A Randomized Double-Blinded, Placebo-Controlled Study of Omalizumab for Idiopathic Anaphylaxis

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Principal Investigator:
Melody Carter, MD, NIAID/LAD

Associate Investigators:
Dean D. Metcalfe, MD, NIAID/LAD
Hirsh D. Komarow, MD, NIAID/LAD
Irina Maric, MD, CC/DLM
Linda M. Scott, CRNP, NIAID/LAD
Hyejeong Bolan, RN, MSN, NIAID/LAD
Andrea Robin Eisch, RN, NIAID/LAD

Collaborators:
Lawrence B. Schwartz, M.D., Ph.D.
Virginia Commonwealth University, School of Medicine
Thomas A.E. Platts-Mills, M.D. University of Virginia, School of Medicine

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Confidentiality Statement

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Statement of Compliance

The study will be conducted in accordance with the design and specific provisions of this IRB approved protocol, in accordance with the ethical principles that have their origin in the Declaration of Helsinki, and that are consistent with Good Clinical Practice (GCP) and the applicable regulatory requirement(s). The Principal Investigator will assure that no deviation from or changes to the protocol will take place without prior agreement from the Sponsor and documented approval from the IRB, except where necessary to eliminate an immediate hazard(s) to the trial participants. The Principal Investigator will promptly report to the IRB and the Sponsor any changes in research activity and all unanticipated problems involving risk to human subjects, or others.

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List of Abbreviations

β-HCG	human choriogonadotropin
5-HIAA	5-hydroxyindoleacetic acid
ADR	adverse drug reaction
AE	adverse event/adverse experience
ALT	alanine aminotransferase
Anti-HTLV I/II	antibody to HTLV virus types I and II
anti-IgE	antibody against human immunoglobulin E
AST	aspartate aminotransferase
AUC	area under the curve
CBC	complete blood count
CFR	Code of Federal Regulations
CIB	clinical investigator's brochure
COI	conflict of interest
CRIMSON	Clinical Research Information Management System of the NIAID
CTCAE	Common Terminology Criteria for Adverse Events
DCR	Division of Clinical Research
DHHS	Department of Health and Human Services
DSMB	Data and Safety Monitoring Board
ESR	erythrocyte sedimentation rate
FcεRI	high-affinity IgE receptor
FDA	Food and Drug Administration
HIPAA	Health Insurance Portability and Accountability Act
ICF	informed consent form
ICH	International Conference on Harmonization
IA	idiopathic anaphylaxis
IgA	immunoglobulin A
IgE	immunoglobulin E
IgG	immunoglobulin G
IgM	immunoglobulin M
IND	Investigational New Drug
IRB	Institutional Review Board
ISM	indolent systemic mastocytosis
MedDRA ©	Medical Dictionary for Regulatory Activities
N	number (typically refers to participants)
NIAID	National Institute of Allergy and Infectious Diseases
NIH	National Institutes of Health
OCRPRO	Office of Clinical Research Policy and Regulatory Operations
OHRP	Office for Human Research Protections
OHSRP	Office of Human Subjects Research Protections
PAF	platelet activating factor
PFT	pulmonary function test
PI	Principal Investigator

List of Abbreviations

PK	pharmacokinetics
PT	prothrombin time
PTT	partial thromboplastin time
QA	quality assurance
RAST	Radioallergosorbent test
RES	reticuloendothelial system
SAE	serious adverse event/serious adverse experience
SC	subcutaneous
SOP	standard operating procedure
UP	Unanticipated Problem
UPnonAE	Unanticipated Problem that is not an Adverse Event
WHO	World Health Organization

Protocol Summary

Full Title	A Randomized Double-Blinded, Placebo-Controlled Study of Omalizumab for Idiopathic Anaphylaxis
Short Title	Omalizumab in the Treatment of Idiopathic Anaphylaxis
Clinical Phase	Phase II
IND Sponsor	OCRPRO/DCR/NIAID/NIH
Conducted By	NIAID/LAD
Principal Investigator	Melody Carter, MD
Sample Size	N=20
Accrual Ceiling	30
Study Population	Adults 18-70 years of age
Accrual Period	72 months
Study Design	Randomized, double-blind, placebo-controlled trial
Study Duration	Start Date: January 2009 End Date: January 2017
Study Agent/ Intervention Description	Omalizumab, FDA-approved for asthma, will be given every 2-4 weeks to patients with idiopathic anaphylaxis. Omalizumab will be administered in a double-blind placebo-controlled manner to assess efficacy in this patient population.
Primary Objective	To determine if treatment with omalizumab will reduce unprovoked anaphylaxis in subjects with a history of idiopathic anaphylaxis.
Secondary Objectives	•Assess pharmacodynamics. • Determine the frequency of the D816V mutation in *c-kit* in patients with idiopathic anaphylaxis. • Identify patients with undiagnosed mastocytosis.
Exploratory Objectives	•Investigate cellular and molecular mechanisms of signaling and the effect of omalizumab on mast cells and/or basophils. •Explore other regulatory pathways that may be involved with modulation of mast cell degranulation.
Endpoints	Primary: Reduction in number and timing of documented anaphylactic events. Secondary: • A ≥50% reduction of the IgE receptor on surface of basophils. • Document changes in mast cell mediator-type symptoms associated with anaphylaxis. • Identify persons with activating mutations of c-kit or other abnormal markers in mast cells.

1.0 Précis

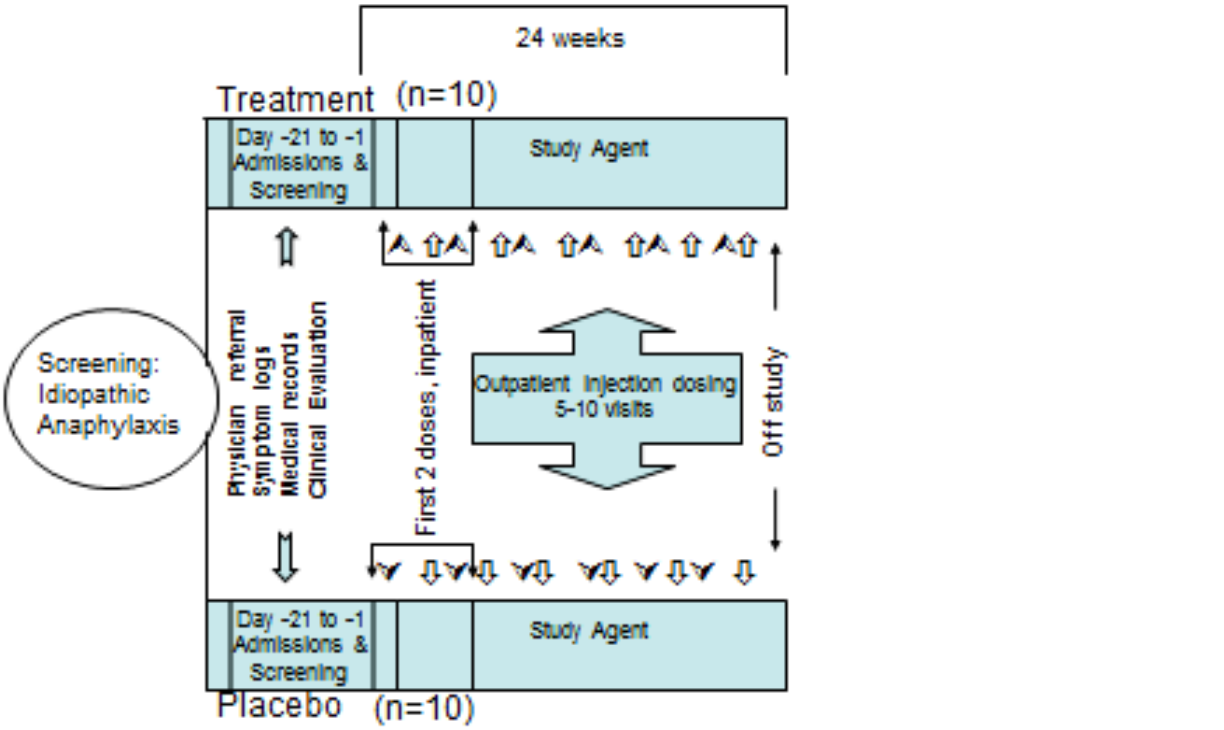
Anaphylaxis is a severe systemic reaction caused by release of mediators from mast cells and basophils. Manifestations include cutaneous, respiratory, cardiovascular, or gastrointestinal signs and symptoms. Although anaphylaxis is frequently attributed to exposure to specific foods, drugs, and insect venoms in sensitive individuals, a causative factor is not identified in 30% to 50% of patients with recurrent anaphylactic episodes (idiopathic anaphylaxis) [1-3].

Currently, therapeutic options for the treatment of idiopathic anaphylaxis are limited with variable efficacy. This pilot study will examine the hypothesis that omalizumab (Xolair®) will decrease episodes of unexplained anaphylaxis in patients with idiopathic anaphylaxis. Omalizumab is approved for use in asthma. We will examine the safety profile and efficacy of omalizumab in patients with anaphylaxis. In addition, the study will investigate whether patients with anaphylaxis have unique molecular and cellular defects in mast cells that result in these cells being more susceptible to degranulation.

The study will enroll patients with idiopathic anaphylaxis. Patients will undergo a clinical evaluation, blood tests, and a bone marrow biopsy and aspirate. Patients will be randomized to either drug or placebo and will receive, in a double-blind placebo-controlled approach, 2 doses of omalizumab or a matched placebo while hospitalized, followed by continued outpatient therapy, every 2 to 4 weeks, for up to 12 months. Patients will remain on the assigned regimen if they have experienced anaphylactic events (post 24-hr window) determined to be unrelated to study agent or have been followed for 6 months, whichever comes first. These unrelated events would be determined by the PI not to jeopardize patient safety or restrict the use of additional therapy such as corticosteroids to control symptoms. After this point, the patient may be discontinued from drug administration until unblinding. This design ensures that no patient will have anaphylactic episodes while on placebo if other therapy is medically indicated. Research studies will be conducted to elucidate other markers or pathways of mast cell regulation.

The primary outcome will be a reduction in the number and timing of anaphylactic events during the randomized phase. Secondary outcomes will include a reduction in surface IgE receptors on basophils, identification of mutations in *c-kit*, and evaluation of the efficacy of omalizumab on other mediator-induced symptoms associated with anaphylaxis. The study will improve the understanding of the mechanisms involved in anaphylactic reactions as a response to the downregulation of mechanisms involved in mast cell activation that could, in turn, lead to development of strategies to better prevent or treat anaphylaxis.

Schematic of Study Design



**Pt on the two-week dosing schedule will receive injections on the 15 day & 30 day time points

§ Pt with > 2 anaphylactic events will discontinue study drug (see Section 4.1)

2.0 Background Information and Scientific Rationale

2.1 Background Information

Anaphylaxis is a systemic reaction associated with release of mediators from mast cells and basophils [4]. Signs and symptoms of anaphylaxis include generalized flushing, urticaria, nasal congestion, conjunctival irritation, bronchospasm, angioedema of the tongue, throat, palms, and soles, gastrointestinal cramping, lightheadedness, and loss of consciousness. The clinical outcome in anaphylaxis varies from a self-limited episode to fatal circulatory collapse. The occurrence of anaphylaxis reported in epidemiologic studies suggest that 1.2% to 16.8% of the U.S. population suffer from an anaphylactic reaction based on the prevalence of allergic patients and that this population have a 0.0002% annual risk of death [5]. Common causes of anaphylaxis include allergic reactions to foods, drugs, and stinging insects. A causative factor, however, is not identified in up to 50% of the patients with recurrent anaphylactic episodes. Therefore, idiopathic anaphylaxis (IA) becomes a diagnosis of exclusion after other causes have been ruled out in these patients. Idiopathic anaphylaxis is categorized as frequent (2 episodes in the past 2 months or 6 episodes in the past year) or infrequent (<6 episodes in the past year) [6].

Tyrosine kinases have been shown to play a key role in the initial stages of high-affinity IgE receptor (FcεRI) activation and subsequent downstream signaling events that lead to mediator release [7]. Animal model studies have demonstrated that other pathways which lead to mast cell activation may play a role in the pathogenesis of anaphylaxis. In mouse models of anaphylaxis, serum levels of sphingosine -1-phosphate, a key mediator of immune cell trafficking, was shown to increase mast cell responsiveness and susceptibility to degranulation [8]. Another mouse model demonstrated abnormal expression of the “regulator of G protein signaling 13” that resulted in increased mast cell degranulation and allergic responses [9]. More recently, it has been reported that platelet activating factor (PAF), a phospholipid secreted by masts cells, and PAF acetylhydrolase levels may correlate with severity of anaphylaxis [10]. Although, other pathways may be involved with mast cell degranulation, the cross-linking of the IgE receptor on the surface of mast cells [7] and basophils [11] remains the major activation pathway.

In human mast cells, the influence of the D816V activating mutation in the tyrosine kinase KIT leads to mast cell proliferation and mastocytosis, which itself is associated with an increase in anaphylactic events. In a clinical study, we evaluated patients with idiopathic anaphylaxis to determine if some might have the D816V mutation. Some of these patients who had syncopal or near-syncopal episodes with 1 or more symptoms suggestive of mast cell degranulation also expressed an aberrant mast-cell population carrying the *c-kit* D816V mutation [12]. Thus, while these patients may have the characteristic aberrant morphology of mast cells associated with mastocytosis, they did not exhibit the skin lesions of

mastocytosis, had minimal pathologic changes in the bone marrow, and presented with recurrent anaphylactic episodes. It is therefore possible that some patients with idiopathic anaphylaxis may have a mutation in KIT, detectable only by sensitive diagnostic techniques, such as flow cytometry, or mutational analysis of the sorted mast cell populations obtained from bone marrow. These techniques are not generally available in local diagnostic laboratories. Although patients with the D816V mutation will not be excluded from the protocol, patients with mastocytosis diagnosed by the WHO criteria (see Appendix C) will not be enrolled in this protocol [13].

Management of anaphylaxis consists of administration of epinephrine, protection of airways, and support of circulation. The pattern of IA is unpredictable as well as the response to therapy and symptoms may cluster with periods of clinical remission. Attempts to control episodes of anaphylaxis with H1 and H2 antihistamines along with systemic corticosteroids cannot be relied upon in all cases to mitigate anaphylactic episodes. Further, corticosteroids are associated with significant side effects which limit dosage and duration of therapy. High-dose prednisone therapy (60-100 mg/day) with daily cetirizine has been shown to control symptoms of anaphylaxis in patients with frequent episodes of idiopathic anaphylaxis. However, patients with frequent episodes of IA were less likely than those with infrequent episodes to respond to corticosteroid therapy and more often required long-term therapy [14]. After 2 to 3 months of therapy, up to 48% of patients from both groups were able to demonstrate remission (no episodes for 1 year and no prednisone) [15]. Although the empiric therapy with prednisone helps to reduce the severity and frequency of episodes, not all patients are able to discontinue prednisone [6]. This lack of targeted therapy for the treatment of anaphylaxis is, in part, a consequence of the relative absence of data on the inflammatory processes that result in systemic anaphylaxis. Thus, anaphylaxis, in general, has been attributed to activation of mast cells and basophils through antigen-induced aggregation of IgE engaged on the high-affinity receptor for IgE, FcεRI, and subsequent release of potent inflammatory mediators such as histamine. However, blockade of such mediators does not prevent anaphylaxis and does not explain why one person allergic to an antigen has a mild reaction while another suffers a severe systemic reaction.

Omalizumab is approved for the treatment of severe asthma, and acts through a mechanism that down regulates the IgE receptor on the surface of basophils, mast cells, and dendritic cells [16]. Recently, omalizumab has been reported to be useful as adjunct therapy in severe food allergy with systemic symptoms (n=84) [17], eosinophilic gastroenteritis (n=9) [18], rush immunotherapy (n=159) [19], chronic urticaria (n=20) [20], chronic autoimmune urticaria (n=12) [21], atopic eczema (n=11) [22], one adult with IA [23], one adult with eczema in the setting of Hyper-IgE syndrome [24], one child with cystic fibrosis and recurrent allergic bronchopulmonary aspergillosis [25], and one child with cold induced-urticaria and anaphylaxis [26]. Similarly, we have reported that omalizumab prevented episodes of spontaneous anaphylaxis in 2 patients with mastocytosis

[27]. In the latter study, in 2 patients with unprovoked episodes of hypotension, omalizumab administration resulted in complete cessation of anaphylactic events that had previously required epinephrine and supportive therapy. In all of these studies there were no reported episodes of anaphylaxis as a result of omalizumab therapy.

Omalizumab now has FDA-approval for the treatment of chronic idiopathic urticaria. Further analysis of adverse event data reported in the 2013 Investigator's brochure states "Xolair treatment was not associated with an increased malignancy risk based on incidence rates per 1000 patient years of 4.14 (14/3382 patient years) for Xolair treated patients and 4.45 (11/2474 patient years) for placebo patients (rate ratio 0.93, 95% confidence interval 0.39-2.27). The overall observed incidence rate of malignancy in the Xolair clinical trial program was comparable to that reported in the general population".
A Recent trial in pediatric asthma have expanded the safety profile in children and was found to be efficacious in children that experienced Fall exacerbations of their allergic diseases [28].

In this protocol, we will enroll patients with IA to assess the efficacy of omalizumab in reducing episodes of anaphylaxis as well as investigate the common and unique features of mast cells in the pathogenesis of anaphylaxis. We will initiate therapy with omalizumab or a matched placebo (every 2-4 weeks) in hospitalized subjects for the first 2 visits (2 consecutive doses at the NIH). Subjects will return to the NIH for subsequent dosing. If subjects experience an anaphylactic event, we will obtain blood for determination of serum tryptase and a tube for research studies at the NIH. The final evaluation will be conducted at the NIH. Research studies will include flow cytometric analysis of blood and bone marrow cells, investigation of mutations or polymorphisms in genes involved in mast cell development, determination of surrogate disease markers, examination of mast cell growth and function, and investigation of alternative pathways involved in regulation of anaphylaxis.

2.1.1 Description of the Study Agents

Omalizumab: Omalizumab (anti-IgE, E25, Xolair®) is a humanized IgG1 monoclonal antibody that binds to the epsilon constant region of IgE and thus prevents the binding of IgE to its high affinity receptor (FcεRI) on mast cells and basophils. Therefore, omalizumab decreases the concentration of free IgE available for binding to mast cells and basophils. By blocking the binding of IgE to FcεRI on effector cells of immediate hypersensitivity, omalizumab inhibits the release of inflammatory mediators [16], inhibits allergic inflammation, improves asthma symptoms, and decreases the need for corticosteroid use [29]. Furthermore, omalizumab treatment in allergic subjects decreases FcεRI surface expression on basophils [30], dendritic cells [31], and presumably mast cells [32]; and as one consequence, basophils and mast cells may be less susceptible to degranulation in general.

Matched-placebo: Matched-placebo study agent will contain the diluents used to reconstitute the active drug and are as follows: sucrose, L-histidine hydrochloride monohydrate, L-histidine, and polysorbate 20.

2.1.2 Summary of Relevant Clinical Studies

Omalizumab significantly increased the tolerance of allergen exposure in oral food challenges [17], and significantly reduced the occurrence of hives in patients with chronic urticaria in a recently completed study [20]. In patients with allergic eosinophilic gastroenteritis, omalizumab reduced IgE expression on basophils, which decreased recruitment of inflammatory cells such as eosinophils in target tissues; patients reported a significant reduction in symptoms scores [18]. Omalizumab administration led to a significant reduction in unprovoked episodes of hypotension in 2 patients with systemic mastocytosis [27]. In these patients, symptoms were reduced from 4-6 episodes per year in the first patient and 14-16 episodes per year in the second patient, to no episodes in either patient while on monthly injections of omalizumab without serious adverse reactions over intervals of 3.5 years and 2 years, respectively.

2.2 Rationale

Omalizumab was initially approved for use in severe allergic asthma, and more recently has been shown to have therapeutic use in other diseases. As mentioned, omalizumab has been shown to have some efficacy in tolerance to oral food challenges [17], the reduction of systemic symptoms including anaphylaxis when utilized in a rush immunotherapy protocol [19], and in a reduction in symptom score as well as a decrease in basophil histamine release in responders with chronic urticaria [20]. Further, there were no serious adverse events associated with administration of omalizumab in these trials. Anaphylactic reactions are life threatening and unpredictable. Symptoms may progress over minutes to hours, and initial signs and symptoms are not always recognized as anaphylaxis as they may be non-specific, such as conjunctival injection. The criteria for the diagnosis of anaphylaxis, as defined in Section 5.1.1, will be used to identify patients for enrollment in this study. An efficacious therapy for management of anaphylaxis would be life-changing for persons with uncontrolled disease. We have shown efficacy in a brief report involving 2 patients with mastocytosis with the D816V mutation and no adverse effects after 2 and 3.5 years, respectively [27]. There are no other studies that have specifically addressed the use of omalizumab as a primary therapy for anaphylaxis.

2.3 Potential Risks and Benefits

2.3.1 Potential Risks of omalizumab

The following are the potential risks and adverse reactions to omalizumab:

2.3.1.1 Anaphylaxis

Anaphylaxis has been reported to occur, on rare occasion, after administration of omalizumab in premarketing clinical trials and in post marketing spontaneous reports. In premarketing clinical trials, the frequency of anaphylaxis attributed to omalizumab use was estimated to be 0.1%. In post marketing spontaneous reports, the frequency of anaphylaxis attributed to omalizumab use was estimated to be 0.2% of patients based on an estimated exposure of about 57,300 patients from June 2003 through December 2006 (Xolair® package insert; Genentech, Inc 2007). Signs and symptoms in these reported cases have included bronchospasm, hypotension, syncope, urticaria, and/or angioedema of the throat or tongue. Some of these events have been life-threatening. Anaphylaxis has occurred as early as the first dose of omalizumab, but also has occurred beyond 1 year after beginning regularly scheduled treatment. In accordance with the most recent data from the FDA, 68% of the anaphylactic reactions occurred in the first 3 doses (39% after 1st dose, 19% after 2nd dose, and 10% after 3rd dose; FDA MedWatch report, July 2007). Further, only 5% of suspected reactions to omalizumab occurred beyond 24 hours. To distinguish anaphylaxis that occurs as a result of the patient's primary disease vs. possible omalizumab-induced episodes of anaphylaxis, the following criterion will be used: anaphylaxis that occurs more than 24 hours after dosing will not be considered to be drug-induced.

In addition, in vitro studies such as the basophil histamine release studies with omalizumab and subject blood samples will be undertaken to evaluate the possibility of a direct cause and effect.

2.3.1.2 Malignancy

Malignant neoplasms were observed in 20 of 4127 (0.5%) omalizumab-treated subjects compared with 5 of 2236 (0.2%) control subjects in clinical studies of asthma and other allergic disorders. The observed malignancies in omalizumab-treated subjects were a variety of types, with breast, non-melanoma skin, prostate, melanoma, and parotid malignancies occurring more than once, and 5 other types occurring once each. The majority of subjects were treated for less than 1 year. The significance or generalizability of these findings are not known, but are currently the focus of Phase 4 studies. The impact of longer exposure to omalizumab or use in subjects at higher risk for malignancy (e.g., elderly, current smokers) is not known (Xolair® package insert; Genentech, Inc 2007).

2.3.1.3 Carcinogenesis, Mutagenesis, Impairment of Fertility, Embryotoxicity, Teratogenicity

No long-term studies have been performed in animals to evaluate the carcinogenic potential of omalizumab. No evidence of mutagenic activity was observed in Ames tests using 6 different strains of bacteria with and without metabolic activation at omalizumab concentrations up to 5000 μg/mL.

The effects of omalizumab on male and female fertility have been assessed in cynomolgus monkey studies. Administration of omalizumab at doses up to and including 75 mg/kg/week did not elicit reproductive toxicity in male cynomolgus

monkeys and did not inhibit reproductive capability, including implantation, in female cynomolgus monkeys. This same study design was used in pregnant cynomolgus monkeys to study the embryotoxicity and teratogenicity of omalizumab. No effects on the fetus were seen at any dose. No reproductive toxicity studies have been performed in humans. These doses studied in monkeys provide a 25- to 50-fold safety factor based on mg/kg dosing, a 2- to 16-fold safety factor based on total dose, and 2- to 5-fold safety factor based on area under the curve (AUC) over the range of adult clinical doses (Xolair® package insert; Genentech, Inc 2007).

Female subjects on study are required to use contraception up to 3 month after the last dose of study agent. Potentially fertile female subjects will have human choriogonadotropin (β-HCG) serum or urine pregnancy tests done prior to every omalizumab injection. Omalizumab will only be administered after a member of the study team confirms a negative pregnancy test result. These procedures will assure that during the period of study agent dosing, all fertile female subjects will have a serum pregnancy test performed a minimum of once every 4 weeks. This frequency is commensurate with the potential risk of the drug as noted above. Omalizumab did not elicit reproductive toxicity or inhibit reproductive capabilities in male cynomolgus monkeys, therefore male subjects do not need to practice contraceptive restrictions but will need to report any pregnancy that occurs with a partner during the study.

2.3.1.4 Other

Since this drug has not yet been used to treat anaphylaxis, there is the possibility of unexpected side effects and unforeseen risks including worsening of symptoms. A 5-year safety study found a slightly higher rate of cardiac and cerebral blood vessel problems occurred in patients being treated with Xolair compared to those patients not treated with Xolair. These included problems such as transient ischemic attacks or TIAs; heart attacks; sudden, unexpected chest pain; pulmonary hypertension; and blood clots in the lungs and veins. Although the data are suggestive of a serious safety signal, due to weaknesses in how the safety study was designed and carried out, the exact increased level of these risks with Xolair cannot be determined.

To further evaluate the cardiac and cerebral risks noted in the 5-year safety study, a review was conducted of a combined analysis of 25 randomized double-blind clinical trials comparing Xolair to placebo. An increased risk of cardiac and cerebral-related problems in patients treated with Xolair was not noted in this combined analysis, but the low number of these events, the young patient population, and the short duration of follow-up prevented reviewers from making any definite conclusions about the absence of a risk.

Since this trial is being conducted for 6 months, the risk for these side effects should be minimal. Because of this possibility, we will collect safety data at all

scheduled visits at the Clinical Center and maintain communication with referring physicians to monitor such side effects while patients are enrolled on protocol.

2.3.2 Potential Risks of other procedures

2.3.2.1 Bone Marrow Biopsy

Subjects will undergo a bone marrow biopsy and aspiration for analyses including for the D816V mutation in KIT as described in Section 7.1.2. This procedure is associated with pain and will result in a small bruise. Anesthesia-conscious sedation will be offered if needed (see below). Infection from the needle puncture is rare, but if this does occur, appropriate treatment will be given. Bleeding at the biopsy site for greater than 2 minutes will be treated with pressure at the site. Pain will be treated with therapy appropriate for severity.

2.3.2.2 Venipuncture

The potential risks of the needle stick for blood drawing include pain, fainting, infection, and bruising or small hematoma. The bruising may last up to 72 hours, and a hematoma is treated with local pressure. Infection from the needle puncture is rare, but if this does occur, appropriate treatment will be given.

2.3.2.3 Skin Testing

Skin testing with allergen extracts is a standard medical procedure that rarely leads to complications. The procedure may lead to mild itching and swelling of the skin. For epicutaneous skin testing, itching and swelling are self-limited and subside within 1-2 hours. The testing leaves no permanent mark on the skin. Skin testing may rarely lead to anaphylaxis. The rate of systemic reactions to skin testing has been reported to be 1 reaction per 3000 patients [33]. Although the risk of anaphylaxis from skin testing is extremely low, medications for treatment of anaphylaxis will be on hand and a physician will be available in the hospital when skin testing is performed. Subjects will stay in the clinic for 30 minutes after the skin testing to monitor for anaphylaxis. RAST testing may also be done as an alternative to skin testing. The risks associated with this procedure are the same for venipuncture, section 2.3.2.2.

2.3.2.4 Anesthesia-Conscious Sedation

In most cases, a bone marrow procedure is done under local anesthesia. Sedation may be required for the performance of the bone marrow biopsy in subjects with a history of prior difficultly with this procedure or extreme anxiety associated with invasive procedures such as syncope. In general, sedation is considered safe; however, there are a number of possible risks including nausea, vomiting, and changes in vital signs (heart rate, breathing rate, and blood pressure). Therefore, this procedure will be conducted in the intensive care unit and administered by specially trained physicians until recovery is complete. A separate consent specific for conscious sedation will be obtained prior to the use of sedation.

2.3.2.5 Pulmonary Function Testing

Pulmonary Function testing is a standard medical procedure that rarely leads to complications.

2.3.3 Potential Benefits

The subjects in the study will benefit from a thorough medical evaluation. Omalizumab has not been used in a controlled clinical trial in subjects with anaphylaxis. Subjects may or may not benefit from the experimental therapy. Subjects may experience a significant reduction in anaphylactic events during the period of omalizumab therapy.

3.0 Study Objectives

3.1 Primary Objective

The primary objective of this study is to determine if treatment with omalizumab over 6 months will produce a reduction in the number and timing of anaphylactic events in subjects with a history of frequent idiopathic anaphylaxis.

3.2 Secondary Objectives

Secondary objectives of this study include the following:

1. Assess the pharmacodynamics of subcutaneously administered omalizumab in subjects with anaphylaxis (free IgE, basophil activation studies).
2. Examine the effects of omalizumab in the immunopathogenesis of anaphylaxis.
3. Identify subjects with the D816V mutation.

3.3 Exploratory Objectives

Exploratory objectives of this study include the following:

1. Investigate cellular and molecular mechanisms of mast cell signaling and the effect of omalizumab on mast cells and/or basophils.
2. Explore other regulatory pathways that may be involved with suppression of mast cell degranulation.

4.0 Study Design

4.1 Description of the Study Design

This is randomized, double-blind, placebo-controlled Phase 2, off-label* study (change in indication, dose and schedule) of commercially available omalizumab and matched placebo in 20 subjects with unprovoked anaphylaxis (10 in each group). Specifically, we intend to use the dosing calculation table in the package insert. This dose has been used safely in other studies where omalizumab was used for off-labeled disease such as chronic urticaria [20, 21]. The first 2 doses will be given at the NIH as an inpatient, then continue on the same interval dosing (every 4 weeks or bi-weekly, depending on the subject's weight and IgE levels) thereafter for up to 6 months with drug being administered at the Clinical

Center's Day Hospital. All subjects will then be followed for 6 months or if they have experienced anaphylactic events (post 24-hr window) determined to be unrelated to study agent, whichever comes first. These unrelated events would be determined by the PI not to jeopardize patient safety or restrict the use of additional therapy such as corticosteroids to control symptoms. After this point, the patient may be discontinued from drug administration until unblinding. These discontinued subjects will complete the follow-up to allow ascertainment of the endpoint. Because of the waiting period for mutational analysis (~4 weeks), subjects will return to begin therapy after the diagnosis of mastocytosis (exclusion criteria) has been ruled out.

*The labeled indication for omalizumab is the treatment of patients with moderate to severe persistent asthma who have a positive skin test or in vitro reactivity to a perennial aeroallergen and whose symptoms are inadequately controlled with inhaled corticosteroids. Omalizumab has been shown to decrease the incidence of asthma exacerbations in these patients.

4.2 Study Endpoints

4.2.1 Primary Endpoint

The primary endpoint for this study is a reduction in the number and timing of anaphylactic events during the 6 month randomized phase.

4.2.2 Secondary Endpoints

The secondary endpoints for this study include the following:

1. Quantify at least a 50% reduction of the IgE receptor on the surface of basophils after 6 months therapy using flow cytometry and correlate with surface expression of IgE on basophils.
2. Document the changes in mast cell mediator-type symptoms associated with anaphylaxis (flushing, vomiting, diarrhea, syncope, pruritus) before and during the 6 months of therapy.
3. Identify persons with the D816V mutation in *c-kit* or other abnormal markers in mast cells with data from flow cytometry and genetic analysis.

4.2.3 Exploratory Endpoints

The exploratory endpoint for this study is to determine if other pathways are involved in the induction of anaphylaxis in these subjects. Exploratory objectives of this study include the following:

- Investigate cellular and molecular mechanisms of mast cell signaling and the effect of omalizumab on mast cells and/or basophils.
- Explore other regulatory pathways that may be involved with suppression of mast cell degranulation.

5.0 Study Population

Volunteers to participate in this study must satisfy all of the following inclusion criteria, but have none of the exclusion criteria.

5.1 **Participant Inclusion Criteria**

Volunteers must satisfy all of the following inclusion criteria to be eligible for this study.

1. Subject must be at least 18 years of age and no older than 70 years of age.
2. Diagnosis of idiopathic anaphylaxis, a diagnosis of exclusion, assigned after other causes of anaphylaxis and other diseases in the differential diagnoses have been considered [6].
3. Anaphylaxis episodes (mild-severe) at least 6 times within the past 1 year period, documented according to medical records, physician report, or patient report, and 1 episode within the last 4 months, and with at least 1 of the following:
    a. Elevated serum tryptase above baseline within 2 hours of the event.
    b. Emergency room visit with documented anaphylaxis without an etiology established by the acute onset of an illness (minutes to several hours) with involvement of the skin, mucosal tissue, or both (e.g., generalized hives, pruritus or flushing, swollen lips-tongue-uvula) [Grade 1]* and at least 1 of the following:
        i. Respiratory compromise or gastrointestinal involvement (e.g., dyspnea, wheeze-bronchospasm, stridor, reduced peak expiratory flow, hypoxemia, nausea, vomiting, or abdominal pain [Grade 2]*).
        ii. Reduced blood pressure or associated symptoms of end-organ dysfunction (e.g., hypotonia [collapse], syncope, or incontinence [Grade 3]*).
    c. Hospitalization for anaphylaxis: hospital records with documented anaphylaxis without known cause established by the acute onset of an illness (minutes to several hours) with involvement of the skin, mucosal tissue, or both (e.g., generalized hives, pruritus or flushing, swollen lips-tongue-uvula) [Grade 1]*) and at least one of the following:
        i. Respiratory compromise or gastrointestinal involvement (e.g., dyspnea, wheeze-bronchospasm, stridor, reduced peak expiratory flow, hypoxemia, nausea, vomiting, or abdominal pain [Grade 2]*).
        ii. Reduced blood pressure or associated symptoms of end-organ dysfunction (e.g., hypotonia [collapse], syncope, or incontinence [Grade 3]*).
4. Letter of referral, with copies of pertinent medical history and laboratory tests, from prospective study participant's local physician.
5. Ability to give informed consent.
6. Women of childbearing potential must have a negative β-HCG serum or urine pregnancy test prior to each injection, and must agree to practice abstinence or effective contraception from initiation of the protocol and for

3 months following the last infusion of the study agent (effective contraception methods include abstinence, surgical sterilization of either partner, barrier methods such as diaphragm, condom, cap, or sponge, or hormonal contraception).

*Severity grading of anaphylaxis [34]

5.2 Participant Exclusion Criteria

A volunteer who satisfies any of the following exclusion criteria will be ineligible to participate in this study.

1. Presence of conditions which, in the judgment of the investigator or the referring physician, may put the subject at undue risk for study participation or travel (such as an acute infection, severe thrombocytopenia, coronary artery disease, uncontrolled hypertension, congestive heart failure, chronic beta blocker therapy such as atenolol or metoprolol, or myeloproliferative disease).
2. History of malignancy
3. Known cause for anaphylaxis or flushing
4. Diagnosis of mastocytosis
5. Inability to provide informed consent
6. Inability or refusal to undergo a bone marrow biopsy and aspirate
7. HIV positive or other known immunodeficiency
8. Active or chronic hepatitis
9. Use of any other investigational agent within 30 days of the study
10. Current use of chronic oral corticosteroids or other immunosuppressant medications
11. Pregnant or nursing women
12. Positive pregnancy test
13. IgE levels and subject's weight that cause dosing to be above dosing guidelines.

5.3 Participation of Children

Children under the age of 18 of age will not be included in the study due to the new data from the FDA (boxed warning) regarding the new risks of omalizumab and anaphylaxis. If this drug is proven safe and efficacious in the adult population, we will consider the addition of children with a protocol amendment.

6.0 Study Agent

6.1 Study Agent Acquisition

The study agent (omalizumab) and placebo-matched control will be obtained from Genentech-Novartis under the OCRPRO Sponsored Trial.

6.2 Study Agent Storage and Stability

Study agent will be stored by the NIH Pharmacy per package insert. The study agent will be prepared in the NIH pharmacy the day of the injection since the drug has to be used within 4 hours of preparation. Unused materials will be returned to Genentech at the end of the study dosing period.

6.3 Preparation, Administration, and Dosage of Study Agent

6.3.1 Study Agent

6.3.1.1 Description

Omalizumab (rhuMAb-E25) is a recombinant DNA-derived, humanized IgG1κ monoclonal antibody that selectively binds to human immunoglobulin E (anti-IgE) (Xolair® package insert; Genentech, Inc 2007. The placebo-matched control will be supplied by Genentech, Inc. and will be an inert product formulated to duplicate the visual appearance as well as physical properties of the drug.

6.3.1.2 Dosing and Administration

The current package insert for using omalizumab is based upon clinical data targeting a reduction in serum IgE to ≤10 IU/mL, and utilizes specifically a dose of 0.008-0.025 mg/kg/IU/mL (IgE) every 2-4 weeks in asthma patients. To simplify dosing calculations for practitioners, the package insert contains a dosing nomogram, based on the subject's serum IgE and weight, which provides drug dosing in this range (Appendix D, Tables 1 and 2). Upper limit of dosing is 375 mg administered subcutaneously. Current understanding of omalizumab pharmacodynamics in asthma and allergic rhinitis suggests that the package insert dose is sufficient to decrease the serum free IgE level by 10- to 30-fold and results in a free serum IgE level of 10 IU/mL. Omalizumab has not been used extensively in anaphylaxis and the pharmacokinetics of the drug in anaphylaxis has not been investigated.

The omalizumab package label limits the maximum dose. Due to this restriction and the requirement for dosing in proportion to the serum IgE, the US package labeling limits omalizumab administration to subjects with high IgE values. For example, the omalizumab package label notes that for a patient weighing more than 70 kg, omalizumab should not be used when serum IgE is greater than 400 IU/mL. Anaphylaxis occurs over a wide distribution of serum IgE values, with some individuals having IgE levels greater than would permit dosing in the current omalizumab dosing scheme in U.S. Thus, the enrollment of anaphylaxis subjects with serum IgE and body mass values that are within the ranges provided by the US package insert will be dosed according to the package insert as shown in Tables 1 and 2. Those subjects whose serum IgE and body mass values are outside of the range of current US package insert will be dosed according to the European dosing guideline (Table 3). Finally, subjects with serum IgE values of <30 IU/mL will receive 150 mg of omalizumab every 4 weeks.

Subsequent dosing (every 2 or 4 weeks) will be administered at the NIH. Patients' whose dosing guideline cannot be determined from the values provided below in US Standard dosing shown in Table 1 or 2, will be dosed according to the guidelines provided in European dosing in Table 3.

Skin testing to determine allergic sensitivity to omalizumab will not done prior to dosing at this time since a specific antigen has not been identified and in accordance with the Joint Task Force of the Academy of Allergy, Asthma, & Immunology and Asthma and Immunology on omalizumab-associated anaphylaxis, it is not currently recommended prior to dosing [35]

6.3.1.3 Omalizumab Dosing Calculation:

Tables 1 and 2 provide omalizumab dosing calculation information obtained from the US package insert. Omalizumab will be dosed at either 4 week intervals, as described in Table 1, or at 2 week intervals, as described in Table 2. Doses for

individuals whose IgE levels fall outside of the ranges provided in Table 1 or 2 will be dosed according to European guidelines provided in Table 3.

Table 1

ADMINISTRATION EVERY 4 WEEKS

Xolair Doses (milligrams) Administered by Subcutaneous Injection

Pre-treatment	**Body Weight (kg)**			
Serum IgE (IU/mL)	30-60	> 60-70	> 70-90	> 90-150
≥ 30-100	150	150	150	300
> 100-200	300	300	300	
> 200-300	300			
> 300-400		**SEE TABLE 2**		
> 400-500				
> 500-600				

Table 2

ADMINISTRATION EVERY 2 WEEKS

Xolair Doses (milligrams) Administered by Subcutaneous Injection

Pre-treatment	**Body Weight (kg)**			
Serum IgE (IU/mL)	30-60	> 60-70	> 70-90	> 90-150
≥ 30-100				
> 100-200		**SEE TABLE 1**		225
> 200-300		225	225	300
> 300-400	225	225	300	
> 400-500	300	300	375	
> 500-600	300	375		
> 600-700	375	**SEE TABLE 3**		

Table 3

ADMINISTRATION EVERY 2 WEEKS

Zolair Doses (milligrams) Administered by Subcutaneous Injection

Pre-treatment	Boby Weight									
Serum IgE (IU/mL)	>20-25	>25-30	>30-40	>40-50	>50-60	>60-70	>70-80	>80-90	>90-125	>125-150
≥ 30-100	SEE TABLE 2									
> 100-200									225	300
> 200-300						225	225	225	300	375
> 300-400				225	225	225	300	300	450	525
> 400-500			225	225	300	300	375	375	525	600
> 500-600			225	300	300	375	450	450	600	
> 600-700		225	225	300	375	450	450	525		
> 700-800	225	225	300	375	450	450	525	600		
> 800-900	225	225	300	375	450	525	600			
> 900-1000	225	300	375	450	525	600				
> 1000-1100	225	300	375	450	600					
> 1100-1200	300	300	450	525	600	DO NOT ADMINISTER-data is unavailable for dose recommendation				
> 1200-1300	300	375	450	525						
> 1300-1500	300	375	525	600						

6.3.1.4 Route of Administration

The drug or placebo-matched product will be injected subcutaneously every 2-4 weeks x 2 total doses at NIH (first two doses as an inpatient and subsequent doses in the day hospital), then every 2-4 weeks thereafter (up to 12 months) based on initial dosing schedule. The placebo dose will be based on the same criteria as the active drug in order to have a uniform volume of the injection material.

6.3.1.5 Dose Adjustments/Modifications/Delays

The dose may be withheld in the event of serious related or unrelated illness or adverse event (e.g., drug related or cardiac arrest). There will be no other dosage modifications.

6.3.1.6 Duration of Therapy

Subjects may remain on the assigned regimen (post 24-hour drug administration period) if they have experienced anaphylactic events determined to be unrelated to study agent or have been followed for 6 months, whichever comes first. These unrelated events would be determined by the PI not to jeopardize patient safety or restrict the use of additional therapy such as corticosteroids to control symptoms. After this point, the patient may be discontinued from drug administration until unblinding. This design ensures that no patient will have repeated anaphylactic episodes while on placebo if other therapy is medically

indicated. If significant efficacy is demonstrated, we will initiate communication with the subject's insurance company for financial support to continue therapy.

6.3.1.7 Tracking of Dose

Dose will be documented on the medication form or in CRIS.

6.3.1.8 Use of Ancillary Medications/OTC Products/Foods

There are no known contraindications with medications or food and omalizumab.

6.3.1.9 Participant Access to Study Agent at Study Closure

We will communicate our findings to the patient's primary physician and insurance company if significant efficacy is demonstrated for continued support for maintenance, off-label therapy.

6.4 Assessment of Participant Compliance with Study Agent

See Appendix F, which will be completed by the study team.

6.5 Prohibited and Precautionary Medications and Procedures

No formal drug interaction studies have been preformed with omalizumab. The concomitant use of omalizumab and allergen immunotherapy has been evaluated in patients receiving rush immunotherapy [19]. Subjects will not be allowed to initiate chronic systemic corticosteroid therapy for anaphylaxis while on the study. If chronic systemic corticosteroids are needed the subject will be removed from the study. Short term corticosteroid use for emergent therapy is permitted as well as inhaled corticosteroids for respiratory illnesses such as asthma.

6.6 Rescue Medications

Use of epinephrine and other drugs for treatment of anaphylaxis are allowed as needed for anaphylaxis events.

7.0 Study Procedures/Evaluations

7.1 Clinical Evaluations (Appendix B) for 2 week (+/- 3 days) and 4 week (+/- 3 days) dosing

7.1.1 Screening Visit – (Inpatient or Outpatient)

If a patient is deemed eligible based on supporting documents, no screening visit is necessary. We will not repeat laboratory tests that have been obtained prior to the first patient visit, if completed within 3 months of the study, with the exception of a pregnancy test for women of childbearing potential, if not done within the past 30 days. Determination of eligibility based on prior bone marrow biopsy studies will be at the discretion of the study PI.

1. Medical History and physical examination.

2. Blood tests in each subject will consist of a complete blood count with differential, acute care panel, hepatic panel, mineral panel, prothrombin time (PT) as medically indicated, partial thromboplastin time (PTT) as medically indicated, total serum IgE, serum tryptase level, hepatitis profiles, HIV test, anti-HTLV I/II, and for women of childbearing potential, a β-HCG serum or urine pregnancy test. Additional tests will be ordered as clinically indicated for each subject's condition. Tests may include urinalysis, urine for 5-hydroxyindoleacetic acid (5-HIAA), radioallergosorbent (RAST) testing for specific allergens and/or skin testing. Additional blood will be collected for research studies as needed (section 4.2.2). The total volume of blood drawn for all testing and during all visits will not exceed 10.5 mL/kg or 550 mL, whichever is smaller, over any 8-week period for adult patients (i.e. those persons 18 years of age or older). This information may be obtained from a prior procedure at the Clinical Center; however these tests will be carried out if not obtained in the last 3 months prior to enrollment.
3. Bone marrow biopsy and aspirate analysis will include routine diagnostic processing and staining of the biopsy and aspirate, tryptase staining of biopsy for mast cells, flow cytometric analysis of the aspirate for abnormal mast cell markers CD2, CD25 or basophil activation studies for degranulation studies, and *c-kit* mutational analysis (if not done prior to enrollment). It is anticipated that most subjects will complete this evaluation as in-patients. Bone marrow biopsy and aspirate will be performed on the 3SW-N procedure unit (sedation will be available on an as-needed basis) by an Associate Investigator (PI) or hematology consult service.
    a. Genetic testing
    Mutations in *c-kit* may be most reliably identified in the mononuclear fraction of a bone marrow aspirate. We also will investigate the presence of polymorphisms or mutations in other genes that regulate mast cell activation.
    This process entails counseling by study investigators as to the significance of positive vs. negative findings. Unanticipated genetic information such as paternity or differences unrelated to a disease process, will not be divulged to the participants in this study and all medical information will remain highly confidential as part of the research records. Information regarding genetic polymorphisms and gene mutations on tested blood specimens will only be given to participants on request. This information will not be shared with any employer or insurance company unless requested by the subject. Such information will only be released when the participant’s DNA base change in KIT or other polymorphisms associated with mast cell growth and differentiation has been confirmed by the appropriate genetic sequencing tests performed in our laboratory. Only the individuals performing the genetic testing on the blood samples will have access to the blood samples of the respective participants. All

information pertaining to the study of genes will be maintained in locked study files.

4. Skin testing will be performed as medically indicated in subjects where a new causative mechanism for anaphylaxis needs to be ruled out prior to enrollment in the treatment protocol.
5. Pulmonary function tests (PFTs) will be performed prior to skin testing, if medically indicated. The subject is instructed to blow hard for ~ 6 seconds into a tube connected to a spirometer to measure the forced expiratory volume during 1 second (FEV_1). An FEV_1 value of >70% of predicted is required to undergo skin testing.
6. Consultations will be requested as medically indicated.
7. Upon completion of testing, the subject will receive the first dose of omalizumab or matched placebo according to directions on the package insert. All subjects will be observed for approximately 24 hours as in-patients.

7.1.2 First Visit- Inpatient

1. Medical history and Physical examination.
2. Blood tests in each subject will consist of a total serum IgE (as needed), serum tryptase level (as needed), research blood (as needed), and for women with child-bearing potential, a β-HCG serum (as indicated) or urine pregnancy test (as indicated). Additional tests will be ordered as clinically indicated by each subject's condition.
3. Consultations will be requested as medically indicated.
4. The subject will receive the first dose of omalizumab or matched placebo. All subjects will be observed for approximately 24 hours as in-patients.
5. There will be standard nursing orders to include: Epi-Pen at bedside, vital signs should be monitored once per shift, or as needed based on the patient’s condition, and other standard orders as appropriate.

7.1.3 Second Visit – Inpatient

1. Medical history and Physical examination.
2. Blood tests in each subject will consist of a serum tryptase level, research blood (as needed), and for women with child-bearing potential, a β-HCG serum or urine pregnancy test. Additional tests will be ordered as clinically indicated by each subject's condition.
3. Consultations will be requested as medically indicated.
4. The subject will receive the second dose of omalizumab or matched placebo. All subjects will be observed for approximately 24 hours as in-patients. (Women will receive the second dose upon receiving the results of pregnancy testing.)

7.1.4 Follow-up Visits – Outpatient (Visits 3, 4 and 5, see appendix for q 2 week dosing)

1. Interval history and physical examination.

2. Upon completion of serum or urine pregnancy testing for women of childbearing potential, the subject will receive the next scheduled dose of omalizumab or matched placebo, and will be observed in the Clinical Center for a period of approximately 2 hours
3. Research blood (at 16 weeks (visit 5 for Q4 week dosing or visit 9 for Q2 week dosing)).

7.1.5 NIH Final Treatment Visit (Visit 6)

1. Focused History and physical examination.
2. Blood tests in each subject: complete blood count with differential, acute care panel, hepatic panel, , serum tryptase levels, hepatitis profiles, anti-HTLV I/II, and for women of childbearing potential, a β-HCG serum or urine pregnancy test. Additional tests will be ordered as clinically indicated for each subject's condition. Additional blood may be collected for research studies.
3. The subject will receive the next scheduled dose of omalizumab or matched placebo, and will be observed in the Clinical Center for a period of approximately 2 hours

7.1.6 Off Treatment Follow-up (Visit 7)

After completion of study agent administration, patients will be monitored by their referring physicians who will continue to document any anaphylactic events. All patients will be scheduled to return to the NIH 6 months (+/- 30 days) after receiving the final dose of study agent or early withdrawal from the protocol due to adverse events or medical conditions determined to be a safety issue by the research team. The following indications may dictate a follow-up visit to the NIH: 1) an adverse event (Grade 3) possibly attributed to study agent, 2) Change in clinical status that may be associated with study agent such as non-anaphylactic adverse events. If necessary, the subject will return to the NIH within 1 month for a follow-up visit which may include:

1. History and physical examination.
2. Blood tests in each subject: complete blood count with differential, acute care panel, hepatic panel (as indicated), IgE, serum tryptase levels, hepatitis profiles (as indicated), anti-HTLV I/II (as indicated), and for women of childbearing potential, a serum or urine β-HCG test for pregnancy. Additional tests will be ordered as clinically indicated for each subject's condition. Additional blood may be collected for research studies.
3. Possible bone marrow procedure for correlation of downregulation of the IgE receptor on the surface of basophils to bone marrow mononuclear cells or mast cells.

7.2 Biohazard Containment

Because HIV and other blood-borne pathogens can be transmitted through contact with contaminated needles, blood, and blood products; appropriate blood and secretion precautions will be employed by all personnel in the drawing of

blood, and in the shipping and handling of all specimens for this study, as currently recommended by the Centers for Disease Control and Prevention and the National Institutes of Health.

8.0 Stored Samples

8.1 Use of Stored Samples

During this study, extra blood and bone marrow aspirate samples will be collected and stored for future research. Samples may be used and tested at a later time but the results of the investigational tests will not be available in the medical records. If the subject is interested in learning about them, someone from the study team will discuss the results with the subject. The subject may also request that those results be shared with the subject's private doctor.

For a select group of enrolled patients, blood samples that are labeled according to a code with no personally identifiable information will be sent to outside collaborators, Lawrence B. Schwartz, M.D., Ph.D. and Thomas A.E. Platts Mills, M.D. for measurement of serum fractionated tryptase levels and galactose-a-1,3-galactose (alpha-gal) assays.

To protect each subject's privacy, all of the subject's samples will be labeled with a code that only the study team can link to that subject. Any identifying information about the subject will be kept confidential to the extent permitted by law. In the future, other investigators (both at NIH and outside) may wish to study these samples. When the study team shares the samples, they will all be labeled with a code. Some general information about the subject such as the subject's gender, age, health history, or ethnicity may also be shared with other investigators. The study team will not sell any samples and the samples will be used only for research purposes. If the future studies require additional information, the study team will contact the subject for separate consent.

In the future, other investigators (both at NIH and outside) may wish to study these samples and/or data. In that case, IRB approval must be sought prior to any sharing of samples. Any clinical information shared about the sample would similarly require prior IRB approval.

8.2 Disposition of Stored Samples

1. Access to stored samples will be limited using [either a locked room or a locked freezer]. Samples and data will be stored using codes assigned by the investigators. Data will be kept in password-protected computers. Only investigators will have access to the samples and data.
2. Samples acquired will be tracked (Biological Specimen Inventory System BSI ®).

3. Any loss or unanticipated destruction of samples of >25% (for example, due to freezer malfunction) or that compromises the scientific integrity of the data collected for the study will be reported to the NIAID IRB.

9.0 Assessment of Safety

9.1 Adverse Event Recording/Documentation

At each contact with the subject, information regarding adverse events will be elicited by appropriate questioning and examinations and will be immediately recorded on a source document. Source documents will include: progress notes, laboratory reports, consult notes, phone call summaries, survey tools, and data collection tools. Source documents will be reviewed in a timely manner by the research team. All grades of adverse events that are possibly, probably, or definitely related to study agent will be recorded on an appropriate case report form (CRF). All AEs will be recorded on a CRF regardless of attribution. The start date, the stop date, the severity of each reportable event, and the PI's judgment of the AEs relationship to the study agent/intervention will also be recorded on the CRF. For the purposes of this study CRIMSON will serve as both source and CRF.

9.1.1 Definitions

Adverse Event (AE)
An adverse event is any untoward or unfavorable medical occurrence in a human subject, including any abnormal sign (e.g., abnormal physical exam or laboratory finding), symptom, or disease, temporally associated with the subject's participation in the research, whether or not considered related to the research.

Adverse Reaction (AR)
An adverse event that is caused by an investigational agent (drug or biologic).

Suspected Adverse Reaction (SAR)
An adverse event for which there is a reasonable possibility that the investigational agent caused the adverse event. 'Reasonable possibility' means that there is evidence to suggest a causal relationship between the drug and the adverse event. A suspected adverse reaction implies a lesser degree of certainty about causality than adverse reaction which implies a high degree of certainty.

Serious Adverse Event (SAE)
A Serious Adverse Event is an AE that results in one or more of the following outcomes:

- death
- a life threatening (i.e., an immediate threat to life) event
- an inpatient hospitalization or prolongation of an existing hospitalization
- a persistent or significant incapacity or substantial disruption of the ability to conduct normal life functions
- a congenital anomaly/birth defect

- a medically important event*

* Medical and scientific judgment should be exercised in deciding whether expedited reporting is appropriate in other situations, such as important medical events that may not be immediately life threatening or result in death or hospitalization but they may jeopardize the subject or may require intervention to prevent one of the other outcomes listed above.

Unexpected Adverse Event
An AE is unexpected if it is not listed in the Investigator's Brochure or Package Insert (for marketed products) or is not listed at the specificity or severity that has been observed. It is the responsibility of the IND Sponsor to make this determination.

Serious and Unexpected Suspected Adverse Reaction (SUSAR)
A SUSAR is a Suspected Adverse Reaction that is both Serious and Unexpected.

Unanticipated Problem (UP)
An Unanticipated Problem is any event, incident, experience, or outcome that is

1. unexpected in terms of nature, severity, or frequency in relation to
   a. the research risks that are described in the IRB-approved research protocol and informed consent document; Investigator's Brochure or other study documents; and
   b. the characteristics of the subject population being studied; and
2. possibly, probably, or definitely related to participation in the research; and
3. places subjects or others at a greater risk of harm (including physical, psychological, economic, or social harm) than was previously known or recognized. (Per the IND Sponsor, an AE with a serious outcome will be considered increased risk.)

Unanticipated Problem that is not an Adverse Event (UPnonAE)
Unanticipated problem that is not an Adverse Event (UPnonAE): An unanticipated problem that does not fit the definition of an adverse event, but which may, in the opinion of the investigator, involve risk to the subject, affect others in the research study, or significantly impact the integrity of research data. Such events would be considered a non-serious UP. For example, we will report occurrences of breaches of confidentiality, accidental destruction of study records, or unaccounted-for study drug

Protocol Deviation: Any change, divergence, or departure from the IRB approved study procedures in a research protocol. Protocol deviations are designated as serious or non-serious and further characterized as

1. Those that occur because a member of the research team deviates from the protocol.
2. Those that are identified before they occur, but cannot be prevented.
3. Those that are discovered after they occur

Serious Protocol Deviation: A deviation that meets the definition of a Serious Adverse Event or compromises the safety, welfare or rights of subjects or others.

Non-compliance: The failure to comply with applicable NIH HRPP policies, IRB requirements, or regulatory requirements for the protection of human subjects. Non-compliance is further characterized as

1. Serious: Non-compliance that
    a. Increases risks, or causes harm, to participants
    b. Decreases potential benefits to participants
    c. Compromises the integrity of the NIH-HRPP
    d. Invalidates the study data
2. Continuing: Non-compliance that is recurring
3. Minor: Non-compliance that, is neither serious nor continuing.

9.2 Assessing Adverse Events

9.2.1 Adverse Event Grading (Severity) Scale

The NCI Cancer Therapy Evaluation Program Common Terminology Criteria for Adverse Events version 3.0 (CTCAE) will be used to grade adverse events which can be found at http://ctep.cancer.gov/protocolDevelopment/electronic_applications/docs/ctcaev3.pdf (see Appendix A)

All other laboratory and clinical AEs that occur in a subject will be assessed for severity and classified into 1of the categories below.

- **Grade 1 (Mild):** The event requires minimal or no treatment and does not interfere with the subject's daily activities.
- **Grade 2 (Moderate):** The event results in a low level of inconvenience or concern with the therapeutic measures. Moderate events may cause some interference with functioning.
- **Grade 3 (Severe):** The event interrupts a subject's usual daily activity and may require systemic drug therapy or other treatment. Severe events are usually incapacitating.
- **Grade 4 (Life Threatening):** Any adverse drug experience that places the subject or participant, in the view of the investigator, at immediate risk of death from the reaction as it occurred, i.e., it does not include a reaction that had it occurred in a more severe form, might have caused death.
- **Grade 5 (Death)**

9.2.2 Adverse Event Relationship to Study Procedures

For all collected AEs, the clinician who examines and evaluates the subject will determine the adverse event's causality based on temporal relationship and his/her clinical judgment. The degree of certainty about causality will be graded using the categories below.

- **Definitely Related:** There is clear evidence to suggest a causal relationship, and other possible contributing factors can be ruled out. The clinical event, including an abnormal laboratory test result, occurs in a plausible time relationship to drug administration and cannot be explained by concurrent disease or other drugs or chemicals. The response to withdrawal of the drug (dechallenge) should be clinically plausible. The event must be pharmacologically or phenomenologically definitive, with use of a satisfactory rechallenge procedure if necessary.
- **Probably Related:** There is evidence to suggest a causal relationship, and the influence of other factors is unlikely. The clinical event, including an abnormal laboratory test result, occurs within a reasonable time sequence to administration of the drug, is unlikely to be attributed to concurrent disease or other drugs or chemicals, and follows a clinically reasonable response on withdrawal (dechallenge). Rechallenge information is not required to fulfill this definition.
- **Possibly Related:** There is some evidence to suggest a causal relationship (e.g., the event occurred within a reasonable time after administration of the trial medication). However, the influence of other factors may have contributed to the event (e.g., the subject's clinical condition, other concomitant events). Although an adverse drug event may rate only as "possibly related" soon after discovery, it can be flagged as requiring more information and later be upgraded to "probably related" or "definitely related", as appropriate.
- **Unlikely:** A clinical event, including an abnormal laboratory test result, whose temporal relationship to drug administration makes a causal relationship improbable (e.g., the event did not occur within a reasonable time after administration of the trial medication) and in which other drugs or chemicals or underlying disease provides plausible explanations (e.g., the subject's clinical condition, other concomitant treatments).
- **Unrelated:** The AE is completely independent of study agent administration, and/or evidence exists that the event is definitely related to another cause. There must be an alternative, definitive cause documented by the clinician.

9.3 Adverse Event Reporting Procedures

9.3.1 Expedited Reporting to the NIAID IRB

Serious and non-serious Unanticipated Problems, deaths, serious deviations, and serious or continuing non-compliance will be reported within 7 calendar days of investigator awareness. Serious Adverse Events that are possibly, probably, or definitely related to the research will be reported to the NIAID IRB within 7 calendar days of investigator's awareness, regardless of expectedness.

9.3.2 Annual Reporting to the NIAID IRB

The following items will be reported to the NIAID IRB in summary at the time of Continuing Review:

- Serious and non-serious unanticipated problems
- Expected serious adverse events that are possibly, probably, or definitely related to the research
- Serious adverse events that are not related to the research
- All adverse events, except expected AEs and deaths granted a waiver of reporting.
- Serious and Non-Serious Protocol deviations
- Serious, continuing, and minor non-compliance
- Any trends or events which in the opinion of the investigator should be reported

Any protocol-specific reporting requirements as per sponsor and pharmaceutical support/provider.

9.3.3 Reporting Adverse Events to Genentech

Adverse events (SAE/AEs) that are possibly, probably, or definitely related to study agent will be reported to Genentech using the same time intervals for reporting to the IRB outlined above in section 9.5.1.1.

9.3.4 Reporting Responsibilities to the Sponsor

9.3.4.1 Adverse Events

Line listings, frequency tables, and other summary AE data will be submitted to the IND Sponsor when needed for periodic safety reviews, review of IND annual reports, review of IND safety reports, and preparation of final study reports.

9.3.4.2 Serious Adverse Events

SAEs (whether or not they are also UPs) must be reported on the SAE/UP Report Form and sent to the Sponsor Clinical Safety Office (CSO) by fax or e-mail attachment. Deaths and immediately life threatening SAEs must be reported within 1 business day after the site becomes aware of the event. All other SAEs must be reported within 3 business days of site awareness.

SPONSOR CLINICAL SAFETY OFFICE CONTACT INFORMATION:

Clinical Safety Office
5705 Industry Lane
Frederick, MD 21704

Phone 301-846-5301
Fax 301-846-6224
E-mail: rchspsafety@mail.nih.gov

9.3.4.3 Unanticipated Problems

Non-Serious AEs that are UPs must also be reported on the SAE/UP Report Form and sent to the CSO by fax or e-mail attachment no later than 7 calendar days of site awareness of the event. The UPs that are not AEs are not reported to the Sponsor CSO.

9.4 Sponsor's Reporting Responsibilities

Serious and unexpected suspected adverse reactions (SUSARs) as defined in 21 CFR 312.32 and determined by the IND Sponsor will be reported to FDA and all participating Investigators as IND Safety Reports.

The IND Sponsor will also submit an IND Annual Report of the progress of the investigation to the FDA as defined in 21 CFR 312.33.

9.5 Type and Duration of the Follow-up of Participants after Adverse Events

AEs may be observed by the Investigator and/or study staff, elicited from the subject and/or family member, reported on subject diary cards, or volunteered by the study subject. Adverse events that had previously been reported by the study subject will also be reassessed for duration, intensity, and possible reoccurrence. Assessment of safety will include clinical observation and monitoring of hematological, chemical, and immunologic parameters.

Any AE that occurs between the times a study participant signs the informed consent form and the time s/he departs the study at the end of the final follow-up visit (or at the time of early discontinuation of the subject from the study for any reason) will be captured and recorded.

Primary care of the subject's initial medical condition will continue to be under the auspices of his or her local medical provider. A letter describing the study will be sent to the subject's primary care physician. The local medical provider will be instructed verbally and with written guidelines to contact the NIH investigators immediately for any adverse event. A toll-free number will be available to provide 24-hour access to the Principal Investigator or designee. The subject's primary

care provider(s) will be encouraged to call the PI should any change in condition be noted as compared to the subject's baseline status. Should the occasion arise, subjects may also be treated at the NIH Clinical Center.

9.5.1.1 Reporting of Pregnancy

The investigators will report within 15 days of the site's awareness this reportable event to the IRB & Genentech. All pregnancies will be followed until outcome, if subject is willing, and any congenital abnormality will be reported to the Sponsor and IRB.

9.5.1.2 Follow-up of Participants after Adverse Events

All SAEs and non-serious AEs reported in this study will be followed until resolution or until the investigator and the clinical/medical monitor are in agreement that the AE/SAE has stabilized and no more follow-up is required. This requirement indicates that follow-up may be required for some events after the patient discontinues participation in the study. Subjects with SAEs that are possibly, probably, or definitely related to drug may be asked to return for a visit in 30 $\pm$ 10 days. These events will be reported to the FDA annually.

9.6 Halting Rules for the Protocol

The protocol will be suspended for new enrollment if two grade 3 severe adverse events documented to be associated with the administration of study agent within 24 hours of the study agent that requires an emergency room visit or hospitalization for anaphylaxis in 2 or more subjects. An urgent review will be requested of the DSMB to determine if the safety of the remaining participants is compromised and if the study should continue. Grade 2 or below serious possibly or probably-related adverse events will not stop the protocol. Medical events determined to be unrelated to study agent administration will not be a reason to halt the protocol; however, a report will be sent to the DSMB and the FDA for documentation of such events.

9.6.1 Unblinding of the Study

9.6.1.1 Scheduled Unblinding

The study will be unblinded after all 20 volunteers have been enrolled and completed the Day 180 study visit. Enrolled subjects that do not complete 180 days due to anaphylactic events deemed associated with study agent or those with more than 2 events will be followed until the end of their projected study period. At that time, efficacy data from Study Days -180 and Day 180 will be reviewed, along with the safety data collected through Study Day 180.

9.6.1.2 Intentional, Unscheduled Unblinding for Treatment Conditions

Prior to breaking the treatment blind, consultation with the PI or the Medically Accountable Investigator will be done. The research pharmacist will keep the

treatment code list locked in a secure area and can be reached 24 hours a day to rapidly access subject unblinding codes if necessary. If a subject's drug assignment is unblinded, the information will be provided to only the individuals needing it for treatment decisions, with documentation of the event and the reason for unblinding recorded in the subject's research record. The PI should immediately report all cases involving emergency unblinding to the Sponsor.

The PI must report all case of unblinding, intentional or unintentional, to the IRB, DSMB, Genentech, and the FDA in writing within 2 business days after the unblinding.

If a serious adverse event (SAE) has resulted in unblinding, this information will be included in the SAE Report Form. Incidences of unblinding in and of themselves will be reported to the OCRPRO Clinical Safety Office.

A detailed report of the event that resulted in the unblinding will be sent to the, NIAID Intramural DSMB, FDA, Genentech, and the NIAID IRB.

Every 6 months, the DSMB will review the data from this trial. The Board may view unblinded anaphylaxis event data (i.e., broken down by treatment group) to assess safety of the study agent. If there is some signal that the active arm is associated with a greater rate of anaphylaxis than the control arm, recommendations regarding termination might be considered; no formal statistical boundaries for harm are specified. Since this is a double-blind, placebo-controlled drug treatment trial, we will continue to elicit the advice of the DSMB for safety and ethical issues. The DSMB will monitor this protocol on a regular schedule and it is within their jurisdiction to evaluate efficacy during these reviews, if appropriate. Furthermore, due to the size of this study (n=20) and time-line for dosing (6 months), the evaluation of efficacy is not statistically powered for interim data.

9.6.2 Stopping Rules for an Individual Participant/Cohort

At any time during the study, subjects may choose to withdraw from the study.

Study agent may be discontinued with a new onset adverse event of Grade 3 or greater (see Appendix A) on one occasion within 24 hours of study medication that occurs in a particular subject and determined by PI to be related to the study agent.

An event will be established by the acute onset of an illness (minutes to several hours) with involvement of the skin, mucosal tissue, or both (e.g., generalized hives, pruritus or flushing, swollen lips-tongue-uvula) [Grade 1] and at least one of the following: 1) Respiratory compromise or gastrointestinal involvement (e.g., dyspnea, wheeze-bronchospasm, stridor, reduced peak expiratory flow, hypoxemia, nausea, vomiting, or abdominal pain [Grade 2]) or 2) Reduced blood pressure or associated symptoms of end-organ dysfunction (e.g., hypotonia

[collapse], syncope, or incontinence [Grade 3]). If these criteria are not met, the episode will not count as an event.

Study agent will also be discontinued if an adverse event occurs that in the opinion of the investigator may compromise the patients' well being.

If the patient is unable or unwilling to keep scheduled appointments for receiving their injections of study agent or follow-up safety visits, subjects will be discontinued from the study.

Study agent will be discontinued and the patient withdrawn from the study if he/she develop a malignancy while on study medication.

During the primary evaluation phase, subjects will continue with the randomized assignment for 6 months, or if they have experienced anaphylactic events determined to be unrelated to study agent or have been followed for 6 months, whichever comes first. Since the primary disease is idiopathic anaphylaxis, patients may experience anaphylactic events that are associated with their underlying disease. Patients will continue to receive study agent, if determined to the best of our ability that these events are unrelated to study agent administration. These unrelated events would be determined by the PI not to jeopardize patient safety or restrict the use of additional therapy such as corticosteroids to control symptoms.

In the event that the subject is withdrawn from the study due to an AE, the event must be recorded on the CRF as such. The subject should be monitored and treated by the investigator until the abnormal parameter or symptom has resolved or stabilized. It is up to the clinician to determine that the AE has either resolved or stabilized, after which no further follow-up is necessary. There should also be documentation to support this determination.

9.6.3 Premature Withdrawal of a Participant

Subjects who withdraw from the study prior to taking at least 1 dose of study medication are not required to complete additional visits. Subjects who receive study agent and either withdraw voluntarily from the study or who meet study criteria for withdrawal may be asked to return to the NIH Clinical Center for additional outpatient follow-up visits, including a focused history and physical exam, research blood tests and safety laboratory tests (CBC, ESR, CHEM-20, serum β-HCG, urinalysis). The timing of these additional visits may correspond to those which may have been previously scheduled for administration of the study agent or may occur at other times according to the availability of the patient and discretion of the PI. Such subjects are not required to complete the additional research tests and procedures typically performed at the sixth month visit but may do so according to patient availability and the discretion of the PI.

9.7 Data and Safety Monitoring

The NIAID Intramural Data and Safety Monitoring Board (DSMB) will review the IRB approved protocol, informed consent documents, the data and safety monitoring plan and any stopping guidelines prior to study initiation. During the course of the study, the DSMB will review cumulative study data twice per year to evaluate safety, efficacy, study conduct, and the scientific validity and integrity of the trial. As part of this responsibility, DSMB members must be satisfied that the timeliness, completeness, and accuracy of the data submitted to them for review are sufficient for evaluation of the safety and welfare of study subjects. The DSMB will convene if stopping criteria are met or other safety issues arise that the Principal Investigator and/or NIAID Clinical Director or designee would like the DSMB to address.

The PI or study coordinator will provide the DSMB Executive Secretary with a sealed copy of the randomization codes needed for the DSMB review of the safety data. The Principal Investigator will notify the DSMB based on the reporting schedule for SAEs of all cases of unblinding, intentional or unintentional, so that the DSMB can assess the potential impact of the unblinding on the overall integrity of the study.

The DSMB will also assess the performance of overall study operations and any other relevant issues, as necessary. Following each review, the DSMB will provide its recommendations to the study sponsor, including whether the study should continue without change, be modified, or terminated. The Principal Investigator will submit all written DSMB recommendations to the IRB upon receipt.

9.7.1 Safety Review and Communications Plan

A Safety Review and Communication Plan (SRCP) has been developed for the protocol. The SRCP is an internal communications document between the PI and the CSO, which delineates the safety oversight responsibilities of the PI, the CSO, and other stakeholders. The SRCP also includes the overall plan for conducting periodic safety surveillance assessments.

9.7.2 Sponsor Medical Monitor (SMM)

A medical monitor, representing the IND Sponsor (OCRPRO), has been appointed for oversight of safety in this clinical study. The SMM will be responsible for performing safety assessments as outlined in an SRCP.

10.0 Statistical Considerations

10.1 Overview and Study Objectives

Eligible subjects will be randomized to receive either placebo or omalizumab in a double-blind fashion with a target of 10 subjects enrolled in each study arm. During the primary evaluation phase, subjects will continue with the randomized assignment for 6 months.. After 6 months, patients will be discontinued from the randomized regimen, and followed for an additional 6 months.

10.2 Description of the Analyses

The primary analysis will employ an exact Wilcoxon Rank Sum Test; this analysis is based completely on a ranking of the 20 subjects. The ranking procedure is as follows. Patients are first sorted according to numbers of events in the 6-month drug period. Ties are broken among patients with the same number of events, by further ranking patients by time of their first event (a patient with a later first event is considered better than a patient with an earlier first event). For example, if there are 5 patients with 0 events, they all get the rank of 1. If there are 3 patients with exactly one event, the one with the latest event time is ranked 6, the one with the middle event time is ranked 7, and the one with the earliest event is ranked 8. This process continues for patients with 2 events, then those with 3 events and so on. To test the hypothesis that the drug reduces anaphylaxis events after the first 24 hours, the primary analysis will exclude events in this time period. However, as a sensitivity analysis, the Wilcoxon Rank Sum Test primary analysis method, described above, will be conducted again, including these early data. The primary analysis will be conducted as a 2-sided α=.05 test. The p-values associated with alternate analyses of the primary endpoint, analyses of secondary endpoints, and exploratory analyses are considered descriptive.

A key secondary analysis of the primary endpoint will analyze the number of events during the 6 months prior to randomization minus the number of events occurring in 6 months after randomization; this analysis will be done by the Wilcoxon Rank Sum Test. Exploratory analyses will also be done comparing the number of events in the 3 study periods: 6 months prior to randomization, 6 months after randomization, and the 6 months after drug discontinuation.

The Cox model using the Wei-Lin-Weissfeld approach to multiple events, with an optimal linear combination for the test of the treatment effect, will also be performed. This alternate analytic method would serve as an additional sensitivity analysis.

Secondary endpoints will be analyzed descriptively, and with comparisons made by t-tests, Wilcoxon Rank Sum Tests, or Fishers Exact test, where appropriate.

10.3 Study Hypotheses

The administration of omalizumab for episodes of unprovoked anaphylaxis in idiopathic anaphylaxis will lead to a decrease in free serum IgE levels, a reduction of FcεRI expression, and result in decreased episodes of anaphylaxis.

10.4 Sample Size Consideration

A simulation study was conducted to estimate statistical power of the primary analysis will be conducted as a two-sided α=.05 test. The power is a function of the hazard ratio (HR); a HR of 5, for example, means that subjects in 1 group would be expected to have 5 times as many events as those in the other group during the same time period. The simulations indicated that with a sample size of 10 per group, the power is likely to be greater than 90% if the true HR=5 and greater than 80% if the true HR=4. The actual power depends somewhat on the assumed true gamma distribution of exponential waiting times. Simulations were conducted on 2 pairs of means and standard deviations of exponential parameters: (0.20, 0.06) and (0.15, 0.05), where for the first parameter set, the true expected time to the first event is 0.20 years for an average person, but that some individuals will have true expected time to first event smaller than 0.10 years and some larger than 0.30 years. The simulated parameters are approximately consistent with the eligibility requirement that enrolled subjects had at least 6 events in the year prior to randomization. The powers did not vary substantially for these parameter sets. In short, if the true HR is very large, namely in the range of 4 to 5, the statistical power is likely to be at least 80%, with this sample size in this population.

10.5 Maintenance of Trial Treatment Randomization Codes

The maintenance of randomization codes will be under the jurisdiction of the Pharmacy and by the DSMB Executive Secretary.

10.6 Randomization and Blinding

The randomization sequence will be obtained by computer-generated random numbers [36] and will be provided by the study pharmacist. Study numbers 1 through 20 will be used for the sequential enrollments with subjects being randomized simultaneously to all cohorts. The study number is assigned after completion of the eligibility checklist in the electronic study database and will be the next sequential number. To reduce the potential for participant dropouts during the period between randomization and initial dosing of the study agent, randomization will occur on Day 0 after eligibility is confirmed and the study consent is signed. The study pharmacist is responsible for maintaining security of the treatment assignments. The subject, the clinical staff, and the Principal Investigator will be blinded to treatment allocation. The pharmacist with primary responsibility for drug dispensing will keep the randomization code. To maintain blinding, any discussion of the treatment assignment between the clinicians and

the pharmacy staff is prohibited until after the assignments are permitted to be known to all. In addition, the placebo-matched controlled drug will be formulated by the parent company (Genentech-Novartis) for consistency between the drug and matched placebo. The nursing staff administering the product will be from a rotating inpatient nursing pool at the NIH for the first 2 doses and subsequent dosing at the NIH will be the same product for the remainder of the study.

11.0 Quality Control and Quality Assurance

Following written standard operating procedures, the monitors (RCHSPP) will verify that the clinical trial is conducted and data are generated, documented (recorded), and reported in compliance with the protocol, GCP, FDA (21 CFR 312.50), and the applicable regulatory requirements.

The investigational site will provide direct access to all source data/documents, and reports for the purpose of monitoring and auditing by the Sponsor, and inspection by local and regulatory authorities.

Quality control procedures will be implemented beginning with the data entry system and data quality control checks that will be run on the database will be generated. Any missing data or data anomalies will be communicated to the site(s) for clarification/resolution.

12.0 Ethics/Protection of Human Subjects

Monitors (RCHSPP) under contract to the NIAID will visit the clinical research site to monitor all aspects of the study in accordance with appropriate regulations. The objectives of a monitoring visit will be: 1) to verify the prompt reporting of data points, including SAEs; 2) to verify the existence of signed informed consent; 3) to examine individual subject CRF and source documents; 4) to ensure protection of study subjects, compliance with the protocol, and accuracy and completeness of records. The monitors also will inspect the clinic site regulatory files to ensure that regulatory requirements [Office for Human Research Protections (OHRP)/ICH-GCP and FDA] are being obeyed. During the monitoring visits, the principal investigator (and/or designee) and other study personnel will be available to discuss the study progress and monitoring visit. The principal investigator (and/or designee) will make study documents (e.g., consent forms) and pertinent CRF and supporting data readily available for inspection by the local IRB, the site monitors, and the NIAID staff for confirmation of the study data.

A specific protocol monitoring plan will be discussed with the principal investigator and study staff prior to enrollment. The plan will outline the frequency of monitoring visits based on such factors as study enrollment, data collection status, and regulatory obligations.

12.1 **Conflict of Interest**

The investigators conducting this clinical trial have completed the appropriate forms that relate to potential conflicts of interest according to NIAID guidelines. Specifically, assets, income, liabilities, outside positions, agreements, arrangements, gifts and travel reimbursements of the investigators, their spouses and their minor children have been reported according to the guidelines. No reportable conflicts of interest have been identified for any of the investigators conducting this trial.

12.2 **Rationale for Subject Selection**

This protocol is open to males and females from all ethnic and racial groups. The study will be listed on ClinicalTrials.gov, Clinical Center research studies and the NIAID patient website. Past, present and future LAD patients, that meet the protocol requirements, will be contacted to see if they are interested in participating. If recruitment goals are not met, a recruitment plan will be developed by the Clinical Center Office of Patient Recruitment.

12.3 **Institutional Review Board**

A copy of the protocol, informed consent forms, and other information to be completed by participants, such as survey instruments or questionnaires, and any proposed advertising or recruitment materials will be submitted to the IRB for written approval.

The investigator must submit and obtain approval from the IRB for all subsequent amendments to the protocol, informed consent documents, and other study documentation referenced above. The investigator will be responsible for obtaining IRB approval of the annual Continuing Review throughout the duration of the study.

12.4 **Informed Consent Process**

When subjects arrive at the NIH Clinical Center, they will be consented by one of the study team investigators using the Standard Consent. Each subject must understand fully the contents of the consent form. The informed consent will be given to the subject in advance so that they can thoroughly read the consent and ask any questions they may have prior to consent being obtained. Upon Admission to the CC the informed consent will be obtained prior to drug administration or any other study procedure and a copy will be given to the subject for their records. According to Title 21 CFR 50.20, the information that is given to the subject or the representative shall be in language understandable to

the subject or the representative. A short form will be used to obtain consent as described in 45 CFR §46.117(b) (2).

Assent or Informed Consent Process (in Case of a Minor)
All subjects will be ≥18 years of age and can legally provide informed consent.

12.5 Justification for Exclusion of Women, Minorities, and Children (Special Populations)

Exclusion of Women: Pregnant or breast feeding mothers are excluded from this study.

Exclusion of Minorities: None will be excluded.

Exclusion of Children: Children under the age of 18 years will be excluded due to new data concerning anaphylaxis and the FDA Boxed warning.

12.6 Compensation

Compensation (money) is not provided as a part of this study. The subjects will be reimbursed for their transportation costs as is permitted by the NIAID travel policy.

13.0 Data Management

The Investigator is responsible for ensuring that the data collected are complete, accurate, and recorded in a timely manner. Source documentation (the point of initial recording of information) should support the data collected in CRIMSON and must be signed and dated by the person recording and/or reviewing the data. Data should be reviewed by the Investigator and signed as required with written or electronic signature, as appropriate. 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 trial. Source documents include, but are not limited to, the subject's medical records, laboratory reports, ECG tracings, x-rays, radiologist's reports, subject's diaries, biopsy reports, ultrasound photographs, progress notes, pharmacy records, and any other similar reports or records of procedures performed during the subject's participation in the study. Data from CRIMSON Data System will be collected directly from subjects during study visits and telephone calls, or will be abstracted from subjects' diaries and medical records. The subject's medical record must record his/her participation in the clinical trial and, after unblinding what medications (with doses and frequency) or other medical interventions or treatments were administered, as well as any adverse reactions experienced during the trial.

14.0 Data Handling and Record Keeping

- Data will be coded, so that subjects will not be able to be identified by persons not listed as investigators. .

- Data will be stored in a secure area, with limited access.

- Data will be collected on a monthly basis from subjects using the weekly event log and physician (both NIH and home) will document each visit on the physician treatment note. (See Appendixes E and F)

15.0 Publication Policy

Following completion of the study, the investigator may publish the results of this research in a scientific journal. The International Committee of Medical Journal Editors (ICMJE) member journals have adopted a trials-registration policy as a condition for publication. This policy requires that all clinical trials be registered in a public trials registry such as ClinicalTrials.gov, which is sponsored by the National Library of Medicine. Other biomedical journals are considering adopting similar policies. It is the responsibility of the NIAID Division or Branch to register this trial in an acceptable registry either on or before the onset of patient enrollment.

Publication of the results of this trial will be governed by NIAID publication policies. Any presentation, abstract, or manuscript will be made available for review (according to division requirements if any), prior to submission.

16.0 Record Retention

The investigator is responsible for retaining all essential documents listed in the ICH Good Clinical Practice Guideline. All essential documentation for all study subjects are to be maintained by the investigators in a secure storage facility for a minimum of three years, per DHHS (45 CFR 46.115(b)). The FDA requires study records to be retained for up to two years after marketing approval or disapproval (21 CFR 312.62), or until at least 2 years have elapsed since the formal discontinuation of clinical development of the investigational agent for a specific indication]. These records are also to be maintained in compliance with IRB/EC, state, and federal medical records retention requirements, whichever is longest. All stored records are to be kept confidential to the extent provided by federal, state, and local law. It is the investigator's responsibility to retain copies of source documents until receipt of written notification to the contrary from the Office of Clinical Research Policy and Regulatory Operations (OCRPRO), Division of Clinical Research (DCR) of the National Institute of Allergy and Infectious Diseases (NIAID). No study document should be destroyed without prior written agreement between OCRPRO/NIAID and the Principal Investigator. Should the investigator wish to assign the study records to another party and/or move them to another location, the investigator must provide written notification

of such intent to OCRPRO/NIAID with the name of the person who will accept responsibility for the transferred records and/or their new location. NIAID must be notified in writing and written NIAID permission must be received by the site prior to destruction or relocation of research records.

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Appendix A. Toxicity Table

The NCI Cancer Therapy Evaluation Program Common Terminology Criteria for Adverse Events version 3.0 (CTCAE) will be used to grade adverse events.

ALLERGY/IMMUNOLOGY						Page 1 of 1
		Grade				
Adverse Event	Short Name	1	2	3	4	5
Allergic reaction/ hypersensitivity (including drug fever)	Allergic reaction	Transient flushing or rash; drug fever <38°C (<100.4°F)	Rash; flushing; urticaria; dyspnea; drug fever ≥38°C (≥100.4°F)	Symptomatic bronchospasm, with or without urticaria; parenteral medication(s) indicated; allergy-related edema/angioedema; hypotension	Anaphylaxis	Death
REMARK: Urticaria with manifestations of allergic or hypersensitivity reaction is graded as Allergic reaction/hypersensitivity (including drug fever).						
ALSO CONSIDER: Cytokine release syndrome/acute infusion reaction.						
Allergic rhinitis (including sneezing, nasal stuffiness, postnasal drip)	Rhinitis	Mild, intervention not indicated	Moderate, intervention indicated	—	—	—
REMARK: Rhinitis associated with obstruction or stenosis is graded as Obstruction/stenosis of airway – *Select* in the PULMONARY/UPPER RESPIRATORY CATEGORY.						
Autoimmune reaction	Autoimmune reaction	Asymptomatic and serologic or other evidence of autoimmune reaction, with normal organ function and intervention not indicated	Evidence of autoimmune reaction involving a non-essential organ or function (e.g., hypothyroidism)	Reversible autoimmune reaction involving function of a major organ or other adverse event (e.g., transient colitis or anemia)	Autoimmune reaction with life-threatening consequences	Death
ALSO CONSIDER: Colitis; Hemoglobin; Hemolysis (e.g., immune hemolytic anemia, drug-related hemolysis); Thyroid function, low (hypothyroidism).						
Serum sickness	Serum sickness	—	—	Present	—	Death
NAVIGATION NOTE: Splenic function is graded in the BLOOD/BONE MARROW CATEGORY.						
NAVIGATION NOTE: Urticaria as an isolated symptom is graded as Urticaria (hives, welts, wheals) in the DERMATOLOGY/SKIN CATEGORY.						
Vasculitis	Vasculitis	Mild, intervention not indicated	Symptomatic, non-steroidal medical intervention indicated	Steroids indicated	Ischemic changes; amputation indicated	Death
Allergy/Immunology – Other (Specify, __)	Allergy – Other (Specify)	Mild	Moderate	Severe	Life-threatening; disabling	Death

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Appendix B. Schedule of Procedures/Evaluations

Each treatment visit may occur within (+/-) 3 days of the scheduled time and the 6 month off-treatment visit may occur within (+/-) 30 days of the scheduled time.

Schedule of Evaluations – 4 week dosing

Preparation and Screening – the following screening procedures may be performed up to 4 weeks prior to the study agent administration. Screening may be either on an inpatient or outpatient basis.

* Women of childbearing potential must have a negative β-HCG serum or urine pregnancy test prior to each injection.

†A serum tryptase and research blood will be obtained subsequent (within 24 hours) to any anaphylactic event in association with study agent administration.

Screening Visit - Day -30 to -1
Admission to the Clinical Center or outpatient clinic for screening (duration 2-3 days)
Inpatient 5SE or Outpatient OP11
Informed consent
Medical history and physical exam
Screening blood work
Bone marrow biopsy (as needed, at the discretion of the PI)
Pulmonary Function Tests (PFTs), if indicated for skin testing
Research blood draws as needed
Consultations will be requested as medically indicated

Visit #1 - Day 0 (1st injection)
Admission to 5SE (duration may be up to 2-3 days)
Medical history and physical exam
Blood draws as needed prior to study agent injection
Initial study agent injection
Observation for approximately 24 hours for adverse reactions
Consultations will be requested as medically indicated
Epi-Pen provided with teaching and take home instructions on the signs and symptoms of anaphylaxis and when to seek medical care. Subjects will be advised to bring Epi-Pen to subsequent visits for staff to check and to carry it with them until otherwise advised.

Day 1
Observation
Discharge

Visit #2 – Week 4 (2nd injection)

Admission to 5SE (duration may be up to 2-3 days)
Focused history and physical
Blood draw
Study agent injection
Observation for aproximately 24 hours
Consultations will be requested as medically indicated
Subjects will be reminded to bring Epi-Pen to subsequent visits for staff to check and to carry it with them until otherwise advised.

Week 4, Day +1
Observation
Discharge

Omalizumab or Placebo-matched control (Study agent) Administration *
All injections administered in the Clinical Center will include an observation period of 2 hours.

Visit #3 – Week 8 (3rd injection)
Study agent administration at the NIH.

Visit #4 – Week 12 (4th injection)
Study agent administration at the NIH.
.
Visit #5 – Week 16 (5th injection)
Research blood draws
Study agent administration at the NIH.
.
Visit #6 – Week 20 (6th injection)
(Final Treatment Visit)
Admission to day hospital
Focused history and physical
Blood draw
Study agent injection
Observation for 2 hours post injection
Subjects will be reminded to bring Epi-Pen to subsequent visits for staff to check and to carry it with them until otherwise advised.

Visit #7 – 6 months post treatment follow up (+/- 30 days)

The subjects will be monitored by their referring physicians, who will continue to document any anaphylactic events, until their follow-up study visit 6 months after drug completion. The subject will return to the NIH for a final follow-up visit which may include:

1) History and physical examination.
2) Blood tests in each subject: complete blood count with differential, acute care panel, hepatic panel (as needed), IgE, serum tryptase levels, hepatitis profiles (as needed), anti-HTLV I/II (as needed),

and for women of childbearing potential, a β-HCG serum or urine test for pregnancy, and research blood (as needed). Additional tests will be ordered as clinically indicated for each subject's condition.

3) Possible bone marrow biopsy

The above schedule will be followed as closely as possible. However, subjects will be allowed a (+/-) 3 day interval unless otherwise noted to meet the schedule timeline for the administration of study agent. Admissions to the th NIH Clinical Center may be extended as necessary to accommodate the subject schedule.

Schedule of Evaluations – 2 week dosing

Preparation and Screening – the following screening procedures may be performed up to 4 weeks prior to the study agent administration. Screening may be either on an inpatient or outpatient basis.

Screening Visit - Day -30 to -1
Admission to the Clinical Center or outpatient clinic for screening (duration 2-3 days)
Inpatient 5SE or Outpatient OP11
Informed consent
Medical history and physical exam
Screening blood work
Bone marrow biopsy (as needed, at the discretion of the PI)
Pulmonary Function Tests (PFTs), if indicated for skin testing
Research blood draws as needed
Consultations will be requested as medically indicated

Visit #1 - Day 0 (1st injection)
Admission to 5SE (duration may be up to 2-3 days)
Medical history and physical exam
Blood draws as needed prior to study agent injection
Research blood draws as neededInitial study agent injection
Observation for approximately 24 hours for adverse reactions
Consultations will be requested as medically indicated
Epi-Pen provided with teaching and take home instructions on the signs and symptoms of anaphylaxis and when to seek medical care. Subjects will be advised to bring Epi-Pen to subsequent visits for staff to check and to carry it with them until other wise advised.

Day 1
Observation
Discharge

Visit #2 – Week 2 (2nd injection)
Admission to 5SE (duration may be up to 2-3 days)
Focused history and physical
Blood draw
Research blood draws as needed
Study agent injection
Observation for approximately 24 hours for adverse reactions
Consultations will be requested as medically indicated
Subjects will be reminded to bring Epi-Pen to subsequent visits for staff to check and to carry it with them until otherwise advised.

Week 2, Day +1
Observation
Discharge

Omalizumab or Placebo-matched control (Study agent) Administration *
All injections administered at the Clinical Center and include an observation period of approximately 2 hours.

Visit #3 – Week 4 (3rd injection)
Study agent administration at the NIH

Visit #4 – Week 6 (4th injection)
Study agent administration at the NIH

Visit #5 – Week 8 (5th injection)
Study agent administration at the NIH

Visit #6 – Week 10 (6th injection)
Study agent administration at the NIH

Visit #7 – Week 12 (7th injection)
Study agent administration at the NIH

Visit #8 – Week 14 (8th injection)
Study agent administration at the NIH

Visit #9 – Week 16 (9th injection)
Study agent administration at the NIH
Research blood draws

Visit #10 – Week 18 (10th injection)
Study agent administration at the NIH

Visit #11 – Week 20 (11th injection)

Study agent administration at the NIH

Visit #12 – Week 22 (12th injection)
(Final Treatment Visit)
Admission to day hospital
Focused history and physical
Blood draw
Research blood draws as needed
Study agent injection
Observation for approximately 2 hours post injection
Subjects will be reminded to bring Epi-Pen to subsequent visits for staff to check and to carry it with them until otherwise advised.

Visit #13 – 6 months post treatment follow up (+/- 30days)

The subjects will be monitored by their referring physicians, who will continue to document any anaphylactic events, until their follow-up study visit 6 months after drug completion. The subject will return to the NIH for one final follow-up visit which may include:

4) History and physical examination.
5) Blood tests in each subject: complete blood count with differential, acute care panel, hepatic panel as needed, IgE, serum tryptase levels, hepatitis profiles as needed, anti-HTLV I/II as needed, and for women of childbearing potential, a β-HCG serum or urine test for pregnancy, and research blood as needed. Additional tests will be ordered as clinically indicated for each subject's condition.
6) Possible bone marrow biopsy
7) The final visit may include counseling by study investigators as to the significance of positive vs. negative findings if data is available.

The above schedule will be followed as closely as possible. However, subjects will be allowed a (+/-) 3 day interval unless otherwise noted to meet the schedule timeline for the administration of study agent. Admissions to the th NIH Clinical Center may be extended as necessary to accommodate the subject schedule.

Appendix C. WHO Criteria for the Diagnosis of Systemic Mastocytosis [13]

1 major criterion + 1 minor criterion or 3 minor criteria

- **Major Criteria:**
  - Characteristic multifocal dense infiltrates of mast cells in bone marrow biopsy
- **Minor Criteria:**
  - Morphology of mast cells: Spindle shaped
  - the D816V mutation in *c-kit*
  - Flow cytometric co-expression of CD117, CD2 and CD25 by the bone marrow mast cell population
  - Serum tryptase >20 ng/mL

Appendix D. Xolair® Package Insert

URL: http://www.gene.com/gene/products/information/pdf/xolair-prescribing.pdf

Appendix E. Physician Treatment Note

MEDICAL RECORD	Outpatient Progress Notes

Date: _____ **Day of omalizumab injection:** _____ **Home Physician Note**

Chief Complaint:

_____

_____

Events since last injection:

_____

_____

Allergies: _____

Medications/Doses: _____

PE: BP_____**Temp**_____ **HR**_____ **Resp** _____**0_2 sat** _____**%**
Pain: Yes/No Pain level (1 to10): _____**Acute pain: Yes/ No Chronic pain: Yes/No**
Weight_____ **Height**_____ **LMP** _____

General: WNL _____ **Abnormal**_____
HEENT: WNL _____ **Abnormal**_____
CVS: WNL _____ **Abnormal**_____
Pulm: WNL _____ **Abnormal**_____
GI: WNL _____ **Abnormal**_____
Integ: WNL _____ **Abnormal**_____

Any adverse events since last injection _____

Local: Description_____
Therapy_____

Systemic: Description_____
Therapy_____

Anaphylaxis (severe systemic): Description_____
Therapy _____

Patient observed for two hours post injection _____

Patient understands how and when to use Epipen _____

Patient given written guidance for signs and symptoms and treatment of anaphylaxis _____

Women using continuous birth control _____

_____ _____
Physician Signature **Date**

Patient Identification	Outpatient Progress Notes NIH-532-10 (8-00) P.A. 09-25-0099 File in Section 2: Progress Notes	1

Appendix F. Weekly Event Log

Week of

Weekly Event Log

Date	Known cause	Event	Symptoms		Interventions	Duration	Comments
			☐ low BP ☐ Throat tightness ☐ wheezing ☐ shortness of breath	☐ hives ☐ flushing ☐ vomiting ☐ diarrhea	☐ PO Meds ☐ IV Meds ☐ IV fluids ☐ Epi-PEN		
			☐ low BP ☐ Throat tightness ☐ wheezing ☐ shortness of breath	☐ hives ☐ flushing ☐ vomiting ☐ diarrhea	☐ PO Meds ☐ IV Meds ☐ IV fluids ☐ Epi-PEN		
			☐ low BP ☐ Throat tightness ☐ wheezing ☐ shortness of breath	☐ hives ☐ flushing ☐ vomiting ☐ diarrhea	☐ PO Meds ☐ IV Meds ☐ IV fluids ☐ Epi-PEN		
			☐ low BP ☐ Throat tightness ☐ wheezing ☐ shortness of breath	☐ hives ☐ flushing ☐ vomiting ☐ diarrhea	☐ PO Meds ☐ IV Meds ☐ IV fluids ☐ Epi-PEN		
			☐ low BP ☐ Throat tightness ☐ wheezing ☐ shortness of breath	☐ hives ☐ flushing ☐ vomiting ☐ diarrhea	☐ PO Meds ☐ IV Meds ☐ IV fluids ☐ Epi-PEN		
			☐ low BP ☐ Throat tightness ☐ wheezing ☐ shortness of breath	☐ hives ☐ flushing ☐ vomiting ☐ diarrhea	☐ PO Meds ☐ IV Meds ☐ IV fluids ☐ Epi-PEN		
			☐ low BP ☐ Throat tightness ☐ wheezing ☐ shortness of breath	☐ hives ☐ flushing ☐ vomiting ☐ diarrhea	☐ PO Meds ☐ IV Meds ☐ IV fluids ☐ Epi-PEN		

Page ____ of ______

Week of

Date	Comments

Page ____ of ____

Appendix G. Expected symptoms and adverse events related to the underlying disease (IA), the study agent omalizumab or protocol procedures.

Idiopathic Anaphylaxis (IA)	Omalizumab	Procedure
Generalized flushing	Anaphylaxis:	Pain
Urticaria	Hypotension	Bruise
Nasal congestion	Syncope	Infection
Conjunctival irritation	Urticaria	Bleeding
Bronchospasm	Malignancy	Fainting
Angioedema (tongue, throat, palms, soles)	Angioedema (throat or tongue)	Infection
Gastrointestinal cramping	Bronchospasm	Bruising
Lightheadedness	Mutagenesis	Small hematoma
Loss of consciousness	Impairment of Fertility	Mild itching
Circulatory collapse	Embryotoxicity	Swelling of the skin
Hives	Teratogenicity	Anaphylaxis
Itching	Carcinogenesis	Nausea
Shortness of breath	Increase in hear diseases	Vomiting
Diarrhea	Lung problems	Changes in vital signs
Vomiting	Cerebrovascular disease(eg. stroke)	Itchy eye, nose, throat
Hypotension	Arthritis/Arthralgia	Runny nose
Laryngospasm	Pain (general)	Tightness in the throat or chest
Hoarseness	Leg pain	Coughing
Uterine cramps	Fatigue	Sneezing
Urinary incontinence	Dizziness	Shortness of breath
	Fracture	Hives
	Arm pain	Flushing
	Pruritus	Lightheadedness
	Dermatitis	Asthma exacerbation
	Earache	Injection site local reaction
	Rash (urticaria or other forms)	Shock
	Fever	Swelling in the throat
	Lymphadenopathy	Death
	Injection site reaction	
	Viral infections	
	Upper respiratory tract infection	
	Sinusitis	
	Headache	
	Pharyngitis	
	Blood Clots	
	Cartiovascular Disease	