Clinical Study Protocol

An Open-Labeled Exploratory Study to Evaluate Safety and Efficacy of FB825 in Adults with Atopic Dermatitis

PROTOCOL NO. FB825CLIIS-01-AD

Study Protocol Number	FB825CLIIS-01-AD
Version and Date of Protocol:	V1.3 Final, 02-March-2018
• **Investigational Product:**	FB825-15D11, FB825, h4B12 (A humanized monoclonal antibody)
• **Indication**	Moderate-to-Severe Extrinsic Atopic Dermatitis
• **Drug Development Phase:**	Exploratory study
• **Principal Investigator:**	Dr. Chia-Yu Chu National Taiwan University Hospital
• **Sponsor:**	Fountain BioPharma Inc 19F-1, No. 3, Yuan Qu St. Taipei 115, Taiwan Telephone: 886-2-2655-8687

Signature Page

PROTOCOL TITLE: An Open-Labeled Exploratory Study to Evaluate Safety and Efficacy of FB825 in Adults with Atopic Dermatitis

PROTOCOL NUMBER: FB825CLIIS-01-AD

Grace Huang President Fountain BioPharma Inc	Date
Nien-Yi Chen, PhD Vice President Fountain BioPharma Inc	Date
David Yeh Senior Director Department of Clinical Research Fountain BioPharma Inc	Date

Investigator Protocol Agreement Page

PROTOCOL TITLE: An Open-Labeled Exploratory Study to Evaluate Safety and Efficacy of FB825 in Adults with Atopic Dermatitis

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I agree to conduct the study as outlined in the protocol "FB825CLIIS-01-AD" in accordance with applicable standard operating procedures, ICH Good Clinical Practices, Good Laboratory Practices (GLP) and all other applicable regulations, including the recommendations laid down in the most recent version of the Declaration of Helsinki. I have read and understood all sections of the protocol.

Dr. Chia-Yu Chu
National Taiwan University Hospital

Date

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Protocol Synopsis

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Title:

An Open-Labeled Exploratory Study to Evaluate Safety and Efficacy of FB825 in Adults with Atopic Dermatitis

Study Phase:

Exploratory study

PI and Study Site:

Dr. Chia-Yu Chu;

National Taiwan University Hospital

Objectives:

Primary Objective

The primary objective of this study is:

- To evaluate the change from baseline in total IgE and allergen-specific IgE in patients with atopic dermatitis after the IV administration of FB825.

Secondary Objectives

The secondary objectives of this study are:

- To evaluate the clinical efficacy in patients with atopic dermatitis after the IV administration of FB825.
- To explore the safety in patients with atopic dermatitis after the IV administration of FB825.
- To monitor the changes in clinical hematology after the IV administration of FB825
- To explore the change from baseline in biomarkers including thymus and activation regulated chemokine (TARC), Eotaxin-3, thymic stromal lymphopoietin (TSLP), periostin, IL-1a, IL-4, IL-5, IL-13, IL-16, IL-31 and M-CSF after IV administration of FB825.

Study Design and Methodology:

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This is an open-labeled exploratory study to evaluate safety and efficacy of FB825 in adults with atopic dermatitis (AD). The study will be conduct at one medical center in Taiwan.

Approximately 12 subjects with atopic dermatitis (AD), who meet the criteria for study entry, will be enrolled to the study. All eligible subjects will receive FB825, 5mg/kg, by 1-hour IV infusion on Day 1 and Day 85. Subjects will be hospitalized after receiving FB825 on Day 1 and Day 85, and will be discharged from the hospital next day for safety observation (at least 12 hours). Subjects will return to the study site on Days 8, 15, 29, 57, 92, 99, 113, 141, and 169 for the safety, efficacy, and biomarker evaluation. Subjects who premature withdraw from the study will have an end of study (EOS) visit within 7 days.

Serum total IgE and antigen-specific IgE will be measured at scheduled visits and evaluated to explore the changes from baseline after the IV administration of 5mg/kg FB825. Subjects will perform the activities at scheduled visits for clinical efficacy evaluation including Pruritus Visual Analogue Scale (VAS), Eczema Area and Severity Index (EASI), Severity Scoring of Atopic Dermatitis Index (SCORAD), Investigator Global Assessment (IGA) for AD and Body Surface Area (BSA) involved in AD symptoms.

Safety data, including AEs and laboratory tests, will be reviewed by the PI. The duration of subject participation the study, excluding screening, is approximately 24 weeks.

Study Drug, Dosage, and Route of Administration:

Investigational Product (IP)

FB825: A humanized monoclonal immunoglobulin G1 (IgG1) targeting the CεmX domain on human B lymphocytic cells expressing membrane-bound IgE (mIgE)

FB825, 5mg/kg, is administered as single 1-hour IV- infusions.

Inclusion criteria:

1. Male or female subjects between 20 and 65 years of age, inclusive.
2. The subject has a physician-confirmed diagnosis of chronic atopic dermatitis based on 3 years history of symptoms defined by the Eichenfield revised criteria of Hannifin and Rajka and supported by positive allergen-specific IgE at the screening visit.
3. Eczema Area and Severity Index (EASI) score ≧14 at the screening and baseline visits.
4. Investigator's Global Assessment (IGA) score ≧ 3 (5-point scale) at the screening and

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baseline visits.

5. ≧10 % body surface area (BSA) of AD involvement at the screening and baseline visits.

6. History of inadequate response to a stable (1 month) regimen of topical corticosteroids or calcineurin inhibitors as treatment for AD within 3 months before the screening visit. (The regimen of topical corticosteroids means medium to high potency, applied for at least 28 days or for the maximum duration recommended by product prescribing information.)

7. Patients must be applying stable doses of emollient provide d for atopic dermatitis twice-daily for at least 7 days before the baseline visit.

8. Female subjects of childbearing potential must use at least two forms of birth control. One must be barrier protection (i.e., condom or female condom) and the other is one of acceptable method of birth control (ie, diaphragm, intrauterine device, hormonal contraceptives, or abstinence) throughout the study. Subjects who are surgically sterile (ie, hysterectomy, bilateral tubal ligation, or bilateral oophorectomy), or postmenopausal (defined as amenorrhea for 12 consecutive months and documented serum follicle-stimulating hormone level >40 mU/mL) will be considered as no childbearing potential. All female subjects must have a negative serum pregnancy test at prior to dosing.

   Note: The subject must use the method of contraception mentioned above during study period and in 16 weeks or 5 half-lives after the last dosing of FB825.

9. The subject has a body weight ≥ 40 kg at screening and a body mass index of 18.0 to 30.0 kg/m^2, inclusive.

10. The subject has a normal, as determined by the investigator, 12-lead electrocardiogram (ECG) with normal cardiac conduction parameters:

    - Heart rate between 45 and 100 bpm;
    - Fridericia-corrected QT interval (QTcF) ≤450 milliseconds (men) or ≤470 milliseconds (women);
    - QRS interval lower than 120 milliseconds.

11. The subject is healthy, except atopic diseases, as determined by the investigator, on the basis of clinical laboratory test results performed at screening. If the results are outside the normal reference ranges, the subject may be included only if the investigator judges

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the abnormalities or deviations from normal not to be clinically significant. This determination must be recorded in the subject's source document and initialed by the investigator. This is not applicable to the laboratory abnormalities listed in the exclusion criterion (using the Division of Microbiology and Infectious Diseases criteria).

12. The subject is able to provide written informed consent.

13. The subject agrees to comply with all protocol requirements.

Exclusion criteria:

1. Female subjects who are pregnant or lactating.

2. The subject is on diet or with poor intake.

3. The subject has a history of heart arrhythmias (any clinically relevant).

4. The subject has a positive test result for hepatitis B surface antigen, hepatitis C virus antibody, or human immunodeficiency virus antibodies at screening.

5. The subject has a history of alcohol or drug abuse that would impair or risk the patients' full participation in the study, in the opinion of the investigator.

6. The subject is under judicial supervision or curatorship.

7. The subject has a clinically relevant, currently active or underlying gastrointestinal, cardiovascular, nervous system, psychiatric, metabolic, renal, hepatic, respiratory (with the exception of uncomplicated allergic rhinitis), inflammatory, immunological, endocrine, diabetes, or infectious disease and ineligible to participate in the study judged by investigator.

8. The subject has any history of a previous anaphylactic reaction.

9. The subject has any condition that, in the opinion of the investigator, would compromise the study or the well-being of the subject or prevent the subject from meeting or performing study requirements.

10. The subject has received any immunoglobulin products or blood products within 3 months prior to dosing.

11. The subject has received a biologic product:

- The subject has received any cell-depleting agents, not only limited to rituximab,

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within 6 months prior to dosing, or before the lymphocyte count returns to normal, whichever is longer.

- The subject has received other biologics within 5 half-lives (if known) or 16 weeks, which is longer, prior to dosing).

12. The subject has one or more of the following laboratory abnormalities at screening as defined by Division of Microbiology and Infectious Diseases Adult Toxicity Table, 2007:

    - Aspartate aminotransferase or alanine aminotransferase (>2 × upper limit of normal [ULN]) or higher
    - Total bilirubin ≥1.5× ULN
    - Serum creatinine ≥1.6 × ULN
    - Any other laboratory abnormality higher than or equal to grade 2 with the exception of IgE level, eosinophil counts, eosinophil cationic protein (ECP) and laboratory values mentioned above.

    Note: Laboratory values may be converted to equivalent standard units. Retesting of abnormal laboratory values that may lead to exclusion will be allowed once (without prior sponsor approval). Retesting will take place during an unscheduled visit in the screening phase (before baseline).

13. The subject has received any approved or unapproved (ie, investigational) immunotherapy treatment within the past 3 months.

14. The subject has used any of the following classes of medication (prescription or over the counter):

    - Intranasal corticosteroid (eg, fluticasone propionate) within 30 days prior to dosing.
    - Systemic corticosteroids (eg, prednisone) within 30 days prior to dosing.
    - Leukotriene modifiers (eg, montelukast) within 30 days prior to dosing.
    - Immunosuppressants (eg, gold salts, methotrexate, azathioprine, cyclosporine) within the past 30 days prior to dosing.
    - Immunomodulating drugs (eg, IFN-γ) within the past 30 days prior to dosing.

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- Anti-IgE (eg, omalizumab) within the past 1 year prior to dosing.
- Allergen immunotherapy within the past 1 year prior to dosing.
- Orally inhaled corticosteroids (eg, budesonide) within the past 30 days prior to dosing.

15. The subject has received phototherapy within 4 weeks prior to dosing.
16. The subject has received live vaccine within 12 weeks prior to dosing.
17. The subject has known or suspected history of immunosuppression, including history of opportunistic infections (eg, TB) per investigator judgment.
18. The subject has history of malignancy within 5 years before the screening period.
19. High risk of parasite infection

• Risk factors for parasitic disease (living in an endemic area, chronic gastrointestinal symptoms, travel within the last 6 months to regions where geohelminthic infections are endemic, and/or chronic immunosuppression)

AND

• Evidence of parasitic colonization or infection on stool evaluation for ova and parasites.

Note: stool ova and parasite evaluation will only be conducted in patients with risk factors and an eosinophil count more than twice the upper limit of normal

Primary Endpoints:

- Change from baseline in total IgE at Day85 and Day 169/EOS.
- Change from baseline in allergen-specific IgE at Day 85 and Day 169/EOS.

Endpoints for Biomarker:

- Change from baseline in total IgE at Day 8, 15, 29, 57, 85, 92, 99, 113, 141, and 169.
- Change from baseline in allergen-specific IgE at Day 8, 15, 29, 57, 85, 92, 99, 113, 141, and 169.
- Change from baseline in biomarkers including thymus and activation regulated

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chemokine (TARC), Eotaxin-3, thymic stromal lymphopoietin (TSLP), periostin, IL-1a, IL-4, IL-5, IL-13, IL-16, IL-31 and M-CSF after IV administration of FB825 at Days 8,15, 29, 57, 85, 92, 99, 113, 141, and 169.

Efficacy Endpoints:

- Changes from baseline in Pruritus Visual Analogue Scale (VAS) at Days 8, 15, 29, 57, 85, 92, 99, 113, 141, and 169.
- Changes from baseline in Eczema Area and Severity Index (EASI) at Days 8, 15, 29, 57, 85, 92, 99, 113, 141, and 169.
- Changes from baseline in Severity Scoring of Atopic Dermatitis Index (SCORAD) at Days 8, 15, 29, 57, 85, 92, 99, 113, 141, and 169.
- Changes from baseline in Investigator Global Assessment (IGA) for atopic dermatitis at Days 8, 15, 29, 57, 85, 92, 99, 113, 141, and 169.
- Changes from baseline in Body Surface Area (BSA) involved in atopic dermatitis at Days 8, 15, 29, 57, 85, 92, 99, 113, 141, and 169.

Safety Assessments:

Safety will be assessed by monitoring and recording of adverse events (AEs) and serious adverse event (SAEs); physical examination findings and vital sign measurements (systolic and diastolic blood pressures, heart rate, respiratory rate, and body temperature), clinical laboratory test results (hematology, coagulation, serum chemistry [including liver function tests, blood glucose level], and urinalysis); 12-lead ECG results.

Sample Size:

Approximately 12 evaluable subjects are planned for this study. The sample size for this study is based on clinical and practical considerations and not on a formal statistical power calculation.

Statistical Methods:

Concentration and change from baseline in total and allergen-specific IgE will be summarized by time point and presented graphically. Change from baseline in total and allergen-specific IgE will also be summarized by the baseline total IgE concentration (serum IgE>1500IU/mL or serum IgE ≤1500IU/mL) and given FB825 doses. The clinical endpoints will be analysed using descriptive statistic (mean of EASI, SCORAD, IGA, VAS, and BSA; SD, CV, number of subjects) by visit and given FB825 doses.

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Adverse events will be coded by preferred term and system organ class (SOC) using the latest version of the Medical Dictionary for Regulatory Activities (MedDRA). Adverse events will also be summarized but not limited to severity, relationship to study drug, serious AEs, and AEs leading to discontinuation of study drug. Clinical laboratory test results including hematology, coagulation, serum chemistry, and urinalysis will be presented in data listings. Actual value and changes from baseline for clinical laboratory test results and vital sign measurements will be summarized by descriptive statistics (number of subjects, mean, SD, median, minimum, and maximum). Shift tables will be generated for clinical laboratory test results. Physical examination and 12-lead ECG findings will be presented in a data listing.		
Date of Protocol: 02-March-2018		

List of Abbreviations

Abbreviation	Definition
AD	Atopic Dermatitis
ADCC	Antibody-Dependent Cellular Cytotoxicity
AE	Adverse Event
ALT	Alanine Aminotransferase
AST	Aspartate Aminotransferase
AUC	Area under the Concentration
BCRs	B-Cell Antigen Receptors
BSA	Body Surface Area
C_{max}	Maximum Observed Concentration
CNS	Central Nervous System
CRF	Case Report Form
CTCAE	Common Terminology Criteria for Adverse Events
EASI	Eczema Area and Severity Index
EC	Ethics Committee
ECG	Electrocardiogram
ECP	Eosinophil Cationic Protein
ELISA	Enzyme-Linked Immunosorbent Assay
EOS	End of Study
FDA	Food and Drug Administration
GCP	Good Clinical Practice
GLP	Good Laboratory Practice
IB	Investigator's Brochure
ICF	Informed Consent Form
ICH	International Conference on Harmonisation
Ig	Immunoglobulin
IGA	Investigator Global Assessment
IFN- γ	Interferon-gamma
IL	Interleukin
IP	Investigational Product
IRB	Institutional Review Board
IV	Intravenous
mAb	Monoclonal Antibody
MedDRA	Medical Dictionary for Regulatory Activities
mIgE	Membrane-bound Immunoglobulin E
M-CSF	Macrophage colony stimulating factor
NOAEL	No Observed Adverse Effect Level
NRS	Numerical Rating Scale
PBMCs	Peripheral Blood Mononuclear Cells

Abbreviation	Definition
PK	Pharmacokinetic
QTc	Corrected QT interval
QTcF	Fridericia-corrected QT Interval
SAE	Serious Adverse Event
SC	Subcutaneous
SCID	Severe Combined Immunodeficiency
SCORAD	Severity Scoring of Atopic Dermatitis Index
SD	Standard Deviation
SOC	System Organ Class
TARC	Thymus and activation regulated chemokine
TEAE	Treatment-emergent adverse event
TSLP	Thymic stromal lymphopoietin
$t_{1/2}$	terminal elimination half-life
TCS	Topical Corticosteroids
ULN	Upper Limit of Normal
UV	Ultraviolet

1 Introduction

1.1 Background

Allergic diseases, such as atopic dermatitis, allergic asthma/ rhinitis, food allergies, and other type I hypersensitivity inflammatory disorders are among the fastest growing chronic diseases in the industrialized countries, and afflict 20%-40% of the population worldwide. Although some of these allergic disorders can be treated by medicines that directly easing the symptoms, many moderate- to-severe diseases remain poorly controlled, which not only exerts a huge impact on the life quality, but also high economic cost to the individual, family, and society. It is recognized that Immunoglobulin E (IgE) plays an important role in mediating hypersensitivity reactions responsible for most of the allergic diseases. IgE is produced by IgE-secreting plasma cells that are generated from continuous differentiation of B lymphocytes expressing membrane-bound IgE (mIgE) on the cell surface (Murphy 2011). The pharmaceutical development of anti-IgE omalizumab has validated the IgE pathway as an effective therapeutic target for treating IgE-mediated allergic diseases (Chang 2000). Omalizumab efficiently neutralizes free IgE, which down-regulates FcεRI on basophils, dendritic cells, and mast cells, thus successfully modulating allergic asthma.

In “atopic” individuals who are at increased risk of developing allergies, IgE concentration in the circulatory system may reach over 10 times the normal level. The concentrations of allergen-specific IgE antibody are closely correlated with clinical symptoms and may be over 1000 times higher in patients with allergic diseases than in those found in healthy individuals. IgE sensitizes effector cells such as basophils, mast cells, and activated eosinophils by occupying the high-affinity IgE receptor, FcεRI, on which they are expressed. In type I hypersensitivity, allergens cross-link IgE molecules bound by FcεRI and subsequently triggers the degranulation of effector cells, releasing pro-inflammatory mediators, such as histamines and leukotrienes. The IgE-mediated allergic pathway, which generates mediator-related allergic symptoms, initiates the immune activities locally or systemically. Basophils and mast cells also release a wide spectrum of inflammatory cytokines and chemokines that not only directly cause clinical symptoms but also activate and recruit various cell types to augment the inflammatory status. Hence, anti-IgE therapy can attenuate both the IgE-mediated pathway and the inflammatory conditions. The neutralization of IgE by humanized IgG antibodies has been studied in many clinical trials of allergic disorders (Vichyanond 2011); one of the anti-IgE IgG antibodies, omalizumab, (Xolair®; Genentech USA, Inc and Novartis Pharmaceuticals Corporation) has been approved for the treatment of allergic asthma and chronic idiopathic urticaria. The success of anti-IgE therapy has confirmed the role of IgE in the pathogenesis of asthma and gradually establishes the concept ‘‘allergic asthma’’.

IgE is biologically expressed in secretory form or membrane-bound form. Membrane-bound IgE forms the core unit of B-cell antigen receptors (BCRs) which determine antigen specificity and are essential for survival and functions of B cells. As a general rule in B-cell activation, besides crosslinking BCRs by specific antigens as the first signal, a second signal of co-stimulatory cytokines and receptor-ligand connection from cognate helper T cells is required. Without the appropriate co-stimulatory signal, a B cell who has its antigen receptors cross-linked will step on processes of energy, a state that is no longer responsive to antigens, or apoptosis. Therefore, an anti-CεmX targeting mIgE-expressing B cells, such as FB825, could be an effective agent to down-regulate activities of IgE-committed B lymphocytic cells. A drug product of mAb designed from similar rationale is being investigated by Roche Genentech which is referred to as quilizumab (h47H4; RG7449; MEMP1972A). Results of clinical studies showed that quilizumab can reduce IgE production in patients with allergic asthma (Gauvreau et al 2014).

1.2 FB825

Fountain Biopharma Inc developed FB825 to block the biological pathway of IgE synthesis; thus it could be used to treat IgE-mediated allergic diseases. FB825 is a humanized monoclonal immunoglobulin G1 specifically targeting the CεmX domain on human B lymphocytic cells expressing mIgE. The CεmX domain of 52 amino acid residues, located between the CH4 domain and membrane-anchor segment of human membrane-bound ε chain on $mIgE^+$ B cells, is a unique antigenic site for the immunological targeting of B cells (Chen et al 2010; Peng et al 1992). Monoclonal antibodies specific for CεmX can potentially affect mIgE-expressing B lymphocytes and memory B cells, down-regulate IgE synthesis, and treat IgE-mediated allergic diseases (Chang 2006; Chang et al 2007). FB825 binds specifically to the CεmX domain of mIgE and does not interact with free IgE; therefore, FB825 is not neutralized by IgE in the circulation.

FB825 can bind to mIgE-expressing human B cells and induce subsequent apoptosis and/or antibody-dependent cellular cytotoxicity (ADCC) (Chan 2012; Cheng 2014). FB825 also reduces the number of IgE-producing plasma B cells in a culture of human peripheral blood mononuclear cells (PBMCs) (Li et al 2013). Furthermore, FB825 suppresses the anti-CD40- and interleukin-4-stimulated production of IgE from human PBMCs in a xenograft mouse model (Chou et al 2013). Based on the aforementioned findings, FB825 should be capable of blocking IgE production driven by allergens and alleviating airway hypersensitive symptoms like allergic asthma and rhinitis. Accumulating data exhibited that decreasing serum IgE levels probably helps alleviate atopic skin conditions like atopic dermatitis and chronic urticaria. If the pharmacological efficacy of FB825 can be proven in human clinical studies, its applications can be expanded to other IgE-mediated disorders.

By targeting CεmX domain, FB825 will not be consumed by free IgE. Therefore, unlike the situation met by omalizumab, its application may not be limited in patients with high serum IgE concentrations. According to Fountain Biopharma Inc pharmacological studies in pre-clinical stage, given the long theoretical half-life ($t_{1/2}$) of human immunoglobulin G1 monoclonal antibodies, the systematic concentration of FB825 in a patient receiving a rational flat dose should be maintained above the minimal effective concentration to decrease the number of mIgE-expressing B cells and IgE production for several weeks. In comparison to omalizumab which is injected every 2 or 4 weeks, a seasonal treatment regimen of FB825 would be practicable, thus a long term control of hypersensitive symptoms would be expected.

Additional details on FB825 are provided in the investigator's brochure (IB) (Fountain BioPharma Inc 2017).

1.3 Non-clinical Data

Various *in vitro,* pharmacodynamic and GLP compliant toxicity studies have been conducted. Details of non-clinical studies are provided in the investigator's brochure of FB825.

1.3.1 Nonclinical Pharmacology

Various *in vitro* and *in vivo* studies were performed to examine mechanisms of actions and pharmacological properties of FB825. Pharmacological properties are summarized as follows:

- FB825 binds to $mIgE^+$ B cells with high specificity.
- FB825 shows similar affinity to the cynomolgus monkey and human CεmX domain.
- FB825 induces cell death of $mIgE^+$ B cells via ADCC and/or apoptosis *in vitro* and inhibits the growth of $mIgE^+$ B-cells in mice. Complement-dependent cytotoxicity of FB825 was not detected.
- FB825 shows pharmacological activities in the depletion of IgE-secreting B cells in primary culture of PBMCs obtained from atopic dermatitis patients.
- FB825 inhibits IgE production of human PBMCs in severe combined immunodeficiency (SCID) mouse model.
- Murine mAb 4B12 (parental clone of FB825) can specifically reduce antigen-specific IgE and reduce airway hyperresponsiveness to inhaled methacholine in an allergic asthma mouse model.

1.3.2 Toxicology Summary

The results of nonclinical toxicology studies of FB825 are summarized as follows:

- FB825 was well-tolerated by cynomolgus monkeys at the maximum dose of 300 mg/kg in the single-dose toxicology studies via IV infusion or subcutaneous injection.
- FB825 was well-tolerated in cynomolgus monkeys at levels of 30, 100, and 300 mg/kg via 10-minute IV infusion once weekly for a total of 4 doses. FB825-related effects were limited to reversible marked increases in alanine aminotransferase (ALT) at FB825 doses of ≥100 mg/kg, and reversible mild increases in aspartate aminotransferase (AST), partially reversible minimal decreases in albumin levels and corresponding albumin:globulin ratios, and reversible minimal increases in monocyte counts at an FB825 dose of 300 mg/kg.
- FB825 was well-tolerated in cynomolgus monkeys at levels of 30, 100, and 200 mg/kg via 20-minute IV infusion once every two weeks for 26 weeks. There are no adverse findings in clinical observations, body weights, body weight change, qualitative food consumption, ophthalmic observations, electrocardiograms, clinical and anatomic pathology, IgE, immunophenotyping (IPT) analysis, thyroid hormone (TSH and T4), and T cell-dependent antibody (anti-keyhole limpet hemocyanin [KLH] antibody) response. Therefore, the no observed adverse effect level (NOAEL) was 200 mg/kg/dose.
- Tissue cross-reactivity of FB825 using cryosections from a full panel of human tissues showed minimal (1+) intensity positive cytoplasmic stainings, which were considered of uncertain specificity to Biotin-FB825, because cytoplasmic staining at very low intensity is occasionally noted as a nonspecific background finding.
- Hyperimmunization study showed that the screening enzyme-linked immunosorbent assay (ELISA) detected FB825-reactive antibodies in the serum collected from all 3 animals tested.

1.3.3 Single-Dose Studies

Two non-GLP single-dose toxicity studies were carried out in cynomolgus monkeys. In an IV injection dose-range-finding study, a single 10-minute IV infusion of FB825 was well tolerated in male and female cynomolgus monkeys at levels of 30, 100, and 300 mg/kg. There were no treatment-related effects on clinical observations, food consumption, body weight, or mortality. FB825-related effects were limited to minimal increases in ALT and AST that recovered by Day 57, and minimal increases to interleukin-6 and interleukin-10 at 6 hours and/or 1 hour after dosing in animals administered at least 100 mg/kg FB825. Based on these results, the no observed adverse effect level (NOAEL) was considered to be 300 mg/kg.

In another single-dose toxicology study, IV administration of FB825 via a single SC injection was well-tolerated in cynomolgus monkeys at 300 mg/kg. There were no FB825-related clinical signs or effects on body weights or clinical pathology parameters (hematology, coagulation, and clinical chemistry).

1.3.4 Repeat-Dose Studies

4-weeks study

Two repeat-dose toxicity studies were carried out in cynomolgus monkeys. The first one IV administration of FB825 by 10 minute intravenous infusion once weekly for a total of 4 doses was well tolerated in cynomolgus monkeys at levels of 30, 100, and 300 mg/kg. The following parameters and end points were evaluated in this study: clinical signs, body weights, food consumption, ophthalmology, electrocardiology, clinical pathology parameters (hematology, coagulation, and clinical chemistry), bioanalysis and toxicokinetic evaluations, anti-therapeutic antibody analysis, flow cytometry, IgE analysis, thyroid hormone levels, gross necropsy findings, organ weights, and histopathologic examinations.

There were no FB825-related clinical signs or effects on body weight, food consumption, ophthalmic, or electrocardiographic examinations, coagulation parameters, and thyroid hormone levels observed in either sex at doses up to 300 mg/kg. Additionally, there were no FB825-related notable gross findings at doses up to and including 300 mg/kg.

FB825-related effects were limited to reversible marked increases in ALT at FB825 doses of ≥100 mg/kg, and reversible mild increases in AST, partially reversible minimal decreases in albumin levels and corresponding albumin:globulin ratios, and reversible minimal increases in monocyte counts at an FB825 dose of 300 mg/kg. The magnitude of increases in ALT and AST levels at 300 mg/kg were considered adverse. Target organ effects were observed at levels of ≥30 mg/kg and consisted of nonadverse follicular colloid depletion of the thyroid and lower thyroid weight. However, the lower thyroid weights were within the range observed in historical control monkeys. Because variation in colloid staining pattern, variation in thyroid follicle size, and vacuolar degeneration have been reported as spontaneous findings in cynomolgus monkeys (Ishida et al 2000; Hatakeyama et al 2011) and because there were no test article-related effects on thyroxine and thyroid stimulating hormone levels, the findings in the thyroid were considered nonadverse under the conditions of this study.

Based on increases in ALT and AST levels at 300 mg/kg, the NOAEL was considered to be 100 mg/kg (C_{max} of 5,330,000 ng/mL and $AUC_{(0-168h)}$ of 520,000,000 ng•hr/mL for males and C_{max} of 5,220,000 ng/mL and $AUC_{(0-168h)}$ of 487,000,000 ng•hr/mL for females)..

26 weeks study

The second repeat dose study is IV administration of FB825 by 20 minute intravenous infusion once every other week for 26 weeks, which means for 13 doses, and assess the reversibility, persistence, or delayed occurrence of any effects after a 9-week recovery phase. FB825 was well tolerated in cynomolgus monkeys at levels of 30, 100, and 200 mg/kg.

Assessment of toxicity was based on mortality, clinical observations, body weights, body weight change, qualitative food consumption, ophthalmic observations, electrocardiograms (ECGs), and clinical and anatomic pathology. Blood samples were collected for analyses of toxicokinetics, IgE, immunophenotyping (IPT), thyroid hormone (T4 and TSH), Immunogenicity (ADA) and T cell-dependent antibody (anti-keyhole limpet hemocyanin [KLH] antibody) response.

All animals survived to the scheduled sacrifice. No FB825-related clinical observations or change in body weight, food consumption (qualitative), ECGs, ophthalmic examinations, hematology, coagulation, urinalysis, organ weights, macroscopic examination, thyroid hormone levels, IgE, IPT, anti-KLH antibody, or immunology were noted.

Several non-progressive FB825-related clinical chemistry effects were observed at multiple time points during the dosing phase in animals administered ≥100 mg/kg/dose; these included a dose-related, minimally to moderately increased alanine aminotransferase activity, and a non-dose-related, minimally to mildly decreased albumin concentration (unclear mechanism), with accompanying minimally to mildly decreased albumin:globulin ratio in animals administered 200 mg/kg/dose and minimally to mildly decreased calcium concentration in males administered ≥100 mg/kg/dose. All changes were reversible, except that for calcium concentration, which was still decreased on Day 64 of recovery phase in males administered ≥100 mg/kg/dose. All changes, except for the increased alanine aminotransferase activity, were considered non-adverse based on their small magnitudes of change, absence of microscopic findings, and/or general evidence of reversibility. No FB825-related findings were observed in hematology, coagulation, or urinalysis test results.

At the terminal sacrifice, FB825-related microscopic findings were noted in the liver (minimal or slight individual hepatocyte necrosis, centrilobular hepatocyte vacuolation/degeneration/necrosis, diffuse leukocytosis in the sinusoidal lumen, and multifocal pigment of Kupffer cells), which were correlated with increased alanine aminotransferase (ALT) activity in most cases; and epidermis of the skin/subcutis (minimal or slight diffuse hyperplasia of the epidermis, accompanied by minimal hyperkeratosis) of animals administered ≥100 mg/kg/dose. These microscopic findings were reversible after a 9-week recovery phase, except the diffuse leukocytosis in the hepatic sinusoidal lumen of one male administered 100 mg/kg/dose; therefore, these microscopic findings were considered non-adverse.

In conclusion, the 26 weeks repeat dose study resulted in no adverse findings in clinical observations. Therefore, the no observed adverse effect level (NOAEL) was 200 mg/kg/dose and this dose level corresponded to mean C_{max} and AUC values are 7,590 µg/mL and 1,100,000 µg*hr/mL, respectively, in male monkeys and 6,300 µg/mL and 882,000 µg*hr/mL, respectively, in female monkeys for FB825 on Day 169 of the dosing phase.

Based on these two repeat-dose study, the no observed adverse effect level (NOAEL) of FB825 was 200 mg/kg/dose.

1.4 Clinical Study

A phase 1, randomized, placebo-controlled, double-blind study to evaluate the safety, tolerability, pharmacokinetics, and immunogenicity of single IV dose of FB825 in normal healthy subjects has been completed in the US, with US FDA approval. The study has included 54 subjects (by 2015) in 6 dose cohorts of FB825: in doses of 0.003, 0.03, 0.3, 1.5, 5, and 10 mg/kg intravenously as a 1-hour infusion. Study cohorts included 7 subjects each in Cohorts A and B (4 active: 3 placebo), and increased in subsequent cohorts to 10 subjects each in Cohorts C, D, E, and F (7 active: 3 placebo).

As of 30 Jan 2016, fifty-four subjects have received treatment with FB825/placebo in phase 1a study. Currently, FB825 were well-tolerated up to 10 mg/kg IV in fifty four healthy volunteers in this phase 1a study.

1.5 Rationale for Study

It is recognized that IgE plays an important role in mediating hypersensitivity reactions responsible for most of the allergic diseases, such as atopic dermatitis, asthma etc. which remain poorly controlled. FB825 blocks the biological pathway of IgE synthesis and thus can be used to treat IgE-mediated allergic diseases.

FB825 was found to be safe when given IV repeat dose in toxicology study in monkey. No adverse effects of FB825 were observed in parameters included electrocardiograms for cardiovascular, ophthalmic examinations and other clinical, CNS and respiratory safety observations.

The safety and tolerability of FB825 was demonstrated in the US phase I randomized, double-blind study with healthy subjects. Also, the FB825 was proved by *in vivo* study that it is able to block the biological pathway of IgE synthesis and thus can be used to treat IgE-mediated allergic diseases. Therefore, in this study, the effects of IgE in patients with atopic dermatitis receiving FB825 treatment will be investigated. The study will evaluate safety and efficacy in adults with atopic dermatitis.

1.6 Rationale for Dose Selection

A phase 1, randomized, placebo-controlled, double-blind study to evaluate the safety, tolerability, pharmacokinetics, and immunogenicity of single IV doses of FB825 in normal healthy subjects has been completed in the US, with US FDA approval. The study has included 54 subjects (by 2015) in 6 dose cohorts of FB825: in doses of 0.003, 0.03, 0.3, 1.5, 5, and 10 mg/kg intravenously as a 1-hour infusion. The results showed that FB825 was safe and well-tolerated up to 10 mg/kg IV in healthy volunteers. Based on the study results, 5 mg/Kg will be selected in the study because it is comparative safe and supposed to be effective.

2 Study Objectives

2.1 Primary Objective

The primary objective of this study is:

- To evaluate the change from baseline in total IgE and allergen-specific IgE in patients with atopic dermatitis after the IV administration of FB825.

2.2 Secondary Objectives

The secondary objectives of this study are as follows:

- To evaluate the clinical efficacy in patients with atopic dermatitis after the IV administration of FB825.
- To explore the safety in patients with atopic dermatitis after the IV administration of FB825.
- To monitor the changes in clinical hematology after the IV administration of FB825.
- To explore the change from baseline in biomarkers including thymus and activation regulated chemokine (TARC), Eotaxin-3, thymic stromal lymphopoietin (TSLP), periostin, IL-1a, IL-4, IL-5, IL-13, IL-16, IL-31 and M-CSF after IV administration of FB825.

3 Study Design

This is an open-labeled exploratory study to evaluate safety and efficacy of FB825 in adults with atopic dermatitis. The study will be conducted at one center in Taiwan.

Approximately 12 subjects with atopic dermatitis (AD), who meet the criteria for study entry, will be enrolled to the study. All eligible subjects will receive FB825, 5mg/kg, by 1-hour IV infusion on Day 1 and Day 85. Subjects will be hospitalized after receiving FB825 on Day 1 and Day 85 and will be discharged from the hospital next day for safety observation (at least 12 hours). Subjects will return to the study site on Days 8, 15, 29, 57, 92, 99, 113, 141, and 169 for the safety, efficacy, and biomarker evaluation.

4 Selection of Study Population

Male or female subjects with atopic dermatitis will enrolled in a single study site. Approximately 15 subjects in total will enrolled to achieve at least 12 evaluable subjects.

4.1 Inclusion Criteria

Each subject must meet all of the following criteria to be enrolled in this study:

1. Male or female between 20 and 65 years of age, inclusive.

2. The subject has a physician-confirmed diagnosis of chronic atopic dermatitis based on 3-year history of symptoms defined by the Eichenfield revised criteria of Hannifin and Rajka and supported by positive allergen-specific IgE at the screening visit.

3. Eczema Area and Severity Index (EASI) score ≧14 at the screening and baseline visits.

4. Investigator's Global Assessment (IGA) score ≧ 3 (5-point scale) at the screening and baseline visits.

5. ≧10 % body surface area (BSA) of AD involvement at the screening and baseline visits.

6. History of inadequate response to a stable (1 month) regimen of topical corticosteroids or calcineurin inhibitors as treatment for AD within 3 months before the screening visit. (The regimen of topical corticosteroids means medium to high potency, applied for at least 28 days or for the maximum duration recommended by product prescribing information.)

7. Patients must be applying stable doses of emollient provided for atopic dermatitis twice-daily for at least 7 days before the baseline visit.

8. Female subjects of childbearing potential must use at least two forms of birth control. One must be barrier protection (i.e., condom or female condom) and the other is one of acceptable method of birth control (ie, diaphragm, intrauterine device, hormonal contraceptives, or abstinence) throughout the study. Subjects who are surgically sterile (ie, hysterectomy, bilateral tubal ligation, or bilateral oophorectomy), or postmenopausal (defined as amenorrhea for 12 consecutive months and documented serum follicle-stimulating hormone level >40

mU/mL) will be considered as no childbearing potential. All female subjects must have a negative serum pregnancy test prior to dosing.

Note: The subject must use the method of contraception mentioned above during study period and in 16 weeks or 5 half-lives after the last dosing of FB825.

9. The subject has a body weight ≥ 40 kg at screening and a body mass index of 18.0 to 30.0 kg/m^2, inclusive.

10. The subject has a normal, as determined by the investigator, 12-lead electrocardiogram (ECG) with normal cardiac conduction parameters:

    - Heart rate between 45 and 100 bpm;
    - Fridericia-corrected QT interval (QTcF) ≤450 milliseconds (men) or ≤470 milliseconds (women);
    - QRS interval lower than 120 milliseconds.

11. The subject is healthy, except atopic diseases, as determined by the investigator, on the basis of clinical laboratory test results performed at screening. If the results are outside the normal reference ranges, the subject may be included only if the investigator judges the abnormalities or deviations from normal not to be clinically significant.

12. The subject is able to provide written informed consent.

13. The subject agrees to comply with all protocol requirements.

4.2 Exclusion Criteria

1. Female subjects who are pregnant or lactating.

2. The subject is on diet or with poor intake.

3. The subject has a history of heart arrhythmias (any clinically relevant).

4. The subject has a positive test result for hepatitis B surface antigen, hepatitis C virus antibody,

or human immunodeficiency virus antibodies at screening.

5. The subject has a history of alcohol or drug abuse that would impair or risk the patients' full participation in the study, in the opinion of the investigator.

6. The subject is under judicial supervision or curatorship.

7. The subject has a clinically relevant, currently active or underlying gastrointestinal, cardiovascular, nervous system, psychiatric, metabolic, renal, hepatic, respiratory (with the exception of uncomplicated allergic rhinitis), inflammatory, immunological, endocrine, diabetes, or infectious disease and ineligible to participate in the study judged by investigator.

8. The subject has any history of a previous anaphylactic reaction.

9. The subject has any condition that, in the opinion of the investigator, would compromise the study or the well-being of the subject or prevent the subject from meeting or performing study requirements.

10. The subject has received any immunoglobulin products or blood products within 3 months prior to dosing.

11. The subject has received an biologic product:
    - The subject has received any cell-depleting agents, not only limited to rituximab, within 6 months prior to dosing, or before the lymphocyte count returns to normal, whichever is longer.
    - The subject has received other biologics within 5 half-lives (if known) or 16 weeks, which is longer, prior to dosing).

12. The subject has one or more of the following laboratory abnormalities at screening as defined by Division of Microbiology and Infectious Diseases Adult Toxicity Table 2007:
    - Aspartate aminotransferase or alanine aminotransferase (>2 × upper limit of normal [ULN]) or higher
    - Total bilirubin ≥1.5 × ULN
    - Serum creatinine ≥1.6 × ULN

- Any other laboratory abnormality higher than or equal to grade 2 with the exception of IgE level, eosinophil counts, eosinophil cationic protein (ECP) and laboratory values mentioned above.

  Note: Laboratory values may be converted to equivalent standard units. Retesting of abnormal laboratory values that may lead to exclusion will be allowed once (without prior sponsor approval). Retesting will take place during an unscheduled visit in the screening phase (before baseline).

13. The subject has received any approved or unapproved (ie, investigational) immunotherapy treatment within the past 3 months.
14. The subject has used any of the following classes of medication (prescription or over the counter):
    - Intranasal corticosteroid (eg, fluticasone propionate) within 30 days prior to dosing.
    - Systemic corticosteroids (eg, prednisone) within 30 days prior to dosing.
    - Leukotriene modifiers (eg, montelukast) within 30 days prior to dosing.
    - Immunosuppressants (eg, gold salts, methotrexate, azathioprine, cyclosporine) within the past 30 days prior to dosing.
    - Immunomodulating drugs (eg, IFN-γ) within the past 30 days prior to dosing.
    - Anti-IgE (eg, omalizumab) within the past 1 years prior to dosing
    - Allergen immunotherapy within the past 1 years prior to dosing
    - Orally inhaled corticosteroids (eg, budesonide) within the past 30 days prior to dosing
15. The subject has received phototherapy within 4 weeks prior to dosing.
16. The subject has received live vaccine within 12 weeks prior to dosing.
17. The subject has known or suspected history of immunosuppression, including history of opportunistic infections (eg, TB) per investigator judgment.
18. The subject has history of malignancy within 5 years before the screening period.
19. High risk of parasite infection.

- Risk factors for parasitic disease (living in an endemic area, chronic gastrointestinal symptoms, travel within the last 6 months to regions where geohelminthic infections are endemic, and/or chronic immunosuppression)

  AND

- Evidence of parasitic colonization or infection on stool evaluation for ova and parasites.

  Note: stool ova and parasite evaluation will only be conducted in patients with risk factors and an eosinophil count more than twice the upper limit of normal

4.3 Restrictions for Subject during the Study

- Subjects must be willing to remain in the hospital overnight after FB825 IV administration for safety observation (at least 12 hours) on Day 1 and Day 85.
- Subjects must be willing to return to the clinic for every follow-up visit up to Day169 (end-of-study visit).
- Subjects must refrain from strenuous physical activity or contact sports 24 hours prior to dosing and during the safety observation period.
- Subjects must refrain from alcohol consumption 48 hours prior to dosing and during the safety observation period.
- Subjects may not travel to where endemic parasitic diseases occur. Site staff should discuss with the sponsor for guidance in cases of uncertainty.

4.4 Withdrawal of Subjects from the Study

4.4.1 Reasons for Withdrawal

Subjects can withdraw consent and discontinue from the study at any time, for any reason, without prejudice to further treatment.

The investigator may withdraw a subject from the study if the subject:

1. Is in violation of the protocol
2. Experiences a serious adverse event (SAE) or intolerable AE

3. Has laboratory safety assessments that reveal clinically significant hematological or biochemical changes from baseline values
4. Develops, during the course of the study, symptoms or conditions listed in the exclusion criteria
5. Requires a medication prohibited by the protocol
6. Requests an early discontinuation for any reason.

The investigator can also withdraw a subject upon the request of Fountain or if Fountain terminates the study. Upon occurrence of an SAE or intolerable AE, the investigator will confer with the sponsor. If a subject is discontinued because of an AE, the event will be followed until it is resolved or until stable.

4.4.2 Handling of Withdrawal

When a subject withdraws from the study, the reason(s) for withdrawal will be recorded by the investigator in the relevant page of the case report form (CRF). Whenever possible, any subject who withdraws from the study prematurely will undergo all end-of-study assessments. Any subject who fails to return for final assessments will be contacted by the site in an attempt to have him or her comply with the protocol.

5 Study Treatments

5.1 Identity of Study Treatments

The Investigational Product (IP) FB825 drug product is manufactured by Cytovance Biologics, 800 Research Parkway, Ste 200 | Oklahoma City, OK 73104

5.1.1 Investigational Product (IP) (FB825)

The FB825 drug substance is a recombinant humanized immunoglobulin gamma-1 mAb directed against the CεmX segment of human mIgE on the progenitors of IgE-secreting B cells. The mature FB825 molecule is a heterotetrameric polypeptide that consists of two 219 residue kappa light chains and two 447-residue heavy chains, with a molecular weight of 147.79 kDa.

FB825 drug product as a sterile solution for injection, supplied as a 3.0-mL solution at a concentration of 20 mg/mL in a solution containing 20 mM L-histidine, 140 mM sodium chloride, and 0.02% Tween 80 at pH 6.5 with water for injection, without any preservative. The visual appearance of the solution of FB825 is clear, colorless, and with no visible particles. The product is packed in serum/lyophilization flint glass vial (5 mL vial, with a total amount of FB825 at 60 mg/vial). The vial is fitted with a 20-mm serum-style stoppers and 20-mm Flip-off TruEdge red matted aluminum seal, intended for intravenous (IV) injection for single use.

5.1.2 Diluent

FB825 (3.0-mL solution in 5 mL glass vial) is to be diluted before use. The diluent, 0.9% sodium chloride solution for injection, will be supplied as a 250-mL volume pack.

5.2 Dosing and IV Administration of Study Treatments

Two doses of 5 mg/kg FB825 will be given to subjects with atopic dermatitis.

Subjects will receive FB825 by 1-hour IV infusion in the morning at Day 1 and Day 85. Fasting for at least 2 hours will be required. There will be no restriction of when subjects can eat again after finishing the infusion. Water intake is not allowed within 1 hour prior to dosing and 1 hour after dosing (water can be had at other times).

The administered amount of FB825 will be adjusted based on subject's body weight, the appropriate amount of drug product will be diluted with 250 mL 0.9% sodium chloride solution.

FB825 will be administered via IV route over 1 hour with the aid of a programmable volumetric infusion device.

The final diluted product with 0.9% sodium chloride, after reconstitution, has to be used as soon as possible, and has to be used with 8 hours. The reconstituted FB825 can be stored at 2°C to 25°C for a maximum of 8 hours, prior to use.

5.3 Management of Clinical Supplies

5.3.1 Study Treatments Storage

Fountain will provide the investigator and study site with adequate quantities of IP FB825 drug. All study drugs must be stored in a secure area (eg, a locked cabinet), protected from moisture and light, and be stored at 2°C to 8°C. The site will be required to keep a temperature log to establish a record of compliance with these storage conditions. All study drugs will be kept in a secure cabinet or room with access restricted to necessary study site personnel.

FB825 drug product vials will be shipped at 2°C to 8°C to the study site. Upon arrival, the vials of FB825 should be transferred to 2°C to 8°C, and may be stored for at least 9 months.

For optimal performance, FB825 drug product should be diluted on the day of injection and used immediately. After the final dilution with 0.9% sodium chloride solution for injection, the FB825 solution can be stored at 2°C to 25°C for a maximum of 8 hours.

5.3.2 Study Drug Accountability

The sponsor “Fountain” is responsible for shipping FB825 to the study site and strict inventory control for the drug accountability of the shipment received at the site should be implemented at the site.

The investigator will maintain accurate records of receipt of all study drugs, including dates of receipt. In addition, accurate records will be kept regarding when and how much study drug is dispensed and used by each subject in the study. Reasons for departure from the expected dispensing regimen must also be recorded. At the completion of the study, to satisfy regulatory requirements regarding drug accountability, the study drug will be reconciled and retained or destroyed according to applicable regulations.

The clinic study site pharmacy will prepare a single dose for each subject. Separate instructions will be provided to the clinic for dose dilution, preparation, storage, and IV administration.

5.3.3 Treatment Compliance

Study drug will be administered in the clinic under direct observation of clinic personnel and recorded in the CRF. Clinic personnel will confirm that the subject has received the dose of study drug.

The date and time of study drug dosing will be recorded in the appropriate page of the CRF. If a subject does not receive study drug, the reason for not receiving study drug will be recorded.

5.4 Prior, Concomitant and Prohibited Medications

5.4.1 Prior Medications and Therapies

Information about prior medications taken by the subject within the 30 days before he or she provides informed consent will be recorded in the subject's CRF.

5.4.2 Pre-treatment/Concomitant Medication and Procedures

Any treatment (including nutritional supplements) or procedure administered from the time of signing of the ICF to the end of study visit is considered concomitant and will be recorded in the CRF. This includes permitted medications ongoing at the time of consent.

The AD basal therapy during the study described below:

- All patients are required to apply moisturizers at least twice daily for at least the 7 consecutive days prior to dosing and to continue the treatment throughout the study. All types of moisturizers are permitted, but patients may not initiate treatment with prescription moisturizers or moisturizers containing additives during the screening period or during the study.

- Patients may continue using stable doses of prescription moisturizers or moisturizers containing additives, if initiated before the screening visit. Starting on day 1/baseline, all patients are required to initiate treatment with topical corticosteroid (TCS) using a standardized regimen according to the following guidelines:

- Apply medium potency TCS daily to areas with active lesions
  - ✓ Low potency TCS should be used on areas of thin skin (face, neck, intertriginous, and genital areas, areas of skin atrophy, etc.) or for areas where continued treatment with medium potency TCS is considered unsafe
- After lesions are under control (clear or almost clear), switch from medium potency to low potency TCS and treat daily for 7 days, then stop
- If lesions return, reinstitute treatment with medium potency TCS, with the step-down approach described above upon lesion resolution
- For lesions persisting or worsening under daily treatment with medium potency TCS, patients may be treated (rescued) with high or super-high potency TCS, unless higher potency TCS are considered unsafe
- Monitor the patient for signs of local or systemic TCS toxicity and step down or stop treatment as necessary

- The type and amount of topical products used during the study will be recorded. The amount of TCS used will be determined by weighing the tube at each visit (see study reference manual for details).
- It is recommended that patients use fluticasone propionate 0.05% cream, mometasone furoate 0.1% cream, or betamethasone valerate 0.06% cream as medium potency TCS, and hydrocortisone 1% ointment for low potency TCS.
- If rescue with TCS is needed, it is recommended that patients use fluocinonide 0.05 % cream, desoximetasone 0.25% ointment as high potency TCS, and clobetasol propionate 0.05% ointment for super high potency TCS.
- Do not use moisturizers and TCS on the same areas at the same time during the day. On areas not treated with TCS, moisturizers will be applied twice daily – morning and evening.

Pre-treatment medications/procedures: medications taken or procedures performed prior to dosing.

Concomitant medications/procedures: medications taken or procedures performed following the IV administration of study drug through the EOS visit.

Prohibited concomitant medications:

- Topical tacrolimus and pimecrolimus
- Systemic corticosteroids, unless the subjects are under rescue medication.
- Leukotriene inhibitors
- Allergen immunotherapy
- Systemic treatment for AD with an immunosuppressive/immunomodulating substance (including, but not limited to, cyclosporine, mycophenolate-mofetil, IFN- γ , azathioprine, methotrexate, or biologics)
- Treatment with a live (attenuated) vaccine
- Traditional Chinese Medicine

Prohibited concomitant procedures:

- Surgical procedures
- Concomitant ultraviolet (UV) procedures (phototherapy [NBUVB, UVB, UVA1, or PUVA])
- Tanning in a bed/booth is not allowed during the study
- Patients are not allowed more than 2 bleach baths per week during study participation

5.5 Handling of Infusion-Related or Allergic Reaction

The IV administration of study drug must be performed under supervision of trained medical staff and where facilities to handle allergic reactions are available. If a subject experiences an infusion-related reaction, the subject must be treated symptomatically with supportive care, further monitoring, and appropriate medical therapy which may include antihistamines and/or corticosteroid if needed. The study infusion may be stopped and the subject will be followed until the end of the study. The amount infused will be recorded. Should a subject experience symptoms typical of an allergic reaction (eg, shortness of breath, anaphylaxis, urticaria, angioedema), then study drug IV administration should be discontinued immediately and permanently.

Suspected anaphylaxis should be assessed according to the clinical diagnostic criteria outlined by the National Institute of Allergy and Infectious Diseases which are provided in Appendix 12-2.

For these and other circumstances, subjects will receive appropriate medical treatment at the discretion of the investigator.

5.5.1 Rescue medications/procedures

At the discretion of the investigator, patients may be rescued with a prohibited medication or procedure to treat intolerable AD symptoms.

- If medically necessary (ie, to control intolerable AD symptoms), rescue treatment with systemic corticosteroids for AD at doses less than 1 mg/kg/day prednisolone and no more than 3 days may be provided to study patients at the discretion of the investigator after week 2.

- Investigators should make every attempt to conduct efficacy and safety assessments (eg, disease severity scores, safety labs) immediately before administering any rescue treatment. An unscheduled visit may be used for this purpose if necessary.

The IV administration of study drug must be performed under supervision of trained medical staff and where facilities to handle allergic reactions are available. The clinic should have a staff trained to manage anaphylaxis and cardiopulmonary arrest. At a minimum, the clinic will have a crash cart with appropriate monitoring and resuscitation equipment including IV replacement fluids, to be

able to deliver supplementary oxygen, and provide appropriate medications including antihistamines, corticosteroids, and epinephrine.

5.6 Precautions

Based on the approved and marketed Xolair anti-IgE antibody product (Genentech 2014), the most common AEs (≥1% more frequent in Xolair-treated patients) in clinical studies for allergic asthma treatment were arthralgia, pain (general), leg pain, fatigue, dizziness, fracture, arm pain, pruritus, dermatitis, and earache. The most common AEs (≥2% Xolair-treated patients and more frequent than in placebo) in clinical studies for chronic idiopathic urticaria treatment were nausea, nasopharyngitis, sinusitis, upper respiratory tract infection, viral upper respiratory tract infection, arthralgia, headache, cough, and injection site reactions. The use of Xolair has also been associated with anaphylaxis (boxed warning); malignancy; acute asthma symptoms; corticosteroid reduction; fever, arthralgia, and rash; and eosinophilic conditions. In controlled trials, a numerical imbalance in the number of arterial thrombotic events was noted between omalizumab and placebo. Cases of idiopathic thrombocytopenia have been noted through spontaneous reporting but the frequency of any potential association is not known. In Genentech's Phase 1a single dose study with MEMP1972A, the most common AEs were headache, fatigue, vessel puncture site hematoma, and nasopharyngitis, and in their Phase IIa multiple-ascending dose study with MEMP1972A, the most common AEs were headache, nasal congestion, back pain, dizziness, and fatigue. Similar reactions may also occur in this study with FB825.

6 Study Procedures and Methods of Assessment

The following sections describe the study procedures and data to be collected. Subjects are to be assessed by the same investigator or site personnel whenever possible.

6.1 Endpoints

6.1.1 Primary Endpoints

- Change from baseline in total IgE at Day85 and Day 169/EOS.
- Change from baseline in allergen-specific IgE at Day 85 and Day 169/EOS.

6.1.2 Secondary Endpoints

- Change from baseline in total IgE at Day 8, 15, 29, 57, 85, 92, 99, 113, 141, and 169.
- Change from baseline in allergen-specific IgE at Day 8, 15, 29, 57, 85, 92, 99, 113, 141, and 169.
- Changes from baseline in pruritus Visual Analogue Scale (VAS) at Days 8, 15, 29, 57, 85, 92, 99, 113, 141, and 169
- Changes from baseline in Eczema Area and Severity Index (EASI) at Days 8, 15, 29, 57, 85, 92, 99, 113, 141, and 169
- Changes from baseline in Severity Scoring of Atopic Dermatitis Index (SCORAD) at Days 8, 15, 29, 57, 85, 92, 99, 113, 141, and 169
- Changes from baseline in Investigator Global Assessment (IGA) for atopic dermatitis at Days 8, 15, 29, 57, 85, 92, 99, 113, 141, and 169
- Changes from baseline in Body Surface Area (BSA) involved in atopic dermatitis at Days 8, 15, 29, 57, 85, 92, 99, 113, 141, and 169
- Change from baseline in biomarkers including thymus and activation regulated chemokine (TARC), Eotaxin-3, thymic stromal lymphopoietin (TSLP), periostin, IL-1a, IL-4, IL-5, IL-13, IL-16, IL-31 and M-CSF after IV administration of FB825 at Days 8, 15, 29, 57, 85, 92, 99, 113, 141, and 169
- Safety will be assessed by monitoring and recording of adverse events (AEs) and serious adverse event (SAEs); physical examination findings and vital sign measurements (systolic

and diastolic blood pressures, heart rate, respiratory rate, and body temperature), clinical laboratory test results (hematology, coagulation, serum chemistry [including liver function tests, blood glucose level], and urinalysis); 12-lead ECG results.

6.2 Biomarker Assessments

Blood samples for the measurement of total, allergen-specific IgE, thymus and activation regulated chemokine (TARC), Eotaxin-3, thymic stromal lymphopoietin (TSLP), periostin, IL-1a, IL-4, IL-5, IL-13, IL-16, IL-31 and M-CSF will be analyzed according to methodology described in a separate report.

Blood samples will be collected. The actual sample collection time and sampling problems, if any, will be recorded on the CRF. Approximately 5 mL sample of venous blood per sample will be drawn at the following time points:

Total Immunoglobulin/ Allergen-specific IgE :

- Screening period: at any time
- Day 1, and 85: (In 2 hours before the start of infusion)
- Days 8, 15, 29, 57, 92, 99, 113, and 141, and 169 after IV administration of FB825 at any time on the day.

TARC, Eotaxin-3, TSLP, periostin, IL-1a, IL-4, IL-5, IL-13, IL-16, IL-31 and M-CSF:

- Day 1 and 85 in 2 hours before the start of infusion, and at any time on Days 8, 15, 29, 57, 92, 99, 113, 141, and 169..

Instructions for sample collection, preparation, and shipping will be provided separately to the clinical site.

6.3 Clinical Efficacy Assessments

Pruritus Visual Analogue Scale (VAS)

The pruritus visual analogue scale (VAS) of SCORAD will be applied for the measurement of pruritus. Patients will be asked to assign a numerical score representing the intensity of their symptoms on a scale from 0 to 10, with 0 for having no symptoms and 10 having worst symptoms. Subjects will be asked to perform the measurement at screening, Day 1 and 85 before dosing, Day 2 and Day 86 before discharge, and any time of Day 8, 15, 29, 57, 92, 99, 113, 141, and 169

Severity Scoring of Atopic Dermatitis Index (SCORAD)

The SCORAD (Index) is the validated scoring system in atopic dermatitis (AD). To measure the extent of AD, the rule of nines is applied on a front/back drawing of the patient's inflammatory lesions. The extent can be graded from 0 to 100. The intensity part of the SCORAD consists of 6 items: erythema, oedema/papulation, excoriations, lichenification, oozing/crusts and dryness. Each item can be graded on a scale from 0 (absent) to 3 (severe). The subjective items include daily pruritus and sleeplessness. The SCORAD Index formula is: $A/5 + 7B/2 + C$. In this formula A is defined as the extent (0–100), B is defined as the intensity (0–18) and C is defined as the subjective symptoms (0–20). The maximal score of the SCORAD Index is 103. Subjects will be asked to perform the measurement at screening, Day 1, and 85 before dosing, Day 2 and Day 86 before discharge, and any time of Day 8, 15, 29, 57, 92, 99, 113, 141, and 169.

Eczema Area and Severity Index (EASI)

The EASI scoring system uses a defined process to grade the severity of the signs of eczema and the extent affected. Extent and severity of signs of eczema will be evaluated in four body regions and the total score will be the sum of the four regions scores adjusted with multipliers. The EASI score is ranged from 0-72. Subjects will be asked to perform the measurement at screening, Day 1 and 85 before dosing, Day 2 and Day 86 before discharge, and any time of Day 8, 15, 29, 57, 92, 99, 113, 141, and 169.

IGA for AD

IGA allows investigators to assess overall disease severity at one given time point, and it consists of a 5-point severity scale from clear to very severe disease (0= clear, 1 =almost clear, 2 = mild disease, 3 = moderate disease, and 4= severe disease). Subjects will be asked to perform the measurement at screening, Day 1 and 85 before dosing, Day 2 and Day 86 before discharge, and any time of Day 8, 15, 29, 57, 92, 99, 113, 141, and 169.

BSA involved in AD symptoms

It will be measured as part A (Extent) of SCORAD. Subjects will be asked to perform the measurement at screening, Day 1 and 85 before dosing, Day 2 and Day 86 before discharge, and any time of Day 8, 15, 29, 57, 92, 99, 113, 141, and 169.

6.4 Safety Assessments

Safety will be assessed by monitoring and recording of Adverse Event (AEs), Serious Adverse Event (SAEs), physical examination findings and vital sign measurements (systolic and diastolic blood pressures, heart rate, respiratory rate, and oral body temperature), clinical laboratory test results (hematology, coagulation, serum chemistry [including liver function tests], and urinalysis), and 12-lead ECG results.

6.4.1 Adverse Events

The Adverse Event section (Section 7) describes the Adverse Event (SAEs), Serious Adverse Event (SAEs) and Adverse Events of Special Interest to be collected during the study.

6.4.2 Physical Examinations

A complete physical examination will be performed at the time points indicated in the schedule of events.

A complete physical examination will include assessment of skin (including any signs for cutaneous erythema), head, ears, eyes, nose, throat, neck, thyroid, lungs, heart, cardiovascular system, abdomen, lymph nodes, and musculoskeletal system/extremities. Interim physical examinations will be performed at the discretion of the investigator, if necessary, to evaluate AEs or clinical laboratory abnormalities.

Height and weight will be measured and body mass index will be calculated at screening only. Weight will also be measured at all other physical examination time points as indicated in the schedules of events for the study. Body weight will be recorded in kilograms (kg) to 1 decimal place in indoor clothing (without coat and shoes) and body height (without shoes) will be measured in centimeters (cm) without decimal places.

6.4.3 Vital Sign Measurements

Vital sign measurements will include systolic and diastolic blood pressures, heart rate, respiratory rate, and body temperature. The subject will be seated for at least 5 minutes before all measurements are taken. Vital signs will be measured at the time points indicated in the schedule of events.

When procedures are overlapping and occurring at the same time point, the order of procedures should be vital sign measurements and then ECGs.

The investigator will determine whether any of the vital sign measurements are clinically significant or not clinically significant. Clinical significance is defined as any variation in results that has medical relevance and may result in an alteration in medical care (eg, active observation, diagnostic measures, or therapeutic measures). If a clinically significant change from the screening values is noted, the clinically significant value and reason for clinical significance will be documented in the AE page of the subject's CRF. The investigator will continue to monitor the subject with additional assessments until the value has reached the reference range or the value at screening or until the investigator determines that follow-up is no longer medically necessary.

6.4.4 Clinical Laboratory Testing

Clinical laboratory tests will be performed by local site. Blood and urine will be collected under fasting conditions (fasted for approximately 2 or more hours) at the time points indicated in the schedule of events.

The following hematology, coagulation, serum chemistry (including liver function and thyroid function tests), urinalysis assessments will be performed:

Hematology: Hematocrit (Hct), hemoglobin (Hb), mean corpuscular hemoglobin (MCH), mean corpuscular hemoglobin concentration (MCHC), mean corpuscular

volume (MCV), platelet count, red blood cell (RBC) count, and WBC and differential count (absolute and percent).

Coagulation: International normalized ratio (INR), partial thromboplastin time (PTT), and prothrombin time (PT)

Serum Chemistry: ALT, albumin, alkaline phosphatase, amylase, anion gap, AST, bicarbonate, bilirubin (total and direct), blood urea nitrogen (BUN), calcium, carbon dioxide, chloride, cholesterol (total, high-density lipoprotein, and calculated low-density lipoprotein), creatine phosphokinase, creatinine, gamma-glutamyltransferase (γ-GT), globulin, glucose, lactate dehydrogenase (LDH), lipase, magnesium, phosphorus, potassium, sodium, total protein, triglycerides, troponin I or T, and uric acid

Thyroid Function: Free T4 and thyroid-stimulating hormone

Urinalysis: Appearance, bilirubin, color, glucose, ketones, leukocyte esterase, microscopy (performed if dipstick is positive; includes bacteria, casts, crystals, epithelial cells, red blood cells, and white blood cells), nitrites, occult blood, pH, protein, specific gravity, turbidity, and urobilinogen

A serum pregnancy test (β-human chorionic gonadotropin) will be performed on all female subjects with potential of children bearing at screening and confirmed result prior to dosing. Urine pregnancy tests will be performed on Days 8, 15, 29, 57, 85, 92, 99, 113, 141, and 169. For female subjects who are postmenopausal, a serum follicle-stimulating hormone test will be performed at screening.

Hepatitis B surface antigen, hepatitis C virus antibody, and human immunodeficiency virus antibody will be assessed at screening.

Abnormal clinical laboratory values will be flagged as either high or low (or normal or abnormal) based on the reference ranges for each laboratory parameter. The investigator will determine whether any of the abnormally high or low results are clinically significant or not clinically significant. Clinical significance is defined as any variation in results that has medical relevance and may result in an alteration in medical care (eg, active observation, diagnostic measures, or

therapeutic measures). If a clinically significant change from the screening value is noted, the clinically significant value and reason for clinical significance will be documented in the AE page of the CRF. The investigator will continue to monitor the subject with additional assessments until the values have reached the reference range or the values at screening or until the investigator determines that follow-up is no longer medically necessary.

Clinically significant laboratory values for individual subjects will be listed. A summary for the number and percentage of subjects with clinically significant laboratory values at any time point will be presented.

6.4.5 Electrocardiograms

Single 12-lead ECGs will be obtained after the subject has been in the supine position for at least 5 minutes at the time points indicated in the schedule of events. Electrocardiogram assessments will include comments on whether the tracings are normal or abnormal, rhythm, presence of arrhythmia or conduction defects, morphology, any evidence of myocardial infarction, or ST segment, T wave, and U wave abnormalities. In addition, measurements of the following intervals will be measured and reported: RR interval, PR interval, QRS width, QT interval, and QTcF.

The investigator will determine whether any of the 12-lead ECG results are clinically significant or not clinically significant. Clinical significance is defined as any variation in results that has medical relevance and may result in an alteration in medical care (eg, active observation, diagnostic measures, or therapeutic measures). If a clinically significant change from screening is noted, the clinically significant value and reason for clinical significance will be documented in the AE page of the subject's CRF. The investigator will continue to monitor the subject with additional assessments until either the values have reached reference range or the values at screening or until the investigator determines that follow-up is no longer medically necessary.

6.5 Other Assessments

6.5.1 Informed Consent and Subject Identification

Before performing any study procedures, all potential subjects will sign an informed consent form (ICF). The investigator must address all questions raised by the subject before the subject signs the consent form. The investigator will also sign the ICF.

6.5.2 Screening and Subject Number

A subject enter the study will be assigned a screening number. Subject when confirmed eligible will be assigned a subject number and this subject number will be used throughout the study.

6.5.3 Demographic Data

Demographic data including date of birth, gender and race will be collected in the CRF at screening (day -28 to -1).

6.5.4 Medical History and Concomitant Medications

A complete medical and medication history for the subjects will be collected in the CRF at screening (Day -28 to -1). Whenever possible, diagnoses but not symptoms should be recorded. Any medical conditions developing during the screening period and any treatment taken from Day -28 to -1 will be recorded in the medical history section in CRF.

6.6 Schedule of events

Subjects will undergo study procedures at the time points specified in the schedule of events.

Table 6.5-1 Schedule of Events

Procedure	**Screening**	**Dose 1 FB825**						**Dose 2 FB825**						
Study Day(s)	**−28 to −1**	**Day 1 [a]**	**Day 2**	**Day 8**	**Day 15**	**Day 29**	**Day 57**	**Day 85 [a]**	**Day 86**	**Day 92**	**Day 99**	**Day 113**	**Day 141**	**Day 169/EOS[b]**
				(±1)	**(±1)**	**(±2)**	**(±2)**	**(±3)**		**(±1)**	**(±1)**	**(±2)**	**(±2)**	**(±3)**
Informed consent	X													
Inclusion /Exclusion criteria	X	X												
Medical history	X													
Physical examination	X	X		X	X	X	X	X		X	X	X	X	X
Vital sign measurements [c, d]	X	X	X	X	X	X	X	X	X	X	X	X	X	X
12-Lead electrocardiogram [e]	X	X	X	X	X	X		X	X	X	X	X		X
AD symptom evaluation [f]	X	X	X	X	X	X	X	X	X	X	X	X	X	X
Serology [g]	X													

Clinical laboratory testing [h]	X	X	X	X	X	X	X	X	X	X	X	X	X	X
Thyroid function testing	X	X			X	X		X			X	X		X
Urine drug, and blood alcohol test	X	X[m]						X						X
Pregnancy test (female subjects) [i]	X	X		X	X	X	X	X		X	X	X	X	X
Serum FSH [j]	X													
Admission to clinic		X						X						
Study drug IV administration		X						X						
Total Immunoglobulin/ Allergen-specific IgE [k]	X	X		X	X	X	X	X		X	X	X	X	X
Biomarker Assessments[l]		X		X	X	X	X	X		X	X	X	X	X
Adverse events assessment	X	X	X	X	X	X	X	X	X	X	X	X	X	X
Prior/Concomitant medications	X	X	X	X	X	X	X	X	X	X	X	X	X	X
Discharge from			X						X					

clinic														

Abbreviations: ALT, alanine aminotransferase; AST, aspartate aminotransferase; EOS, end of study; FSH, follicle-stimulating hormone; Ig, immunoglobulin.

a. Subjects will check into the clinic on Day 1 and Day 85 and have check-in procedures performed.
b. Subjects early withdraw from the study will be requested to have an EOS visit and perform required activities.
c. Vital sign measurements (systolic and diastolic blood pressures, heart rate, respiratory rate, and body temperature) will be obtained at screening; Day 1, and 85 before the start of infusion and all study visits. Vital sign measurements will be obtained at 1.25 (end of infusion), 2, 4, 8 hours (± 5 minutes in each time points) after the start of the infusion on Day 1, and Day 85,and prior to discharge on Day 2 and Day 86. During the infusion, vital sign measurements will be obtained every 15 minutes (± 5 minutes).
d. When procedures are overlapping and occurring at the same time point, the order of procedures should be vital sign measurements and then ECGs.
e. Twelve-lead electrocardiograms will be obtained at screening; on Day 1 and Day 85 within 2 hours before the start of infusion and at 1.25 (end of infusion, ± 5 minutes), 8 hours (± 5 minutes) after the start of the infusion; prior to discharge; and all other study visits, except Day 57, and 141.
f. AD symptom evaluation is determined by VAS, EASI, SCORAD, IGA, and BSA. These are evaluated by Investigator at screening; on Day 1 prior to dosing, and all other study visits.
g. Serology testing will include hepatitis B surface antigen, hepatitis C virus antibody, and human immunodeficiency virus antibodies.
h. Clinical laboratory tests (hematology, coagulation, serum chemistry [including liver function tests and glucose test], and urinalysis) will be performed at screening; on Day 1 and Day 85 before the start of infusion and at 1.25 (end of infusion, ± 5 minutes), 8 hours (± 5 minutes) after the start of the infusion; prior to discharge, and all other study visits.
i. A serum pregnancy test will be performed for females of childbearing potential only at screening and at the end-of-study visit. Urine pregnancy tests will be performed on all other study visits, in Day 1 only to confirm the results, no need to have a test again.
j. Female subjects who are postmenopausal will have a serum FSH test at screening.
k. Blood samples for the measurement of total immunoglobulin/ Allergen-specific immunoglobulin E will be collected at screening, on Day 1 and 85 (in 2 hours before the start of infusion); and on all other study visits.
l. Blood samples for the measurement of biomarkers including thymus and activation regulated chemokine (TARC), Eotaxin-3, thymic stromal lymphopoietin (TSLP), periostin, IL-1 , IL-4, IL-5, IL-13, IL-16, IL-31 and M-CSF will be collected at Day 1 and 85 (in 2 hours before the start of infusion), and on Days 8, 15, 29, 57, 92, 99, 113, and 141.
m. The X in Day 1 of Urine drug and blood alcohol test means to confirm the results, no need to have a test again.

7 Adverse Events

The investigator is responsible for reporting all AEs that are observed or reported during the study, regardless of their relationship to study drug or their clinical significance. If there is any doubt as to whether a clinical observation is an AE, the event should be reported.

7.1 Definitions

7.1.1 Adverse Event (AE)

An AE is defined as any untoward medical occurrence associated with the use of a drug in humans, whether or not considered drug related. Subjects will be instructed to contact the investigator at any time during the study period if any symptoms develop.

A TEAE is defined as any event not present before exposure to study drug or any event already present that worsens in intensity or frequency after exposure.

An adverse reaction is any AE caused by a drug. Adverse reactions are a subset of all suspected adverse reactions for which there are reasons to conclude that the drug caused the event.

A suspected adverse reaction is any AE for which there is a reasonable possibility that the study drug caused the AE. For the purposes of investigational new drug safety reporting, “reasonable possibility” means that there is evidence to suggest a causal relationship between the study drug and the AE. A suspected adverse reaction implies a lesser degree of certainty about causality than adverse reaction, which means any AE caused by a study drug.

An AE or suspected adverse reaction is considered “unexpected” if it is not listed in the IB or at the specificity or severity that has been observed with the study drug being tested; or, if an IB is not required or available, is not consistent with the risk information described in the general investigational plan or elsewhere in the current application. For example, under this definition, hepatic necrosis would be unexpected (by virtue of greater severity) if the IB referred only to elevated hepatic enzymes or hepatitis. Similarly, cerebral thromboembolism and cerebral vasculitis would be unexpected (by virtue of greater specificity) if the IB listed only cerebral vascular accidents. "Unexpected," as used in this definition, also refers to AEs or suspected adverse reactions that are mentioned in the IB as occurring with a class of drugs or as anticipated

from the pharmacological properties of the drug, but are not specifically mentioned as occurring with the particular drug under investigation.

7.1.2 Serious Adverse Event (SAE)

An AE or suspected adverse reaction is considered an SAE if, in the view of either the investigator or sponsor, it results in any of the following outcomes:

- Death
- Life-threatening AE
- Inpatient hospitalization or prolongation of existing hospitalization
- Persistent or significant incapacity or substantial disruption of the ability to conduct normal life functions
- Congenital anomaly or birth defect

Important medical events that may not result in death, be life threatening, or require hospitalization may be considered serious when, based upon appropriate medical judgment, they may jeopardize the subject and may require medical or surgical intervention to prevent one of the outcomes listed in this definition. Examples of such medical events include allergic bronchospasm requiring intensive treatment in an emergency room or at home, blood dyscrasias or convulsions that do not result in inpatient hospitalization, or the development of drug dependency or drug abuse.

An AE or suspected adverse reaction is considered “life threatening” if, in the view of either the investigator or sponsor, its occurrence places the subject at immediate risk of death. It does not include an AE or suspected adverse reaction that, had it occurred in a more severe form, might have caused death.

7.1.3 Adverse Events of Special Interest

Adverse events of special interest include the following events:

1. Any subject experiences a treatment-emergent AE (TEAE) of anaphylaxis
2. Any subject experiences an SAE (Section 7.1.2)
3. Any subject experiences a persistent QT prolongation (>500 milliseconds, or ≥60 milliseconds change from baseline) for at least 30 minutes or ischemic changes on repeated ECGs, or persistent symptomatic arrhythmia
4. Hypersensitivity reactions including anaphylaxis, thyroid abnormalities, cutaneous erythema, thrombocytopenia, anemia, hemolysis, neutropenia, hepatotoxicity, and nephrotoxicity
5. The following laboratory parameters are encountered in any individual subject:
   - ALT or AST ≥5 × ULN
   - Bilirubin ≥2 × ULN
   - Platelet count grade 1 ≤99.999*10^9/L
   - Hemoglobin ≤105 g/L
   - Absolute neutrophil count grade 1 ≤1.5*10^9/L
   - Blood urea nitrogen or creatinine rise to >2 × ULN

7.2 Eliciting of Adverse Events

The investigator is responsible for ensuring that all AEs and SAEs are recorded in the CRF and reported to Fountain. Adverse events will be assessed from the time of screening period until completion of all study procedures and discharge from the study.

At every study visit or assessment, subjects will be asked a standard question to elicit any medically-related changes in their well-being. They will also be asked if they have been hospitalized, had any accidents, used any new medications, or changed concomitant medication regimens (both prescription and over-the-counter medications).

In addition to subject observations, AEs will be documented from any data collected in the AE page of the CRF (eg, laboratory values, physical examination findings, and ECG changes) or other documents that are relevant to subject safety.

7.3 Documenting Adverse Events

All AEs reported or observed during the study will be recorded in the AE page of the CRF. Information to be collected includes drug treatment, type of event, time of onset, dosage, investigator-specified assessment of severity and relationship to study drug, time of resolution of the event, seriousness, as well as any required treatment or evaluations, and outcome. The AEs resulting from concurrent illnesses, reactions to concurrent illnesses, reactions to concurrent medications, or progression of disease states must also be reported. All AEs will be followed until they are resolved or stable or judged by the investigator to be not clinically significant. The Medical Dictionary of Regulatory Activities (MedDRA) will be used to code all AEs.

Any medical condition that is present at the time that the subject is screened but does not deteriorate should not be reported as an AE. However, if it deteriorates at any time during the study, it should be recorded as an AE.

7.3.1 Assessment of Severity

The severity (or intensity) of an AE using the Common Terminology Criteria for Adverse Events (CTCAE) will be used for infusion reaction severity grading.

- Grade 1 Mild: Transient or mild discomfort (<48 hours); no medical intervention/therapy required.
- Grade 2 Moderate: Mild to moderate limitation in activity - some assistance may be needed; no or minimal medical intervention/therapy required.
- Grade 3 Severe: Marked limitation in activity, some assistance usually required; medical intervention/therapy required, hospitalization possible.
- Grade 4 Life threatening: Extreme limitation in activity, significant assistance required; significant medical intervention/therapy required, hospitalization or hospice care probable.

Changes in the severity of an AE should be documented to allow an assessment of the duration of the event at each level of intensity to be performed. An AE characterized as intermittent requires documentation of onset and duration of each episode.

7.3.2 Assessment of Causality

The investigator's assessment of an AE's relationship to study drug is part of the documentation process but is not a factor in determining what is or is not reported in the study.

The investigator will assess causality (ie, whether there is a reasonable possibility that the study drug caused the event) for all AEs and SAEs. The relationship will be characterized using the following classification:

- Unrelated: This relationship suggests that there is no association between the study drug and the reported event.
- Possible: This relationship is based on evidence suggesting a causal relationship between the study drug and the AE, ie, there is a reasonable possibility that the drug caused the event. The event follows a reasonable temporal sequence from the time of drug IV administration or follows a known response pattern to the study drug, but could also have been produced by other factors.
- Probable: This relationship suggests that a reasonable temporal sequence of the event with drug IV administration exists and, based upon the known pharmacological action of the drug, known or previously reported adverse reactions to the drug or class of drugs, or judgment based on the investigator's clinical experience, the association of the event with the study drug seems likely.
- Definite: This relationship suggests that a definite causal relationship exists between drug IV administration and the AE, and other conditions (concurrent illness, progression/expression of disease state, or concurrent medication reaction) do not appear to explain the event.

7.3.3 Follow-up of Adverse Events

All AEs must be reported in detail in the appropriate page of the CRF and followed until they are resolved or stable or judged by the investigator to be not clinically significant.

7.4 Reporting Serious Adverse Events

Any AE considered serious by the investigator or that meets SAE criteria (Section 7.1.2) must be reported to the sponsor immediately (after the investigator has confirmed the occurrence of the SAE). The investigator will assess whether there is a reasonable possibility that the study drug caused the SAE. The sponsor will be responsible for notifying the relevant regulatory authorities of any SAE as outlined in the ICH Guideline for Good Clinical Practice (GCP) and the National Statement on Ethical Conduct in Research Involving Humans 2007. The investigator is responsible for notifying the IRB/EC directly.

Information regarding serious adverse events will be transmitted to the sponsor using the Serious Adverse Event Form, which must be signed by investigator. The initial report of a serious adverse event may be made by facsimile (fax) or telephone. It is preferable that serious adverse events be reported via fax. A telephone report of a serious adverse event must be followed by a completed Serious Adverse Event Form from the investigator.

In addition, the suspected unexpected serious adverse reactions (SUSAR) should also forward to IRB and health authority by the sponsor within the time frame according to the regulation of the health authority.

8 Statistical Analysis

8.1 General Statistics

Details of all statistical analyses will be described in a statistical analysis plan. All data collected will be presented in data listings. Data from subjects excluded from an analysis population will be presented in the data listings but not included in the calculation of summary statistics.

For categorical variables, frequencies and percentages will be presented. Continuous variables will be summarized using descriptive statistics (number of subjects, mean, median, SD, minimum, and maximum).

Baseline demographic and background variables will be summarized by dose and overall for all subjects. The number of subjects who enroll in the study and the number and percentage of subjects who complete the study will be presented. Frequency and percentage of subjects who withdraw or discontinue from the study, and the reason for withdrawal or discontinuation, will also be summarized. Analysis for this study will be demonstrated with descriptive statistics for each period and group. No significance test will be applied.

A statistical analysis plan (SAP) will be written to address statistical analysis work in detail. The clinical database lock will occur after all data are reconciled (i.e., “cleaned”) after the last patient completes the study.

8.2 Sample Size Calculations

A total of approximately 12 evaluable subjects are planned for this study. The sample size for this study is based on clinical and practical considerations and not on a formal statistical power calculation.

8.3 Analysis Sets

Full Analysis Set (FAS) is defined as subjects who received at least 1 dose of study drug. All efficacy evaluation will be performed in FAS population.

The Safety population is defined as subjects who received at least 1 dose of study drug. All safety evaluation will be performed in safety population.

8.4 Statistical Analysis

8.4.1 Biomarker Analyses

Concentration and change from baseline in total and allergen-specific IgE and biomarkers listed as endpoints will be summarized by visit and presented graphically. Change from baseline in total and allergen-specific IgE will also be summarized by the baseline total IgE concentration (serum IgE>1500IU/mL or serum IgE ≤1500IU/mL) and given FB825 doses (1 dose or 2 doses).

In subjects who receive the second dose of FB825, the data collected for the second dose will be analysis and summarized as same as those collected for the first dose.

8.4.2 Clinical Efficacy Analysis

The evaluation index will be assessed by PI or co-PI during every visit for each subject. The clinical endpoints will be analyzed using descriptive statistic (mean of EASI, SCORAD, IGA, VAS, and BSA; SD, CV, number of subjects) by visit time points and given FB825 doses (1 dose or 2 doses).

The change of mean index versus scheduled visit time profiles will be presented graphically

In subjects who receive the second dose of FB825, the data collected for the second dose will be analysis and summarized as same as those collected for the first dose.

8.4.3 Safety Analyses

Adverse events will be coded by preferred term and system organ class using the latest version of the Medical Dictionary for Regulatory Activities and summarized by treatment, dose level, and overall. Adverse events will also be summarized by severity, relationship to study drug, SAEs, and AEs leading to discontinuation of study drug.

Actual values and changes from baseline for clinical laboratory test results, vital sign measurements, and 12-lead ECG results will be summarized by treatment and dose at each time point using descriptive statistics (number of subjects, mean, SD, median, minimum, and maximum). Shift tables will be generated for clinical laboratory test results. Clinical laboratory data, vital sign measurements, 12-lead ECG results, and physical examination findings will be presented in data listings.

8.5 Handling of Missing Data

Concentrations that are below the limit of quantification (BLQ) will be treated as zero for descriptive statistics. Mean BLQ concentrations will be presented as BLQ, and the SD and CV will be reported as not applicable. Missing concentrations will be excluded from the calculations.

Last observation carry forward (LOCF) will be applied to handle missing data. No imputation will be available for safety data.

8.6 Interim Analyses

No interim analysis is planned.

8.7 Data Quality Assurance

All aspects of the study will be monitored for compliance with applicable government regulations with respect to current International Conference on Harmonisation (ICH) harmonised tripartite guideline E6 (R1): Good Clinical Practice and current standard operating procedures. There may be an internal quality review audit of the data and additional reviews by the clinical monitor.

9 Investigator Obligations

The following administrative items are meant to guide the investigator in the conduct of the study and may be subject to change based on industry and government standard operating procedures, working practice documents, or guidelines. Changes will be reported to the IRB/EC but will not result in protocol amendments.

9.1 Confidentiality

All laboratory specimens, evaluation forms, reports, and other records will be identified in a manner designed to maintain subject confidentiality. All records will be kept in a secure storage area with limited access. Clinical information will not be released without the written permission of the subject (or the subject's legal guardian), except as necessary for monitoring and auditing by the sponsor, its designee, regulatory authorities such as the FDA, or the IRB/EC.

The investigator and all employees and coworkers involved with this study may not disclose or use for any purpose other than performance of the study, any data, record, or other unpublished, confidential information disclosed to those individuals for the purpose of the study. Prior written agreement from the sponsor or its designee must be obtained for the disclosure of any said confidential information to other parties.

9.2 Institutional Review

ICH E6 (R1) guidelines and applicable regulatory requirements require that approval be obtained from an IRB/EC before participation of human subjects in research studies. Before study onset, the protocol, informed consent, advertisements to be used for the recruitment of study subjects, and any other written information regarding this study to be provided to the subject or the subject's legal guardian must receive written approval by each IRB/EC. Documentation of all IRB/EC approvals and of the IRB/EC compliance with the ICH E6 (R1) guidelines will be maintained by the site and will be available for review by the sponsor or its designee.

All IRB/EC approvals should be signed by the IRB/EC chairman or designee and must identify the IRB/EC name and address, the clinical protocol by title or protocol number or both and the date approval or a favorable opinion was granted.

9.3 Subject Consent

Written informed consent in compliance with ICH E6 (R1) guidelines and applicable regulatory requirements shall be obtained from each subject before he or she enters the study or before any unusual or nonroutine procedure that involves risk to the subject is performed. If any institution-specific modifications to study-related procedures are proposed or made by the site, the consent should be reviewed by the sponsor or its designee or both before IRB/EC submission. Once reviewed, the investigator will submit the ICF to the IRB/EC for review and approval before the start of the study. If the ICF is revised during the course of the study, all active participating subjects must sign the revised form.

Before recruitment and enrollment, each prospective subject or his or her legal guardian will be given a full explanation of the study and be allowed to read the approved ICF. Once the investigator is assured that the subject/legal guardian understands the implications of participating in the study, the subject/legal guardian will be asked to give his or her consent to participate in the study by signing the ICF.

The investigator will provide a copy of the signed ICF to the subject or legal guardian. An original signed ICF shall be maintained in the subject's medical records at the site.

9.4 Study Reporting Requirements

By participating in this study, the investigator agrees to submit reports of SAEs according to the time line and method outlined in this protocol. In addition, the investigator agrees to submit annual reports to his or her IRB/EC as appropriate.

9.5 Financial Disclosure and Obligations

The investigator is required to provide financial disclosure information to allow the sponsor to submit the complete and accurate certification or disclosure statements. In addition, the investigator must provide to the sponsor a commitment to promptly update this information if any relevant changes occur during the course of the investigation and for 1 year following the completion of the study.

9.6 Investigator Documentation

Prior to beginning the study, the investigator will be asked to comply with ICH E6 (R1) 8.2 by providing the following essential documents, including but not limited to:

IRB/EC approval,

An original investigator-signed investigator agreement page of the protocol,

Form FDA 1572, fully executed, and all updates on a new fully executed Form FDA 1572,

Curriculum vitae for the principal investigator and each subinvestigator listed on Form FDA 1572. Current licensure must be noted on the curriculum vitae. They will be signed and dated by the principal investigators and subinvestigators at study start-up, indicating that they are accurate and current,

Financial disclosure information to allow the sponsor to submit complete and accurate certification or disclosure statements. In addition, the investigators must provide to the sponsor a commitment to promptly update this information if any relevant changes occur during the course of the investigation and for 1 year after the completion of the study,

An IRB/EC-approved ICF, samples of site advertisements for recruitment for this study, and any other written information about this study that is to be provided to the subject or legal guardians, and

Laboratory certifications and reference ranges for any local laboratories used by the site.

9.7 Study Conduct

The investigator agrees that the study will be conducted according to the principles of ICH E6 (R1). The investigator will conduct all aspects of this study in accordance with all national, state, and local laws or regulations.

9.8 Data Collection

9.8.1 Case Report Forms and Source Documents

The study site will maintain source documentation and enter subject data into the CRF as accurately as possible and will respond to any reported discrepancies rapidly.

Electronic CRFs will be utilized and accessed through an electronic data capture (EDC) system. This electronic data capture system is validated and compliant with 21 Code of Federal Regulations 11. Each person involved with the study will have an individual identification code and password that allows for record traceability. Thus, the system, and subsequently any investigative reviews, can identify coordinators, investigators, and individuals who have entered or modified records, as well as the time and date of any modifications. There is an internal quality review audit of the data and additional reviews by the clinical monitor.

Each eCRF is presented as an electronic copy, allowing data entry by site personnel, who can add and edit data, add new subjects, identify and resolve discrepancies, and view records. This system provides immediate direct data transfer to the database, as well as immediate detection of discrepancies, enabling site coordinators to resolve and manage discrepancies in a timely manner.

Paper copies of the eCRFs and other database reports may be printed and signed by the investigator. This system provides site personnel, monitors, and reviewers with access to hardcopy audits, discrepancy reviews, and investigator comment information.

9.9 Adherence to Protocol

The investigator agrees to conduct the study as outlined in this protocol in accordance with ICH E6 (R1) and all applicable guidelines and regulations.

9.10 Reporting Adverse Events

By participating in this study the investigator agrees to submit reports of SAEs according to the time line and method outlined in this protocol. In addition, the investigator agrees to submit annual reports to his or her IRB/EC as appropriate. The investigator also agrees to provide the sponsor with an adequate report, if applicable, shortly after completion of the investigator's participation in the study.

9.11 Investigator's Final Report

Upon completion of the study, the investigator, where applicable, should inform the institution; the investigator/institution should provide the IRB/EC with a summary of the study's outcome and the sponsor and regulatory authority(ies) with any reports required.

9.12 Records Retention

Essential documents should be retained until at least 2 years after the last approval of a marketing application in an ICH region and until there are no pending or contemplated marketing applications in an ICH region or at least 2 years have elapsed since the formal discontinuation of clinical development of the study drug. These documents should be retained for a longer period, however, if required by the applicable regulatory requirements or by an agreement with the sponsor. It is the sponsor's responsibility to inform the investigator/institution as to when these documents no longer need to be retained.

9.13 Publications

After completion of the study, the data may be considered for reporting at a scientific meeting or for publication in a scientific journal. In these cases, the sponsor will be responsible for these activities and will work with the investigators to determine how the manuscript is written and edited, the number and order of authors, the publication to which it will be submitted, and other related issues. The sponsor has final approval authority over all such issues.

Data are the property of the sponsor and cannot be published without their prior authorization, but data and publication thereof will not be unduly withheld.

10 Study Management

10.1 Monitoring

10.1.1 Monitoring of the Study

The clinical monitor, as a representative of the sponsor, is obligated to follow the study closely. In doing so, the monitor will visit the investigator and study facility at periodic intervals, in addition to maintaining necessary telephone and letter contact. The monitor will maintain current personal knowledge of the study through observation, review of study records and source documentation, and discussion of the conduct of the study with the investigator and staff.

All aspects of the study will be carefully monitored by the sponsor or its designee for compliance with applicable government regulation with respect to current ICH E6 (R1) guidelines and standard operating procedures.

10.1.2 Inspection of Records

The investigator and institution involved in the study will permit study-related monitoring, audits, IRB/EC review, and regulatory inspections by providing direct access to all study records. In the event of an audit, the investigator agrees to allow the sponsor, their representatives, the FDA, or other regulatory agency access to all study records.

The investigator should promptly notify the sponsor of any audits scheduled by any regulatory authorities and promptly forward copies of any audit reports received to the sponsor.

10.2 Management of Protocol Amendments and Deviations

10.2.1 Modification of the Protocol

Any changes in this research activity, except those necessary to remove an apparent, immediate hazard to the subject, must be reviewed and approved by the sponsor or designee. Amendments to the protocol must be submitted in writing to the investigator's IRB/EC and receive approval before subjects are enrolled by an amended protocol.

10.2.2 Protocol Violations and Deviations

The investigator or designee must document and explain in the subject's source documentation any deviation from the approved protocol. The investigator may implement a deviation from, or a

change to, the protocol to eliminate an immediate hazard to study subjects without prior IRB/EC approval. As soon as possible after such an occurrence, the implemented deviation or change, the reasons for it, and any proposed protocol amendments should be submitted to the IRB/EC for review and approval, to the sponsor for agreement, and to the regulatory authorities, if required.

A deviation from the protocol is an unintended or unanticipated departure from the procedures or processes approved by the sponsor and the IRB/EC and agreed to by the investigator. Deviations usually have an impact on individual subjects or a small group of subjects and do not involve inclusion/exclusion or primary endpoint criteria. A protocol violation occurs when the subject or investigator does not adhere to the protocol, resulting in a significant, additional risk to the subject. Protocol violations can include nonadherence to inclusion or exclusion criteria, enrollment of the subject without prior sponsor approval, or nonadherence to local regulations or ICH E6 (R1) guidelines.

Protocol violations and deviations will be documented by the clinical monitor throughout the course of monitoring visits. The investigator will be notified in writing by the monitor of violations and deviations. The IRB/EC should be notified of all protocol violations and deviations, if appropriate, in a timely manner.

10.3 Study Termination

Although the sponsor has every intention of completing the study, they reserve the right to discontinue it at any time for clinical or administrative reasons.

The end of the study is defined as the date on which the last subject completes the last visit (includes the end-of-study visit and any additional long-term follow-up). Any additional long-term follow-up that is required to monitor the resolution of a finding or AE may be reported through an amendment to the clinical study report.

10.4 Final Report

Whether the study is completed or prematurely terminated, the sponsor will ensure that clinical study reports are prepared and provided to the regulatory agency(ies) as required by the applicable regulatory requirement(s). The sponsor will also ensure that clinical study reports in marketing applications meet the standards of the ICH harmonised tripartite guideline E3: Structure and content of clinical study reports.

Where required by applicable regulatory requirements, an investigator signatory will be identified for the approval of the clinical study report. The investigator will be provided reasonable access to statistical tables, figures, and relevant reports and have the opportunity to review complete study results.

Upon completion of the clinical study report, the sponsor will provide the investigator(s) with the final approved clinical study report.

11 Reference List

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12 Appendices

12.1 Appendix 1: National Cancer Institute Common Terminology Criteria for Adverse Events v4.03

The National Cancer Institute Common Terminology Criteria for Adverse Events v4.03 can be accessed at the following website link:
http://evs.nci.nih.gov/ftp1/CTCAE/CTCAE_4.03_2010-06-14_QuickReference_5x7.pdf.

12.2 Appendix 2: Second symposium on the definition and management of anaphylaxis: Summary report—Second National Institute of Allergy and Infectious Disease/Food Allergy and Anaphylaxis Network symposium

Second symposium on the definition and management of anaphylaxis: Summary report-Second National Institute of Allergy and Infectious Disease/Food Allergy and Anaphylaxis Network symposium can be accessed at the following website link:

https://www.google.com/url?url=https://wao.confex.com/wao/wisc12/webprogram/Handout/Paper4600/2nd%2520Anaphylaxis%2520Symposium-JACI-02-06.pdf&rct=j&frm=1&q=&esrc=s&sa=U&ei=pRt2VL2TJ4uZNoG9gGA&ved=0CB8QFjAC&usg=AFQjCNExbzj-VOSsAgnLsLq0VAXG-aV8gA

Clinical criteria for diagnosing anaphylaxis are presented in Table 12.2–1.

Table 12.2-1 Clinical Criteria for Diagnosing Anaphylaxis

Anaphylaxis is highly likely when any <u>one</u> of the following 3 criteria are fulfilled:
1. Acute onset of an illness (minutes to several hours) with involvement of the skin, mucosal tissue, or both (eg, generalized hives, pruritus or flushing, swollen lips-tongue-uvula) AND AT LEAST ONE OF THE FOLLOWING: a. Respiratory compromise (eg, dyspnea, wheeze-bronchospasm, stridor, reduced PEF, hypoxemia) b. Reduced BP or associated symptoms of end-organ dysfunction (eg, hypotonia [collapse], syncope, incontinence)
2. Two or more of the following that occur rapidly after exposure to a <u>likely</u> allergen for that patient (minutes to several hours): a. Involvement of the skin-mucosal tissue (eg, generalized hives, itch-flush, swollen lips-tongue-uvula) b. Respiratory compromise (eg, dyspnea, wheeze-bronchospasm, stridor, reduced PEF, hypoxemia) c. Reduced BP or associated symptoms (eg, hypotonia [collapse], syncope, incontinence) d. Persistent gastrointestinal symptoms (eg, crampy abdominal pain, vomiting)
3. Reduced BP after exposure to known allergen for that patient (minutes to several hours): a. Infants and children: low systolic BP (age specific) or greater than 30% decrease in systolic BP[1] b. Adults: systolic BP of less than 90 mm Hg or greater than 30% decrease from that person's baseline

Abbreviations: PEF, peak expiratory flow; BP, blood pressure.
Low systolic blood pressure for children is defined as less than 70 mm Hg from 1 month to 1 year, less than (70 mm Hg + [2 × age]) from 1 to 10 years, and less than 90 mm Hg from 11 to 17 years.

12.3 Appendix 3: Division of Microbiology and Infectious Disease (DMID) Adult Toxicity Table November 2007 Draft (For Screening)

	Grade 1	**Grade 2**	**Grade 3**	**Grade 4**
HEMATOLOGY				
Hemoglobin	9.5 - 10.5 gm/dL	8.0 - 9.4gm/dL	6.5 - 7.9 gm/dL	< 6.5 gm/dL
Platelets	75,000-99,999/mm3	50,000-74,999/mm3	20,000-49,999/mm3	<20,000/mm3
WBCs	11,000-13,000/mm3	13,000- 15,000 /mm3	15,000-30,000/mm3	>30,000 or <1,000 /mm3
Prothrombin Time (PT)	1.01 - 1.25 x ULN	1.26-1.5 x ULN	1.51 -3.0 x ULN	>3 x ULN
Activated Partial Thromboplastin (APPT)	1.01 -1.66 x ULN	1.67 - 2.33 x ULN	2.34 - 3 x ULN	> 3 x ULN
CHEMISTRIES				
Hyponatremia	130-135 mEq/L	123-129 mEq/L	116-122 mEq/L	< 116 mEq/L or abnormal sodium *with* mental status changes or seizures
Hypernatremia	146-150 mEq/L	151-157 mEq/L	158-165 mEq/L	> 165 mEq/L or abnormal sodium *with* mental status changes or seizures
Hypokalemia	3.0 - 3.4 mEq/L	2.5 - 2.9 mEq/L	2.0 - 2.4 mEq/L or intensive replacement therapy or hospitalization required	< 2.0 mEq/L or abnormal potassium*with* paresis, ileus or life-threatening

	Grade 1	**Grade 2**	**Grade 3**	**Grade 4**
				arrhythmia
Hyperkalemia	5.6 - 6.0 mEq/L	6.1 - 6.5 mEq/L	6.6 - 7.0 mEq/l	> 7.0 mEq/L or abnormal potassium *with* life-threatening arrhythmia
Hypoglycemia	55-64 mg/dL	40-54 mg/dL	30-39 mg/dL	<30 mg/dL or abnormal glucose *with* mental status changes or coma
Hyperglycemia (nonfasting and no prior diabetes)	116 - 160 mg/dL	161- 250 mg/dL	251 - 500 mg/dL	> 500 mg/dL or abnormal glucose *with* ketoacidosis or seizures
Hypocalcemia (corrected for albumin)	8.4 - 7.8 mg/dL	7.7 - 7.0 mg/dL	6.9 - 6.1 mg/dL	< 6.1 mg/dL or abnormal calcium *with* life threatening arrhythmia or tetany
Hypercalcemia (correct for albumin)	10.6 - 11.5 mg/dL	11.6 - 12.5 mg/dL	12.6 - 13.5 mg/dL	> 13.5 mg/dL or abnormal calcium *with* life threatening arrhythmia
Hypomagnesemia	1.4 - 1.2 mEq/L	1.1 - 0.9 mEq/L	0.8 - 0.6 mEq/L	< 0.6 mEq/L or abnormal magnesium *with* life-threatening

	Grade 1	**Grade 2**	**Grade 3**	**Grade 4**
				arrhythmia
Hypophosphatemia	2.0 - 2.4 mg/dL	1.5 -1.9 mg/dL or replacement Rx required	1.0 -1.4 mg/dL intensive therapy or hospitalization required	< 1.0 mg/dL or abnormal phosphate *with* life-threatening arrhythmia
Hyperbilirubinemia (when accompanied by any increase in other liver function test)	1.1 - <1.25 x ULN	1.25 - <1.5 x ULN	1.5 – 1.75 x ULN	> 1.75 x ULN
Hyperbilirubinemia (when other liver function are in the normal range)	1.1 - <1.5 x ULN	1.5 - <2.0 x ULN	2.0 – 3.0 x ULN	> 3.0 x ULN
BUN	1.25 - 2.5 x ULN	2.6 - 5 x ULN	5.1 - 10 x ULN	> 10 x ULN
Hyperuricemia (uric acid)	7.5 – 10.0 mg/dL	10.1 – 12.0 mg/dL	12.1 – 15.0 mg/dL	>15.0 mg/dL
Creatinine	1.1 - 1.5 x ULN	1.6 - 3.0 x ULN	3.1 - 6 x ULN	> 6 x ULN or dialysis required
ENZYMES				
AST (SGOT)	1.1 - <2.0 x ULN	2.0 – <3.0 x ULN	3.0 – 8.0 x ULN	> 8 x ULN
ALT (SGPT)	1.1 - <2.0 x ULN	2.0 – <3.0 x ULN	3.0 – 8.0 x ULN	> 8 x ULN
GGT	1.1 - <2.0 x ULN	2.0 – <3.0 x ULN	3.0 – 8.0 x ULN	> 8 x ULN
Alkaline Phosphatase	1.1 - <2.0 x ULN	2.0 – <3.0 x ULN	3.0 – 8.0 x ULN	> 8 x ULN
Lipase	1.1 - 1.5 x ULN	1.6 - 2.0 x ULN	2.1 - 5.0 x ULN	> 5.1 x ULN
URINALYSIS				
Proteinuria	1+ or 200 mg - 1 gm loss/day	2-3+ or 1- 2 gm loss/day	4+ or 2-3.5 gm loss/day	nephrotic syndrome or > 3.5 gm loss/day
Hematuria	microscopic only <10 rbc/hpf	gross, no clots >10 rbc/hpf	gross, with or without clots, OR red blood cell casts	obstructive or required transfusion