3. NON-TECHNICAL ABSTRACT

Allertein Therapeutics, LLC (Allertein) is developing EMP-123 for the treatment of peanut allergy. EMP-123 consists of three modified peanut proteins encapsulated within dead bacteria that are suspended in a thick solution for rectal administration. This product is designed to act as a vaccine, or immunotherapy, in which peanut allergic patients are gradually vaccinated against progressively larger doses of EMP-123 to reduce or eliminate sensitivity to peanut allergens and to prevent potentially life-threatening or fatal reactions in peanut allergic patients who are inadvertently exposed to small quantities of peanut proteins.

Peanut allergy is estimated to occur in 0.5-1% of the population, and there is evidence that the prevalence of peanut allergy in the US is rising. There is no approved drug currently available to treat peanut allergy (i.e., to reduce or eliminate sensitivity to peanut allergens). The standard of care for peanut allergy is dietary avoidance and emergency treatment for accidental ingestions of peanut. However, strict avoidance diets can be complicated due to difficulty in interpreting food labels and by the presence of undeclared or hidden peanut allergens in commercially prepared foods. Accidental ingestions are common, with up to 50% of food-allergic patients having an allergic reaction over a two-year period. Allergic reactions to peanut can be severe and life threatening; and peanut and/or tree nut allergies account for the vast majority of fatal food-induced anaphylaxis. This combination of strict avoidance diets, the high incidence of accidental exposures, and the risk of severe or even fatal reactions with accidental exposures adds a tremendous burden and stress on patients and their families. Further complicating matters is the fact that only about 20% of children will outgrow peanut allergy, meaning that the majority of people with peanut allergy will have it for the rest of their lives. Developing an effective treatment for peanut allergy is imperative.

Allertein, in conjunction with the National Institute of Allergy and Infectious Diseases, Division of Allergy, Immunology, and Transplantation, and the Consortium for Food Allergy Research proposes to conduct a phase 1 clinical study of EMP-123. EMP-123 has never been studied in humans. The main purpose of this study is to determine if EMP-123 can be given safely to humans. At first, 5 non-peanut allergic subjects will be given EMP-123. If these subjects do not experience any severe side effects, then 10 peanut allergic subjects will be given EMP-123. The study will also evaluate if peanut allergic subjects are less sensitive to peanut allergens after 13 doses of EMP-123, although, due to the limited duration of this first trial, no direct medical benefit is anticipated. The study will also include tests to help further understand the underlying mechanisms of peanut allergy and to identify tools that might be used to follow the course and treatment of the disease.

The purpose of this submission is to provide the protocol for the above clinical trial to National Institutes of Health Office of Biotechnology Activities and Recombinant DNA Advisory Committee for review. Deoxyribonucleic acid (DNA) is a nucleic acid molecule that contains the genetic instructions used in the development and functioning of living organisms. The DNA

segments that contain the instructions needed to construct other components of cells, such as proteins and RNA molecules are called genes. Recombinant DNA is a form of artificial DNA that combines DNA sequences that would not normally occur together. Recombinant DNA will be transferred into human participants in the process of EMP-123 therapy. However, EMP-123 is not intended as a gene therapy. In gene therapy, the objective is to deliver nucleic acid into an individual's cells with the intent of replacing or repairing a defective gene that is responsible for disease. For this purpose, the nucleic acids must be taken up by the cell, transported to the nucleus where the cell DNA is located, and integrated into the genome (cell DNA).

EMP-123 is not designed to deliver nucleic acids into human cells, nor is it designed to integrate recombinant DNA into the human genome. The objective of EMP-123 therapy is to deliver modified peanut allergens (i.e., proteins) encapsulated inside of dead bacteria to the rectal lining where they can suppress/elicit immune responses that will reduce or eliminate sensitivity to peanut allergens. The modified peanut allergens are expressed from recombinant DNA within the bacteria during the manufacturing process, and the bacteria are subsequently killed during the last steps in manufacturing. The encapsulated modified peanut allergens are suspended in a thick solution for rectal administration to humans with a syringe and flexible rectal adaptor (similar to how a suppository medication or enema is administered). The DNA present in the final EMP-123 product is essentially carryover from the process used to manufacture the encapsulated allergens. The likelihood that DNA from EMP-123 bacteria that break open within the body will be taken up by human cells and integrated into the genome is minimal. Further, in the event of such an occurrence, the cells of the gastrointestinal (GI) tract lining have a relatively short lifespan, and such an event would be short lived.

A bacterial infection within a subject given EMP-123 or transmission of a bacterial infection between a subject given EMP-123 and other individuals (e.g., relatives or study doctors and nurses) is unlikely, as the bacteria in the EMP-123 product are dead. Further, the bacteria used to manufacture EMP-123 have been shown to lack well-recognized pathogenic (disease causing) mechanisms, and are considered nonpathogenic (non-disease causing). Transmission of bacterial infection directly from mother to baby during the period immediately before and after birth is unlikely for the same reasons listed above. Regardless, pregnant or lactating females will not be allowed to participate in the proposed clinical study, and sexually active patients will be required to use an effective method of contraception throughout the study.

The characteristics of EMP-123 that define it as a good lead compound for the treatment of peanut allergy via immunotherapy can be broken down into four main areas: 1) selection of the three peanut proteins, 2) modification of the peanut proteins, 3) encapsulation of the modified peanut proteins in dead bacteria, and 4) rectal administration of EMP-123. The rationale for each of these areas is described below.

Selection of the Three Peanut Proteins: In order to treat peanut allergy, EMP-123 should protect against exposure to the main peanut antigens (i.e., proteins) responsible for anaphylactic

reactions. Ara h 1, Ara h 2, and Ara h 3 were selected as the peanut proteins for EMP-123 as they represent the three major peanut allergens that are responsible for peanut allergy.

Modification of the Peanut Proteins: The DNA sequences coding the peanut proteins were modified to interfere with known IgE binding epitopes. The rationale for modifying the peanut proteins to disrupt IgE binding epitopes was to potentially reduce the ability of these proteins to produce allergic responses following administration of the proteins during immunotherapy. However, regardless of the scientific rationale for using modified peanut proteins, and the safety profile demonstrated in animal models, it has not been proven that EMP-123 has reduced IgE binding, or has an "improved" safety profile over wild type proteins because of reduced IgE binding.

Encapsulation of the Modified Peanut Proteins in Dead Bacteria: One therapeutic strategy for suppressing the immune responses responsible for allergy (antigen-specific Th2 responses) is to activate antigen-specific Th1 T-cells. The bacteria of EMP-123 provide an activating component necessary for the induction of Th1 immunity, as well as the antigen (the modified peanut allergens) to which the Th1 cell response is desired. Further, encapsulation of the modified peanut allergens is thought to provide an additional level of protection from any potential allergic response following administration of the modified peanut proteins, by shielding the proteins from cells that trigger allergic responses. Dead bacteria are used to avoid the risk of infection.

Rectal Administration of EMP-123: Rectal administration of dead bacteria is anticipated to pose minimal risk, as the lower colon and rectum are colonized with millions of bacterial organisms, which the local immune system tolerates. It is also thought that the immune response of the lower colon may favor tolerance induction (long-term reduction or elimination of sensitivity to peanut allergens). Furthermore, given that absorption of peanut antigen following accidental peanut ingestion occurs via the GI tract, it is also desirable to choose a route of administration that might specifically alter the gut immune response to peanut antigens.

Allertein is currently conducting two animal studies of EMP-123 in support of the proposed clinical trial: 1) a study to measure desensitization to peanut allergens in a mouse model of peanut anaphylaxis that also serves as a safety study of the anaphylactic potential of EMP-123 in peanut sensitized mice, and 2) a 16-week repeated dose toxicity study of rectally administered EMP-123 in dogs. In the mouse model of peanut anaphylaxis, mice treated with EMP-123 showed no symptoms of anaphylaxis during the EMP-123 treatment period, indicating that EMP-123 itself lacks anaphylactic potential. Therefore, EMP-123 appears to be safe in peanut sensitized mice. Further, rectal administration of EMP-123 once a week for three consecutive weeks in peanut sensitized mice resulted in desensitization of some but not all of the mice to orally administered peanuts. Further assessments are underway. In the dog study, no adverse findings attributed to EMP-123 were observed during the 16 weeks of dosing and the 2-week follow-up. Further assessments are underway.