Open Label Peanut Oral Immunotherapy in Children: IMPACT Follow Up Study

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Open Label Peanut Oral Immunotherapy in Children: IMPACT Follow Up Study (IND #17784)

1. Abstract

This application is being submitted as a follow-up to Protocol NA_00077852 “Oral Immunotherapy for Induction of Tolerance in Peanut Allergic Children.” The “IMPACT” protocol was a double-blind, placebo-controlled study of peanut oral immunotherapy in children 12-48 months of age. As part of the IMPACT protocol, all participants who received placebo treatment were promised the opportunity to receive open label treatment at the conclusion of the doubleblind phase and initial follow-up. At the time of submitting IMPACT, we did not specify any detailed protocol for the open label crossover treatment, as this is an evolving field, but we are now ready to offer this open label treatment as promised.

There are no specific hypotheses to be tested. The main research questions will focus on the safety and efficacy of the treatment.

2. Objectives

1. The primary objectives of this protocol is to provide open label peanut oral immunotherapy (OIT) for those subjects who received placebo treatment in the doubleblind phase of the above noted study and to assess safety, as measured by the incidence of adverse events and the proportion of subjects who discontinue treatment due to adverse events.

Secondary objective will include:

2. Efficacy of the treatment, as defined by an end of treatment oral peanut challenge.

3. Background

Anaphylaxis is a severe, potentially fatal, systemic allergic reaction that occurs suddenly after contact with an allergy-causing substance[1]. Peanut allergy affects 1-2% of US children and is associated with a high risk of life-threatening anaphylaxis.[2,3] Even more concerning, peanut is the allergen most commonly associated with death and near-death following food-induced anaphylaxis and is frequently encountered in common food products. Peanut allergy also persists into adulthood in the majority of affected individuals, with less than 25% of peanutallergic children naturally developing tolerance.

Currently, treatment for peanut allergy is limited to dietary avoidance and ready access to selfinjectable epinephrine. However, immunotherapy for food allergy has been evaluated extensively over the last decade with studies focusing on oral, sublingual and epicutaneous immunotherapy to treat peanut, milk and egg allergy.[3] When comparing these forms of immunotherapy for peanut allergy, oral immunotherapy (OIT) has proven to be the most efficacious to date.

The rationale for this study is that peanut OIT will induce immune modulation resulting in suppression of allergic responses allowing for desensitization to peanut and protection from anaphylaxis. The use of peanut flour for this study is similar to other single allergen OIT studies.[5] The study product will be manufactured by the University of North Carolina. We have selected a dosing strategy based on all available information that is most likely to best balance safety with efficacy.

4. Study Procedures

This study will provide open label peanut OIT, with a maintenance dose of 1000 mg of peanut protein. Treatment will be initiated on a single day in which multiple doses are given. Peanut flour will be given incrementally and increased every 15-30 minutes until a maximum dose of 6 mg peanut protein is given. This visit may take up to 6 hours to complete:

Initial Day Dose Escalation	
Dose #	Peanut Protein (mg)
1	0.8
2	1.5
3	3.0
4	6.0

A minimum of 1.5mg must be achieved on the initial dose escalation day. In other studies all subjects have achieved at least 1.5 mg with no more than mild symptoms reaction. After the initial dose escalation day, subjects will return to the research unit the next day for an observed dose administration of the highest tolerated dose from the initial escalation day. Subjects who tolerate 6 mg during initial dose escalation and again on the observation day following initial dose escalation will proceed with dosing per the table below. Subjects who do not reach 6 mg on the initial dose escalation day will require additional up-doing visits to escalate to the 6 mg dose (Example: from 1.5 to 3.0 to 6.0) mg before beginning the dose build up schedule described below. Once subjects have tolerated a dose under observation, they will then continue dosing at home with OIT and return to the research unit every 2 weeks for a 1-step dose escalation to a maximum daily dose of 1000 mg (see table below). Subjects may remain on a single-maintenance dose for longer than 2 weeks if necessary. The dosing escalations will be consistent with previous OIT studies. Participants who do not reach the 1000mg dose during the build-up phase may enter the maintenance phase at their highest tolerated dose. Subjects must achieve a minimum of 200mg during the build up to enter the maintenance phase.

Mild symptoms with dosing such as transient nausea, mild abdominal pain, and/or oral pharyngeal pruritus are common and are not considered dose limiting. Dose limiting symptoms include those that do not respond to antihistamine and/or require the use of epinephrine.

Subjects who experience dose limiting symptoms during an up-dosing visit will continue on the previously tolerated dose for an additional 2 weeks. Subjects who experience dose limiting symptoms with a home dose will be seen in the research unit for down-dosing to the last tolerated dose. Subjects will remain on the last tolerated dose for at least 2 weeks before attempting another up-dosing. A subject may attempt a specific dose level 3 separate times before the dose is considered “not tolerated”. In that case, the dose previously tolerated will become the maintenance dose and the subject will not attempt additional up-dosing.

Dose Build-Up Schedule			
Dose #	Peanut protein	Interval (weeks)	% Increase
5	10 mg	2	66%
6	20 mg	2	100%
7	30 mg	2	66%
8	50 mg	2	60%
9	75 mg	2	33%
10	125 mg	2	60%
11	200 mg	2	62.5%
12	300 mg	2	33%
13	500 mg	2	60%
14	750 mg	2	50%
15	1000 mg	2	25%

Consent will be obtained at the last visit in IMPACT Study. For subjects who have already completed the last visit of that protocol and/or families who request additional time to review the consent, consent will be obtained at the 1st visit in the Pediatric Clinical Research Unit prior to

any research specific procedures. The study will be explained in age appropriate terms to the participants and they will be given the opportunity to ask questions. Some of the older subjects may have some context to comprehend the assent process. The assent process will be documented in the clinical note.

At each dosing visit, the following procedures will be performed prior to dose administration:

- Vital signs
- Review of adverse events including any accidental exposure to peanut
- Review of concomitant medications
- Review of home dosing diaries
- Physical exam
- Peak flow

The build-up phase will comprise up to 22-52 weeks. Subjects will then enter the Maintenance phase and will continue on daily OIT at the maximum tolerated dose established during the Build-up phase. The Maintenance phase will consist of at least 12 weeks and may continue as long as through week 64. Subjects will be seen every 6-8 weeks during the Maintenance phase. The window between maintenance visits may be extended to longer than 6-8 weeks if necessary. At the end of the Maintenance phase, subjects will undergo an open peanut oral food challenge to a maximum of 4000 mg of peanut protein using the following dosing regimen:

Dose #	Peanut Protein (mg)	Cumulative Dose (mg)
1	100	100
2	300	400
3	600	1000
4	1000	2000
5	2000	4000

After this food challenge all participants will be given individualized guidelines for the introduction of peanut into their diet based on the outcome of the open peanut challenge.

5. Inclusion/Exclusion Criteria

Inclusion:

1. Parent guardian must be able to understand and provide informed consent
2. Subjects enrolled in Protocol NA_00077852 “Oral Immunotherapy for Induction of Tolerance in Peanut Allergic Children” who meet at least one of the following criteria:

a. a reaction to a cumulative dose of ≤1000 mg of peanut protein during the End-ofTreatment food challenge

b. subjects determined to be assigned to the placebo cohort **Exclusion:**

1. Inability or unwillingness of a parent guardian to give written informed consent or comply with study protocol
2. History of severe anaphylaxis to peanut, defined by severe hypoxia, hypotension, neurological compromise, confusion, cardiovascular collapse, or loss of consciousness
3. Significant chronic disease (other than asthma, rhinitis, or atopic dermatitis) requiring therapy; e.g., heart disease or cystic fibrosis which is judged by the investigator to have potential impact on study outcomes or safety.
4. Severe or poorly controlled atopic dermatitis per investigator's discretion
5. Past or current history of eosinophilic gastrointestinal disease
6. Diagnosis of asthma that meets any of the following criteria:
   - Uncontrolled asthma (as per Global Initiative for Asthma [GINA] latest guidelines)
   - History of 2 or more systemic corticosteroid courses in the last year or 1 systemic course within the 3 previous months prior to visit 1 for treating wheezing
   - Prior intubation/mechanical ventilation for asthma
7. Currently receiving β-blocking agents, angiotensin-converting enzyme inhibitors, angiotensin-receptor blockers, calcium channel blockers or tricyclic antidepressant therapy.
8. Current participation in another clinical trial or participation in another clinical trial in the last 90 days

6. Drugs/ Substances/ Devices

The treatment agent, a de-fatted peanut flour, will be provided by the University of North Carolina (UNC) GMP manufacturing facility under an Investigational New Drug (IND) application to the FDA. All study product will be obtained from the same manufacturer; a certificate of analysis obtained according to FDA standards will be stored as per manufacturer's recommendations to ensure stability. Research staff will administer food flour to the subject orally in an appropriate age-appropriate food vehicle. Each peanut flour/powder is weighed into a separate container to be dispensed to the subject. Dosage will be done according to the protocol as set forth above. For home administration, the family will be provided with an adequate supply of individually packaged peanut OIT. The powder may be added to apple juice, milk, applesauce, pudding or other age-appropriate food. The product must be consumed promptly after mixing. If there is a prolonged delay in consumption (>2 hours), the product should be discarded and a new product package mixed and consumed. Subjects or their parents will be instructed to take/administer the dose of OIT at approximately the same time of the day each day. At least approximately 12 hours should pass between doses.

Drug Accountability: Under Title 21 of the Code of Federal Regulations (21CFR §312.62) the investigator is required to maintain adequate records of the disposition of the investigational agent, including the date and quantity of the drug received, to whom the drug was dispensed (subject-by-subject accounting), and a detailed accounting of any drug accidentally or deliberately destroyed. Records for receipt, storage, use, and disposition will be maintained by the study sites. A drug-dispensing log will be kept current for each subject. This log will contain the identification of each subject and the date, lot and quantity of drugs dispensed. All records

regarding the disposition of the investigational products will be available for inspection by the IRB and FDA.

7. Study Statistics

As an open label follow-on study, statistics will be purely descriptive, describing the proportion of subjects achieving desensitization as well as measures of safety.

Early stopping rules: Study enrollment and treatment will be suspended pending expedited review of all pertinent data by the IRB and FDA if the following occur:

- Any death.
- More than one severe anaphylactic reaction related to peanut immunotherapy dosing at any stage of the protocol.
- More than three subjects require 2 or more injections of epinephrine to treat one allergic adverse event during peanut OIT dosing.
- More than 3 subjects require epinephrine on 2 or more occasions to treat dosingrelated reaction over the course of the study

8. Risks

OIT: The primary risk of the study is related to the peanut OIT. Previous studies have shown that mild reactions, such as oral pruritus, are very common, while more severe respiratory or systemic reactions occur in less than 1% of doses. The dosing schema to be used on the initial escalation day followed by the build-up phase of immunotherapy is based on previous experience with peanut, egg, milk, and wheat OIT.[5] In addition to acute reactions, 10-20% of treated subjects experience more chronic abdominal pain, which is the most common reason to discontinue treatment. Some of those subjects have eosinophilic esophagitis, which has been estimated to occur in 2-5% of children receiving OIT.[7] Subjects who persist with symptoms consistent with eosinophilic esophagitis such as swallowing difficulty, food impaction, persistent vomiting, abdominal pain, nausea and/or heartburn beyond 4 weeks of OIT avoidance will be referred to GI.

Oral food challenge: Since the subjects will have already undergone an End-of-Treatment oral food challenge in the IMPACT study, a baseline food challenge will not be needed to establish a peanut allergy diagnosis. An end-of- treatment challenge will be conducted to determine safe levels of peanut to eat, but the subjects will be substantially desensitized at that time, making reactions less likely overall. However, it is important to recognize that there is still risk of a reaction that could even be severe. Common symptoms may include urticaria, angioedema, nausea, abdominal discomfort, vomiting and/or diarrhea, rhinorrhea, sneezing and/or mild wheezing. The major risks involved include severe breathing difficulties, and rarely, a drop in blood pressure. While a severe outcome is theoretically possible (i.e. death), this has only occurred once in the world in medically supervised oral food challenges. To date the primary investigator has performed more than 5000 oral food challenges without a serious lifethreatening anaphylactic reaction or need for hospitalization

Trained staff will be present to administer study food challenges and a physician will be at the bedside to provide oversight, evaluation, and treatment as needed. The risks of oral food challenges are minimized by the following procedures:

- Children must have a stable baseline examination prior to undergoing the challenge without significant symptoms of flaring atopic dermatitis, exacerbations of rhinorrhea, current urticarial, or other symptoms evaluated during food challenges
- Children must have no wheezing or repetitive cough prior to challenge
- Children must have no current illnesses (e.g. fever) at time of oral challenge
- Medications (epinephrine, intravenous fluids, antihistamines, ranitidine, vasopressors, beta-agonists, and steroids), personnel and equipment (oxygen, resuscitation equipment) will be immediately available to treat allergic reactions should they occur.
- Children will have discontinued antihistamines and bronchodilators for appropriate periods prior to challenge, thereby allowing investigators to perform challenges only when participants are stable without influence of medications.
- The food will be provided gradually, at 15 minute intervals, beginning with a dose unlikely to trigger a reaction and progress stepwise with escalating doses.
- Vital signs (heart rate, blood pressure, respiratory rate) and physical examination will be undertaken at baseline and as indicated throughout the challenge.
- Challenges will be stopped, and medications administered, in the event of any objective symptoms.
- Children who have experienced an allergic reaction will be observed until 2 hours have passed for a local reaction, or 4 hours for a generalized reaction, from the time of resolution of symptoms.

Plan for reporting and collecting adverse events

Reporting will occur as follows:

i. Toxicity will be graded according to the NCI-CTC for application in adverse event reporting. The NCI-CTC has been reviewed specifically for this protocol and is appropriate for this study population. The purpose of using the NCI-CTC system is to provide standard language to describe toxicities, and to facilitate tabulation and analysis of the data and assessment of the clinical significance of treatmentrelated toxicities. The investigator will try to determine the relationship of toxicity to peanut immunotherapy as not related, possibly related, or definitely related using standard criteria for clinical trials. All grades of toxicity will be noted. Toxicity grades are assigned by the study site to indicate the severity of adverse experiences and toxicities.

ii. Adverse events, not included in the NCI-CTC listing, should be recorded and graded 1-5 according to the General Grade Definition provided below:

Table 7: General Grade Definitions

Grade 1	Mild	Transient or mild discomforts (< 48 hours), no or minimal medical intervention/therapy required, hospitalization not necessary (non-prescription or single-use prescription therapy may be employed to relieve symptoms, e.g., aspirin for simple headache, acetaminophen for post-surgical pain). Examples of anticipated events include: oral/pharyngeal pruritus, localized hives/swelling, skin flushing and/or pruritus, rhinorrhea/sneezing, nasal congestion, occasional cough, throat discomfort, mild abdominal discomfort, nausea or single episode of vomiting.
Grade 2	Moderate	Mild to moderate limitation in activity, some assistance may be needed; no or minimal intervention/therapy required, hospitalization possible. Examples of anticipated events include: systemic hives, throat tightness without hoarseness, persistent cough, wheezing without dyspnea, persistent moderate abdominal pain/cramping/ nausea, repeated vomiting
Grade 3	Severe	Marked limitation in activity, some assistance usually required; medical intervention/therapy required hospitalization possible. Examples of anticipated include: laryngeal edema, throat tightness with hoarseness, wheezing with dyspnea, persistent severe abdominal pain with repetitive vomiting, change in mental status, hypotension
Grade 4	Life-threatening	Extreme limitation in activity, significant assistance required; significant medical/therapy intervention required hospitalization or hospice care probable. Example include any severe symptoms that do not respond to treatment.
Grade 5	Death	Death

All adverse events related to the experimental procedures will be reported to the DSMB and IRB in an expedited manner if they are Grade 3 and above in severity Subject deaths are reportable within 24 hours. The investigator will continue to follow or obtain documentation of the resolution course of such an event. A copy of the annual DSMB report of all adverse events will be reported to the IRB.

Data and Safety Monitoring:

A Data Safety Monitoring Board will be convened for overview of this study. The Principal Investigator and Co-Investigators are responsible for collecting and recoding all clinical data. As these results are collected, all toxicities and adverse events will be identified and reported to the PI. Adverse events will be reported as described above. The Principal Investigator will determine the relationship of the event to the study intervention and decide the course of action for the study participant.

The use of epinephrine to treat dosing-related symptoms will be classified as a serious adverse event. The location of the event (home or clinic) and number of doses of epinephrine will be reported to the DSMB.

Any new diagnosis of eosinophilic esophagitis made during the treatment period will be classified as a serious adverse event and reported to the DSMB.

Yearly reports will be made to the DSMB and proper Institutional Committees, as required. All adverse events will be kept in a computerized file by numerical identifier.

In the event that the study is stopped because of adverse event(s), it will not be resumed until information regarding the adverse event(s) has been discussed with the DSMB and the DSMB concurs with resumption of the studies.

Legal risks such as the risks that would be associated with breach of confidentiality.

The risk of breach of confidentiality will be minimized by using unique identifiers for participants and keeping the record that links the identifier to the participant in a locked file cabinet accessible only to the investigators.

Financial risks to the participants.

The study does not provide routine care or any medications or treatments for general health or allergic problems (although we will be available for phone consultation regarding possible reactions). All costs associated with study visits, skin testing, spirometry, blood drawing, food challenges, and OIT protein are covered by the investigators. All participants will be required to provide a food matrix (juice, milk, applesauce, pudding or other age-appropriate food) to consume the daily doses at home . This will be provided by the family so that flavor/variety can be altered for each child's preference. All participants will be required to have an epinephrine auto-injector available at home during immunotherapy treatment. If they do not already have one, they will be responsible for the cost of this medication.

9. Benefits

The benefits for the participant include the possibility of a change in sensitivity to peanut and decreased allergic reactions following an accidental ingestion of peanut. Another possible benefit is the possibility of altering the natural course of the peanut allergy, including tolerance to peanut protein in someone that is unlikely to naturally "outgrown" his/her allergy. If tolerance is achieved, this then make impact quality of life.

10. Payment and Remuneration

Subjects will receive a parking coupon for each visit.

11. Costs

The study does not provide routine care or any medications or treatments for general health or allergic problems (although we will be available 24 hours a day for phone consultation regarding possible reactions). All participants will be required to have an epinephrine autoinjector available at home during immunotherapy treatment. If they do not already have one, they will be responsible for the cost of this medication. All costs associated with study visits and OIT are covered by the investigator.

References

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