

Full Title: A Phase 2 Study of Multi Oral Immunotherapy in Multi Food Allergic Patients to Test Immune Markers after Minimum Maintenance Dose

Short Title: Multi Immunotherapy to test Minimum dose using Xolair (MIMiX)

Statistical Analysis Plan

NCT03181009

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## Statistical Analysis Plan

### MIMIX

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**Objective:** To determine if the combination of omalizumab and multi OIT will increase the IgG<sub>4</sub>:IgE ratio of at least 2 allergens by  $\geq 25\%$  at week 18 from baseline in multi food allergic patients.

**Study Design:** This phase 2 multisite study was conducted at two centers in the U.S. All participants received oral immunotherapy for their specific food allergies. Further, all participants received three doses of Omalizumab over 8 weeks. The subject's allergens were introduced on desensitization Day 1 of week 0, after receiving the third omalizumab dose. Participants returned to clinic to escalate the dose of their allergens until 300 mg (group A) or 1200 mg (group B) total protein daily dose was reached. Subjects were randomized 1:1 to either group A or group B after meeting eligibility criteria.

**Primary endpoint:** Indicator for whether or not a participant had an IgG<sub>4</sub>:IgE increase of at least 25% for at least 2 allergens from baseline to week 18.

**Exposure:** Treatment group – 300 mg (group A) vs 1200 mg (group B)

#### Methods:

Baseline characteristics will be summarized overall and by treatment group using medians and ranges, and counts and percentages. Categorical and continuous variables will be tested across treatment arms using Fisher's exact test and the Wilcoxon rank sum test, respectively.

To evaluate the primary endpoint of the overall proportion of participants who had an IgG<sub>4</sub>:IgE increase of at least 25% for at least 2 allergens from baseline to week 18, a one-sided exact binomial test will be used, with a null hypothesis that the probability of success (i.e. meeting the primary endpoint) is no better than chance (i.e.  $H_0: p = 0.50$  vs  $H_1: p > 0.50$ ). The probability of success and 95% confidence interval will be reported. Fisher's exact test will be used to determine whether the probability of success differs by treatment group. The odds ratio of group A vs group B and 95% confidence interval will be reported. Similar methods will be used to evaluate secondary endpoints of a ratio increase of at least 25% for 3, 4, and 5 allergens.

The continuous change in the IgG<sub>4</sub>:IgE ratio from baseline for each allergen will also be reported descriptively overall and by treatment group.

Logistic regression models will be used to determine whether any baseline characteristics predict success of the primary endpoint, adjusting for treatment arm.

The proportion of doses in which an adverse event occurred will be summarized by treatment arm. To determine whether adverse event rates are different by treatment group and across home doses, a mixed effect Poisson regression model will be fit to the number of AEs as a

function of group and home dose amount, with an offset for  $\log(\text{number of home doses})$  and a random subject effect.

A Cox proportional hazards model will be used to determine whether time-to-OIT-maintenance differed between groups A and B. Participants who do not reach maintenance will be censored at their end of study visit. The p-value from the log-rank test will be reported.