Determining the Efficacy and Value of Immunotherapy on the likelihood of peanut tolerance: The DEVIL Study

Statistical Analysis Plan

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Sample size

No placebo-controlled studies have been published that evaluated the development of tolerance/SU after years of treatment with peanut OIT. Published data from our own uncontrolled pilot study in older children with long-standing disease suggest that SU developed in 12 of 24 (50%) peanut-allergic subjects completing high-dose OIT. (Vickery, et al. Sustained unresponsiveness to peanut in subjects who have completed peanut oral immunotherapy. J Allergy Clin Immunol. 2014 Feb;133(2):468-75. doi: 10.1016/j.jaci.2013.11.007). On the basis of preliminary data that were available to us at the time this study was conceived in 2008, and according to our hypothesis, we predicted before the study that 70% of low-dose subjects would develop SU, compared with the expected rate of spontaneous peanut allergy resolution of 20% as shown in multiple cohort studies. At a 2-sided significance level of .05, 15 subjects in each treatment arm would have at least 80% power to detect a 50% absolute average difference between the proportion of subjects in each arm passing the exit SU OFC and the 20% rate of spontaneous tolerance expected in untreated controls. On the basis of a prestudy assumption of 15% to 20% dropout, we enrolled 20 subjects per arm to ensure adequate power.

Practical considerations prevented a trial large enough to show definitive comparisons of high- and low-dose therapy directly. Twenty subjects in each arm would have 63% power to identify a 40% difference in SU acquisition between regimens. Even if underpowered to show a difference between low-dose and high-dose therapy, we reasoned a priori that a type II error in this setting may still be clinically meaningful so long as the proportion achieving SU in the low-dose group significantly exceeded 20%. This would be especially true if low-dose therapy offers other advantages (fewer visits, better safety profile, improved palatability, etc).

Randomization

For the primary outcome analysis, subjects were considered a single intervention group on open label peanut OIT. For exploratory analyses, subjects were randomized 1:1 to be on either low dose OIT (300mg peanut protein) or high dose (3000mg peanut protein). Masking was achieved by the addition of oat flour to the low dose OIT in order to match the weight of the high dose OIT product. Patients, patient families, study coordinators and investigators were blinded to the dose allocation. Randomization was conducted by unblinded laboratory staff in the Burks lab using a block randomization scheme.

Statistical Analysis

We computed averages, variances, frequencies, proportions, and graphical displays for all variables and examined them to ensure parametric distributional assumptions were met. Nonparametric test statistics were used as appropriate. Baseline demographics and categorical peanut consumption outcomes were compared between E-OIT and controls using Fisher's exact test. Analyses were performed with GraphPad Prism 6 for Mac (La Jolla, CA) or Stata/SE 13.1 (College Station, TX). To achieve approximate normality and variance stabilization for longitudinal immune analyses, psIgE and psIgG4 were log-transformed, while for SPT raw data were employed. Models were fit separately for each group in R (www.r-project.org) for each outcome with functions of time using generalized estimating equations. Linear and quadratic,

and cubic models in time were considered, with the best fitting model selected for each group for each outcome selected using QIC. All hypothesis tests were two-sided, with $p<0.05$ considered significant.