The Wall Street Journal[1]

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Silent Treatment: How Genentech, Novartis Stifled A Promising Drug

Biotech Firm Tried to Pursue Peanut-Allergy Injection, But Contract Got in Way

Zach Avoids a 'Kiss of Death'

By DAVID P. HAMILTON

NEWPORT NEWS, Va. – For years, the onset of the peanut harvest was enough to send Zach Williams to the hospital.

Every fall, Zach's family would watch peanut dust rise from fields to the south and trigger his allergies, making him labor for air as fluid swelled his tissues and constricted his breathing passages. Some attacks laid him in a hospital bed for weeks, where he wore an oxygen mask as drugs dripped into his veins.

Five years ago Zach, then 15 years old, joined a clinical trial of an experimental drug called TNX-901, produced by Tanox Inc., a Houston biotechnology company. Monthly injections of the drug tamed Zach's runaway immune reactions. For the first time in years, his parents sent him to school without worrying that a peanut exposure might kill him.

More than 1.5 million Americans have an allergy to peanuts, and some can die in minutes if accidentally exposed. Food allergies lead to 30,000 emergency-room visits and more than 150 deaths a year, many the result of peanut exposure, says the Food Allergy and Anaphylaxis Network, a nonprofit organization in Fairfax, Va. If further testing had proven successful, TNX-901 might now be nearing approval as the first preventive treatment for these people.

Instead, the drug sits on the shelf, abandoned after Tanox's own corporate partners forced it to end development. The U.S. biotech giant Genentech Inc. and Swiss drug maker Novartis AG insisted that Tanox kill TNX-901 in favor of a Genentech drug called Xolair that has yet to prove effective against peanut allergy. When Tanox refused, its partners took it to court. The ensuing legal fight to kill TNX-901 spanned five years and consumed well over $100 million in legal fees. The battle over TNX-901 highlights a common paradox in the drug business. While companies sell many drugs that help both patients and their bottom lines, they can sometimes also advance their commercial interests by stifling potential medical advances. That may mean postponing in-house projects to prevent competition with a drug the company already sells or demanding a halt to allegedly patent-infringing research at a rival.

TNX-901 represents an unusual twist on such cases: Genentech and Novartis, relying on disputed contract language, successfully blocked a third, independent company from moving ahead with a promising drug – despite the absence of alternative treatments at the time. The long court record provides a window into the vigor with which big companies can fight to stop a potential breakthrough. "It's critical that we get that clinical trial . . . shut down," a lawyer representing Genentech told a judge in 2000, referring to the TNX-901 trial that Zach later joined.

No one knows whether TNX-901 would have ultimately proven successful. Regulatory approval would have required more rigorous testing. In the trial Zach joined, tests in more than 80 people showed that TNX-901 could bolster their tolerance to the equivalent of nine whole peanuts. Those receiving a placebo could tolerate less than half a peanut.

Novartis declined to make officials available for comment. Genentech officials cast the fight with Tanox as a straightforward contract dispute, and otherwise declined to comment.

Tanox itself, despite its long resistance, ultimately gave up and signed a settlement with Novartis and Genentech in February 2004. The three companies agreed to start testing Xolair as a peanut-allergy treatment. In a joint statement to The Wall Street Journal, the three say their current focus on Xolair is "the most

rapid and efficient approach" for helping patients. Xolair, approved in 2003 as an asthma treatment, is now in mid-stage human trials for peanut allergy, and those tests may produce data sometime next year. Formal approval by the Food and Drug Administration for use in peanut allergy could take years more.

Like other food sensitivities, peanut allergy is growing more common in the U.S., particularly among children. A 2003 study found that the incidence of peanut allergy in children doubled between 1997 and 2002 for reasons no one fully understands.

LaDonna Williams knew her son Zach faced a lifetime of allergies almost from the moment he was born red and wheezing in 1985. Tests by Hugh Sampson, an allergy specialist then at Duke University, showed a severe allergy to peanuts. In subsequent years, Zach would keep his distance from outside food to avoid trace amounts of peanut or oil that might cling to utensils or cooking surfaces. When the family ate at a local Italian restaurant, Zach's mother would bring her own spaghetti and meatballs, ask for a plate and wash it in the bathroom before serving Zach's meal on it. In 2000 Dr. Sampson, who had moved to Mount Sinai Medical Center in New York, called Ms. Williams with news of a potentially life-changing drug. It was TNX-901, and the Williamses jumped at the chance to enroll Zach in a clinical trial.

The odyssey of TNX-901 began with an allergy-prone molecular biologist, Tse-wen Chang, and his wife, Nancy, a fellow scientist. The Taiwanese couple founded Tanox in 1986 and soon embarked on a project to attack allergic inflammation. Their target: an immune-system antibody known as immunoglobulin E, or IgE.

Floating through the bloodstream and across mucous membranes, the Y-shaped IgE molecule sweeps up viral and bacterial particles in its outstretched arms, and then docks its tail to a particular immune-system cell. That alerts the body's defenses, usually triggering sneezing, rashes and watery eyes – the body's somewhat crude initial attempt to expel invaders.

Life-Threatening Reaction

Unfortunately, in some people IgE also grabs innocuous substances such as pollen or peanut protein, making the body respond to a nonexistent threat. In some allergies, such as sensitivity to peanuts or penicillin, such reactions can escalate to life-threatening anaphylactic shock. Other researchers had long tried to block IgE with experimental drugs but failed because the drugs themselves triggered allergic reactions. Tse-wen Chang thought Tanox could tailor-make a genetically engineered antibody that would latch onto IgE's tail, preventing it from docking and setting off an allergic reaction. Tanox scientists created several such antibodies. One was TNX-901. Like many young biotech companies, Tanox was chronically short of cash. Nancy Chang, who handled the company's business side, looked for a corporate partner and found interest from Genentech and Ciba-Geigy of Switzerland, which later merged with another Swiss company in 1996 to become Novartis. In 1989, Dr. Chang sent data and samples of an early anti-IgE antibody to Genentech, but talks with Genentech foundered. Tanox then signed a partnership with Ciba in mid-1990. Worried that the anti-IgE project might stall in Ciba's bureaucracy, Tanox negotiated a provision allowing it to move ahead with any antibody candidate that Ciba rejected.

A few years later, Genentech unveiled its own anti-IgE program, one that Dr. Chang says she considered suspiciously familiar. Tanox filed suit in Harris County district court in December 1993 accusing Genentech of misappropriating its work. The case dragged on into 1996, and Tanox officials began to fear that Genentech was outgunning them in the development race.

Eventually, the three companies reached a deal. Genentech, Ciba (soon to be renamed Novartis) and Tanox would combine their anti-IgE programs. Genentech and Ciba would take the lead in testing, manufacturing and selling any resulting drugs. Tanox, meanwhile, licensed its anti-IgE patents to the partnership in exchange for royalties and other rights. The deal explicitly incorporated the 1990 Ciba-Tanox pact – but, significantly, it failed to clarify whether Tanox still had the right to independently develop any anti-IgE drug rejected by the bigger partners.

The two big companies quickly chose Genentech's anti-IgE antibody — the future Xolair — as the partnership's lead candidate. TNX-901 was relegated to backup status. Tanox executives began to get frustrated when the bigger partners insisted on testing Xolair solely as an asthma and hay-fever treatment, says David Anderson, a former Tanox vice president. Tanox wanted to go after food allergies, too. In mid-1997, Tanox told Genentech and Novartis that it would assert its rights to study TNX-901 in medical conditions the collaboration wasn't addressing.

Back to Court

Tanox argued that Genentech and Novartis had effectively rejected TNX-901 — triggering the old clause that said Tanox could research such drugs on its own. Not so, said the two big companies. They maintained that all anti-IgE drugs identified before the formation of the three-way collaboration belonged to the partnership, whether or not it was actively working on them. In April 1999, Genentech and Novartis sued Tanox in federal district court and demanded that it stop working on TNX-901. Tanox refused, and soon after started the clinical tests of TNX-901 that involved Dr. Sampson and Zach Williams.

Zach joined the trial in October 2000. Several months later, a test revealed that his tolerance had risen substantially, apparently thanks to TNX-901. Zach's reactions to the dust from peanut harvests ceased. When he accidentally ate some jelly beans made in a factory that also processed peanuts, he didn't feel a thing.

For Ms. Williams, a 15-year burden lifted. She was no longer plagued by the fear that an unsuspecting girl would eat a peanut-butter candy, then grab her attractive son and plant a kiss on his lips. "It would literally be the kiss of death," she says.

Genentech and Novartis were worried about the commercial threat TNX-901 might pose to Xolair, court documents show. At the time, Genentech and Novartis weren't testing Xolair against food allergies, but their officials could foresee the possibility that they might end up competing against their own business partner.

In 2001, Genentech General Counsel Stephen Juelsgaard blasted "Tanox's unilateral decision to compete against the collaboration" and noted concerns that TNX-901 might "compete with the Xolair antibody." In a mid-2000 courtroom status conference, an outside lawyer for Genentech, Dana Haviland, told presiding U.S. district judge Marilyn Patel that Tanox's tests of TNX-901 threatened the "heart" of the collaboration and the coming launch of Xolair. "We really need to not have a competing product in the market from our strategic partner," Ms. Haviland said.

Judge Patel urged a settlement. One day she surveyed the attorneys in her courtroom and declared: "This is why you never had an agreement that you could agree upon. . . . There are too many lawyers." Later, she added, "I can't imagine this is really helping, you know, further the cause of medicine and science or anything else."

On Oct. 9, 2001, Judge Patel ruled the partnership agreements allowed Tanox to pursue TNX-901. But Genentech and Novartis quickly asked the judge to suspend the case and let them proceed with arbitration, which Tanox had earlier sought. Judge Patel agreed. A year later, an arbitrator ruled that Tanox had no right to work on TNX-901. Nancy Chang decided to end a multiyear fight that she says had cost Tanox as much as $75 million. "The biggest lesson was that money is more important than right or wrong," she said in an interview last year.

The joint statement by Genentech, Novartis and Tanox issued to the Journal says Dr. Chang's comments reflected a "general feeling about the legal system" and didn't specifically refer to the dispute with Genentech and Novartis. The statement says Tanox is "fully supportive" of the partnership's decision to pursue Xolair against peanut allergy.

As a bittersweet coda, Dr. Sampson and his team published findings from the TNX-901 trial in the New England Journal of Medicine in March 2003, triggering a wave of publicity and lifting the spirits of allergy

sufferers. But the drug was on its last legs. In February 2004, the two sides settled remaining litigation. Tanox agreed to drop TNX-901 and forgo certain rights to Xolair in exchange for a payment of $6.6 million.

At the same time, Genentech and Novartis announced plans to test Xolair against peanut allergy. The drug is similar to TNX-901, so researchers like Dr. Sampson think it will also work well against food allergies. No one will know for certain, however, until results of that 150-person trial are released. Even if successful, the delay in bringing a peanut-allergy treatment to market would be significant since TNX-901 completed its similar trial in 2001.

The three-company statement defends the decision to go with Xolair, noting that it has an extensive safety record because it was tested in more than 6,000 asthma patients. It states that doctors and allergists are gaining experience with the drug and that Xolair can easily be manufactured in large quantities, neither of which was true of TNX-901.

Since Xolair is already approved as an asthma treatment, doctors could in theory prescribe it "off label" for peanut allergy as well. That might be risky, though, because no one knows the proper dose for peanut allergy. People receiving too low a dose might relax their watchfulness and end up in the emergency room. In addition, insurers generally don't cover off-label drug use so most patients would have to pay thousands of dollars a year out of pocket.

Tanox is now pursuing an AIDS treatment and drugs targeting asthma and inflammatory diseases. Nineteen years after its founding, the company is still unprofitable.

Tanox still supplies TNX-901 to former clinical-trial patients such as Zach Williams via the study's original researchers. But patients typically must travel at their own expense to clinics in New York City or Denver, and some have been asked to pay several hundred dollars a month to cover the cost of administering the drug.

Gregory Rogers, a 51-year-old Monument, Colo., carpenter who participated in a TNX-901 trial, stopped taking the drug last summer because he couldn't afford it. Other allergies like hay fever and a serious skin rash, once also suppressed by the drug, have come roaring back. "After having that [drug] for a while, I sure got spoiled," he says.

Write to David P. Hamilton at david.hamilton@wsj.com

The Wall Street Journal[2]

MAY 19, 2005

Xolair Is the Better Drug for Peanut Allergy Therapy

We are writing to express our disappointment and strong exception to your page-one article "SilentTreatment: How Genentech, Novartis Stifled a Promising Drug" (April 5). The article included an incomplete discussion of the scientific facts regarding the development of a potential therapy for peanut allergies. Because science is at the center of our efforts to develop a treatment for peanut allergy, the article's neglect of some important facts had the potential to be misleading to your readers.

Genentech, Novartis and Tanox together strived to identify the most promising medicine that could be brought to patients with peanut allergies most rapidly. The fundamental question was simply, what was the best way to develop an effective treatment for patients suffering from peanut allergy quickly and safely?

Two similar compounds with an identical mechanism of action — Xolair, which was on the market, and TNX-901, in early development – were considered as potential drug candidates to treat peanut allergy reactions. Because Xolair was already on the market and TNX-901 would require many years of development activities, Xolair was chosen as the most promising project.

It is imperative that we conduct the right trials to determine safety and efficacy. Xolair already has a record of safety and efficacy based on trials involving more than 6,000 patients as well as physician prescriptions for more than 40,000 patients. TNX-901 did not have a similar patient database. Secondly, Xolair already had a well-developed, FDA-approved manufacturing process and was on the market for a different indication. Therefore, the best way to move forward as quickly as possible for treating peanut allergies was to focus the trial program on Xolair. Genentech, Novartis and Tanox have always focused on bringing innovative medicines to patients as quickly as possible, and we have kept this mission at the center of our efforts in developing a treatment for peanut allergies.

Susan Desmond-Hellmann, M.D.
President, Product Development
Genentech
South San Francisco, Calif.

James Shannon, M.D.
Global Head, Clinical Development & Medical Affairs
Novartis Pharma AG
Basel, Switzerland

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The Wall Street Journal[3]

Thursday, February 26 2004

Tanox, Genentech and Novartis Settle Disputes Surrounding Xolair(R) And TNX-901

Tanox, Inc. *(Nasdaq:TNOX)*, Novartis Pharma AG, an affiliate of Novartis AG *(NYSE:NVS)* and Genentech, Inc. *(NYSE: DNA)* announced today that they have settled all litigation among them and finalized the detailed terms of their three-party collaboration,begun in 1996, to develop and commercialize certain anti-IgE antibodies including Xolair(R) (omalizumab) and TNX-901.

The following details of the settlement were disclosed: Genentech and Novartis will each reimburse Tanox $3.3 million for a portion of its TNX-901 development costs; Tanox will relinquish any rights to manufacture Xolair and, in exchange, will receive payments tied to the quantity of Xolair produced; and Tanox will benefit from an accelerated forgiveness of a loan to finance the construction of its biologics manufacturing plant in the mid-1990s.

As in the original agreement, Genentech and Novartis share U.S. marketing rights for all collaboration products, while Novartis has marketing rights outside the U.S. The existing royalty and profit-sharing percentages will remain unchanged. Committees with representatives from all three companies have been established to cooperatively oversee further development and commercialization of Xolair, and possibly other collaboration products.

“We are pleased to end the disputes with respect to Xolair and TNX-901 and look forward to working with Genentech and Novartis to further develop and support anti-IgE therapy for asthma and allergy,” said Nancy Chang, CEO of Tanox.

Peanut allergy

The partners are committed to developing Xolair as the lead antibody for peanut allergy. An Investigational New Drug (IND) application for Xolair in this indication was filed with the U.S. Food and Drug Administration (FDA) in November 2003. Patient enrollment in a Phase II proof of concept clinical trial is expected to begin early this year.

About Tanox

Tanox, Inc. is a biopharmaceutical company with demonstrated expertise in monoclonal antibody technology. The Company is engaged in the discovery and development of therapeutic monoclonal antibodies designed to address significant unmet medical needs in the areas of asthma, allergy, inflammation and other diseases affecting the human immune system. In June 2003, the FDA approved Xolair(R) (omalizumab) For Subcutaneous Use for treatment of adults and adolescents (12 years of age and above) with moderate-to-severe persistent asthma who have a positive skin test or in vitro reactivity to a perennial aeroallergen and whose symptoms are inadequately controlled with inhaled corticosteroids. Xolair, Tanox's first approved drug, is an anti-immunoglobulin E, or anti-IgE, antibody that was developed under a collaboration agreement among Genentech, Inc., Novartis Pharma AG and Tanox.

This release and other information about Tanox, Inc. can be found on the World Wide Web at http://www.tanox.com .

This release contains certain "forward-looking statements" relating to the expected timing of patient enrollment in a Phase II proof of concept clinical trial. Those statements reflect the current views of Tanox with respect to future events and are subject to certain risks, uncertainties and assumptions. Many factors could affect the actual timing of trial enrollment, including but not limited to the discussions with the FDA, recruitment of investigators and study site initiation.

SOURCE Tanox, Inc.

The Wall Street Journal[4]

JANUARY 16, 2006

Genentech Stops Trial on Concerns Over Safety of Peanut-Allergy Test

By DAVID P. HAMILTON

Genentech Inc. stopped a clinical trial of a drug it hopes can be used to prevent peanut-allergy reactions, citing safety concerns not with the drug itself but with an allergy test.

The South San Francisco, Calif., biotechnology company said two children in the 150-person trial experienced "severe hypersensitivity reactions" when given a trace amount of peanut protein, an initial step designed to gauge the severity of a patient's allergies. Neither child had received the drug, called Xolair, the company said. Xolair is on the market, approved as a treatment for allergic asthma.

"We had always been very nervous about that study," said Susan Desmond-Hellmann, head of product development for Genentech. "We are not going to do that anymore."

Cancellation of the Xolair trial means that an approved treatment for peanut allergy remains years away at the earliest. Dr. Desmond-Hellmann said Genentech may explore the possibility of moving straight to a large-scale trial that wouldn't involve a peanut "challenge," as the allergic-reaction test is called. Instead, such a trial might track volunteers over an extended period of time, to determine if those receiving Xolair experienced fewer accidental peanut reactions than those taking a placebo.

"It's going to take a long time, and it's going to be hard work, but it's better than exposing someone we know to be allergic" to peanuts, Dr. Desmond-Hellmann said.

The setback is the latest delay in a long and fitful effort to find a drug that can blunt the serious consequences of peanut allergy. The condition, which affects an estimated 1.5 million Americans, can lead to life-threatening anaphylactic shock if allergic individuals ingest even a trace amount of peanut flour or oil. In November, a 15-year-old Canadian girl with the allergy died reportedly after a kiss from her boyfriend, who had earlier eaten a peanut-butter snack. Several years ago, a drug called TNX-901 from a Houston biotechnology company called Tanox Inc. appeared to reduce peanut sensitivity in a similar clinical trial of allergic individuals. But Tanox's corporate partners, Genentech and Novartis AG, objected to continued development of the drug, wanting to focus on Xolair instead. After years of legal tussles, Tanox agreed to shelve TNX-901 in early 2004. The decision to shelve Tanox was the subject of a page-one article last year in The Wall Street Journal.

The three companies next agreed to test Xolair as a possible peanut-allergy treatment. The clinical trial was similar to the earlier test of TNX-901, and some researchers had anticipated that it might produce results later this year. Volunteers, however, were slow to sign up, Genentech officials said.

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The Wall Street Journal[5]

NOVEMBER 10, 2006

Genentech to Acquire Asthma-Drug Partner Tanox

By DAVID P. HAMILTON

Genentech Inc. agreed to acquire Tanox Inc. for $919 million, allowing the larger biotechnology concern to absorb a smaller partner that once posed a potential competitive threat. The agreement — which the South San Francisco, Calif., company said is the first acquisition in its 30-year history — highlights the hot market for acquisitions of biotech companies. With the exception of the Genentech-Tanox deal, pharmaceutical companies and large biotechs have snapped up seven smaller biotech concerns at a total cost of more than $16 billion in the past two months. "It looks like the party is going to continue for a while, when even Genentech steps up," said Geoffrey Porges, an analyst with Sanford C. Bernstein & Co.

Genentech, Tanox and Novartis AG of Switzerland worked together to develop Xolair, a drug for allergic asthma that had U.S. sales of $107 million in the third quarter. Starting in the late 1990s, however, the three companies battled over Tanox's attempt to independently develop a similar drug called TNX-901 as a preventative treatment for potentially fatal peanut allergy. The fight over TNX-901 spanned five years, during which a midstage clinical trial suggested that the drug could mitigate the peanut-allergy effects. Tanox, of Houston, won a federal lawsuit, allowing it to continue the drug's development, but subsequently ended up in an arbitration proceeding that ruled against the smaller company. The three companies settled the matter in 2004, with Tanox agreeing to drop TNX-901 development in exchange for $6.6 million.

Although the three companies agreed to proceed with a test of Xolair against peanut allergy, Genentech canceled that trial nearly a year ago after two children experienced severe reactions to an allergy test before receiving the drug. Genentech officials have said they are interested in devising a new trial, but haven't announced plans for further testing in peanut allergy. Tanox has several potentially promising drug candidates under development, including an AIDS drug designed to prevent HIV from entering cells. Genentech Chief Financial Officer David Ebersman, however, said the deal primarily aims to improve Genentech's return on sales of Xolair.

With the acquisition, Genentech will hold onto Tanox's share of Xolair-related royalties, profit-sharing and manufacturing-related payments, which analysts estimate at between 8% and 12% of the drug's net sales. As a result, the deal will add "modestly" to the company's bottom line starting in 2008, Mr. Ebersman said.

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The Wall Street Journal[6]

AUGUST 3, 2007

Genentech Completes A Deal to Buy Tanox

By DAVID P. HAMILTON

Genentech Inc. said it completed its $20-a-share, or $919 million, acquisition of its asthma-drug collaborator Tanox Inc., following expiration of the waiting period under the Hart-Scott-Rodino Act. Genentech, Tanox and Novartis AG worked together to develop Xolair, a drug for asthma that had U.S. sales of $120 million in the second quarter, a 14% increase over the year-earlier period. Under the deal, Genentech, of South San Francisco, Calif., will halt its royalty payments to Tanox, and will collect them from Novartis.

Xolair recently received a black-box warning from the Food and Drug Administration cautioning physicians and patients about the risks of anaphylaxis, a severe immune reaction. The biotech giant had collaborated on Xolair for over a decade with the small Texas based biotech amid periods of rivalry.

While the asthma drug was the main driver of the deal, a Genentech spokeswoman said that the company is interested in several Tanox experimental drugs including other compounds against asthma, eye disease and AIDS.

Notes

[1] http://online.wsj.com/article/SB111265511632497703.html
[2] http://online.wsj.com/article/SB111645532618537399.html
[3] http://www.prnewswire.com/news-releases/tanox-genentech-and-novartis-settle-disputes-surrounding-xolairr-and-tnx-901-71837927.html
[4] http://online.wsj.com/article/SB113737301838547294.html
[5] http://online.wsj.com/article/SB116313101820019558.html
[6] http://online.wsj.com/article/SB118609942303686786.html

ORIGINAL ARTICLE

Effect of Anti-IgE Therapy in Patients with Peanut Allergy

Donald Y.M. Leung, M.D., Ph.D., Hugh A. Sampson, M.D., John W. Yunginger, M.D., A. Wesley Burks, Jr., M.D., Lynda C. Schneider, M.D., Cornelis H. Wortel, M.D., Ph.D., Frances M. Davis, Ph.D., John D. Hyun, B.S., and William R. Shanahan, Jr., M.D., for the TNX-901 Peanut Allergy Study Group*

ABSTRACT

BACKGROUND

Peanut-induced anaphylaxis is an IgE-mediated condition that is estimated to affect 1.5 million people and cause 50 to 100 deaths per year in the United States. TNX-901 is a humanized IgG1 monoclonal antibody against IgE that recognizes and masks an epitope in the CH3 region of IgE responsible for binding to the high-affinity Fcε receptor on mast cells and basophils.

METHODS

We conducted a double-blind, randomized, dose-ranging trial in 84 patients with a history of immediate hypersensitivity to peanut. Hypersensitivity was confirmed and the threshold dose of encapsulated peanut flour established by a double-blind, placebo-controlled oral food challenge at screening. Patients were randomly assigned in a 3:1 ratio to receive either TNX-901 (150, 300, or 450 mg) or placebo subcutaneously every four weeks for four doses. The patients underwent a final oral food challenge within two to four weeks after the fourth dose.

RESULTS

From a mean base-line threshold of sensitivity of 178 to 436 mg of peanut flour in the various groups, the mean increases in the oral-food-challenge threshold were 710 mg in the placebo group, 913 mg in the group given 150 mg of TNX-901, 1650 mg in the group given 300 mg of TNX-901, and 2627 mg in the group given 450 mg of TNX-901 ($P<0.001$ for the comparison of the 450-mg dose with placebo, and P for trend with increasing dose <0.001). TNX-901 was well tolerated.

CONCLUSIONS

A 450-mg dose of TNX-901 significantly and substantially increased the threshold of sensitivity to peanut on oral food challenge from a level equal to approximately half a peanut (178 mg) to one equal to almost nine peanuts (2805 mg), an effect that should translate into protection against most unintended ingestions of peanuts.

From the National Jewish Medical and Research Center, Denver (D.Y.M.L.); Mount Sinai School of Medicine, New York (H.A.S.); Mayo Clinic, Rochester, Minn. (J.W.Y.); Arkansas Children's Hospital, Little Rock (A.W.B.); Children's Hospital, Boston (L.C.S.); ClinQuest, Marlborough, Mass. (C.H.W.); and Tanox, Houston (F.M.D., J.D.H., W.R.S.). Address reprint requests to Dr. Sampson at the Department of Pediatrics, Box 1198, Mount Sinai School of Medicine, 1 Gustave L. Levy Pl., New York, NY 10029-6574, or at hugh.sampson@mssm.edu.

*The members of the study group are listed in the Appendix.

N Engl J Med 2003;348:986-93.

Peanut allergy is characterized by symptoms and signs after ingestion that may include nausea, vomiting, diarrhea, abdominal pain, urticaria, angioedema, bronchospasm, hypotension, loss of consciousness, and death.[1,2] Although data from animals demonstrate that allergic reactions are mediated by antigen-specific IgE bound to high-affinity receptors for IgE (FcεRIs) on mast cells and basophils,[3,4] non-IgE pathways for anaphylaxis exist, at least in mice,[5,6] and direct clinical evidence of IgE involvement in peanut allergy in humans is lacking.

Approximately 1.5 million people in the United States have peanut allergy,[7,8] 50 to 100 of whom die each year from unintended ingestion.[9,10] Severe reactions can occur at any age,[2,11] the previous reaction cannot be used reliably to predict the course of the next, and even the first reaction may be severe.[1,11-13] Current treatment for peanut allergy is avoidance or rescue with epinephrine.[12,14-16] Only a small minority of patients who are allergic to peanuts carry epinephrine, and even timely injection may not prevent death.[8,11] Avoidance is extremely difficult,[1,11,17] and the risk–benefit ratio for hyposensitization is unfavorable.[18]

TNX-901 is a humanized IgG1 monoclonal antibody against IgE that binds with high affinity to an epitope in the CH_3 domain, masking a region responsible for binding to both FcεRIs and low-affinity Fcε receptors (FcεRII, or CD23).[19-21] In addition to inhibiting binding of IgE to mast cells and basophils, anti-IgE also markedly down-regulates the expression of FcεRIs on basophils[22,23] and may inhibit allergen-specific activation of T cells through interference with the processing of antigen-presenting cells mediated by FcεRIIs or FcεRIs.[24]

METHODS

PATIENTS

Patients 12 to 60 years of age with a history of peanut allergy manifested by urticaria, angioedema, lower respiratory tract symptoms, or hypotension were eligible for enrollment. Inclusion criteria were a serum total IgE level between 30 and 1000 IU per milliliter, good health, body weight within 20 percent of ideal, a positive skin-prick test to peanut and a negative skin-prick test to tuna oil, and no prior exposure to monoclonal antibodies. Eligible patients could not be pregnant. Any asthma was to be under control, with a forced expiratory volume in one second that was at least 80 percent of the predicted value. Systemic corticosteroids, beta-blockers, and acetylcholinesterase inhibitors were prohibited before screening and throughout the study, and aspirin, antihistamines, and antidepressants were prohibited for three days, one week, and two weeks, respectively, before skin testing or oral food challenge. Race was determined by the investigators.

STUDY DESIGN

This was a randomized, double-blind, placebo-controlled, dose-ranging study. Prospective patients underwent a screening physical examination and laboratory tests. Before enrollment, allergy to peanut was confirmed and the threshold for reactivity was established by a randomized, double-blind oral food challenge, as described below. Central randomization was performed in blocks of four per site. Patients were randomly assigned in groups of 28 and in a 3:1 ratio to receive 150 mg, 300 mg, or 450 mg of TNX-901 or placebo subcutaneously every four weeks for four doses. They then underwent a final oral food challenge with peanut flour within two to four weeks after the last dose. Enrollment at each dose level was completed before enrollment at the next level began. Every four weeks, blood and urine samples were obtained and patients were evaluated for adverse events. The final evaluation occurred eight weeks after the last dose (week 20).

The study was approved by institutional review boards at all participating centers, and all patients provided written informed consent. The data from all participating centers were sent to and monitored by ClinQuest, and all data were entered and locked before data analysis commenced. The data were analyzed by Abt Associates Clinical Trials. The study was designed by five of the investigators, three of whom had full access to the data. The sponsor did not limit the investigators' right to publish the results.

STUDY DRUG

Each dose of TNX-901 and placebo was supplied as a 150-mg lyophilized cake in a 5-ml clear-glass vial. A pharmacist reconstituted each cake with 1 ml of sterile water in an unblinded fashion and placed the solution in a syringe, which was masked to prevent study personnel from identifying the contents, for subcutaneous injection.

ASSESSMENT OF EFFICACY

The primary measure of efficacy was the change from base line in the threshold dose that induced

hypersensitivity to peanut flour, as assessed by an oral food challenge. The threshold dose was log-transformed (on a base 10 scale). Peanut flour was made by grinding equal portions of Valencia, runner, and Spanish peanuts (Greer Laboratories), the types used in virtually all peanut products consumed in the United States. The peanuts were defatted, and then various doses (1 mg to 2 g) were loaded into gel capsules. Matching placebo capsules were filled with similar amounts of cornstarch. For masking purposes, the capsules were rolled in tuna oil before administration.

The screening double-blind, placebo-controlled oral food challenge was administered on two days within a five-day period. At base line, spirometry was performed, intravenous access established, and continuous cardiac monitoring initiated. Vital signs were checked, chest auscultation was performed, and peak expiratory flow rates were monitored every 30 minutes during the food challenge and for at least 2 hours after the last dose or the abatement of any symptoms or signs. Patients were given increasing doses of placebo or peanut flour every 40 minutes until the principal investigator at each site judged that a definite reaction was occurring. To maximize safety and prevent severe reactions, the end point for the oral food challenge was the threshold dose for an allergic reaction. At screening, the initial dose was 1 mg, followed successively by 5, 10, 20, 50, 100, 200, 500, 1000, and 2000 mg of peanut flour or matching placebo capsules. Patients who could tolerate 2000 mg were considered to have had a negative test. To enter the study, each patient was required to have one positive and one negative result at screening, under the assumption that the positive result was to peanut. The final oral food challenge with peanut flour alone was initiated at 1 mg or 100 mg, depending on the screening threshold, and escalated to 4000 mg and then 8000 mg if tolerated. The dose escalation was terminated when an investigator believed there were clear-cut symptoms or signs of a hypersensitivity reaction, and the patient was then given activated charcoal slurry (Liqui-Char, Jones Pharma), which is believed to adsorb residual peanut protein in the stomach. Specific treatment protocols were followed in the event of asthma or other systemic reactions.

ASSESSMENT OF SERUM IgE, PEANUT-SPECIFIC IgE, TNX-901, AND ANTI–TNX-901 ANTIBODY LEVELS

Total IgE and free IgE (unbound by TNX-901), TNX-901, and anti–TNX-901 antibodies were measured in blood samples with use of a modification of the enzyme-linked immunosorbent assays described for CGP 51901, the chimeric version of TNX-901.[25] Total peanut-specific IgE was measured by a fluorescence enzyme immunoassay (CAP-System, FEIA, Pharmacia Upjohn).[26]

STATISTICAL ANALYSIS

The predefined primary efficacy measure was the change from base line in the log-transformed threshold dose of peanut flour that induced hypersensitivity. Since there were no clinical data on which to estimate the variability in this measure, the sample size was estimated on the basis of a dichotomous variable. Success was defined as an increase in the threshold dose of at least 0.9 log (by a factor of at least 7.9 or by three steps in the oral food challenge). Success constituted a secondary efficacy measure thought to be both clinically meaningful and unlikely to be due to placebo. Assuming a success rate of 80 percent for TNX-901 and 20 percent for placebo, a two-sided type 1 error rate of 0.05, a statistical power of 90 percent, and a multiple-comparison approach, 20 patients per group were required. To allow for a 5 percent dropout rate, the number was increased to 21 per group.

Safety and efficacy were analyzed on a predefined, modified intention-to-treat basis. Inclusion in the intention-to-treat analysis of efficacy required the receipt of at least one dose of study drug and values for base-line and repeated oral food challenges; safety analyses included any patient who received at least one dose of study drug. For the primary efficacy measure, pairwise comparisons of each TNX-901 group with placebo used Dunnett's test based on an analysis-of-covariance model with terms for treatment, site, base-line weight, base-line IgE levels, and base-line peanut-specific IgE levels. The proportion of patients who had an increase in the threshold dose of at least 0.9 log (success) was assessed by pairwise comparisons of each TNX-901 group with placebo with the use of Fisher's exact test, with adjustment for multiple comparisons. All reported P values are two-sided. No interim analysis was conducted.

RESULTS

STUDY POPULATION

The study was conducted between July 1999 and March 2002 at seven centers in the United States: 164 patients were screened, 84 patients under-

went randomization, and 81 completed the study. Two patients (one each in the 150-mg and 300-mg groups) were found to have had a positive placebo and a negative peanut challenge at screening. For both, a base-line threshold dose of 2000 mg (the highest dose administered at screening) was assigned, and the threshold dose was determined to be 100 mg at the final oral food challenge. In the 300-mg group, one patient discontinued the study on day 7 because of a myocardial infarction, and one stopped on day 43 because of a brain tumor. The efficacy analyses therefore included 82 patients. A total of 23 patients were randomly assigned to receive placebo, 19 to receive 150 mg of TNX-901, 19 to receive 300 mg of TNX-901, and 21 to receive 450 mg of TNX-901. One patient in the 450-mg group completed efficacy evaluations but withdrew consent before the final two visits. Base-line characteristics were similar among the groups (Table 1).

EFFICACY AND PHARMACODYNAMICS

Allergic reactions to peanut were generally well controlled by termination of the oral food challenge followed by the oral administration of charcoal and treatment with epinephrine, bronchodilators, antihistamines, and corticosteroids, as appropriate. One patient required overnight hospitalization for hypotension. The mean time from the final dose to the final oral food challenge was similar among the four groups (range, 21.2 to 24.5 days).

In all patients, the threshold of sensitivity to peanut was determined by a constellation of signs and symptoms typical of allergic reactions to food, at least one of which was judged to be moderate or severe in nature in all but 14 of the 166 challenges to peanut flour. Nausea, abdominal pain, vomiting, throat tightness, chest tightness, wheezing, persistent cough, rhinitis, conjunctivitis, pruritus, hives, and angioedema were among the most common

Table 1. Characteristics of the Patients Included in the Efficacy Analysis.

Characteristic	Placebo (N=23)	150 mg of TNX-901 (N=19)	300 mg of TNX-901 (N=19)	450 mg of TNX-901 (N=21)	Total (N=82)
Age (yr)					
Mean	34.4	34.9	28.3	31.6	32.4
Range	14–59	13–49	13–52	13–53	13–59
No. 12–17 yr of age	5	3	6	4	18
Sex (M/F)	10/13	11/8	12/7	12/9	45/37
Weight (kg)					
Mean	75.1	71.5	76.7	70.1	73.4
Range	59–99	45–114	43–100	45–95	43–114
Race or ethnic group (no.)					
White	20	16	19	20	75
Black	2	1	0	0	3
Hispanic	0	0	0	1	1
Asian	1	1	0	0	2
Other	0	1	0	0	1
Threshold sensitivity to peanut flour (mg)					
Mean	300.0	435.5	433.2	177.6	330.9
Range	1–2000	5–2000	5–2000	5–2000	1–2000
Serum IgE (IU/ml)					
Mean	251.3	349.8	205.1	286.7	272.5
Range	36–955	101–902	11–496	33–1017	11–1017
Serum peanut-specific IgE (U/ml)					
Mean	24.0	21.7	24.3	32.9	25.9
Range	0.34–100	0.34–100	0.34–100	0.69–100	0.34–100
Peanut-specific IgE (%)					
Mean	9.7	7.4	12.2	12.6	10.6
Range	0.15–42.7	0.14–30.5	0.20–34.5	0.47–30.4	0.14–42.7

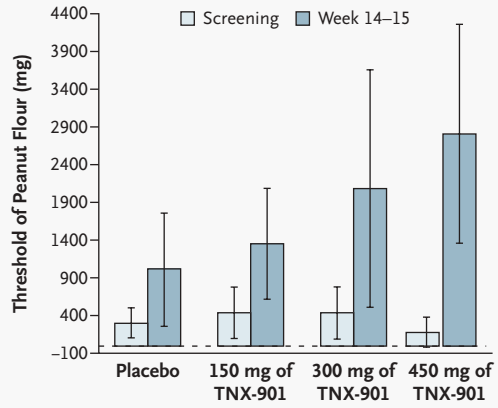

Figure 1. Mean Threshold Dose of Peanut Flour Eliciting Symptoms in Patients Receiving TNX-901 or Placebo.

The mean increase in the threshold of sensitivity, as compared with that in the placebo group, reached significance only in the 450-mg group (P<0.001); however, results of the test for trend with increasing doses were significant (P<0.001). I bars are 95 percent confidence intervals.

signs and symptoms that led to the termination of the oral food challenge.

The mean threshold of sensitivity to peanut at the final oral food challenge increased from base line in a dose-responsive manner. Although the increase, as compared with that in the placebo group, only reached statistical significance for the 450-mg group (P<0.001) (Fig. 1), a strong trend was associated with increasing doses (P<0.001). The proportion of patients who had an increase in the threshold of sensitivity of at least 0.9 log was greater in all the TNX-901 groups than in the placebo group, but again this difference was significant only in the 450-mg group (P=0.002): 22 percent in the placebo group, 53 percent in the 150-mg group, 47 percent in the 300-mg group, and 76 percent in the 450-mg group (P for trend=0.001). The proportions of patients in each group who tolerated a 0.5-, 1-, 2-, 4-, and 8-g challenge at screening and during the final oral food challenge, at week 14 to 15, are shown in Figure 2. In the placebo group, 4 percent of patients reached the highest level tested — 8 g — as compared with 0 percent of those in the 150-mg group, 21 percent of those in the 300-mg group, and 24 percent of those in the 450-mg group. Although pairwise comparisons with placebo of the proportions of patients who tolerated a given dose were not significant, significant trends with increasing dose were noted for the 4-g and 8-g threshold (P=0.02 for both).

Changes from base line in the log-transformed threshold dose correlated similarly with the dose

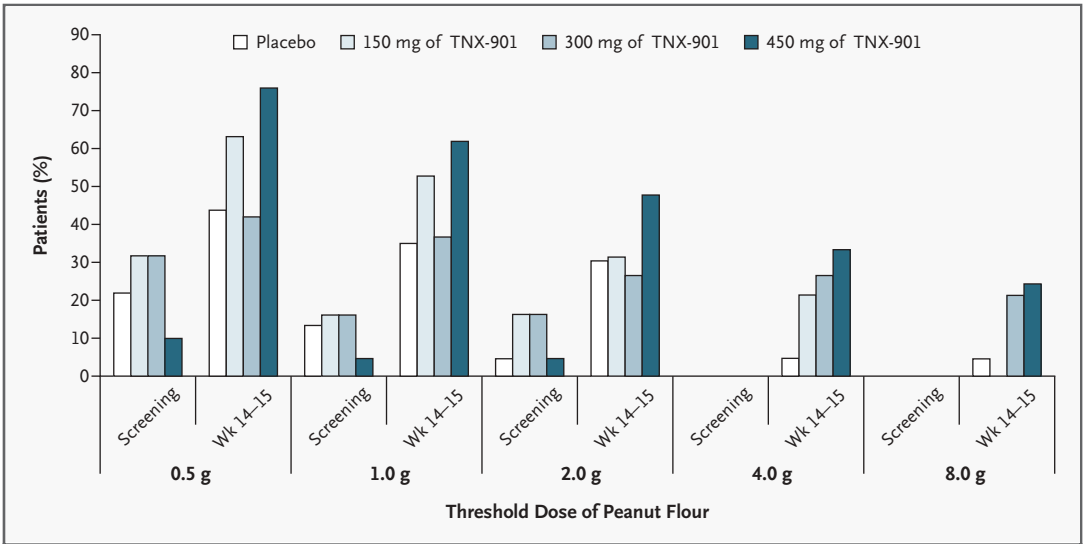

Figure 2. Percentage of Patients Who Tolerated Specified Dosing Thresholds during the Oral Food Challenge at Screening and Week 14 to 15.

Although pairwise comparisons with placebo did not reach statistical significance at any threshold level, the trend for increasing doses of TNX-901 at the 4-g and 8-g threshold levels was significant (P=0.02 for both).

on an absolute basis in terms of milligrams of anti-IgE (Fig. 3), milligrams of anti-IgE per kilogram of body weight, and milligrams of anti-IgE per kilogram per total IgE level at base line, and these relations were statistically significant. Efficacy correlated less well with the dose on the basis of milligrams per kilogram per peanut-specific IgE level at base line and milligrams per kilogram per percent of total IgE that was peanut-specific at base line, and these correlations were not significant.

Trough drug levels were roughly dose proportional and reached steady state at week 12 (mean, 11.6 μg per milliliter in the 150-mg group; 32.2 μg per milliliter in the 300-mg group; and 57.5 μg per milliliter in the 450-mg group). Taking the trough level at week 12 as a measure of drug exposure, we found that the correlation between the change in the threshold dose and trough drug levels ($r=0.392$, $P<0.001$) was similar to that between threshold dose and the dose of TNX-901 ($r=0.381$, $P<0.001$).

Serum free IgE levels were measured every four weeks, just before each injection, and substantial reductions were obtained and sustained at all three doses of TNX-901. From base-line levels of 199.5 IU per milliliter in the placebo group, 262.0 IU per milliliter in the 150-mg group, 158.9 IU per milliliter in the 300-mg group, and 242.0 IU per milliliter in the 450-mg group, free IgE levels were 207.4 (an increase of 4.0 percent), 30.4 (a decrease of 88.4 percent), 17.0 (a decrease of 89.3 percent), and 16.6 (a decrease of 93.2 percent) IU per milliliter, respectively, at the end of week 4, just before the second injection, and similar reductions were observed throughout the dosing period. Eight weeks after the last dose of TNX-901, the last time point assessed, free IgE levels were still reduced from base line by 71.6 percent in the 150-mg group, 79.1 percent in the 300-mg group, and 88.7 percent in the 450-mg group.

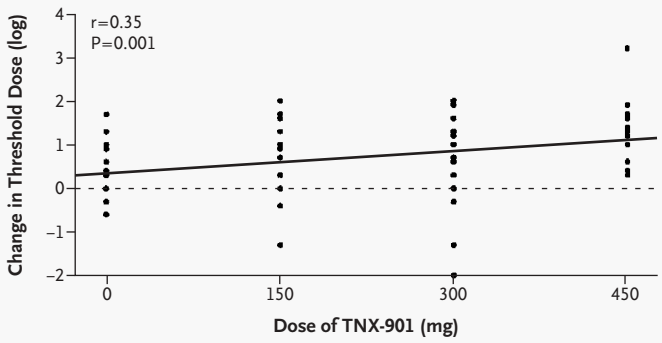

Figure 3. Scatter Plot of the Correlation between the Dose of TNX-901 and the Increase in the Threshold of Sensitivity to Peanut Flour from Screening to Week 14 to 15.

Not all of the data points can be individually distinguished, since the protocol-specified dose-escalation scheme for the oral food challenge limited the number of possible values on either an absolute or, as shown here, a log-transformed basis; hence, many of the data points overlie one another.

SAFETY

TNX-901 was well tolerated. The incidences and spectrum of systemic adverse events and local adverse events were similar in the TNX-901 and placebo groups. The total number of systemic adverse events reported (range, 45 to 50 per group) and the number of patients who had such events (range, 15 to 19 per group) were similar among the four groups. Systemic adverse events that occurred more than once in a TNX-901 group are given in Table 2. With respect to local adverse events, injection-site reactions were noted in 13 to 14 patients in each group and consisted primarily of erythema and, to a lesser extent, swelling and burning. All injection-site reactions were considered mild in nature except in one patient in the 450-mg group who had moderate erythema or edema on two occasions. There were no significant changes in the results of routine hematologic variables (including platelet count), serum chemical analyses, and urinalysis. There was no evidence of anti–TNX-901 antibodies in any patient.

DISCUSSION

In the absence of reliable epidemiologic data and given the impracticability of conducting a large, placebo-controlled trial in which episodes of anaphylaxis owing to accidental ingestions served as end points, we elected to use an increase in the amount of peanut flour required to elicit symptoms in an oral challenge as a valid substitute. A substantial increase in the threshold of peanut flour required to provoke symptoms should serve as a proxy for the level of protection against unintended ingestion. The double-blind, placebo-controlled oral food challenge is the standard for diagnosing food allergy and has been used as an efficacy end point in several studies.[17,27-30] Although we discontinued the oral food challenge only when patients had symptoms or signs that typically precede more severe symptoms, this end point is not devoid of subjective interpretation, since some of these symptoms can be produced by anxiety. Reliable confirmation of an aller-

Table 2. Adverse Events Other Than Local Events That Occurred in More Than One Patient in a TNX-901 Group.

Adverse Event	Placebo (N=23)		150 mg of TNX-901 (N=19)		300 mg of TNX-901 (N=21)		450 mg of TNX-901 (N=21)	
	No. of Patients	No. of Events	No. of Patients	No. of Events	No. of Patients	No. of Events	No. of Patients	No. of Events
Diarrhea	1	1	4	5	1	1	1	2
Nausea	1	1	3	3	1	2	1	1
Vomiting	2	2	1	2	2	2	1	1
Fatigue	0	0	3	3	2	2	0	0
Fever	1	1	1	1	3	3	1	1
Food allergy*	6	7	4	4	7	7	5	6
Upper respiratory tract infection	7	8	7	12	10	12	3	4
Headache	3	4	4	5	2	2	2	2
Arthralgia	1	1	2	2	3	3	2	3

* Events related to food allergy were reported by the patient and were unrelated to oral food challenge. Reactions were due to exposure to a variety of foods, including tree nuts and seafood. Four food reactions occurred more than six weeks after the last dose of study drug: one each in the placebo, 300-mg, and 450-mg groups and two in the 150-mg group. Many of the food reactions were subjective in nature, and all were considered mild or moderate, except one event rated as severe in the placebo group. All reactions were treated expectantly or symptomatically. Approximately half the food reactions were considered mild and approximately half moderate in all groups except the 450-mg group, in which five food reactions were rated mild and only one was rated moderate.

gic response is not readily available, since plasma histamine (a marker of the allergic response) is very labile and difficult to measure,[31] serum tryptase rarely increases during allergic reactions to peanuts,[11] and signs such as the heart rate are subject to anxiety on the part of the patient. A placebo effect was clearly seen. Two patients had negative peanut and positive placebo challenges at base line, with positive challenges to peanut at the final oral food challenge. In spite of these limitations, in experienced hands, the oral food challenge appears to be a reliable method of determining sensitivity to peanut in most patients. In general, the thresholds of sensitivity to peanut flour at screening and at the final evaluation were remarkably similar in the placebo group; only 5 of 23 patients had more than a two-step increase in the threshold.

Although the average amount of peanut consumed in an accidental exposure has not been accurately quantified, it is generally believed to be no more than one or two peanuts, or the equivalent of approximately 325 to 650 mg of peanut flour. The thresholds achieved in the 300-mg and 450-mg groups — 2083 and 2805 mg, respectively — are equivalent to approximately six and eight peanuts, respectively, and should therefore provide substantial protection in most patients. In addition, 21 percent of patients in the 300-mg group and 24 percent of those in the 450-mg group were effectively tolerized and able to ingest at least 8 g of peanut flour (approximately 24 peanuts), the final dose in the food challenge, before having a reaction.

In patients with peanut allergy, there is currently no adequate treatment of or protection against the accidental ingestion of peanuts other than avoidance, although epinephrine modulates the reaction and can be lifesaving. Our clinical data confirm the direct role of IgE in peanut-induced hypersensitivity reactions and demonstrate that TNX-901, at a dose of 450 mg subcutaneously every four weeks, significantly increases the threshold of sensitivity to peanut antigen, as assessed by oral food challenge, to a level that should translate into at least partial protection against most unintended ingestions of peanut. Although these results are highly encouraging, TNX-901 is still an experimental drug, and approval for general use will require confirmation of these results in additional studies.

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APPENDIX

The TNX-901 Peanut Allergy Study Group consisted of the following investigators: A.W. Burks, Jr., L. Christie, and K. Althage, Arkansas Children's Hospital, Little Rock; H.A. Sampson, S.H. Sicherer, A. Nowak-Wegrzyn, and S.A. Noone, Mount Sinai School of Medicine, New York; L.C. Schneider, A. Alangari, and I. Borras, Children's Hospital, Boston; J. Spergel, Children's Hospital of Philadelphia, Philadelphia; S.A. Tilles, Asthma, Inc., Seattle; D.Y.M. Leung, H.S. Nelson, F.D. Atkins, and J. Murray, National Jewish Medical and Research Center, Denver; and J.W. Yunginger, G. Volcheck, M. DeBolt, K.A. Bachman, and C. Wiginton, Mayo Clinic, Rochester, Minn.

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