

---

# Correspondence

---

## SUBLINGUAL-ORAL ADMINISTRATION OF STANDARDIZED ALLERGENIC EXTRACTS: PHASE 1 SAFETY AND DOSING RESULTS

**To the Editor:** Recently, Esch et al<sup>1</sup> reported on a phase 1 safety and dosing trial for single allergen sublingual immunotherapy (SLIT). The authors note that a dose “up to more than 100 times the cumulative monthly doses currently used in subcutaneous immunotherapy (SCIT) is generally safe and without serious adverse effects.” They conclude this trial is the first step toward approval of home SLIT administration. Although this was a phase 1 trial, we think that important data were not presented.

The maximum tolerable dose is unclear. Although the paper cites the doses achieved during the 1-day build-up phase, it does not cite the doses participants took in the ensuing 8 weeks of treatment. We think that this information is critical for a safety analysis because the dose could be adjusted, up or down, at clinic visits every 2 weeks. What doses did patients take during the 8-week treatment course? What were the effects of dose adjustments on adverse effects (AEs)?

Also, the 2 methods used to report AEs are unclear. The primary method used was an arbitrary scale of mild, moderate, or severe. An AE was considered severe if it was “hard to tolerate, caused interference with activities of daily living or sleep, or prompted a call to the study physician.” For this method, they report that 13.6% of participants had a “severe” AE. Yet, what does this tell us? It says nothing about the safety concern of prime importance with respect to allergen immunotherapy, namely, anaphylaxis. One could argue that anaphylaxis would be graded as severe. However, what about the patient with 2 to 3 urticarial lesions and cough that resolves spontaneously? Perhaps patients perceive these symptoms as “mild” or “moderate.” Would this patient have their dose adjusted? Should they have used their EpiPen? Should this patient be administering SLIT unsupervised?

Regarding the second AE reporting method, a systemic AE was defined as symptoms involving either the lung and/or skin. By this definition, of 24,756 AEs, 9.1% were considered systemic. However, the actual number or percentage of patients who experienced a lung or skin manifestation was not reported and neither were the types of lung (eg, dyspnea) or skin (eg, urticaria) manifestations. These factors are relevant and reported in studies evaluating SCIT.<sup>2,3</sup> Last, one could argue that throat symptoms be considered separately from mouth symptoms—just how far does the “large local” reaction of SLIT go?

We commend the authors for their work and hope future trials will report the aforementioned data that we believe are necessary for allergists to make safe, evidence-based treatment decisions.

MAJ MARK S. LA SHELL  
MAJ CHRISTOPHER W. CALABRIA  
Department of Allergy, Asthma, and Immunology  
59th Medical Group  
Lackland AFB

---

**Disclosures:** Authors have nothing to disclose.

**Disclaimer:** The views expressed in this article are those of the authors and do not reflect the official policy of the Department of Defense or other Departments of the US Government.

San Antonio, Texas  
mark.lashell@lackland.af.mil

1. Esch RE, Bush RK, Peden P, Lockey RF. Sublingual-oral administration of standardized allergenic extracts: phase 1 safety and dosing results. *Ann Allergy Asthma Immunol.* 2008;100:475–481.
2. Lockey RF, Nicoara-Kasti GL, Theodoropoulos DS, Bukantz SC. Systemic reactions and fatalities associated with allergen immunotherapy. *Ann Allergy Asthma Immunol.* 2001;87(suppl 1):47–55.
3. Harvey SM, Laurie S, Hilton K, Khan DA. Safety of rush immunotherapy to multiple aeroallergens in an adult population. *Ann Allergy Asthma Immunol.* 2004;92:414–419.

**Author Response:** The maximum tolerable dose was initially estimated during the 1-day dose-escalation phase, and dose adjustments were made, if necessary, during the 8-week treatment course.<sup>1</sup> In general, the patients were maintained on this maximum tolerable dose during the 8-week treatment course. Dose adjustments were made in 31 (35%) of the 88 patients, and there were no adverse events (AEs) among the 20 patients whose doses were increased.

We apologize that our reporting of AEs was at times unclear. We followed regulatory guidelines in collecting and reporting safety data such that all AEs occurring after initiating study treatment were included, even those events likely to be related to the underlying disease. These AEs, which included the daily morning and evening rhinoconjunctivitis and asthma symptoms, were captured using electronic diaries. Most if not all of these AEs, regardless of whether they were local or systemic, were attributed to the underlying allergic disease. These symptoms were controlled by using their routinely prescribed antiallergy medications. We hope to address the relevance and frequencies of these AEs with respect to sublingual immunotherapy (SLIT) in subsequent placebo-controlled trials. Nevertheless, during our trials, it became evident that certain types of AEs could be attributed to SLIT. They included 20 AEs in 12 patients. The most commonly reported AEs were sore tongue, throat, or lips and headache. The only severe AE attributed to SLIT was gastrointestinal complaints with diarrhea, which resolved after dose reduction.

There is a wide range of opinions regarding the appropriate clinical use of epinephrine. In our trials, we required subjects to be trained on the emergency use and administration of epinephrine, and those who refused were excluded. The correspondent asks practical and relevant questions regarding dose adjustments, the use of epinephrine, and the level of supervision required during SLIT. It is our opinion that epinephrine should be available anywhere immunotherapy is given, including at home. Dose adjustments were based on individual patients' tolerance, and this seemed to be a safe approach. Finally, it is our opinion that SLIT, like subcutaneous immunotherapy, should be supervised by physicians who are experienced in the administration of allergen immunotherapy.

ROBERT E. ESCH, PhD\*  
ROBERT K. BUSH, MD†  
DAVID PEDEN, MD‡  
RICHARD F. LOCKEY, MD§  
\*Research and Development

---

**Disclosure:** R. Esch is employed by Greer Laboratories.

---

Greer Laboratories  
Lenoir, North Carolina  
esch@greerlabs.com  
†Section of Allergy/Immunology, Pulmonary,  
Department of Medicine  
University of Wisconsin-Madison  
William S. Middleton Memorial Veterans' Hospital  
Madison, Wisconsin  
‡Division of Pediatric Immunology and  
Infectious Diseases  
Center for Environmental Medicine  
Asthma and Lung Biology, School of Medicine

University of North Carolina  
Chapel Hill, North Carolina  
§Division of Allergy and Immunology  
Department of Internal Medicine  
University of South Florida College of Medicine  
James A. Haley Veterans' Hospital  
Tampa, Florida

1. Esch RE, Bush RK, Peden D, Lockey RF. Sublingual-oral administration of standardized allergenic extracts: phase 1 safety and dosing results. *Ann Allergy Asthma Immunol.* 2008;100:475–481.