secukinumab. Ustekinumab was recently evaluated for psoriasis therapy, such as ustekinumab and 5 to 7 patients per month. The algorithm clearly identified a single cluster of CD3+CD4+CCR4+CCR6+CXCR3+ cells in our patient that was absent in the controls. This cluster matched the phenotype of T-helper 17 (Th17) cells and consisted of 53.4% effector-memory cells and 45.4% central-memory cells (Fig. S1A in the Supplementary Appendix). In our patient, the frequency of Th17 cells was 30 times that in the controls, and the frequency of interleukin-17–producing T cells was 67 times that in the controls (Fig. 1D and 1E and Fig. S1B). The plasma level of interleukin-17A was 38 times that in the controls (83.4 pg per milliliter and 2.2 pg per milliliter, respectively). A Th17 dysregulation was confirmed in a second patient with genetic confirmation of SAM syndrome (see the Results section in the Supplementary Appendix).

Available treatments targeting Th17 cells include biologic drugs that are currently licensed for psoriasis therapy, such as ustekinumab and secukinumab. Ustekinumab was recently evaluated, with encouraging results, in two patients with DSP mutations, but we had obtained little cutaneous improvement in another patient with SAM syndrome who had DSP1 mutations. Because 99% of the Th17 cells in our patient had a memory phenotype, we hypothesized that long-survival memory Th17 cells would not be vulnerable to the neutralization of interleukin-23 (as with ustekinumab), whereas secukinumab could neutralize the effect of the preformed Th17 pool by blocking the action of interleukin-17A on the skin.

We initiated therapy with 75 mg of secukinumab subcutaneously at weeks 0, 1, 2, 3, and 4 and then monthly on a compassionate-use basis when our patient was 18 months of age. The improvement was evident 3 weeks after treatment initiation (Fig. S3). At week 35, the patient showed a marked cutaneous improvement (Fig. 1B), the pruritus had almost disappeared, her weight and length charts had improved dramatically (Fig. 1F and 1G), and the weight-for-height z score had increased from −2.3 SD to +1.9 SD (Table S3).

The major effect of secukinumab on our patient’s quality of life supports interleukin-17A as a new target to treat patients with serious skin disorders, such as SAM syndrome. Furthermore, our study proposes an innovative strategy to identify individualized immune biomarkers to exploit with precision the biologic therapeutic arsenal.

Angela Hernández-Martín, M.D., Ph.D.
Hospital Infantil Universitario Niño Jesús
Madrid, Spain
ahernandez@aedv.es
Rafael Correa-Rocha, Ph.D.
Instituto de Investigación Sanitaria Gregorio Marañón
Madrid, Spain
and Others

A complete list of authors is available with the full text of this letter at NEJM.org.

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**Trial of SAGE-217 in Patients with Major Depressive Disorder**

**TO THE EDITOR:** Gunduz-Bruce et al. (Sept. 5 issue) report promising results for acute anti-depressant effects of SAGE-217. The drug is a positive allosteric modulator of γ-aminobutyric acid (GABA) receptors, which can improve mood and reduce anxiety in patients with major depressive disorder. To further evaluate the efficacy and safety of SAGE-217, additional clinical trials are needed to confirm these findings.
Benzodiazepines are often used in combination with antidepressants to manage anxiety and insomnia in patients with major depressive disorder. However, there is little evidence that benzodiazepines have clinically meaningful effects on the core symptoms of depression when used as monotherapy. Thus, benzodiazepines are almost never used alone to treat major depressive disorder. In contrast, in our trial SAGE-217 was largely administered as monotherapy. Moreover, the mechanism of action of SAGE-217 is distinct from that of benzodiazepines. Benzodiazepines bind only GABA<sub>λ</sub> receptors expressing γ subunits in combination with α1, α2, α3, or α5 subunits that largely mediate phasic inhibition, and these drugs have no activity on α4- or δ-subunit-containing extrasynaptic receptors that mediate tonic inhibition, which neurosteroids such as SAGE-217 potently modulate. Consistent with these pharmacologic characteristics, the reduction in depression scores by SAGE-217 occurred across several scales and was not driven by improvements in anxiety and insomnia, which would have been expected if efficacy were a consequence of selective modulation of phasic inhibition alone.

Handan Gunduz-Bruce, M.D.
Stephen J. Kanes, M.D., Ph.D.
Sage Therapeutics
Cambridge, MA
handan.gunduz-bruce@sagerx.com

Charles F. Zorumski, M.D.
Washington University School of Medicine
St. Louis, MO

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