Tuberous Sclerosis Alliance

WE'LL GIVE EVERYTHING. BUT UP.

November 7, 2018

Kendall Marcus, MD
Director, Division of Dermatology and Dental Products
Center for Drug Evaluation and Research
US Food and Drug Administration
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Dear Dr. Marcus:

We are writing on behalf of the Tuberous Sclerosis Alliance (TS Alliance) to update the Division on the unmet medical need of tuberous sclerosis complex (TSC) patients for access to safe and effective treatment of facial angiofibromas. As detailed in the *Voice of the Patient* report[1] we submitted to CDER in October 2017, facial angiofibromas can have significant physical and psychosocial impact on patients' quality of life.

TSC is a genetic disorder that causes non-malignant tumors to form in many organs. TSC is caused by mutations in either the TSC1 or TSC2 gene. The protein products of these genes form a protein complex in the cell which regulate the activity of the mechanistic target of rapamycin, or mTOR. Over the last 15 years, orally bioavailable mTOR inhibitors have been tested for beneficial effects in TSC, leading to FDA approval of everolimus for treatment of subependymal giant cell astrocytomas, renal angiomyolipomas, and adjunctive treatment of partial onset seizures in TSC, and to approval of rapamycin, or sirolimus, for treatment of lymphangioleiomyomatosis, a progressive lung manifestation associated with TSC.

The impact of TSC on individuals is highly variable, even between identical twins. Many TSC patients are heavily burdened by seizures, intellectual disability, and autism, while others may experience only one or none of those manifestations. However, nearly all people with TSC have skin manifestations of the disorder. Among the most burdensome skin manifestations are angiofibromas–skin growths which initially may appear in early childhood as flat red "spots" on the face, or as diffuse redness in the cheeks. The lesions tend to be progressive and become nodular in adolescence due to increased amounts of fibrous tissue. They may bleed spontaneously or as a result of abrasions, creating a risk of infection.

Facial angiofibromas are often the most visible sign of TSC. Several participants in our Externally-Led Patient Focused Drug Development Meeting in June 2017 mentioned that they (or their affected children) were teased for the bumps on their faces. However, the risks of angiofibromas are physical as well as psychological. For instance, one panelist recalled her angiofibromas bled during sports, leading to her being removed from play to avoid infection of herself and others.

The Dermatology and Dentistry Subcommittee of the 2012 International TSC Clinical Consensus Conference recommend laser treatments, surgical excision, and topical mTOR inhibitors as potential interventions for angiofibromas that are symptomatic, disfiguring, or negatively affecting function.[2]

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In our 2017 International TSC Drug Development Survey, dermatological procedures were the most commonly reported in-office procedures for TSC patients of all age groups.[1,a] General anesthesia is often necessary, especially for those individuals with severe developmental disabilities. All in-office procedures for facial angiofibromas have short-lived results and may need to be repeated because the underlying disease process is not addressed by physical procedures.

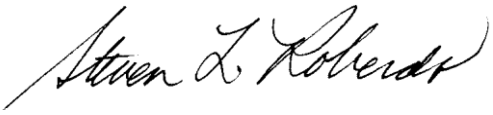
There is no FDA-approved treatment for facial angiofibromas in TSC. Several clinical trials and smaller case studies have tested topical formulations of the mTOR inhibitor sirolimus, or rapamycin, in TSC patients. Topical treatment appears to be well-tolerated, with no evident local or systemic adverse effects, and results in dramatic improvement of the skin lesions.[3-8]

Because no FDA-approved product exists in the United States, and because the various clinical trials and case studies utilized different concentrations and formulations, physicians routinely prescribe an mTOR inhibitor off-label in a cream or ointment preparation in accordance with TSC consensus guidelines. These treatments are generally compounded by pharmacies, although several participants in our 2017 survey indicated they mix oral sirolimus into a topical formulation at home to avoid the expense of compounding. Even pharmacist-compounded topical mTOR inhibitor preparations are not subject to regulated quality control or stability testing and are usually not covered by insurance.

The TS Alliance hopes FDA will consider the unmet need of TSC patients in its benefit-risk analysis when evaluating new or repurposed treatments for TSC, including potential new treatments for angiofibromas. We sincerely appreciate your commitment to improving the lives of those affected by TSC.

Sincerely,

Kari Luther Rosbeck
President and CEO



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[a] 21% of children with TSC; 45% of dependent adults with TSC diagnosis only; 45% of independent adults with TSC diagnosis only; 41% of dependent adults with TSC and LAM; 53% of independent adults with TSC and LAM