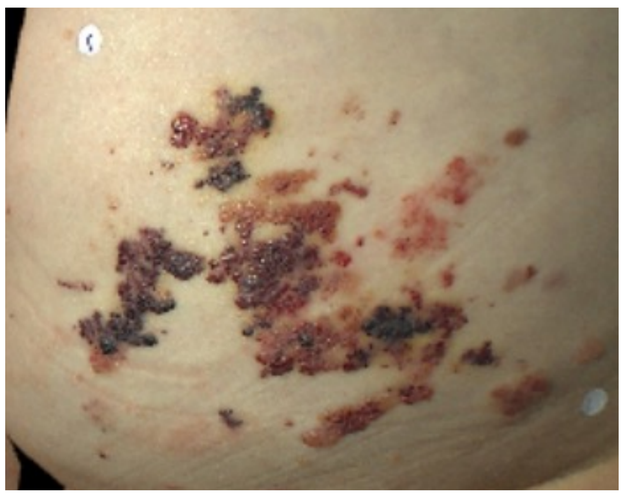
SELVA: A Phase 3 Study with a Fit-For-Purpose Primary Endpoint Evaluating QTORIN3.9% Rapamycin Anhydrous Gel in the Treatment of Microcystic Lymphatic Malformations.

Joyce Teng MD PhD[1], Stacie Hudgens[2], Jim Treat[3], Emily Cook[4], Jeffrey Martini PhD[4]

1) Stanford University School of Medicine; Lucile Packard Children's Hospital at Stanford in Stanford, CA; 2) Clinical Outcomes Solutions, Tucson, AZ 3) Children's Hospital of Philadelphia, Philadelphia, PA; 4) Palvella Therapeutics, Wayne, PA

1. Background: Microcystic Lymphatic Malformation

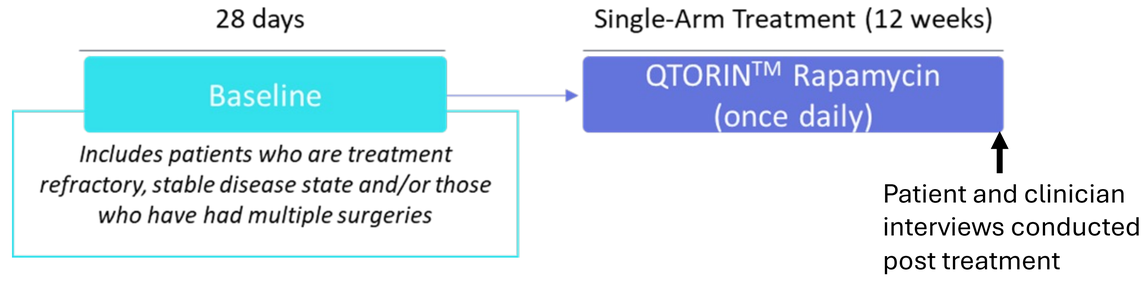


1) Gallagher et. al, Annual prevalence estimation of lymphatic malformation with a cutaneous component: observational study of a national representative sample of physicians, *Orphanet J of Rare Diseases*, 2022

- Chronically debilitating genetic disease of uncontrolled overgrowth of the lymphatic system.
- Estimated > 30,000 U.S. individuals living with microcystic LMs. (1)
- Arise from somatic mutations resulting in hyperactivated PI3K/mTOR pathway.
- Present at birth with continued proliferation throughout life.
- No FDA approved therapies.

- *Prior to this Phase 2 study, no clinically agreed upon key signs/ symptoms or endpoints*
- *Patient and clinician interviews are needed to understand the disease burden, determine clinically meaningful endpoints, and inform clinical trial design*

2. Qualitative Interviews to Identify Signs & Symptoms to Inform Clinical Design and Endpoints



Qualitative interviews conducted in Phase 2 clinical study aimed to identify critical signs and symptoms for microcystic LM

Key Objectives:

1. Understand which signs and symptoms patients valued and prioritized in assessing severity of disease and change
2. Determine how clinician preferred endpoints relate to patient change
3. Understand meaningful change from the patient and clinician perspective
4. Select a clinically meaningful primary endpoint for Phase 3

3. Patients Describe Microcystic LM as a Debilitating Disease

"The LM has always kept me from doing things that I wanted to do, which has held me back a lot in life…. The infections are debilitating. They're just horrible."

"It's kind of part of my whole life and my whole personality and my whole way of doing things. And it is totally part of how I socialize and just how I am."

"Just not knowing when it's going to leak or bleed, or what's going to trigger it. … Having to be cautious a lot of the time to what I'm doing, just kind of making sure I don't agitate it or cause it to bleed…It was a daily occurrence of having leaking, or the bleeding."

"I would have infections at least two or three times a month…I went to the emergency room four to five times a month."

"I was in church one day, and I had a white shirt on. I thought I was sweating. A guy said, 'You're bleeding.' I had to go around the back steps to check, and I had to go right home. Right between a song."

4. Change Scales Are a Clinically Meaningful Endpoint

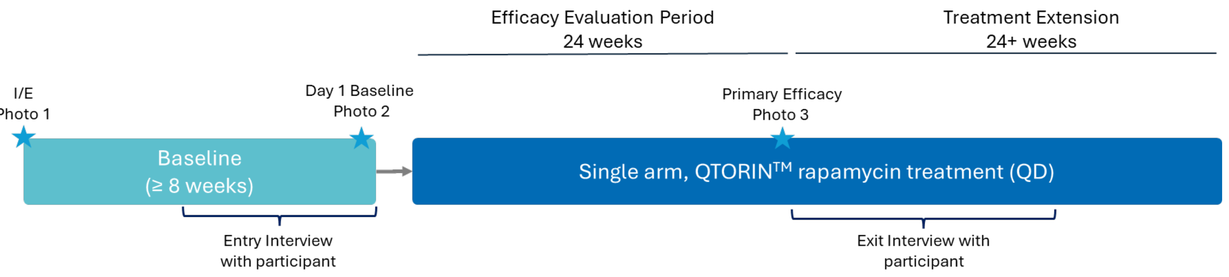
Patient	PGI-C	Patient Quote (Patient Numbers Refer to Patient Report)
Patient 1	+2	"When I first started, there were bumps there. Within two weeks, I put it on my hand, it started sliding right on down. The bumps were gone."
Patient 2	+3	"The reddening, the vesicles with color. It's soft, it's not as hard. I just see a huge difference."
Patient 3	+2	"That area just looks a little more normal. Less clustery, red, wart-looking. More just—again, it just looks a lot more appealing."
Patient 4	+2	"The height decreased significantly. And the redness went away. … and then the overall just kind of redness went away as well."
Patient 5	+2	"The bleeding, that was a problem beforehand. But then it stopped, so I didn't have to deal with it anymore. And the size of the strawberries and like the pigmentation—that also went down. So that also was really nice, because it's not as noticeable."

5. Clinician Interviews and Clinical Data Support a Clinician Change Scale as Clinically Meaningful Endpoint

- Clinician-reported change in severity is supported by large effect sizes observed in Phase 2 and exit interviews conducted with the clinicians.
- Clinicians were able to accurately reflect change in disease severity across each level of disease activity.
- Physicians identified key signs of disease as height, leaking/ bleeding, and vesicle appearance.
- Live clinician assessments provide the most objective analysis of efficacy.
- Physicians unanimously supported the use of a live change scale as the primary endpoint for a Phase 3 clinical trial.

- *The mLM-IGA is a "Fit for Purpose" endpoint specifically designed for microcystic LM incorporating physician and patient views*
- *The mLM-IGA is a dynamic 7-point change instrument evaluating microcystic LM severity over time*
- *Completed live by the clinician; utilizes pre-treatment photographs*

6. SELVA*: Phase 3 (NCT06239480) Evaluating QTORIN™ rapamycin** for the treatment of microcystic LM



SELVA Phase 3 Study: Single-Arm, Baseline-Controlled
n=40; QD dose

Primary Efficacy
- mLM-IGA, a 7-point clinician change scale

Key Secondary
- Blinded mLM Multi-Component Static Scale (mLM- MCSS)

* Palvella Therapeutics Awarded Up to $2.6 million Grant from the FDA Office of Orphan Products Development to Support Phase 3 Single-Arm, Baseline-Controlled Trial in Microcystic LM

** QTORIN rapamycin has received FDA Breakthrough Designation, Fast Track Designation, and Orphan Drug Designation

Children's Hospital of Philadelphia

palvella THERAPEUTICS

Lucile Packard Children's Hospital Stanford