

Phase 3 SELVA: Investigational QTORIN™ Sirolimus Topical Gel 3.9% Improved Disease Severity and Key Lesion Characteristics in Children With Microcystic Lymphatic Malformations

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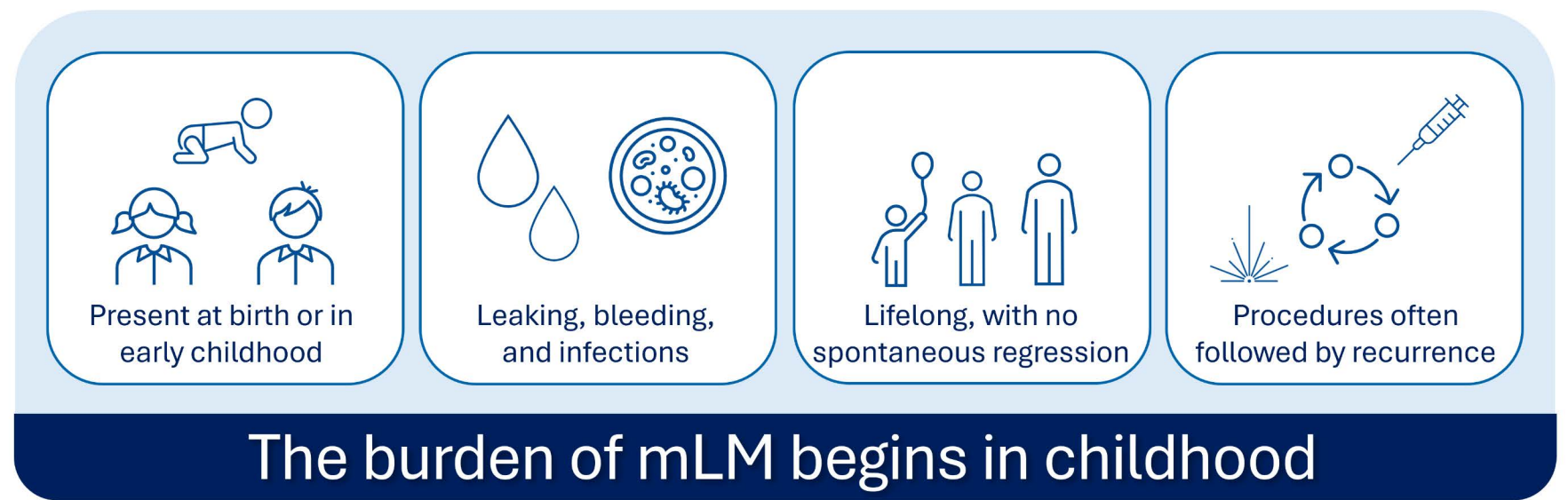
INTRODUCTION

Microcystic lymphatic malformations (mLMs) are rare, congenital slow-flow lymphatic anomalies that often present during infancy or early childhood and can result in lifelong morbidity^{1,2}. Lesions are characterized by clusters of abnormal lymphatic vesicles involving the skin and underlying soft tissues and are associated with recurrent complications that can substantially affect patients' daily functioning and quality of life.

Recent advances have shown that mLMs are predominantly driven by somatic activating *PIK3CA* mutations, resulting in activation of the PI3K/AKT/mTOR signaling pathway⁴. This biologic understanding has provided a rationale for targeted mTOR inhibition^{1,3}. Investigational QTORIN™ sirolimus topical gel 3.9% is a novel, anhydrous topical formulation designed to deliver localized mTOR inhibition directly to affected skin while minimizing systemic exposure. The Phase 3 SELVA study evaluated its efficacy, safety, and pharmacokinetics in patients with mLM.

OBJECTIVE

To evaluate the efficacy and safety of once-daily investigational sirolimus topical gel 3.9% in children and adolescents with mLM enrolled in the Phase 3 SELVA study.



CLINICAL STUDY DESIGN

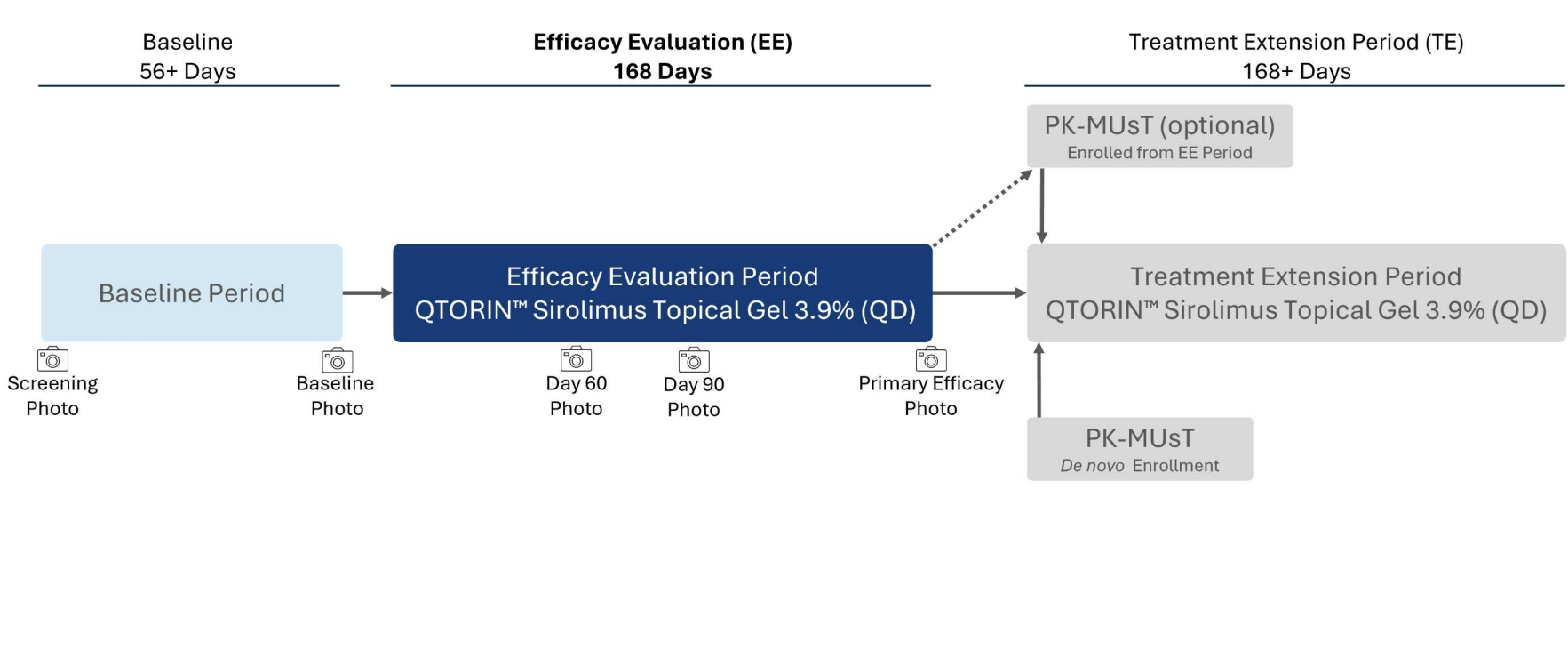


Figure 1. SELVA Phase 3 study design. After a baseline period (≥56 days), participants applied investigational sirolimus topical gel 3.9% once daily (QD) for 168 days and could then continue into an optional treatment extension, which included an optional pharmacokinetic maximal use substudy (PK-MUSt). The primary endpoint was the clinician-rated microcystic lymphatic malformation Investigator's Global Assessment (mLM-IGA; 7-point dynamic change scale). The key secondary endpoint was the microcystic lymphatic malformation Multicomponent Static Score (mLM-MCSS), assessed by a blinded Independent Endpoint Assessment Committee (IEAC).

RESULTS

Clinically Meaningful Improvement in the mLM-IGA Was Observed Across Pediatric Age Groups Through Day 168

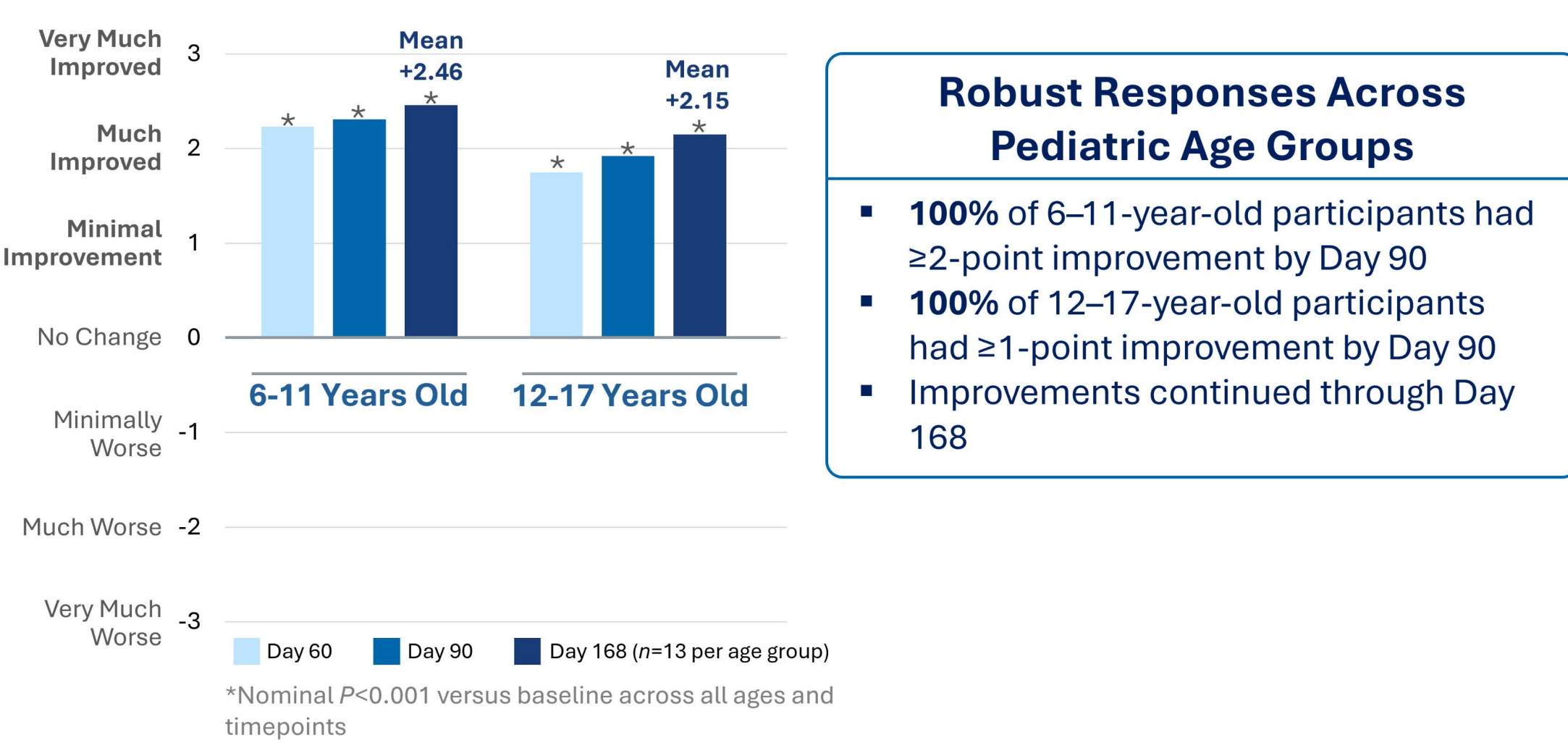


Figure 2. Clinically meaningful improvement in microcystic lymphatic malformation Investigator's Global Assessment (mLM-IGA) across pediatric age groups through Day 168. Mean change from baseline in mLM-IGA score was assessed at Days 60, 90, and 168 following once-daily treatment with investigational sirolimus topical gel 3.9%. Improvement was observed across all pediatric age groups through Day 168. Among participants aged 6–11 years, 100% ($n=13$) achieved ≥2-point improvement by Day 90, while 100% of participants ($n=13$) aged 12–17 years achieved ≥1-point improvement by Day 90. Clinically meaningful improvements were observed through Day 168. All mean changes from baseline were statistically significant (nominal $P<0.001$).

Blinded Review Showed Reduced Severity on a Combined Score of Lesion Height, Leaking/Bleeding, and Vesicles Across Pediatric Age Groups at Day 168

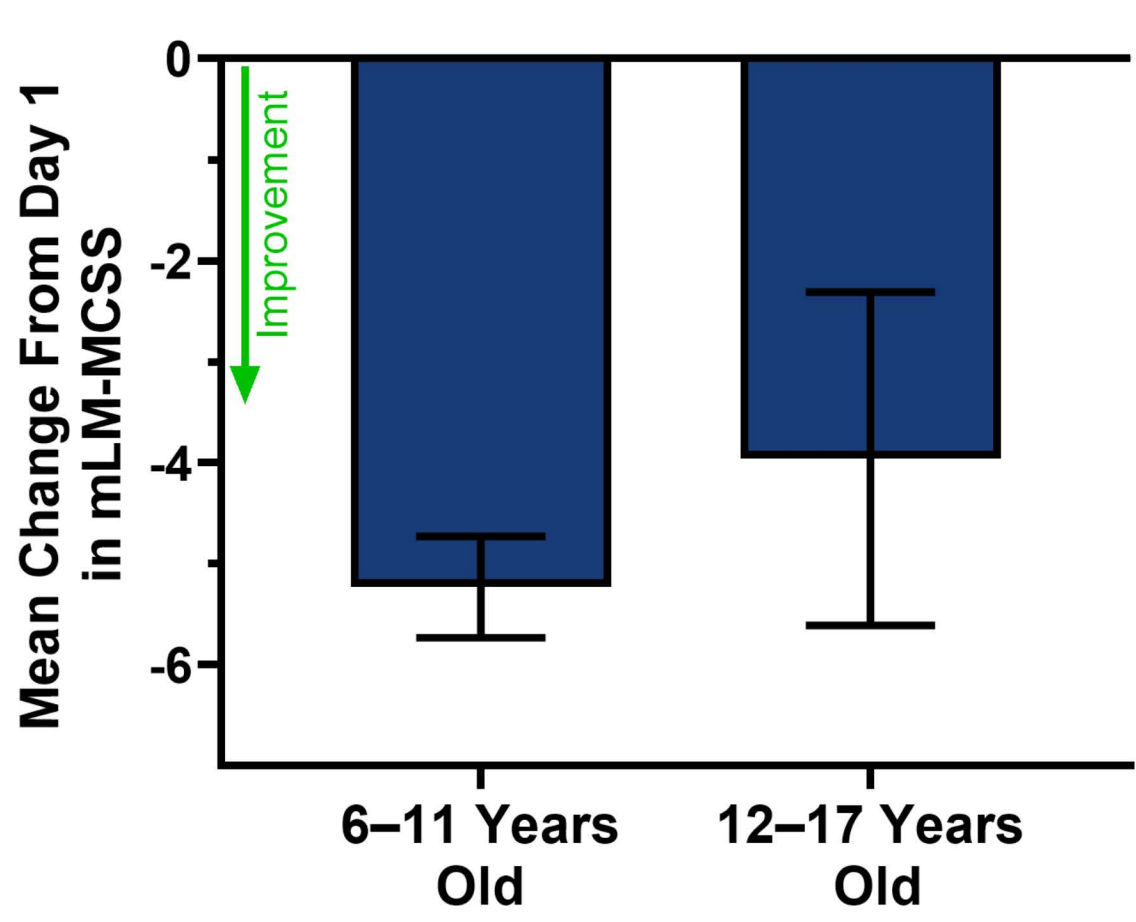


Figure 3. Reduced lesion severity in the microcystic lymphatic malformation Multicomponent Static Score (mLM-MCSS) across pediatric age groups at Day 168. Change from baseline to Day 168 in the mLM-MCSS was assessed from photographs by the blinded Independent Endpoint Assessment Committee in participants aged 6 to 11 years ($n=13$) and 12 to 17 years ($n=13$). The mLM-MCSS is the sum of lesion height, leaking/bleeding, and vesicle appearance scores (each rated 1 to 5; total range 3 to 15). Mean (95% CI) change was -5.23 ($-5.73, -4.73$) and -3.96 ($-5.61, -2.31$), respectively; negative values indicate improvement. Both changes were statistically significant versus baseline (nominal $P<0.001$).

Age 7, Female, mLM-IGA: +3 “Very Much Improved”

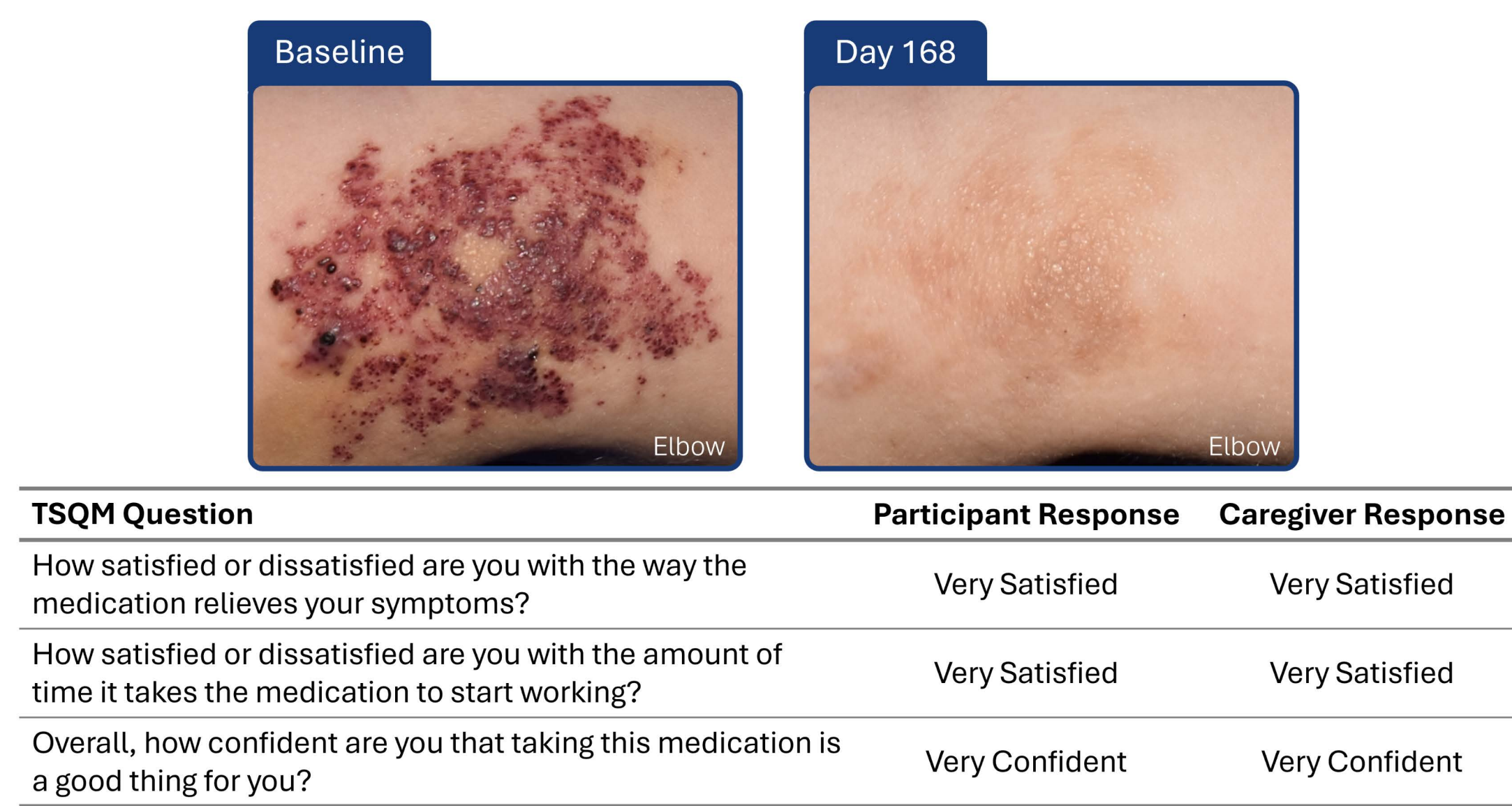


Figure 4. Clinical response in a pediatric participant with microcystic lymphatic malformation (mLM). Baseline and Day 168 images are shown for a 7-year-old female participant with an elbow mLM treated with once-daily investigational sirolimus topical gel 3.9%. Images were cropped to highlight the treatment area but were otherwise unaltered. This participant had a 3-point improvement in mLM-IGA (Very Much Improved) at Day 168. Participant and caregiver responses to the Treatment Satisfaction Questionnaire for Medication (TSQM) are shown. Photographic and questionnaire data are selected examples and are not intended to represent the results observed in all study participants. Conclusions regarding study outcomes should be based on the complete study dataset and prespecified analyses.

PATIENT JOURNEY

High treatment satisfaction was accompanied by a 98% rollover rate into the treatment extension

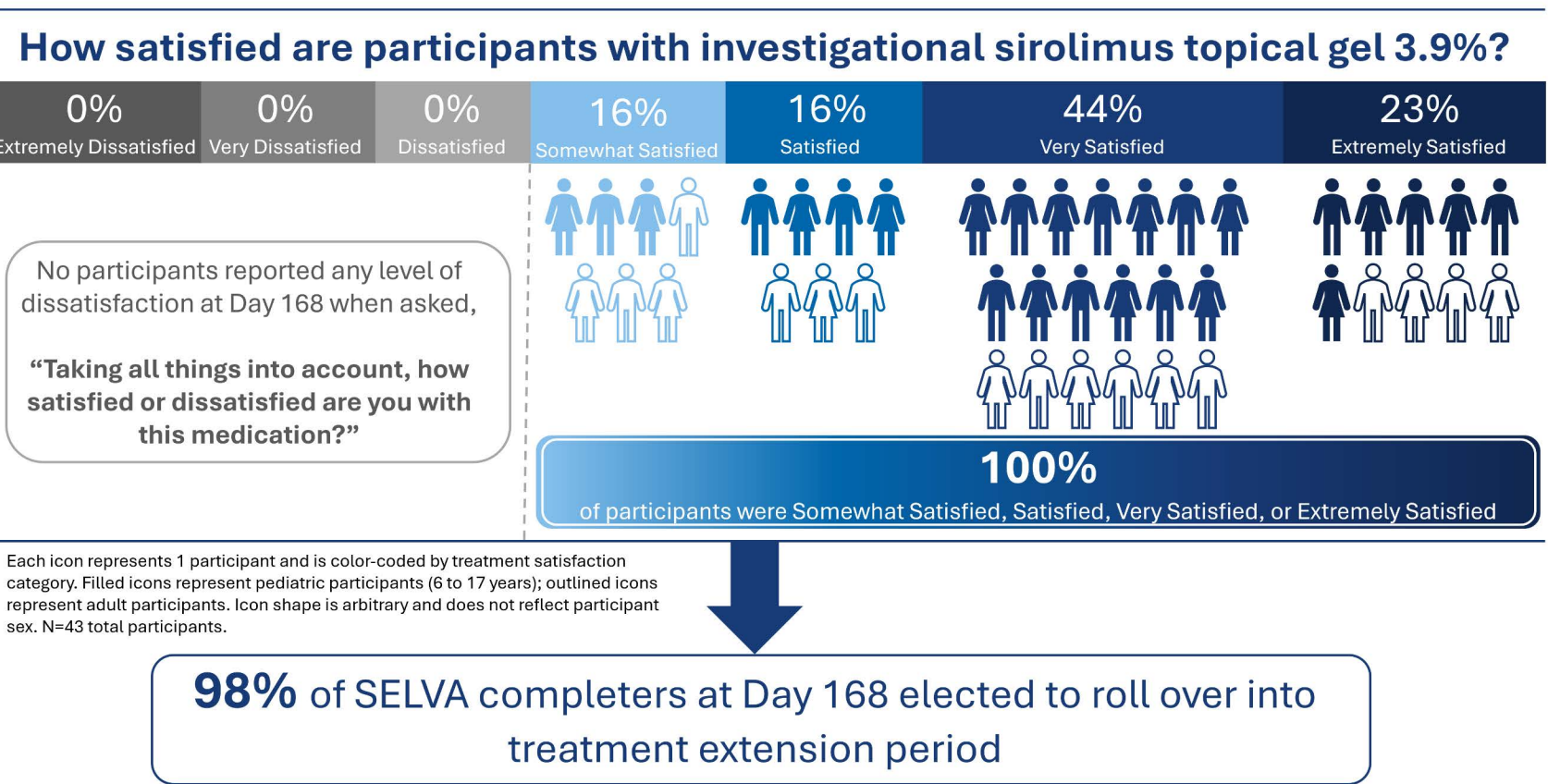


Figure 5. Treatment satisfaction among all participants receiving investigational sirolimus topical gel 3.9%. Satisfaction was assessed as a supportive endpoint using TSQM Item 9 at Day 168. Each icon represents 1 participant ($N=43$); filled icons represent pediatric participants (6 to 17 years; $n=26$), and outlined icons represent adult participants ($n=17$). Overall, 98% (43 of 44) of participants who completed the 168-day efficacy evaluation period elected to continue into the optional treatment extension.

SAFETY

Investigational sirolimus topical gel 3.9% was generally well tolerated; the most common adverse events were application-site reactions. All systemic sirolimus concentrations measured in the study were below 2 ng/mL.

CONCLUSIONS

- Investigational sirolimus topical gel 3.9% demonstrated clinically meaningful improvement in mLM-IGA in pediatric participants with mLM; 100% improved by Day 90.
- Improvements in mLM-IGA were observed by Day 60 and continued through Day 168. Blinded photographic review also showed reduced lesion severity at Day 168.
- Robust responses among pediatric participants are particularly meaningful given that mLMs typically present in childhood, persist throughout life, and are associated with substantial morbidity and treatment burden.
- All pediatric participants who completed the TSQM reported being at least somewhat satisfied with treatment.
- Investigational sirolimus topical gel 3.9% was generally well tolerated with minimal systemic sirolimus exposure.
- Overall, 98% of participants who completed Day 168 chose to continue treatment. Together with the tolerability and low systemic exposure observed, this supports the potential for long-term, chronic administration in children with mLM.

These data demonstrate the potential of investigational sirolimus topical gel 3.9% to provide a targeted, noninvasive therapeutic option for children with mLMs, addressing a significant unmet need in a disease with no approved medical therapies.

REFERENCES

- Teng, J.M.C., et al. "Sirolimus in the Treatment of Microcystic Lymphatic Malformations: A Systematic Review," *Lymphat Res Biol*, vol. 21, no. 2, pp. 101-110, 2023.
- Elluru, R.G., et al., "Lymphatic malformations: diagnosis and management," *Semin Pediatr Surg*, vol. 23, no. 4, pp. 178-185, 2014.
- Hathaway, B.A., et al., "Lymphatic and Mixed Malformations," *Lymphat Res Biol*, vol. 19, no. 1, pp. 41-50, 2021.
- Castillo, S.D., et al., "Somatic activating mutations in PIK3CA cause sporadic venous malformations in mice and humans," *Sci Transl Med*, vol. 8, no. 332, 2016.