Systemic Pharmacokinetics of Investigational Sirolimus Topical Gel 3.9% Under Maximal Use Conditions in Microcystic Lymphatic Malformations: Results From the Phase 3 SELVA PK-MuST

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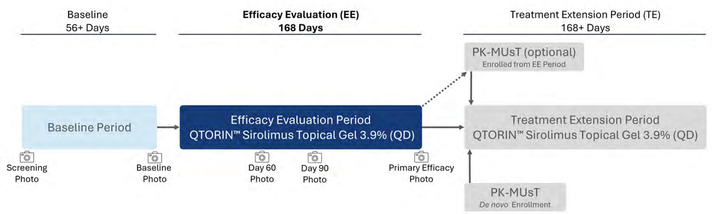
SYNOPSIS: Microcystic lymphatic malformations (mLM) are rare, serious, lifelong vascular anomalies with no FDA-approved therapies. Investigational sirolimus topical gel 3.9%, developed on the proprietary QTORIN™ platform, was engineered for sustained dermal penetration with limited systemic absorption. A pharmacokinetic maximal use substudy (PK-MuST), conducted as part of the Phase 3 SELVA trial, characterized systemic sirolimus exposure under maximal use conditions across a broad range of ages, disease severities, and treated lesion areas. Systemic concentrations remained low and stable over 24 hours, substantially below reported oral sirolimus therapeutic thresholds[1], supporting a favorable systemic exposure margin for investigational sirolimus topical gel 3.9% in patients with mLM. The Phase 3 SELVA trial met its primary endpoint, with 95% of participants achieving improvement at Day 168, and all secondary endpoints.

OBJECTIVE

To characterize the systemic pharmacokinetic profile of investigational sirolimus topical gel 3.9% under maximal use conditions and contextualize exposure relative to known oral sirolimus PK parameters[1].

METHODS



Entry pathway	Rollover (post-EE): 15 • Direct entry: 9 • Total: N=24
Age groups	5 children (6–<12y) • 4 adolescents (12–<18y) • 15 adults (≥18y)
Disease severity	Clear/almost clear to very severe
Lesion area treated	10–375 cm^2 (up to 3.57% BSA)
Dose	21 participants: 1 g (39 mg) QD• 3 participants: 2 g (78 mg) QD[1]

[1]*Dose adjusted for lesion size.*

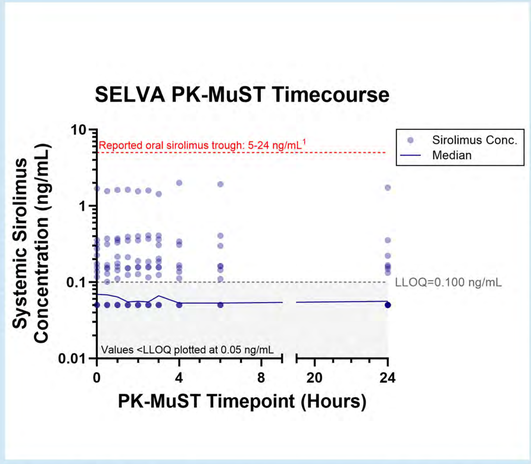
Figure 1. Phase 3 SELVA study design and PK-MuST participant characteristics. PK-MuST was an optional substudy that evaluated systemic sirolimus exposure at the upper bound of anticipated clinical use during the Phase 3 SELVA trial. Participants enrolled either after completing the Efficacy Evaluation Period or directly, 10–28 days after treatment initiation, and both groups continued on study drug during the Treatment Extension Period. Serial blood samples were collected on a single intensive PK sampling day and quantified using a validated, high-sensitivity LC-MS/MS assay (LLOQ 100 pg/mL), 20-fold more sensitive than standard commercial assays (LLOQ 2 ng/mL).

PK-MuST SUMMARY

Median (range)	Children (6 to <12 y) *n*=5	Adolescents (12 to <18 y) *n*=4	Adults (≥18 y) *n*=15	Overall N=24	*Oral Sirolimus Reference*[1]
AUC_{0-24} (ng·h/mL)	2.3 (0.7–11.9)	3.4 (0.2–42.5)	1.6 (0.6–9.4)	1.8 (0.2–42.5)	AUC_{0-24}=230-466
C_{trough} (ng/mL)	0.095 (0.031–0.495)	0.139 (0.010–1.766)	0.064 (0.026–0.391)	0.074 (0.010–1.766)	C_{trough}=5-24 ng/mL

Table 1. Systemic sirolimus exposure was low across all age groups. Pharmacokinetic parameters for all 24 PK-MuST participants, presented as median (range). AUC_{0-24}, C_{max}, and C_{trough} were estimated from a population PK model to account for the reduced sampling schedule in participants <12 years of age. Reference values for oral sirolimus are shown for context[1].

RESULTS



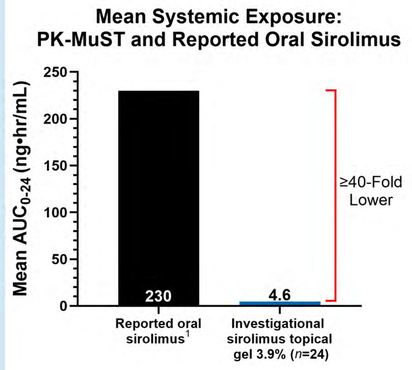


Figure 2. Systemic exposure was >40 fold lower with investigational sirolimus topical gel 3.9% versus reference levels for oral sirolimus. (Left) Individual sirolimus blood concentrations for 24 PK-MuST participants from predose through 24 hours postdose; participants <12 years (n=5) were sampled at predose, 1, and 3 hours per protocol. Values below the LLOQ (0.100 ng/mL; 63.5% of samples) are plotted at 0.05 ng/mL. Stable concentrations are consistent with slow dermal absorption. (Right) Mean sirolimus AUC_{0-24} for all PK-MuST participants with investigational sirolimus topical gel 3.9% (N=24) and the lowest reported oral sirolimus AUC_{0-24}[1]. Oral sirolimus was not evaluated in SELVA; oral values are from the US prescribing information[1] and reflect different studies and patient populations.

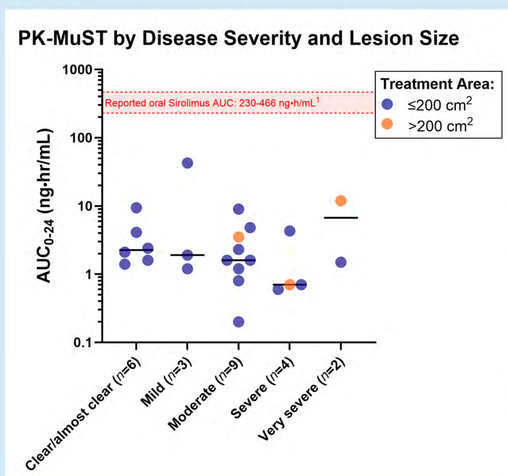


Figure 3. Systemic exposure did not increase with disease severity. Individual sirolimus AUC_{0-24} values by Clinical Global Impression of Severity (CGI-S) during PK-MuST, with group medians. Dosing was based on treatment area at study entry: ≤200 cm² (n=21), 1 g of investigational sirolimus topical gel 3.9% (39 mg sirolimus) daily; >200 cm² (n=3, orange), 2 g (78 mg sirolimus) daily. The highest exposure (42.5 ng·h/mL) occurred in a participant with mild disease.

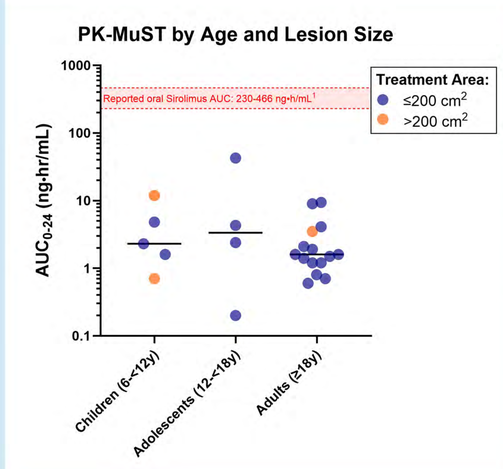


Figure 4. Systemic exposure was low across all age groups. Individual sirolimus AUC_{0-24} by age group, with group medians; orange indicates treatment area >200 cm². No clinically meaningful difference was observed by age or treatment area/dose. Reported oral sirolimus AUC_{0-24} is approximately 40- to 100-fold higher than mean systemic exposure following topical application[1].

CONCLUSIONS

- Mean systemic exposure (AUC_{0-24}) under maximal use conditions remained substantially below (at least 40-fold) that reported in the oral sirolimus USPI (230–466 ng·h/mL)[1], supporting a favorable systemic exposure for investigational sirolimus topical gel 3.9%.
- Most samples (63.5%) were below the LLOQ (0.100 ng/mL) of a validated, high-sensitivity assay 20-fold more sensitive than standard commercial assays (LLOQ 2 ng/mL).
- Systemic exposure was consistent across age, treatment area/dose, and disease severity.
- In the Phase 3 SELVA trial (N=59), most treatment-emergent adverse events (TEAEs) with investigational sirolimus topical gel 3.9% were mild or moderate in severity. The most common TEAEs were localized application site reactions; no serious adverse events were considered related to treatment, and there were no safety signals in clinical laboratory results, vital signs, or physical findings.
- The Phase 3 SELVA trial met its primary endpoint and all secondary endpoints. Together, these data support the potential of investigational sirolimus topical gel 3.9% as a targeted, non-invasive treatment option for patients with mLM, a rare, serious disease with no currently approved therapies.

DISCLOSURES AND FUNDING

Study funded by Palvella Therapeutics and FDA Orphan Products Development grant FD-R-08196-01-A1; ClinicalTrials.gov NCT06239480.

This poster's production and display were fully supported by Palvella Therapeutics.

REFERENCES

1. RAPAMUNE® (sirolimus oral solution and tablets, for oral use) [US prescribing information]. Pfizer; 2024.

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