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First-in-disease therapies for patients with rare skin diseases

Phase 2 TOIVA Topline Data in Cutaneous Venous Malformations
December 15, 2025

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Phase 2 TOIVA Topline Data: Today's Presenters

Wes Kaupinen
Founder and CEO

Jeff Martini, PhD
Chief Scientific Officer

Bohan Wei
VP Corporate Development &
New Product Planning

Michael Kelly, MD, PhD

Cleveland Clinic

- Pediatric hematologist-oncologist at Cleveland Clinic
- Study investigator in Phase 2 TOIVA study
- Member of Palvella Medical and Scientific Advisory Board

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Agenda

EXECUTIVE SUMMARY	Wes Kaupinen, Founder and CEO
DISEASE OVERVIEW	Michael Kelly, MD, PhD, Cleveland Clinic
PHASE 2 TOIVA TOPLINE RESULTS	Jeff Martini, PhD, CSO Michael Kelly, MD, PhD, Cleveland Clinic
SUMMARY	Wes Kaupinen, Founder and CEO
Q&A	

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QTORIN™ Rapamycin for Cutaneous Venous Malformations: Phase 2 TOIVA Topline Data

- **Achieved statistical significance on multiple pre-specified clinician-reported and patient-reported efficacy endpoints, including dynamic change endpoints and static severity endpoints**
  - **Overall Cutaneous Venous Malformations-Investigators' Global Assessment (cVM-IGA):** 7-point clinician-assessed change scale ranging from "Very Much Worse" (-3) to "Very Much Improved" (+3)
    - Mean effect size at week 12: **+1.5 (p<0.001)**
    - **73%** of participants (11/15 participants) demonstrated 1-point improvement or greater at Week 12
    - **67%** of participants (10/15 participants) rated as either "Much Improved" (+2) or "Very Much Improved" (+3) at Week 12
- **QTORIN™ rapamycin was generally well-tolerated, consistent with previous clinical trials**

Planned discussions with FDA in early 2026 regarding the potential for Breakthrough Therapy Designation and a Phase 3 pivotal study

Note: Statistical significance (p<0.05) is nominal as there was no adjustment for multiplicity amongst efficacy endpoints. Data analyzed per statistical analysis plan; Intent-to-Treat (ITT) population analyzed with no imputation of values for missing data.

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Dr. Michael Kelly, Cleveland Clinic

Michael Kelly, MD, PhD

Cleveland Clinic

Pediatric hematologist-oncologist at Cleveland Clinic

- One of the leading physician-scientists advancing modern, mutation-informed treatment paradigms in the vascular anomalies field
- Involved in over 100 clinical trials for novel oncology and vascular anomaly therapeutics
- More than two decades of clinical and research experience in care of patients with complex venous, lymphatic, and mixed vascular malformations
- Treated thousands of vascular anomaly patients, including those with cutaneous venous malformations and microcystic lymphatic malformations
- Clinical investigator in Phase 2 TOIVA trial evaluating QTORIN™ rapamycin for the treatment of cutaneous venous malformations
- Consultant to Palvella and investigator in the Phase 3 SELVA trial evaluating QTORIN™ rapamycin for microcystic lymphatic malformations

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QTORIN™ Rapamycin for
Cutaneous Venous Malformations

Disease Overview

Dr. Michael Kelly,
Cleveland Clinic

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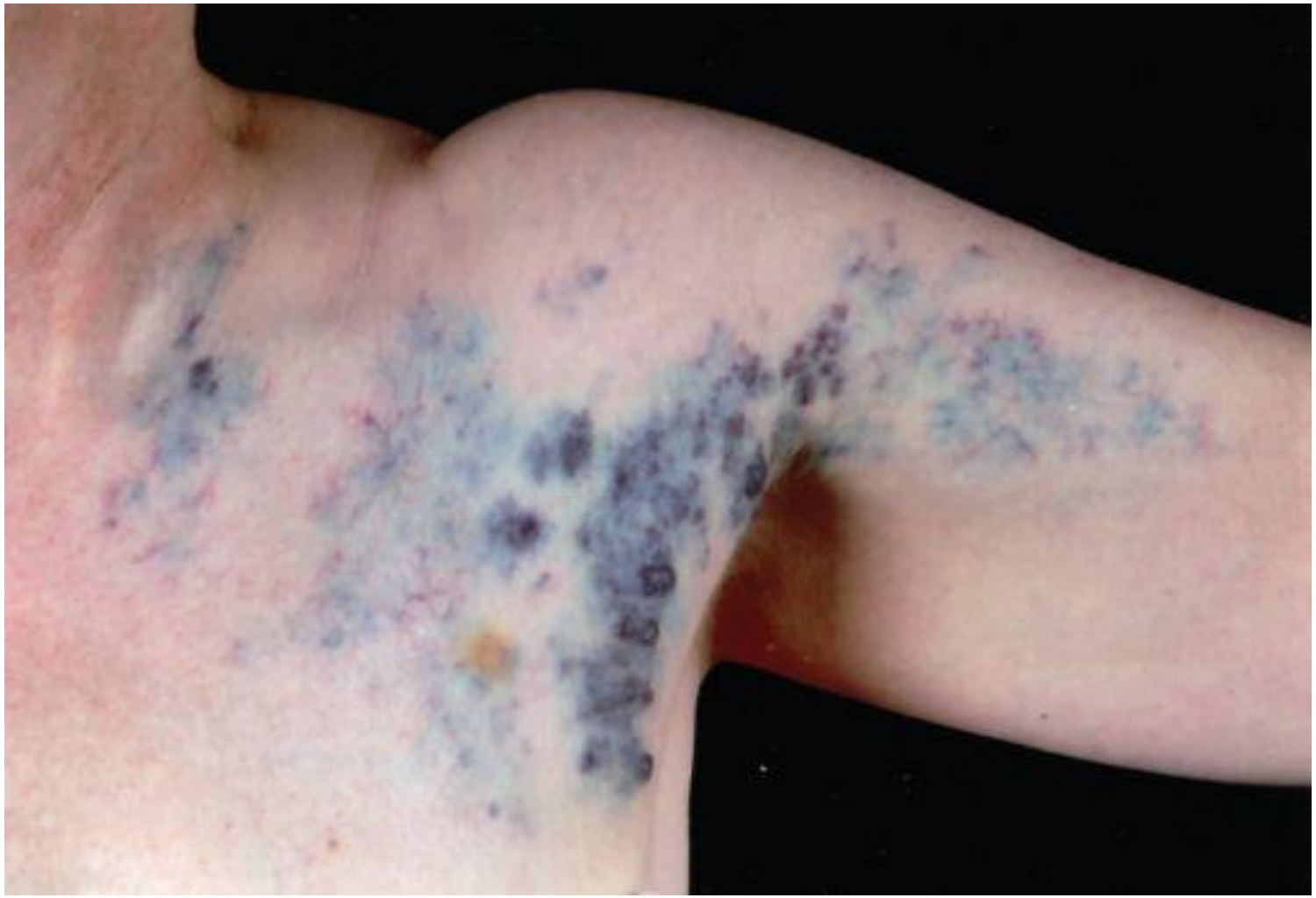
Cutaneous Venous Malformations: High Unmet Medical Need



One of the most significant unmet medical needs in vascular malformations field

Most common vascular malformation, affecting estimated > 75k patients in the U.S.[1]

Chronic, lifelong disease course

1. Gallagher et al, *Orphanet Journal of Rare Diseases*, (2025).

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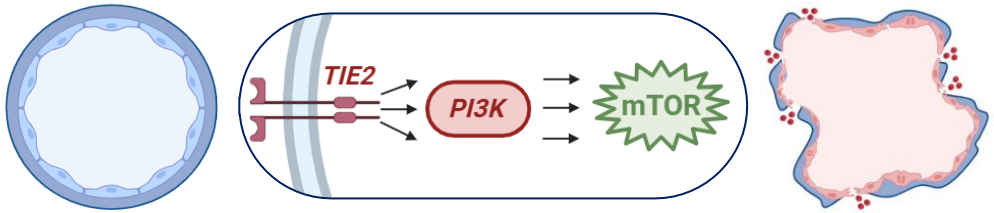
Cutaneous Venous Malformations: Relentless Cycle of Microthromboses and Functional Loss

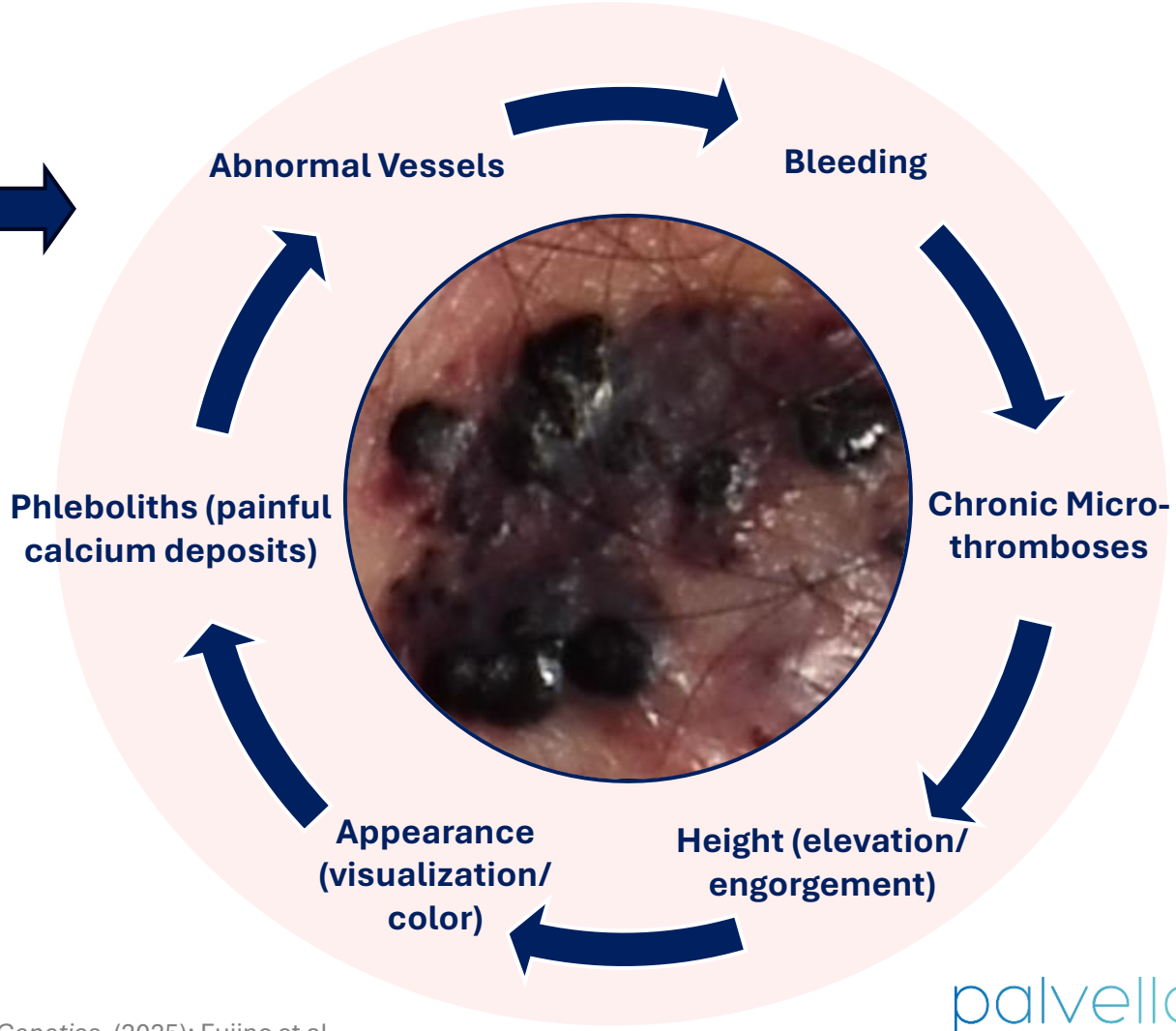
TEK/PIK3CA/Other VM Mutations



mTOR Hyperactivation

Endothelial Dysfunction

No Spontaneous Regression



Therapeutic goal: slow/halt the biological progression and/or improve clinical signs of disease

Sources: Eng et al, *American Journal of Medical Genetics Part C: Seminars in Medical Genetics*, (2025); Fujino et al, *Lymphatic Research and Biology*, (2024); Hirose et al, *Human Pathology*, (2024).

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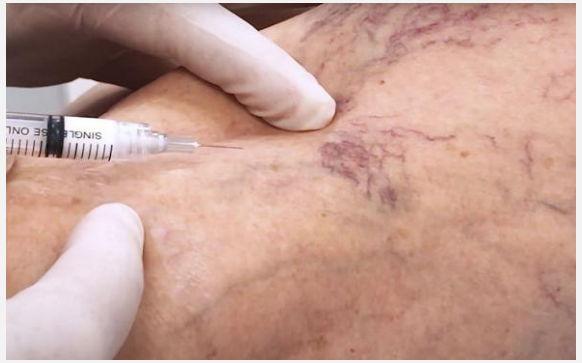
Constitutively Active Biological Signaling is Not Addressed by Non-specific, Episodic Treatments

Sclerotherapy

Laser

Surgery



- ☒ **Does not address underlying causal biology of disease**
- ☒ **Highly invasive and traumatic**
- ☒ **Any improvement likely to be limited and short-term**

Disease will reliably recur, often more extensively than before

Sources: Ali S, Mitchell SE *Semin Intervent Radiol*. 2017 Sep;34(3):288-293; Hassanein, AH, *Plastic and Reconstructive Surgery* 125(6):p 48, June 2010.
Image Source: Vein Health Medical Clinic.

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QTORIN™ Rapamycin for
Cutaneous Venous Malformations

Phase 2 TOIVA Topline Results

Dr. Jeff Martini, Chief Scientific Officer
Dr. Michael Kelly, Cleveland Clinic

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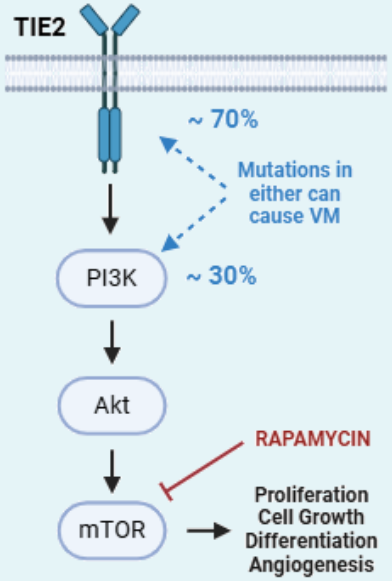
Venous Malformations: Progress Towards the Potential First Targeted Therapy for Unaddressed Cutaneous Disease

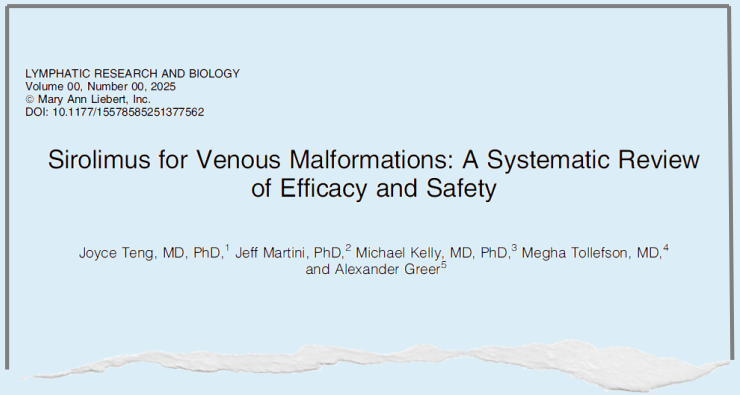
Known Genetics / Clear Biology



Plausible mechanism

Limaye et al (2009, 2015)

Real-world Evidence



Real-world evidence supports rapamycin's off-label use in primarily internal manifestations of VMs…

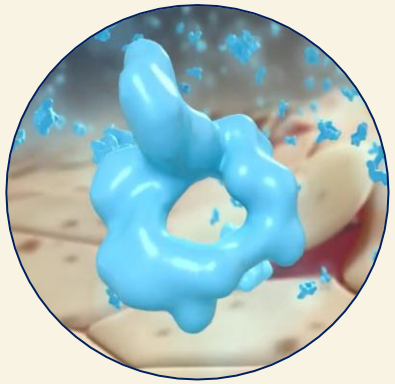
…however, poor patient outcomes persist in cutaneous disease

Teng et al (2025)

On Target, In Tissue

QTORIN™

RAPAMYCIN



3.9% concentration
Dermal penetration
Extensive CMC package

Phase 2 TOIVA Data (2025)

QTORIN™ 3.9% rapamycin anhydrous gel is for investigational use only and has not been approved or cleared by the FDA or by any other regulatory agency. The safety or efficacy has not been established for any use.

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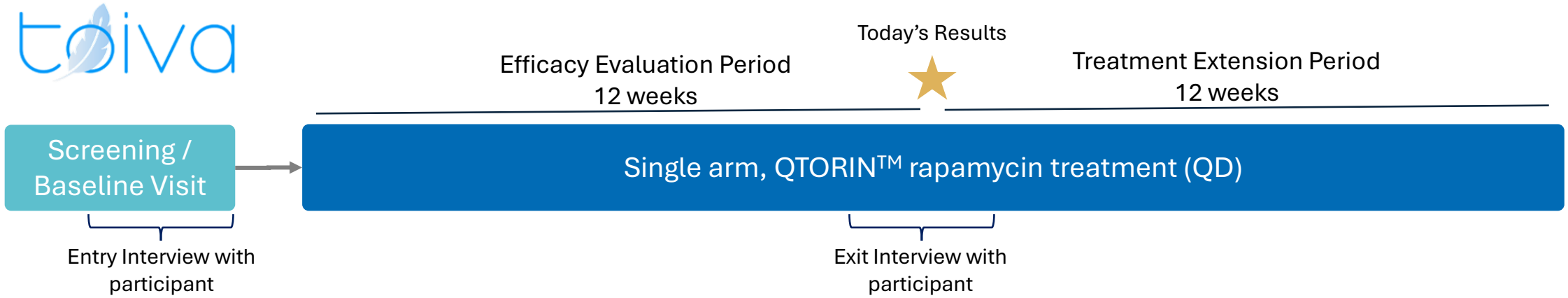
Phase 2 TOIVA Study in cVMs: 24-Week Study

Single-arm, baseline-controlled, QD dose, age 6+



Safety and Tolerability

Efficacy (no pre-specified primary endpoint): cVM-IGA (7-point clinician change scale), cutaneous VM multi-component static scale (cVM-MCSS), other clinician- and patient-reported outcomes

Statistics: Intent-to-Treat (ITT) population, based on available data at each time point and analyzed per statistical analysis plan

Key Entry Criteria: Enriched for patients with cutaneous disease and confirmed by third party eligibility consult team; genetics not required

Enrollment: 16 participants enrolled and dosed; 1 dosed participant lost to follow up

Sites: Mayo Clinic; Cleveland Clinic; Children's Hospital of Philadelphia; Stanford Medicine; UCI; Children's Hospital Colorado; Children's Healthcare of Atlanta; Johns Hopkins Medicine; University of Utah Health; UNC Health; Minnesota Clinical Study Center

Note: Statistical significance ($p<0.05$) is nominal as there was no adjustment for multiplicity amongst efficacy endpoints. Data analyzed per statistical analysis plan; ITT analyzed with no imputation of values for missing data.

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Statistically Significant Improvements on Dynamic Change Scales

Note: 7-point scales ranging from -3 to +3; positive values indicate improvements from baseline	**Participants (n=15) at Week 12** Mean Change / p-value
Overall Cutaneous Venous Malformations Investigator Global Assessment (cVM-IGA)	**+1.5** ($p < 0.001$)
cVM-IGA Height/Engorgement	**+1.3** ($p < 0.001$)
cVM-IGA Appearance *(visualization/color of affected veins)*	**+1.5** ($p < 0.001$)
cVM-IGA Bleeding	**+0.7** ($p = 0.045$)
Overall Patient Global Impression of Change (PGI-C)	**+1.1** ($p < 0.001$)

Note: Statistical significance ($p<0.05$) is nominal as there was no adjustment for multiplicity amongst efficacy endpoints. Data analyzed per statistical analysis plan; ITT analyzed with no imputation of values for missing data.
cVM-IGA Ulceration assessed with no disease present at baseline.

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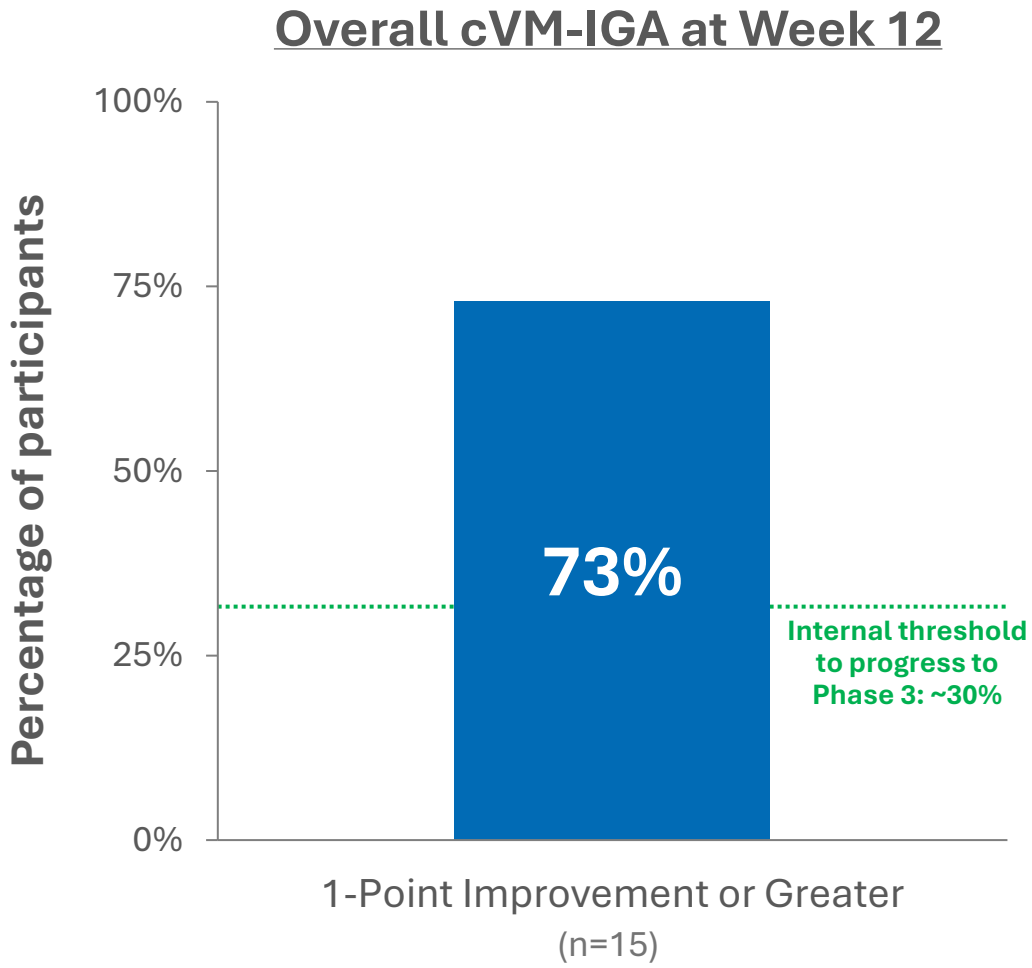
Overall cVM-IGA: 73% of Participants Demonstrated Improvement at Week 12

Single-arm, baseline-controlled, QD dose, age 6+



- **Overall cVM-IGA:** 7-point clinician-assessed dynamic change scale ranging from “Very Much Worse” (-3) to “Very Much Improved” (+3)
  - Mean effect size at week 12: **+1.5 (p<0.001)**
- **73%** of participants (11/15 participants) demonstrated at least a 1-point improvement on the Overall cVM-IGA at Week 12
- **67%** of participants (10/15 participants) were rated as either “Much Improved” (+2) or “Very Much Improved” (+3) on the Overall cVM-IGA at Week 12; represented in these 10 participants were:
  i. Genetically confirmed TEK mutations
  ii. Genetically confirmed PIK3CA mutations
  iii. Non-TEK/PIK3CA mutation or unconfirmed genotype
- Based on analysis of data at Week 12, the Company does not anticipate requiring confirmed genotypes or genetic testing in future studies

Note: Statistical significance (p<0.05) is nominal as there was no adjustment for multiplicity amongst efficacy endpoints. Data analyzed per statistical analysis plan; ITT analyzed with no imputation of values for missing data.
1. Genetic testing was not required as part of the protocol; Palvella is continuing efforts to collect genetic data on trial participants.

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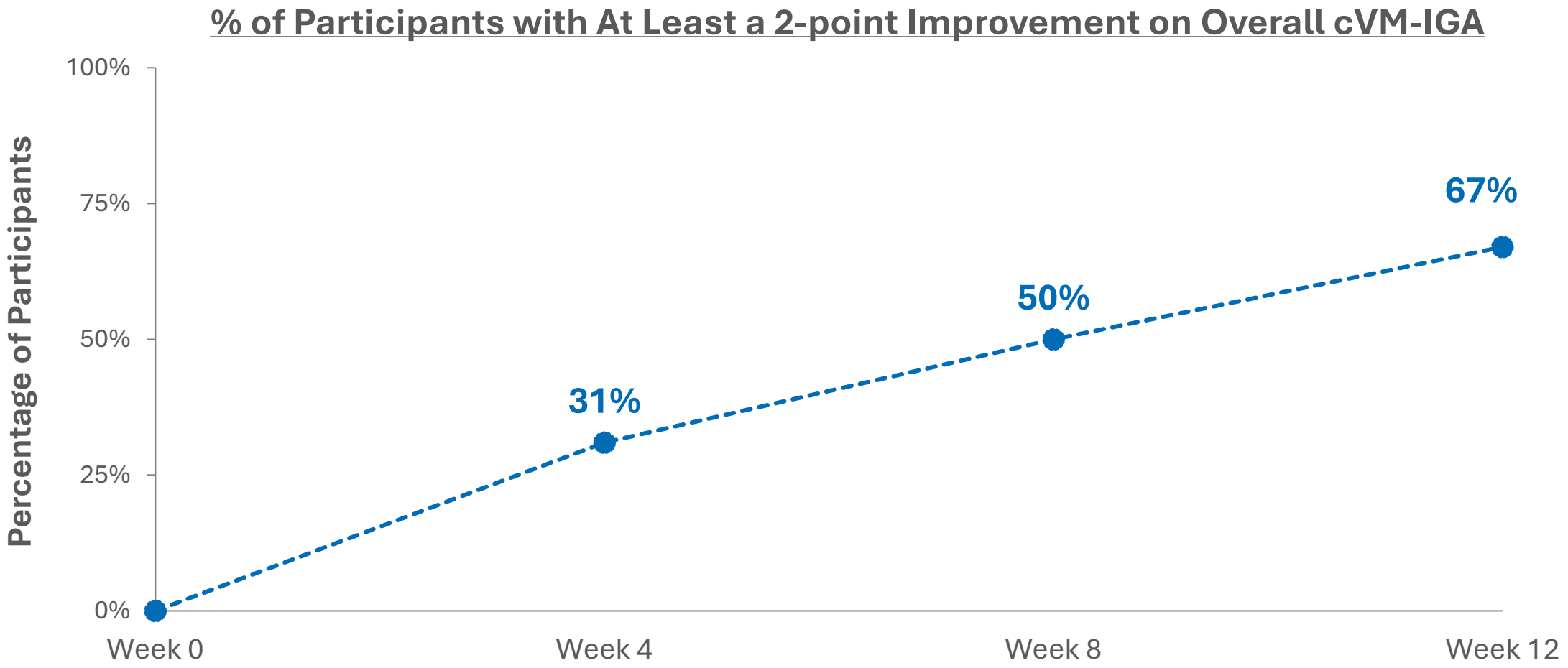
Overall cVM-IGA: Rapid, Time Dependent Response Observed

Single-arm, baseline-controlled, QD dose, age 6+



Note: Statistical significance ($p<0.05$) is nominal as there was no adjustment for multiplicity amongst efficacy endpoints. Data analyzed per statistical analysis plan; ITT analyzed with no imputation of values for missing data.

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Statistically Significant Improvements on Key Static Severity Scales

Note: 5-point scales ranging from 1 to 5; negative values indicate improvements from baseline	**Participants (n=15) at Week 12** Mean Change / p-value
Overall Clinician Global Impression of Severity (CGI-S)	**-1.0** ($p < 0.001$)
cVM-MCSS (Cutaneous VM Multi-Component Static Scale) Severity of Height/Engorgement	**-1.3** ($p < 0.001$)
cVM-MCSS Severity of Appearance *(visualization/color of affected veins)*	**-1.1** ($p < 0.001$)
Overall Patient Global Impression of Severity (PGI-S)	**-0.5** ($p = 0.027$)

Note: Statistical significance ($p<0.05$) is nominal as there was no adjustment for multiplicity amongst efficacy endpoints. Data analyzed per statistical analysis plan; ITT analyzed with no imputation of values for missing data.
CGI-S Ulceration assessed with no disease present at baseline. CGI-S Bleeding assessed with limited disease present at baseline.

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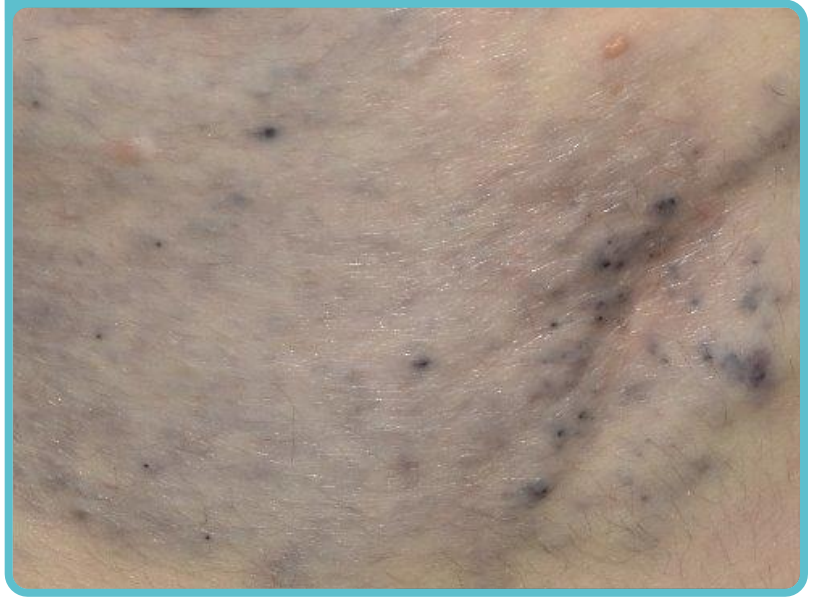
Phase 2 Results: Visible Improvement

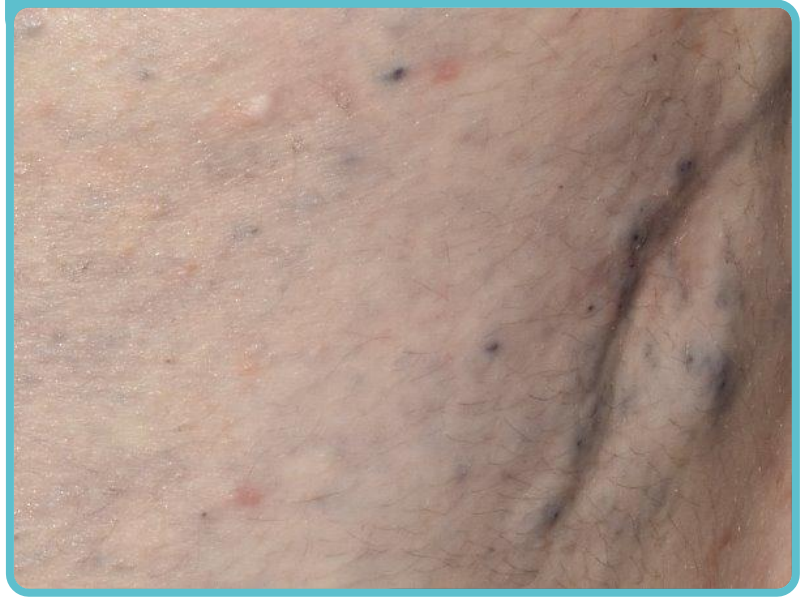
Site: CHOP
Investigator: Dr. Denise Adams

Participant Age: 17
Mutation: TEK
cVM-IGA at Week 12:
Very Much Improved (+3)

Baseline



Week 12



Participant Qualitative Interview: *"I've definitely noticed some improvements…it's definitely had a positive effect…It's more comfortable to wear a bra now…I've had less pain in that specific area"*

Note: Selective photos.

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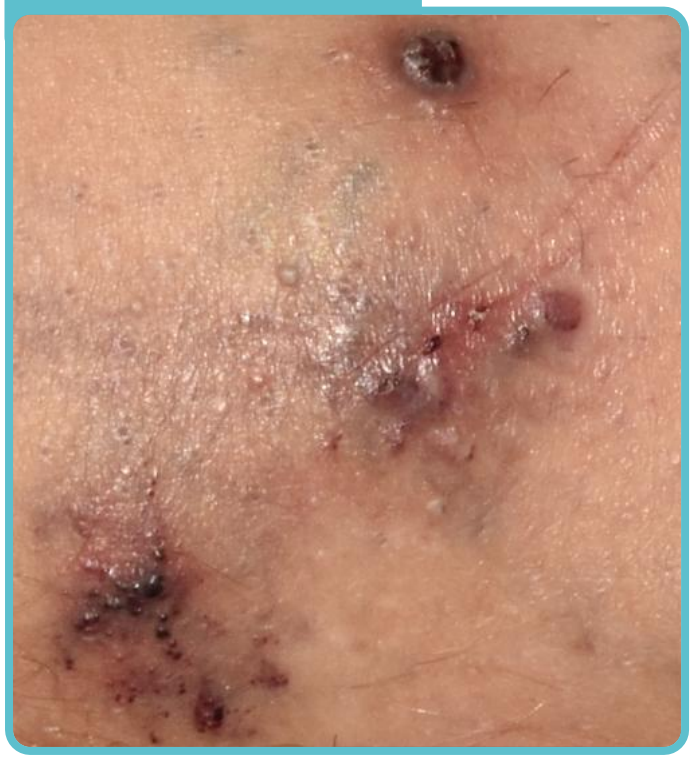
Phase 2 Results: Visible Improvement

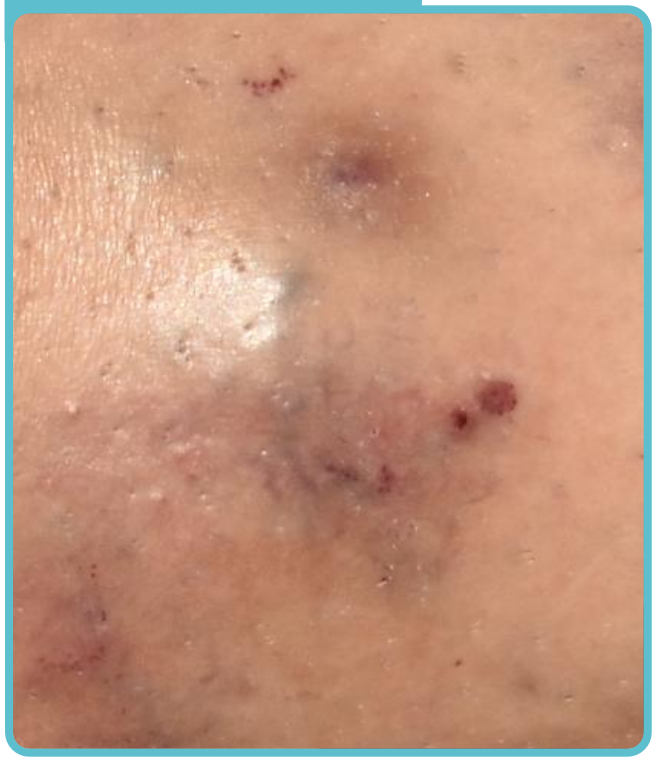
Site: Cleveland Clinic
Investigator: Dr. Michael Kelly

Participant Age: 13
Mutation: PIK3CA
cVM-IGA at Week 12:
Much Improved (+2)

Baseline



Week 12



Participant Qualitative Interview: *"It's slowed down bleeding and the color has changed…There's a bump on my leg that went away…it shrunk in size and now it's not there really"*

Note: Selective photos.

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Phase 2 Results: Safety and Tolerability

- QTORIN™ rapamycin was generally well-tolerated, similar to previous clinical trials
- Most common Treatment-Emergent Adverse Events were application site reactions (erythema, 25%)
- All Treatment-Related Adverse Events were moderate or mild (no severe events)
  - Majority of AEs were mild
  - No SAEs related to study drug
  - No unexpected AEs

Rapamycin levels were below the lower limit of quantification (2 ng/mL) in systemic circulation on a standard lab assay for all participants at all timepoints in the study

Significantly below 5 ng/mL which is the lower boundary where rapamycin begins to exert immunosuppressive effects

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QTORIN™ Rapamycin for
Cutaneous Venous Malformations

Summary

Wes Kaupinen
Chief Executive Officer

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QTORIN™ Rapamycin has the Potential to Be the First FDA-Approved Therapy for Cutaneous Venous Malformations

1. Achieved statistical significance on multiple pre-specified clinician-reported and patient-reported efficacy endpoints, including **73% of participants (11/15 participants) demonstrated a 1-point improvement or greater on Overall cVM-IGA at Week 12**

2. Planning for near-term discussions with **FDA regarding potential for Breakthrough Therapy Designation and a Phase 3 pivotal study,** as well as the newly announced Plausible Mechanism Pathway

3. QTORIN™ rapamycin has the **potential to become the first FDA-approved therapy and standard of care** for the estimated more than 75,000 individuals with cutaneous venous malformations in the U.S.

The Phase 2 results further support Palvella's "pipeline-in-a-product" strategy for QTORIN™ rapamycin, with programs advancing in microcystic LMs, cVMs, and angiokeratomas

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Thank You

Striving to be first for rare disease patients

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