

Phase 2 TOIVA: Overall Disease Severity and Lesion Bleeding Were Reduced in Pediatric Participants With Cutaneous Venous Malformations Treated With Investigational QTORIN™ Sirolimus Topical Gel 3.9%

Maria Gnarra Buethe¹, Megha Tollefson², Michael Kelly³, Steve Kempers⁴, Jeffrey Martini⁵, Kristen Kahle⁵, Eduardo Weiss⁶, Taizo Nakano⁷, Sally Cohen-Cutler⁸, Denise Adams⁸, Elizabeth Nieman⁹, Amy Theos¹⁰, Joyce M.C. Teng¹¹

¹ University of California, Irvine; ² Mayo Clinic and Mayo Clinic Children's Rochester; ³ Cleveland Clinic; ⁴ Minnesota Clinical Study Center; ⁵ Palvella Therapeutics; ⁶ International Dermatology Research; ⁷ Children's Hospital of Colorado; ⁸ Children's Hospital of Philadelphia; ⁹ University of North Carolina at Chapel Hill, Department of Dermatology; ¹⁰ University of Utah; ¹¹ Stanford University, Lucile Packard Children's Hospital

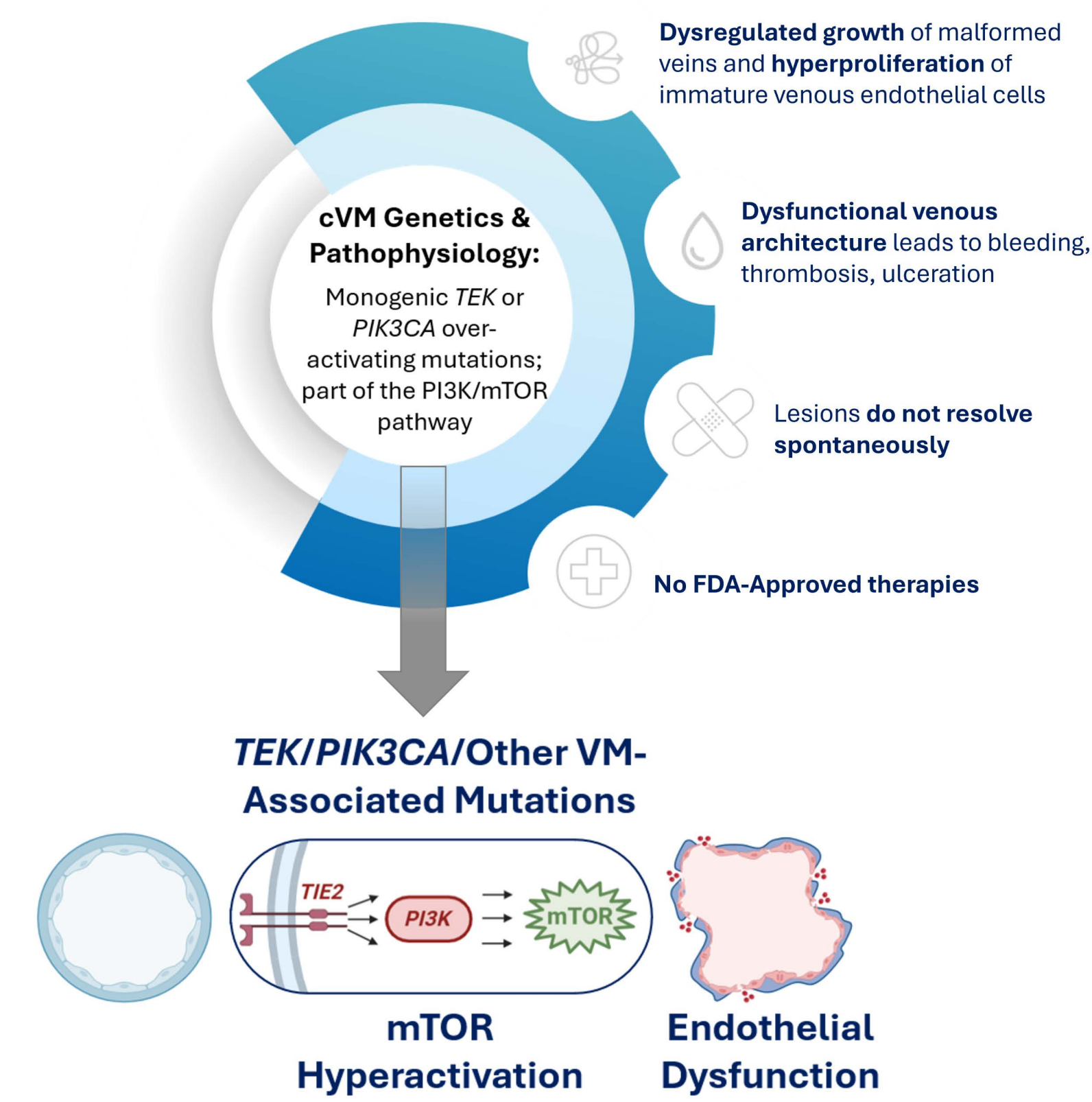
INTRODUCTION

Cutaneous venous malformations (cVMs) are rare, progressive vascular anomalies caused most commonly by somatic activating mutations in *TEK* or *PIK3CA*, leading to hyperactivation of the PI3K/mTOR signaling pathway. Dysregulated mTOR signaling promotes abnormal venous endothelial proliferation, impaired vessel maturation, and progressive lesion enlargement, venous stasis, thrombosis, bleeding, pain, and functional impairment^{1,2}.

cVMs frequently present during childhood and do not spontaneously regress³, resulting in cumulative disease burden over a patient's lifetime. Despite substantial morbidity, there are currently no FDA-approved pharmacologic therapies, and management remains largely dependent on invasive procedural interventions including surgery, sclerotherapy, laser therapy, and cryotherapy, which are associated with procedural morbidity, scarring, incomplete responses, and high rates of recurrence¹.

Investigational QTORIN™ sirolimus topical gel 3.9% is a novel topical formulation designed to locally inhibit mTOR signaling within affected skin while minimizing systemic exposure.

Cutaneous Venous Malformations: Serious, High Unmet Need



OBJECTIVE

The objective of this analysis was to characterize the clinical response to investigational QTORIN™ sirolimus topical gel 3.9% in pediatric participants (6–17 years) enrolled in the Phase 2 TOIVA study, including changes in lesion bleeding.

REFERENCES

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2. Hammer J, et al. Sirolimus is efficacious in treatment for extensive and/or complex slow-flow vascular malformations: a monocentric prospective phase II study. *Orphanet J Rare Dis*. 2018 Oct 29;13(1):191.

3. Kato M, Watanabe S, Kato R, Kawashima H, Iida T, Watanabe A. Spontaneous Regression of Lymphangiomas in a Single Center Over 34 Years. *Plast Reconstr Surg Glob Open*. 2017 Sep 25;5(9):e1501.

CLINICAL STUDY DESIGN AND RESULTS

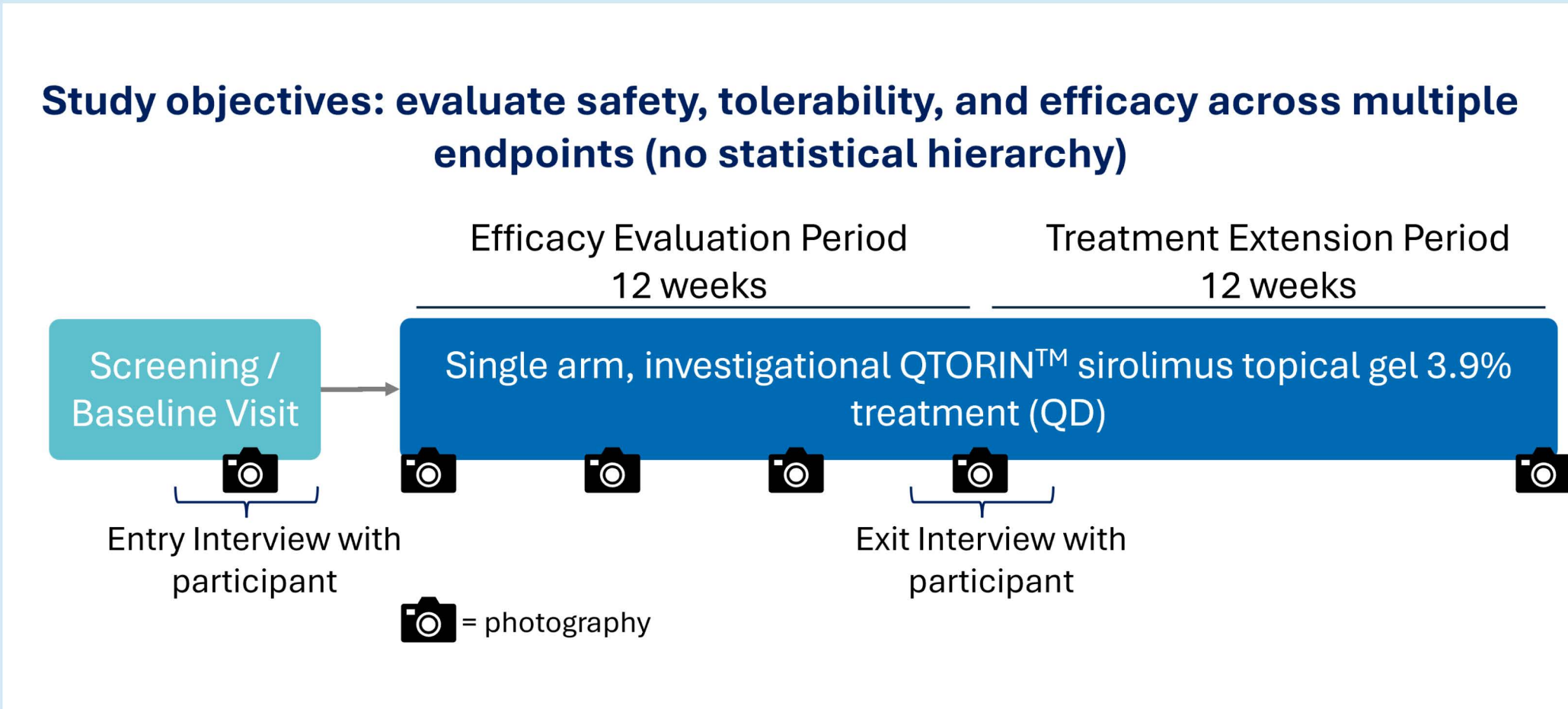


Figure 1. TOIVA Phase 2 study design. The single-arm, baseline-controlled design is appropriate for a rare, serious condition such as cVM, which has a well-characterized natural history and no spontaneous improvement^{1,3}. Participants applied investigational QTORIN™ sirolimus topical gel 3.9% once daily for a 12-week efficacy evaluation period, followed by a 12-week treatment extension. Prespecified outcomes (no statistical hierarchy) included the cVM Investigator Global Assessment (cVM-IGA; 7-point dynamic change scale) and Clinician Global Impression of Severity (CGI-S), with photographs taken at multiple timepoints.

Clinically Meaningful Overall Improvement Observed in Pediatric Participants by Week 12, Sustained Through Week 24

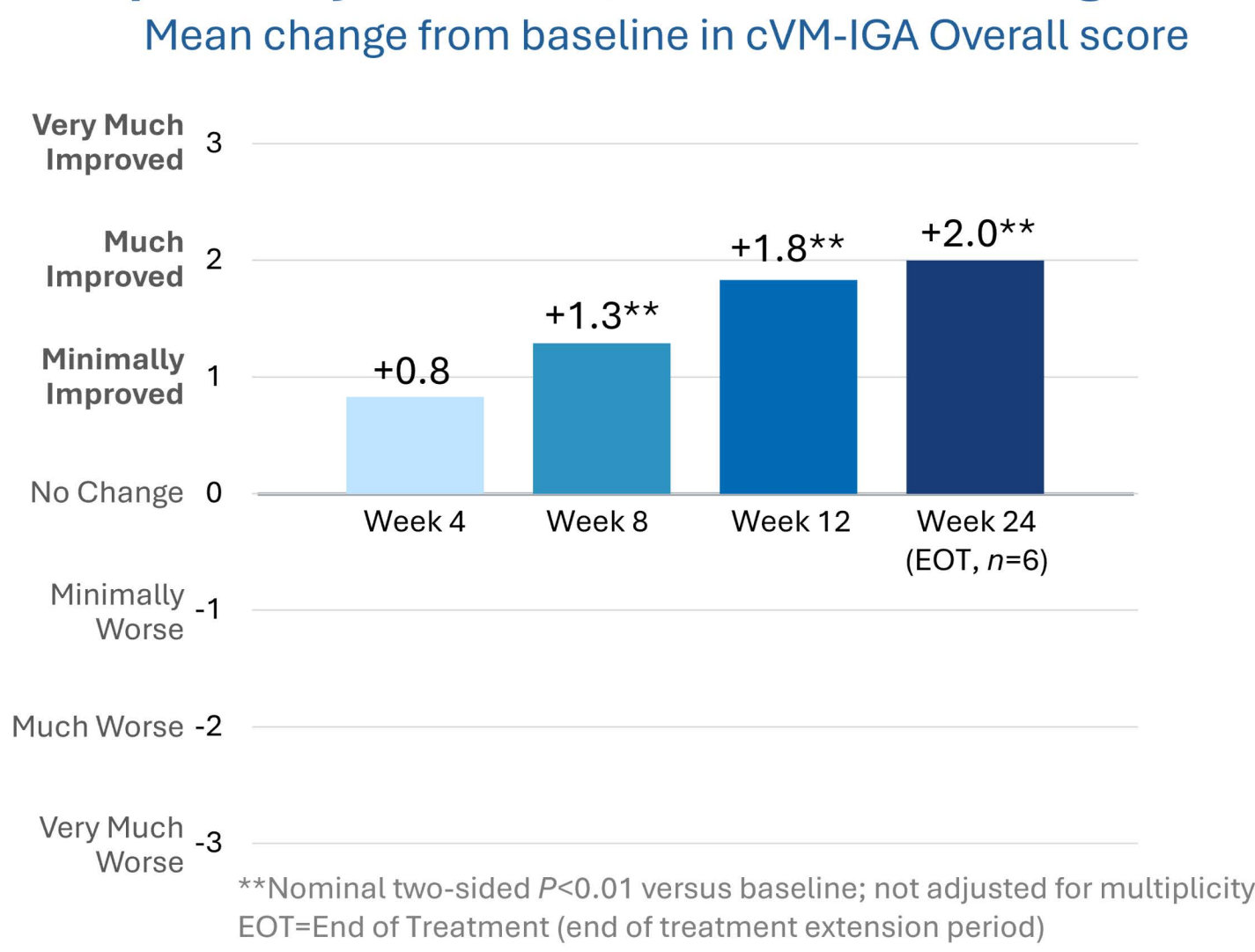


Figure 2. Mean change in cVM Investigator Global Assessment (cVM-IGA) over time in pediatric participants (n=7). Mean change from baseline in cVM-IGA Overall score is shown for pediatric participants (6–17 years) at Weeks 4, 8, 12 (end of efficacy evaluation period), and 24 (end of treatment extension period) of once-daily treatment with investigational QTORIN™ sirolimus topical gel 3.9%; positive values indicate improvement. One pediatric participant missed the Week 4 visit, and another was lost to follow-up after Week 8. At baseline, 4 of 7 participants had severe disease on the CGI-S; by Week 24, 5 of 6 were rated mild. Mean cVM-IGA scores improved versus baseline beginning at Week 8, and 5 of 6 participants were Much Improved or Very Much Improved at Weeks 12 and 24.

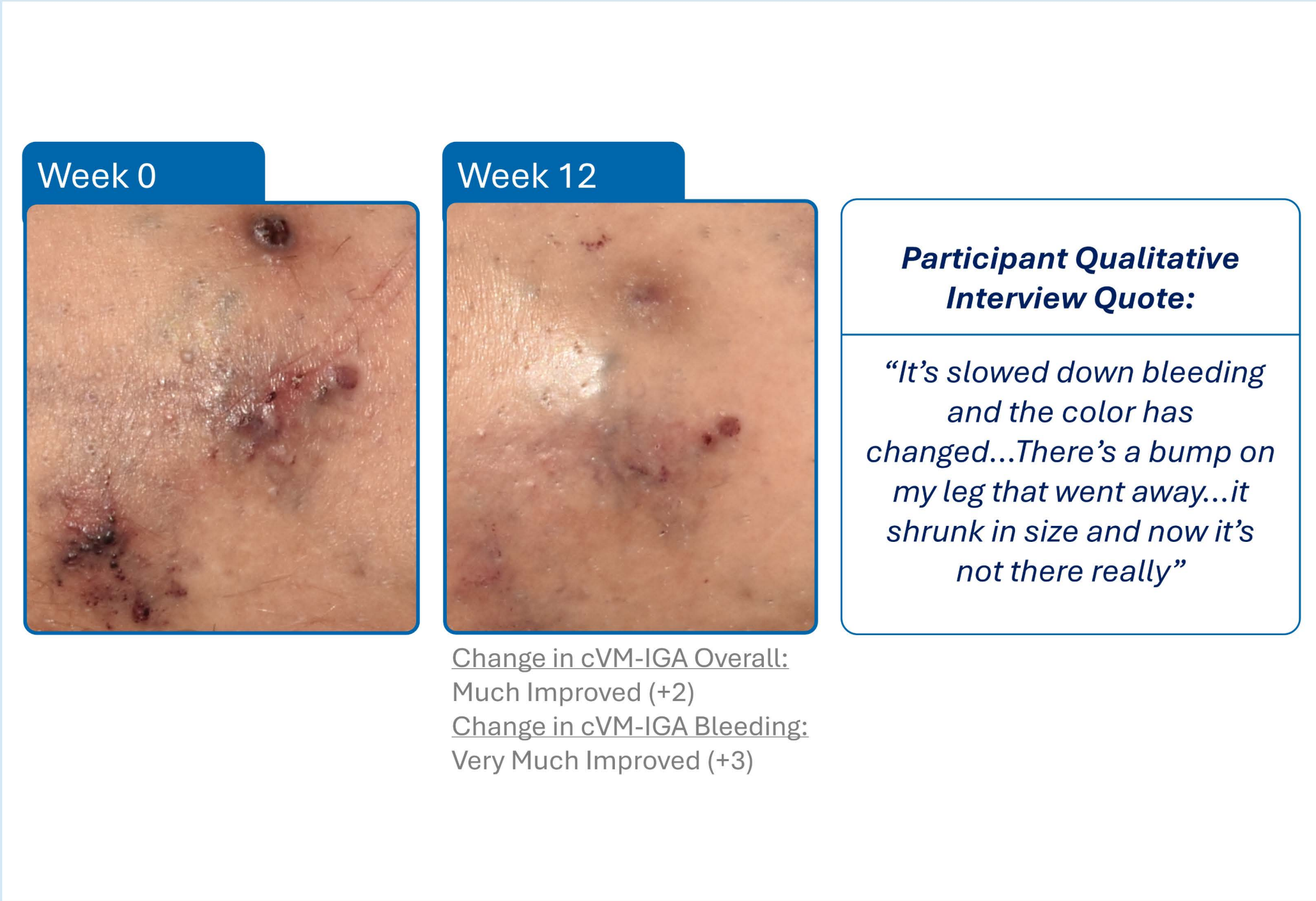


Figure 3. Reduced bleeding and visibly improved lesions in a 13-year-old with cVM. Baseline (Week 0) and Week 12 images are shown for a 13-year-old male participant with a confirmed *PIK3CA* mutation and cVM lesions on the lower leg. Images were cropped to highlight the treatment area but were otherwise unaltered. Improvements in lesion appearance, height/engorgement, and bleeding at Week 12 resulted in a 2-point improvement in cVM-IGA Overall score and a 3-point improvement in cVM-IGA Bleeding score for this participant, who is also included in Figure 4. Photographic and interview 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 OUTCOMES

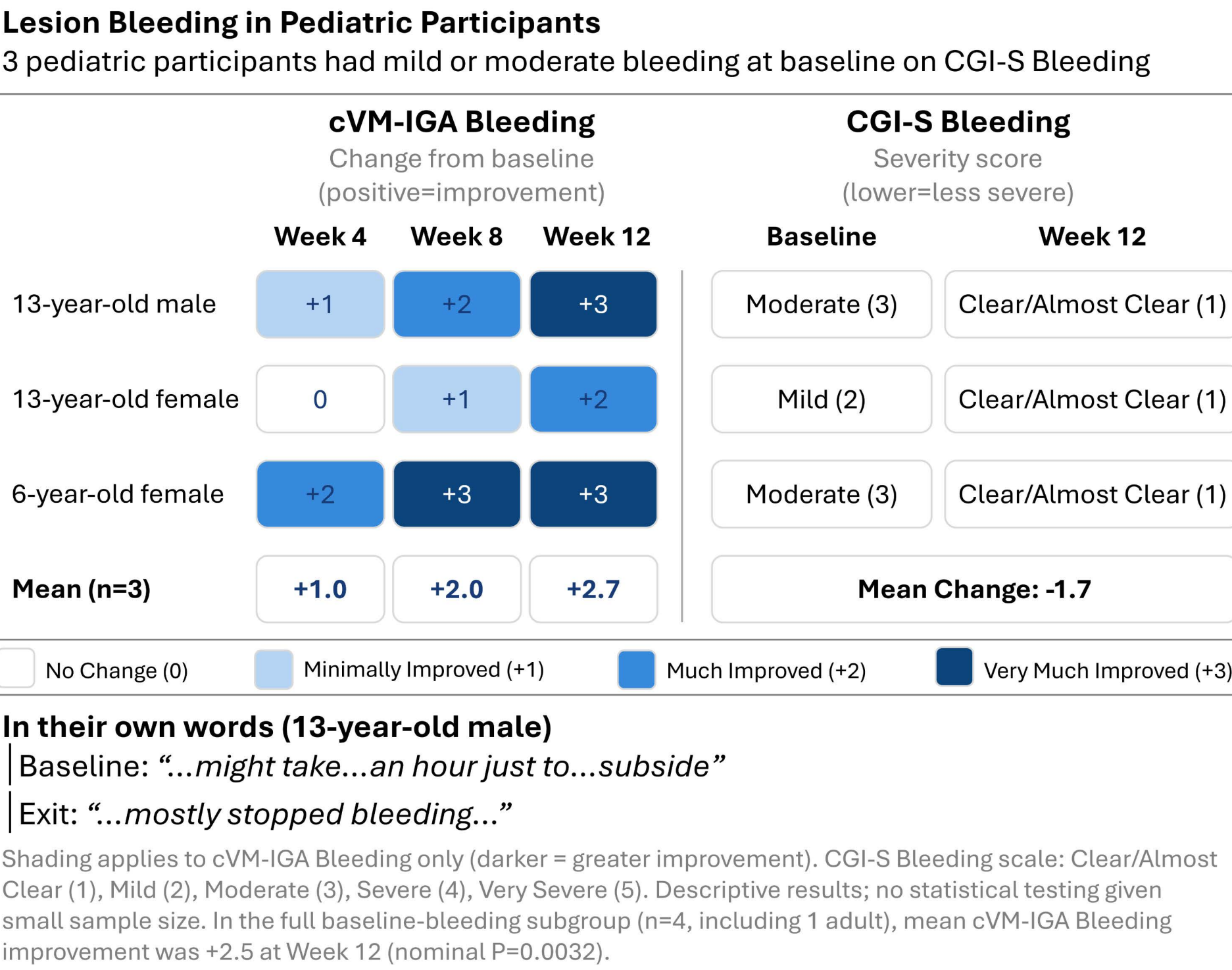


Figure 4. Lesion bleeding in pediatric participants with baseline bleeding. Changes from baseline in individual cVM-IGA Bleeding and CGI-S Bleeding scores are shown for the 3 pediatric participants with mild or moderate bleeding at baseline. At Week 12, all 3 participants were rated Much Improved or Very Much Improved on cVM-IGA Bleeding and Clear/Almost Clear on CGI-S Bleeding. Quotes are from the participant's entry and exit qualitative interviews.

Participant	Prior cVM interventions	TSQM satisfaction response (Week 12)
1 (13-year-old male)	Bandage/compression dressing (1x)	Very Satisfied
2 (13-year-old female)	Sclerotherapy (2x); Bandage/compression dressing (1x); Resection (1x)	Satisfied
3 (17-year-old female)	Sclerotherapy (6x)	Very Satisfied
4 (15-year-old female)	Sclerotherapy (1x)	Satisfied
5 (6-year-old female)	Sclerotherapy (1x); Bandage/compression dressing (1x)	Very Satisfied
6 (9-year-old male)	Sclerotherapy (2x)	Extremely Satisfied
7 (13-year-old male)	Sclerotherapy (1x)	Lost to follow-up after Week 8

Figure 5. High treatment satisfaction in pediatric participants with persistent cVM despite prior interventions. Pediatric participants had a history of prior cVM-directed therapies, including sclerotherapy, compression therapy, and surgical resection. Following treatment with investigational QTORIN™ sirolimus topical gel 3.9%, all participants with available assessments reported being at least satisfied with treatment at Week 12 (Treatment Satisfaction Questionnaire for Medication [TSQM], Question 9).

CONCLUSIONS

- Investigational QTORIN™ sirolimus topical gel 3.9% was associated with clinically meaningful improvements in pediatric participants with cVM.
- Improvements were evident by Week 8 and increased over time across clinician global assessment and lesion-specific endpoints.
- All 3 pediatric participants with baseline bleeding were rated Much Improved or Very Much Improved on cVM-IGA Bleeding and Clear/Almost Clear on CGI-S Bleeding at Week 12.
- The robust responses observed in these pediatric participants are particularly encouraging given that cVM typically presents during childhood and progresses over time without spontaneous regression.
- Treatment was generally well tolerated, with low systemic sirolimus exposure (all pediatric concentrations <1 ng/mL).
- Among pediatric participants with available TSQM responses, all reported being at least satisfied with treatment.
- These findings support further development of investigational QTORIN™ sirolimus topical gel 3.9% as a non-invasive targeted therapy for pediatric cVM.

Cutaneous venous malformations typically begin in childhood, with disease burden accumulating over a lifetime. The consistent and clinically meaningful improvements observed with investigational QTORIN™ sirolimus topical gel 3.9%, including reductions in lesion bleeding, support the potential for early, targeted intervention in this disease.