Significant Reductions in Lesion Bleeding with QTORIN™ 3.9% Rapamycin in Cutaneous Venous Malformations

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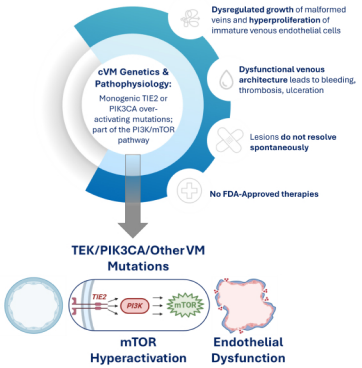
INTRODUCTION

Cutaneous venous malformations (cVMs) are caused by somatic activating mutations, most commonly in TEK or PIK3CA, that lead to downstream hyperactivation of the PI3K/mTOR signaling pathway in venous endothelial cells. Aberrant mTOR signaling results in dysregulated endothelial proliferation, impaired vessel maturation, and the formation of structurally abnormal, dilated venous channels, driving progressive lesion enlargement, venous stasis, thrombosis, bleeding, and pain[1,2]. QTORIN™ Rapamycin is a novel, targeted topical therapy designed to locally inhibit mTOR signaling at the site of disease while minimizing systemic exposure and associated toxicities observed with oral sirolimus.

Cutaneous Venous Malformations:
Serious, High Unmet Need



Given the lack of FDA-approved therapies for the treatment of cVM, clinical management is limited to invasive and often iterative destructive procedural approaches, including surgery, sclerotherapy, laser therapy, and cryotherapy, which are associated with procedural morbidity, scarring, incomplete responses, and high rates of recurrence[1].

OBJECTIVE

While lesion height and appearance are commonly assessed, lesion bleeding is a high-impact manifestation that affects daily functioning and quality of life. Bleeding occurs in only a subset of patients, complicating evaluation of treatment effects.

The objective of this work is to evaluate changes in lesion bleeding following QTORIN™ rapamycin anhydrous gel treatment in the Phase 2 TOIVA cVM study.

CLINICAL STUDY DESIGN AND RESULTS

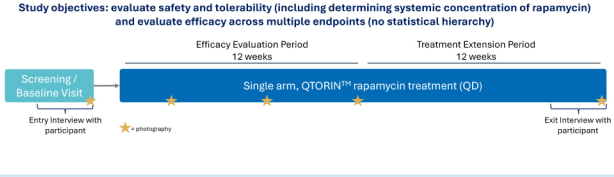


Figure 1: TOIVA Phase 2 Study Design. The TOIVA Phase 2 study employed a single-arm, baseline-controlled design, which is appropriate for a rare and serious condition such as cVM with a well-characterized natural history and no spontaneous improvement[1,3]. Patients applied once-daily QTORIN™, a proprietary topical rapamycin formulation engineered for high local skin exposure with minimal systemic absorption. Photographs and outcome analyses were taken at multiple timepoints during the 12-week efficacy evaluation period. Pre-specified clinician- and patient-reported outcomes included the Overall cVM Investigator's Global Assessment (cVM-IGA; 7-point dynamic change scale), static severity measures (lesion height, appearance/engorgement, bleeding), and patient global impression of change.

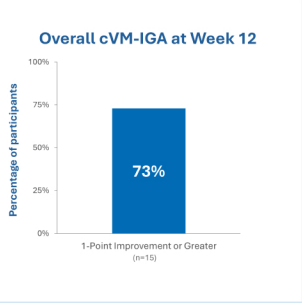


Figure 2. Overall cVM Investigator Global Assessment (cVM-IGA) Improvement at Week 12. Overall cVM-IGA is a 7-point clinician-assessed dynamic change scale ranging from "Very Much Worse" (-3) to "Very Much Improved" (+3). At Week 12, 73% of participants (11/15) demonstrated at least a 1-point improvement in Overall cVM-IGA score. Mean effect size at Week 12 was +1.5 ($p<0.001$) and median effect was +2.0.

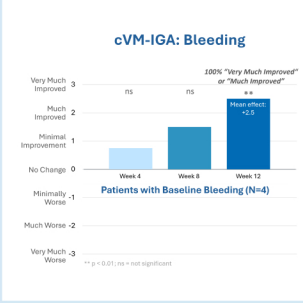


Figure 3. cVM-IGA:Bleeding improvement over time in patients with baseline bleeding. Change from baseline in cVM-IGA:Bleeding scores at Weeks 4, 8, and 12 is shown for patients with baseline bleeding (N=4). Scores range from −3 to +3, with higher scores indicating greater improvement in lesion bleeding. Patients with baseline bleeding demonstrated statistically significant improvement at Week 12, with a mean effect size of +2.5 (**p = 0.0032).

Figure 4. Clinical images of treatment response in a patient with baseline bleeding. Baseline (Week 0) and Week 12 images are shown for a 13 year old male participant carrying a PIK3CA mutation with cVM lesions on his lower leg. Images were cropped to highlight the treatment area but are otherwise unaltered. Improvements at Week 12 on the cVM-IGA: Overall and cVM-IGA: Bleeding scales are shown.

CONCLUSIONS

Bleeding and Leaking in cVM: the Patient Experience

- **Four out of 15** ITT patients experienced bleeding at baseline.
- Participants described both **bleeding/leaking from a trigger (e.g., bumping the area) or spontaneously occurring.**
- The duration of bleeding/leaking varied across participants, but **some reported bleeding/leaking for days**

Treatment Satisfaction in Patients with Baseline Bleeding

100% of patients rated their experience as **'very satisfied'** or **'satisfied'** with the medication at week 12 on the TSQM question related to satisfaction with medication

Figure 4. Bleeding and leaking were meaningful symptoms impacting patient experience in participants with cVM. Among participants reporting baseline bleeding symptoms, 100% of patients were either satisfied or very satisfied with the medication at Week 12 (N=4).

QTORIN™ 3.9% rapamycin produced rapid, progressive, and clinically meaningful improvement in cutaneous venous malformations over 12 weeks. Significant improvement in overall cVM severity (cVM-IGA) was observed across all evaluated timepoints in the overall study population.

Clinically meaningful reductions in lesion bleeding were also observed, with a statistically significant mean improvement of +0.7 points on the cVM-IGA bleeding scale across all patients ($p=0.045$, n=15). In participants with baseline bleeding (n=4), a markedly greater effect was observed, with a statistically significant mean improvement of +2.5 points at Week 12 ($p= 0.0032$), reflecting a clinically meaningful reduction. Improvements in bleeding were accompanied by significant improvements in lesion height and appearance.

Patient-level trajectories, photographic assessments, and clinician-reported outcomes demonstrated consistent treatment-associated improvement over time. Together, these findings support lesion bleeding as a clinically meaningful, patient-relevant endpoint and further support localized mTOR inhibition with QTORIN™ 3.9% rapamycin as a promising disease-modifying therapeutic strategy for cutaneous venous malformations.

REFERENCES

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