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Preliminary results from an open-label escalating-dose cohort study of VT30, a topically formulated phosphatidylinositol 3-kinase inhibitor (PI3K), intended as a treatment for patients with cutaneous vascular malformations associated with underlying *PIK3CA* or *TEK* mutations (Study VT30-101)

ClinicalTrials.gov Identifier: NCT04409145

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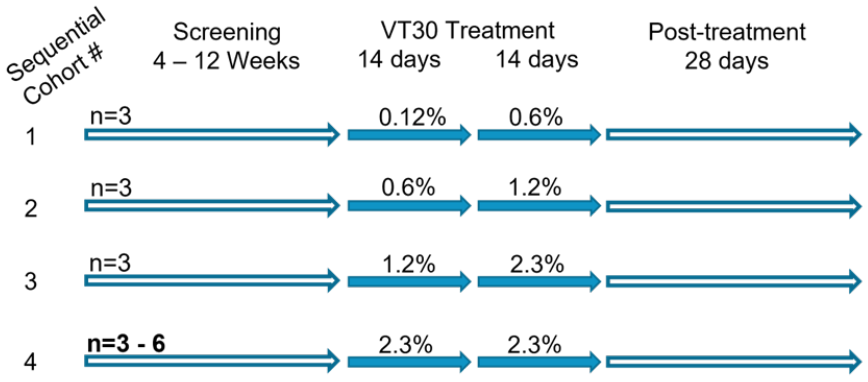
Disclosures

- Founder: Venthera
- Speaker: Novartis; Sanofi; Pfizer; Leo; Pierre Fabre Dermatologie
- PI: Novartis; Sanofi; Pierre Fabre Dermatologie; Leo; Eli Lilly; Pfizer

VT30-101 First-in-Human Study Objectives

- Characterize the safety & tolerability of VT30 Topical Gel
  - Define maximum tolerated dose (MTD) or maximum feasible dose (MFD)
- Assess plasma drug levels
- Exploratory
  - Tissue drug levels
  - Tissue pharmacodynamics
  - Imaging
  - Efficacy – patient and investigator assessments
- Note – results presented reflect available open-label data to date – database is not yet complete or finalized

VT30-101 Study Design



Visit 1 = screening
Visit 2 = allocation to daily topical treatment (study treatment area = 140 cm2)
Visit 3 = 2 weeks on treatment – intra-cohort escalation (Cohorts 1, 2 & 3)
Visit 4 = last on-treatment visit (4 wks)
Visit 5 = post-treatment follow up

Biopsies for genotyping & baseline pharmacodynamics: Visit 1
Biopsies for post-treatment pharmacodynamics & tissue drug levels: Visit 4
Plasma drug levels, pre and post-application: V2, V3 & V4

Key Inclusion Criteria

- 18 to 60 years of age
- Informed consent
- Have a clinically or phenotypically defined VM, LM, or mixed VLM affecting the skin (may also have capillary involvement and/or extend to affect subcutaneous tissue)
- Lesion amenable to defining a contiguous study-treatment area of 140 cm2
- Lesion genotyping confirms either PIK3CA or TEK mutation, likely or known to be pathogenic

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VT30-101: Subject Disposition & Characteristics

- 29 potential subjects formally screened
- 15 were allocated to treatment
  - Most common reasons for screen failure
    - Non-qualifying genotype (9)
    - Withdrawn consent/lost to follow up (5)
  - Of the 15 allocated patients, 14 completed the full treatment period
    - 109-001 completed treatment but was unable to return for the 1-month post-treatment follow up due to travel issues and family commitments
    - 118-001 in Cohort 3 (receiving 2.3%) skipped the final dose because of a local dermatitis/rash
    - 101-003 in Cohort 4 (receiving 2.3%) discontinued treatment ~1 week early because of a local dermatitis/rash
  - *Note – dose lowered to 0.6% for the final 4 patients in Cohort 4 (due to rash)*

Cohort	Subject Number	Sex	Age (yrs)	Treatment	Genotype	Lesion Type	Location
1	112-001	M	30	0.12 -->0.6%	TEK	VM	abdomen
	112-003	F	47	0.12 -->0.6%	PIK3CA	VM (cap)	prox left leg
	108-001	F	21	0.12 -->0.6%	TEK	VLM (cap)	prox left leg (buttock)
2	111-001	F	37	0.6 -->1.2%	PIK3CA	VM (cap)	distal right leg
	113-001	F	22	0.6 -->1.2%	PIK3CA	VM (cap)	prox left leg
	112-004	M	21	0.6 -->1.2%	TEK	VM (cap)	prox right leg
3	109-001	M	46	1.2 -->2.3%	PIK3CA	VLM (cap)	prox right leg
	105-001	M	18	1.2 -->2.3%	PIK3CA	LM	back
	118-001	F	33	1.2 -->2.3%	TEK	VM	back
4	118-003	F	27	2.30%	PIK3CA	VM	buttock
	101-003	M	26	2.30%	TEK	VM	back
	109-004	M	46	0.60%	PIK3CA	VLM (cap)	prox right leg
	109-005	F	25	0.60%	PIK3CA	LM (cap)	abdomen
	113-004	M	30	0.60%	PIK3CA	VLM	abdomen
	114-001	F	36	0.60%	PIK3CA	VM	distal right leg

VM = venous malformation; LM = lymphatic malformation; VLM = mixed (venolymphatic); cap = capillary involvement

VT30 Safety & Tolerability: Rash – only finding of note
Apparent dose or exposure relationship with observed incidence

- 4 patients developed a local dermatitis/rash on gel strengths of 1.2% or higher (2 missed 1 or more applications as a result and 1 discontinued treatment)
- 1 patient at 0.6% presented with a local rash 4 days after completing study treatment (114-001)
- Clinical presentation and histopathology consistent with a contact dermatitis
  - Perivascular mononuclear cell infiltrates
  - No indication of an IgE-mediated phenomenon
- All cases were limited to treatment area and resolved after cessation of treatment

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	109-005	F	25	0.6%	PIK3CA	LM (cap)	abdomen
	113-004	M	30	0.6%	PIK3CA	VLM	abdomen
	114-001	F	36	0.6%	PIK3CA	VM	distal right leg

XXX = dermatitis/rash
VM = venous malformation; LM = lymphatic malformation; VLM = mixed (venolymphatic); cap = capillary involvement

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Tissue-Drug Levels in Multiple-fold Excess of IC50 for PI3Kα Inhibition

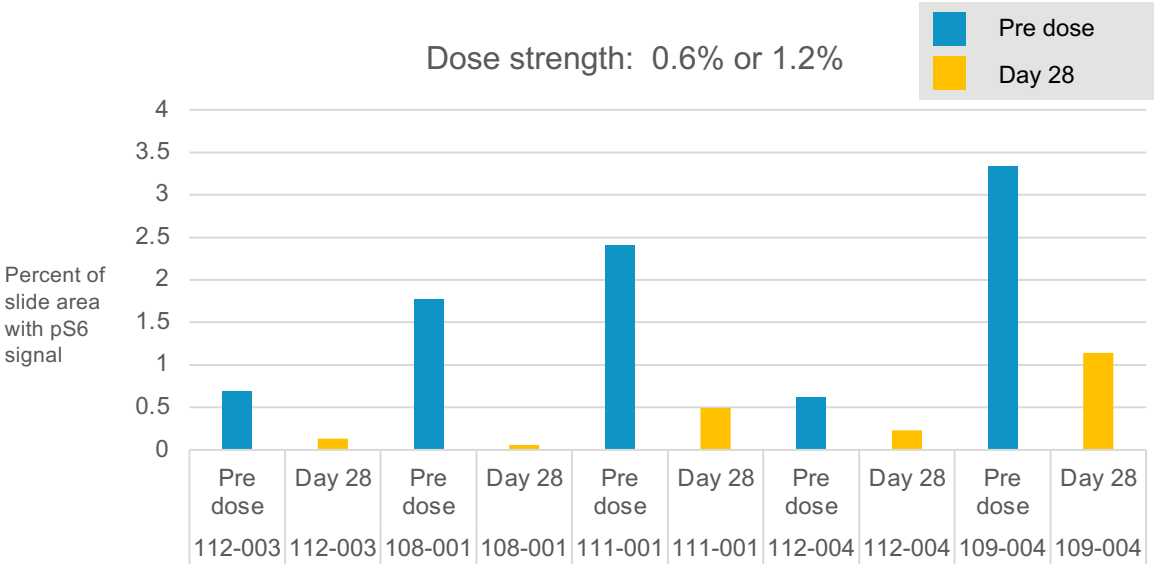
- VT30 is efficiently converted to VT10 after permeation of the epidermal stratum corneum
  - *VT10 is the active drug form in and in proximity to the dermis*
- VT10 IC_{50} for pS6rp in cell-based assays = 200 – 400 nM; IC_{50} for PI3Kα enzymatic activity = 5 – 10 nM
- Skin biopsies taken after 28 days of treatment; **no detectable drug levels in plasma (VT30 or VT10)**
- *Drug-level biopsy results not available for all subjects*

Cohort	Subject Number	Final Dose-strength	VT30 μM	VT10 μM
2	111-001	1.2%	6.16	**8.92**
	112-004	1.2%	46.4	**114**
3	105-001	2.3%	21.6	**16.3**
	109-001†	2.3%	.00844	**1.63**
4	118-003	2.3%	4.87	**54.4**
	109-004	**0.6%**	46.4	**20.6**
	109-005	**0.6%**	21.3	**9.50**
	113-004	**0.6%**	3.38	**27.92**
	114-001	**0.6%**	5.49	**9.57**

† Biopsy taken from peripheral region of scarring due to bleeding concerns

Tissue Pharmacodynamics: suppression of dermal pS6rp levels on immunofluorescent staining

Preliminary Data – Patients with biopsies unconfounded by skin rash
Median pS6rp area, assessed by immunofluorescence, normalized to evaluable dermis – pre and post dosing



- Consistent with high drug levels documented in tissue
- Quantitative assessment made on dermis - excludes epidermis and sebaceous glands/hair follicles (due to nonspecific staining)
- Reproducible decrease in signal with dose strengths ≤ 1.2%

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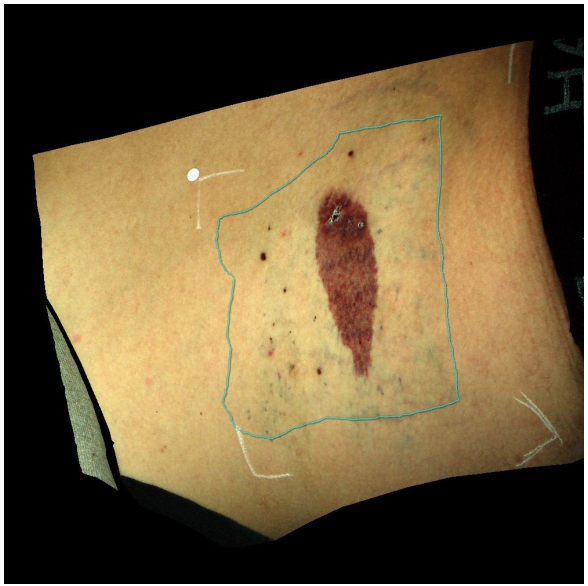
Standardized Imaging of Treatment Area Conducted as an Exploratory Methodology

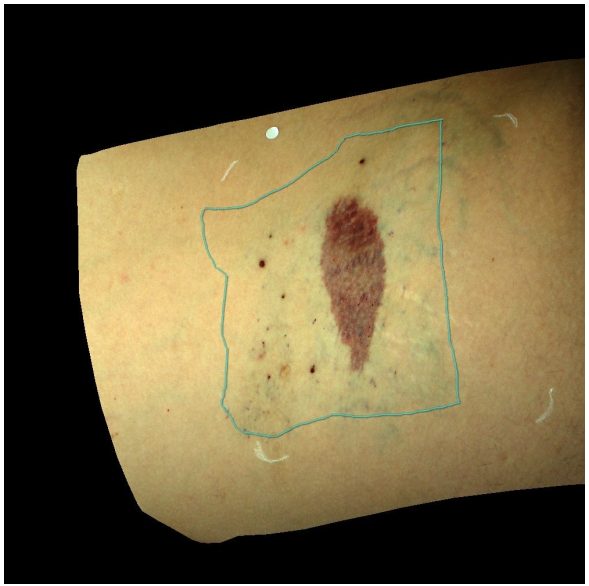
- Feasibility and utility confirmed
  - Investigators sized treatment areas, per protocol, via digital tracing
  - Successful documentation of biopsy sites and of lesion space within the treatment area
  - High resolution 3D renderings created from 2D stereo-images
  - Can serve as basis for future centralized evaluation
- Consistent with expectations for a 4-week treatment period, definitive treatment effects were not observed on sequential images
  - Subtle changes consistent with improvement potentially noted on some patients

Patient 113-004: 0.6% x 4 wks

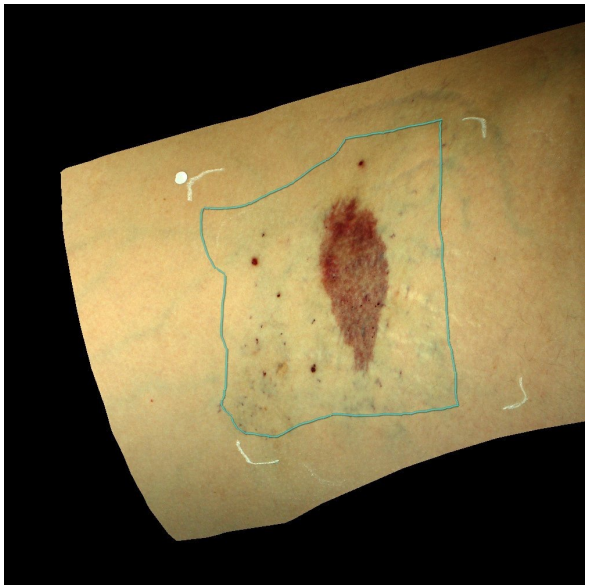
Visit 2, pre-treatment



Visit 4, day 28 of treatment



Visit 5, post-treatment follow up



Genotype: PIK3CA mutation E453_L455 del

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Exploratory Efficacy: Baseline Mean and Mean Change after 4 Weeks of Topical Study Treatment

- *Preliminary Results: Pending Completion of Database*
- We measured Investigator Global, Pain, Bleeding and oozing, and Patient Global assessment
- Observed a slight improvement in Bleeding and Oozing and Investigator Global
  - **Dose escalating study was limited by duration and treatment area**

VT30-101: Summary and Conclusions

- **0.6% VT30 Topical Gel (once daily) is appropriate as a dose-strength for longer term study**
  - Acceptable tolerability out to 4 weeks
    - Potential for contact dermatitis requires further clarification
  - **Generates drug levels in the skin well in excess of concentrations necessary for meaningful PI3Kα inhibition**
    - **Suppresses pS6rp levels in the dermis**
  - No circulating drug detected (with up to a 2.3% formulation)
- *Anticipate completed database and lock late 2Q2022*
  - *Next steps – 12-week pilot efficacy cohort and follow-up work to clarify rash potential*