venthera
a bridgebio company

BBP-681 Overview

Non-confidential

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The Venthera team is dedicated to developing meaningful medicines for patients with Vascular Anomalies

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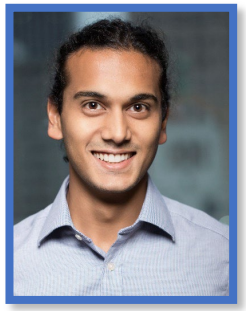
Core Team

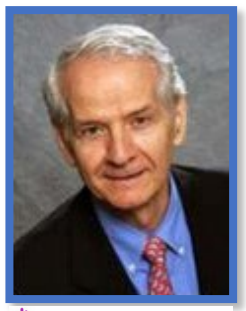
Thomas Rossi, PhD
CEO
Formerly CEO of Agile Tx, Kore Pharma, and SVP, Board member for The R.W. Johnson Pharmaceutical Research Institute



Kahlil D'Souza
Assoc. Director of BD and Operations

Ken Truitt, MD
CMO
Formerly CMO at ImmusanT, Inc. and SVP of Internal Medicine at Daiichi Sankyo

Lisa Pugliese
VP of Clinical Operations



Agis Kydonieus, PhD
Head of Formulation Development
Formerly VP of R&D Bristol-Myers Squibb
Has published extensively in transdermal delivery

Founders

José Baselga, MD, PhD

Eulàlia Baselga Torres, MD
SJD Barcelona Children's Hospital

Pau Castel, PhD
New York University

Overview of BBP-681 opportunity in Venous and Lymphatic Malformations

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Venous and Lymphatic Malformations (VM/LM) affect over 110,000 people in US+EU and can cause significant morbidity

VM/LMs are **driven by dysregulated activation of the PI3K/AKT signaling pathway**, representing a logical potential treatment target

BBP-681 is designed to potently inhibit PI3Kα and is optimized for skin permeation to target cutaneous lesions

Phase 1/2 trial was initiated in 2021 with an interim readout expected in 1H2022

Venthera is potentially positioned to address the **broader Vascular Anomalies space,** consisting of several druggable monogenic diseases with a high unmet medical need

Venous and Lymphatic Malformations are heterogenous overgrowth anomalies that can dramatically impact patients

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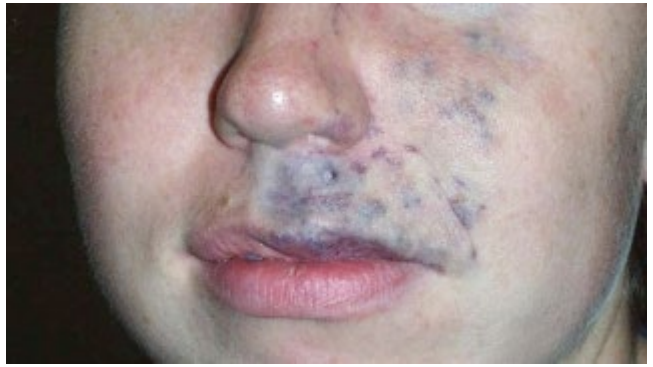
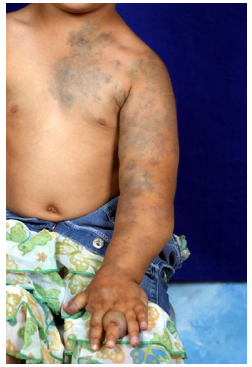
Venous Malformations

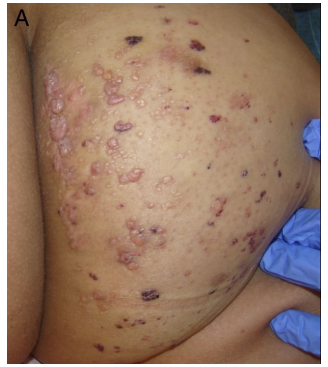
- Dilated and dysfunctional slow-flow venous channels, deficient in smooth muscle cells
- Present at birth, and grow slowly and unpredictably throughout life
- Arise in any location, but a large portion involve the skin
- Cause pain, bleeding, disfigurement and functional impairment
- Current treatments include compression bandages, analgesics, laser ablation, surgical resection, sclerotherapy, and in rare cases off label rapamycin
- Thromboembolic complications may require anti-platelet agents or anticoagulants

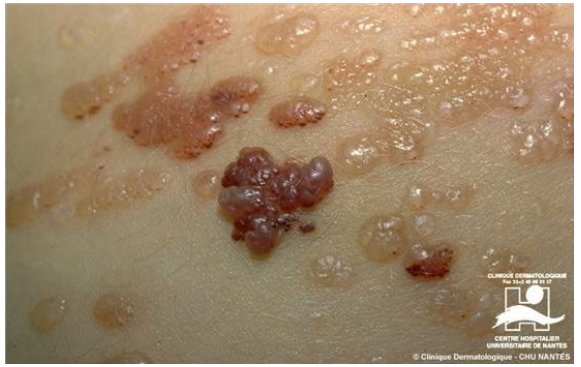




Lymphatic Malformations

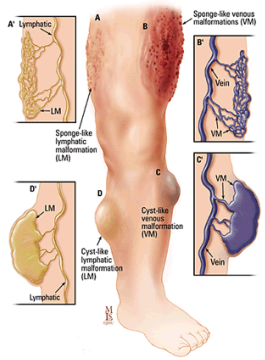
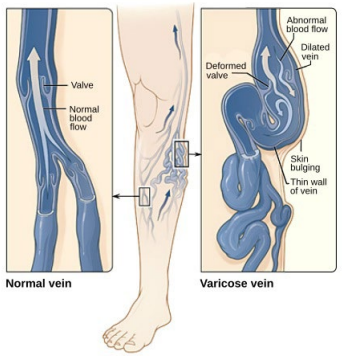
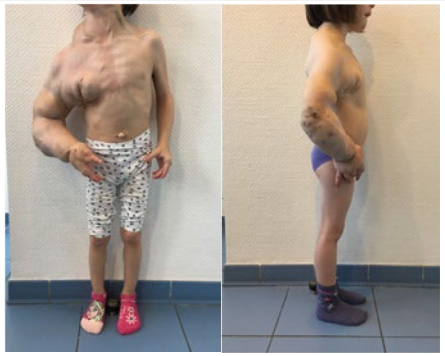
- Immature lymphatic structures that fails to communicate with normal vasculature
- Classified as macrocystic (cysts are >1 cm), microcystic (cysts are <1 cm), and mixed
- Superficial or deep and can arise in any location, tissue, or organ
- Cause pain, disfigurement, bleeding or ‘weeping’ of lymphatic fluid and functional impairment
- Current treatments include compression bandages, laser ablation, surgical resection, sclerotherapy, and off label rapamycin





Cutaneous lesions have no effective treatments, leaving a need for a targeted topical like BBP-681; existing therapies are invasive and there are no approved drugs

Venous and Lymphatic Malformation Standard of Care

	Cutaneous lesions	Deep isolated lesions	Syndromic disease
Lesion Description	*~50% of VM/LM are cutaneous, can have pain (~30%), bleeding and oozing, discoloration, functional impairment*	*Often painful, disfiguring lesions, with functional impairment*	*Deep, bulky, highly disfiguring, may have skin, muscle and bone involvement, functional impairment*
Typical Treatments	*Analgesics, compression dressings, anticoagulants, laser (at limited centers)*	*Analgesics, compression dressings, anticoagulants, laser, sclerotherapy*	*Surgery, sclerotherapy, sirolimus (off-label)*
Treatment Strategy	***"Watch and Wait": very little to offer for cutaneous lesions***	*Patient-specific therapy: Highly practitioner-dependent*	Systemic therapy as tolerated; repeat procedures
Visual example			

Source: Castel P, Carmona FJ, Grego-Bessa J, et al. Somatic PIK3CA mutations as a driver of sporadic venous malformations. Science translational medicine. 2016; 8(332):332ra42; Behravesh S, Yakes W, Gupta N, et al. Venous malformations: clinical diagnosis and treatment. Cardiovasc Diagn Ther. 2016; 6(6):557-569.; Rikihisa N, Akita S, Osuga K, Mimura H, Yuzuriha S, Sasaki S. Evaluation of pain incidence due to venous malformation based on data from 85 institutions in Japan. J Vasc Surg Venous Lymphat Disord. 2020 Mar;8(2):244-250.; https://www.hopkinsmedicine.org/interventional-radiology/conditions/malformations/; https://icloudhospital.com/specialties/congenital-vascular-malformation

VMs and LMs result from mutations leading to dysregulated activation of the PI3K/AKT pathway; both preclinical and clinical evidence support PI3K inhibition as a therapeutic strategy

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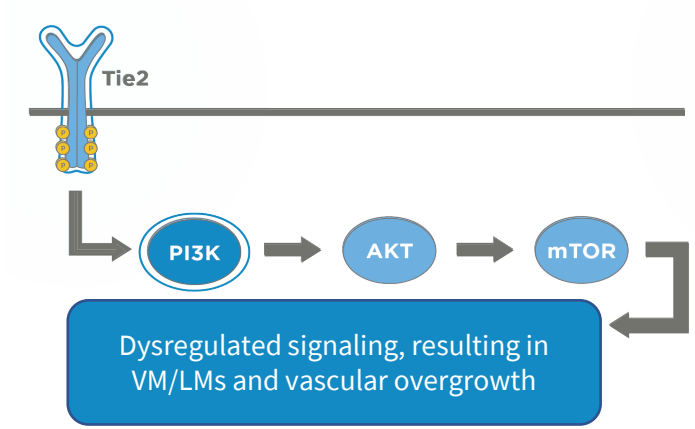
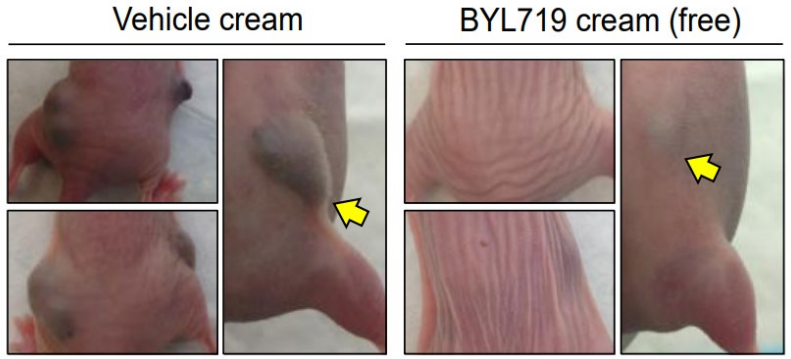
VM/LMs result from somatic gain of function (GOF) mutations that activate PI3K signaling

- VMs: 30% driven by GOF mutations in PIK3CA; 60% by TEK2 (Tie2) GOF mutations
- LMs: 90% driven by PIK3CA GOF mutations



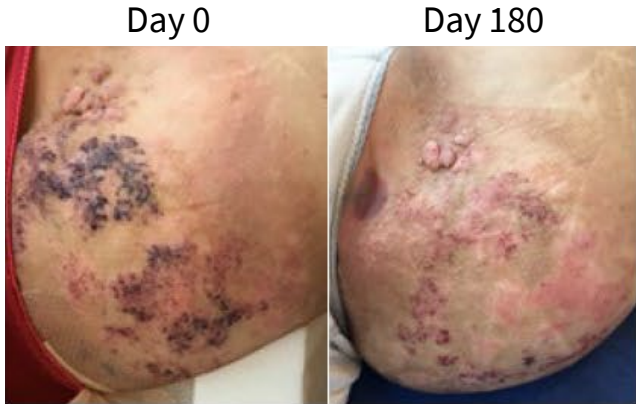
PI3K inhibition causes regression of lesions in a VM mouse model

- Rapid regression of VM lesions upon topical application of a PI3Kα-specific inhibitor (BYL719, alpelisib)



Compassionate use of Alpelisib in PROS provides clinical proof of target

- PROS is a collection of syndromes driven by somatic PI3K mutation, leading to widespread VM/LMs and associated overgrowth
- Oral treatment with alpelisib shrinks both superficial and deep lesions



Source: Castel P, Carmona FJ, Grego-Bessa J, et al. Somatic PIK3CA mutations as a driver of sporadic venous malformations. Science translational medicine. 2016
Venot, Q et al. Targeted Therapy in Patients with PIK3CA-Related Overgrowth Syndrome. Nature, June 2018
Luks VL et al. Lymphatic and other vascular malformative/overgrowth disorders are caused by somatic mutations in PIK3CA. J Pediatr. 2015

BBP-681 is a topical prodrug designed to inhibit PI3Kα signaling in cutaneous vascular malformations

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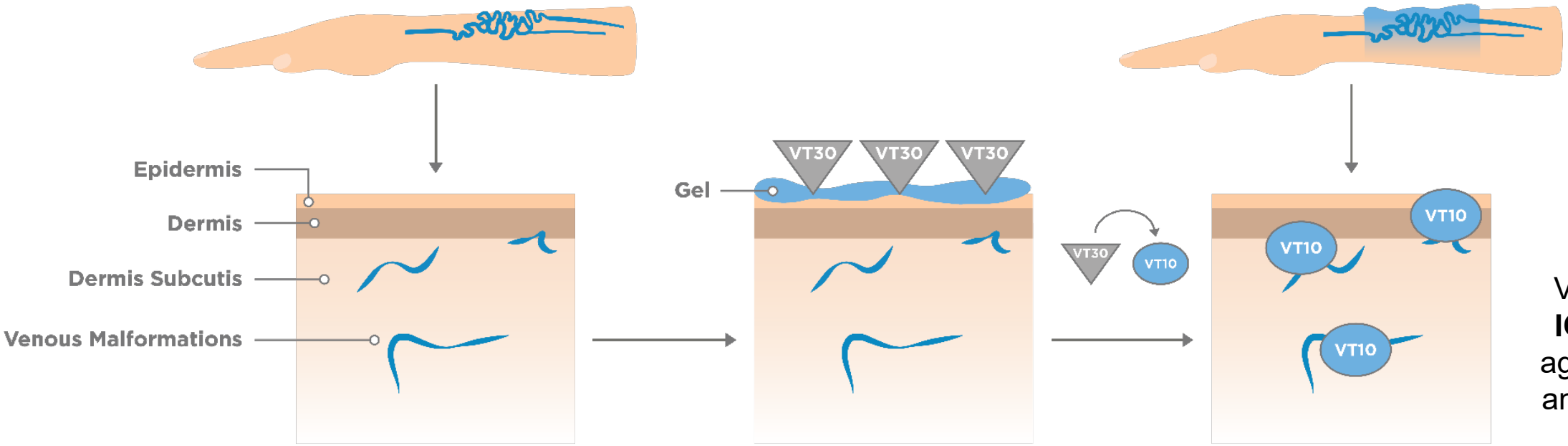


The prodrug, BBP-681 (VT30), is designed to permeate the epidermis

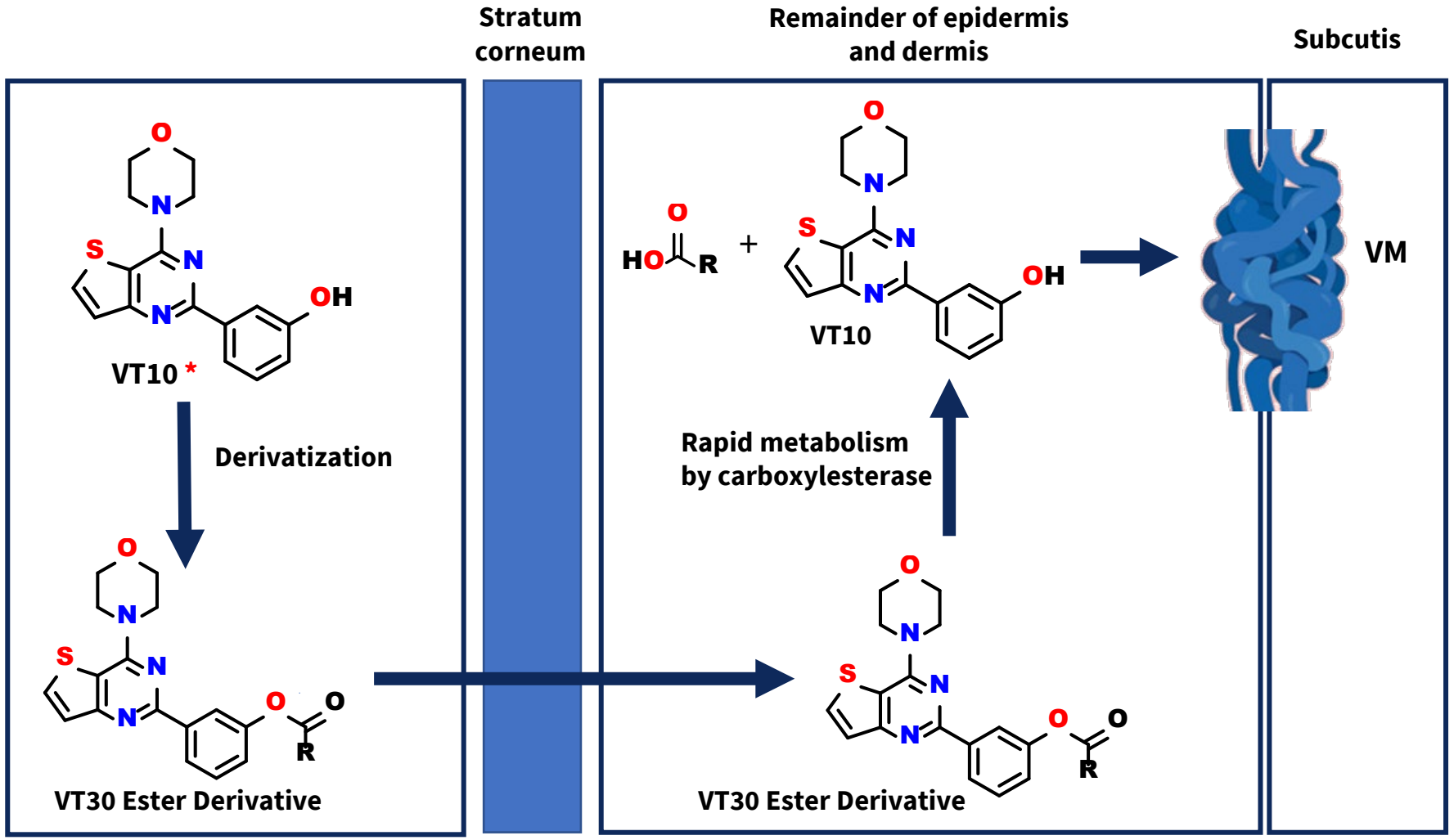
The gel formulation is **optimized for permeation** of the epidermal stratum corneum

VT30 Prodrug is cleaved by resident carboxylesterases in the dermis **to produce the more active drug form, VT10**

VT10 has an **IC50 of 5nM** against mutant and WT PI3Ks

VT30 provides local delivery to cutaneous lesions and is designed to minimize the risks of systemic side effects

A prodrug approach allows Venthera to optimize delivery of active drug into the target lesion



*Hayakawa, M.; et al. Bioorg. Med. Chem. 2006, 14(20), 6847–6858
*Hayakawa, M.; et al. Bioorg. US 6,838,457 B2. January. 2005

Venthera is approaching an interim readout in our First in Human study of VT30

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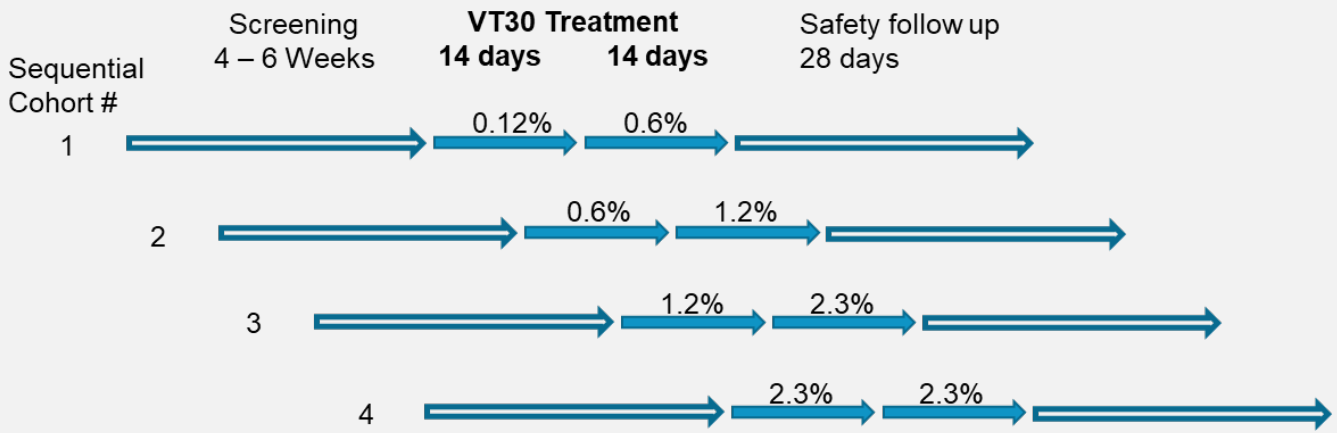
- Dose escalation phase is nearing completion
- 16 affected patients have been dosed
- Dose selected for phase II
- Data on
  - Safety and tolerability
  - Intra-lesional tissue drug levels
  - Investigator and patient reported outcomes
  - Pharmacodynamic marker for target engagement



Clinical data demonstrate that BBP-681 topical gel is performing as designed: high local drug levels and no systemic exposure

Local tissue concentrations of VT10/VT30 from skin biopsies taken 4h after day 28 dosing:

	Dose (QD)	Local VT10 concentration (uM)
Cohort 2	0.60%->1.20%	**8.9**
Cohort 2	0.60%->1.20%	No biopsy
Cohort 2	0.60%->1.20%	**114.2**
Cohort 3	1.20% ->2.30%	**16.2**
Cohort 3	1.20% ->2.30%	**1.6**
Cohort 3	1.20% ->2.30%	No biopsy
Cohort 4	2.30%	**54.2**
Cohort 4	0.6%	**9.5**
Cohort 4	0.6%	**20.6**

- VT10 (IC50 = 5nM) has >1000-fold coverage over PI3K based on measured concentrations. Variability in skin flux is expected due to natural differences in skin thickness by location and investigator technique, but all samples were within uM range.
- BBP681 (VT30) is applied to the skin, and VT10 is measured in the samples. VT30->VT10 conversion occurs after VT30 has penetrated the stratum corneum and can access the lesion.
- No systemic drug exposure: **all patients below LLOQ** (1ng/ml for VT10; 0.1ng/ml for VT30)

*Cohort 1 samples lost by CRO due to protocol deviation during processing.

Pharmacodynamics: BBP-681 suppresses dermal pS6rp in all patients treated with 0.6% as measured with immunofluorescent staining

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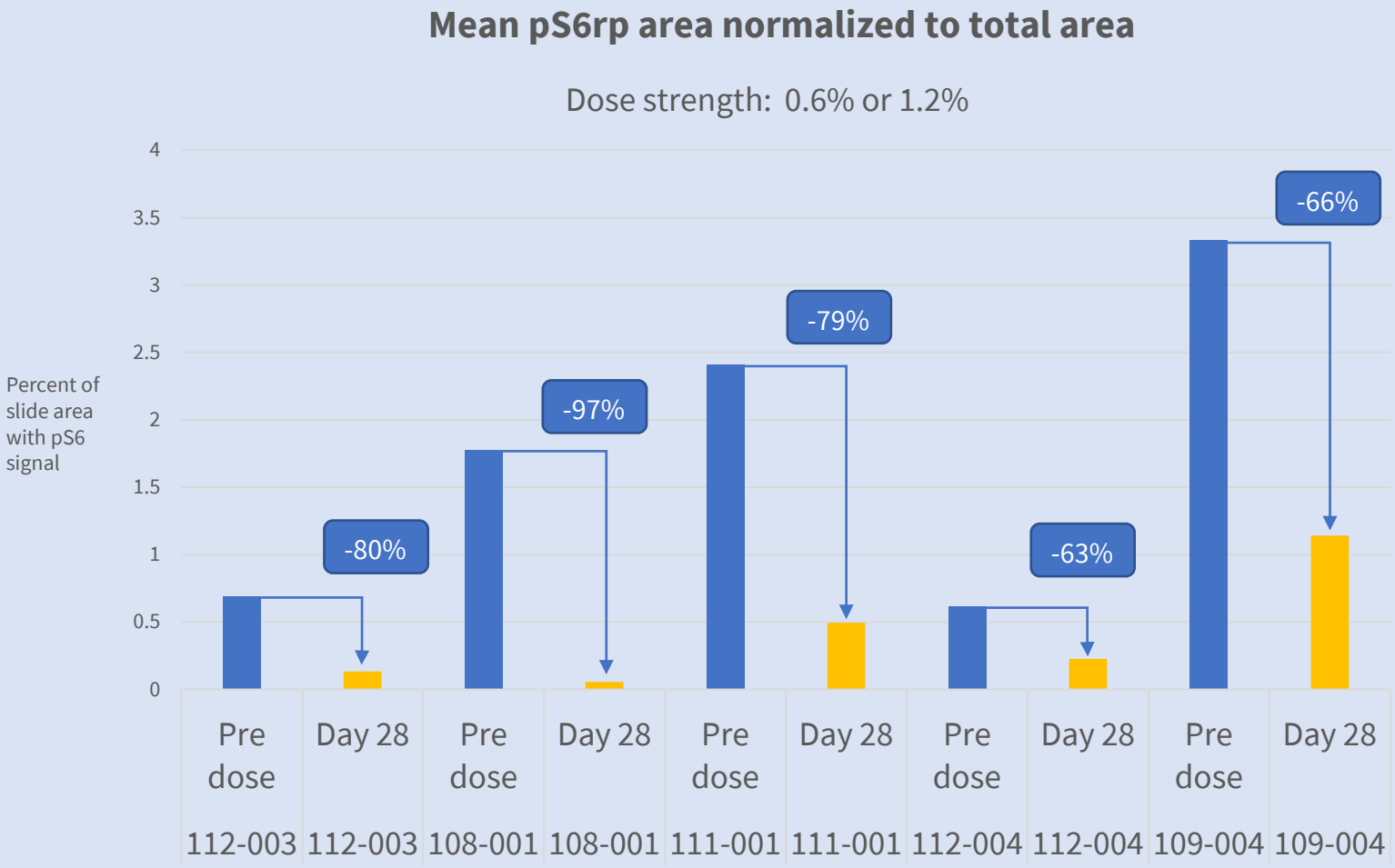

Patient ID	Dose
112-003	0.12% (2 wks) then 0.6% (2 wks)
108-001	0.12% (2 wks) then 0.6% (2 wks)
111-001	0.6% (2 wks) then 1.2% (2 wks)
112-004	0.6% (2 wks) then 1.2% (2 wks)
109-004	0.6% (4 wks)

Study in progress with additional data pending

The utility of pS6rp levels to reflect PI3K inhibition in sequential biopsies from patients dosed at 2.3% was confounded by the development of activated cellular (inflammatory) infiltrates (that may correlate with the appearance of rashes).

BBP-681 has potential to reach $1.1B+ in worldwide product sales at peak

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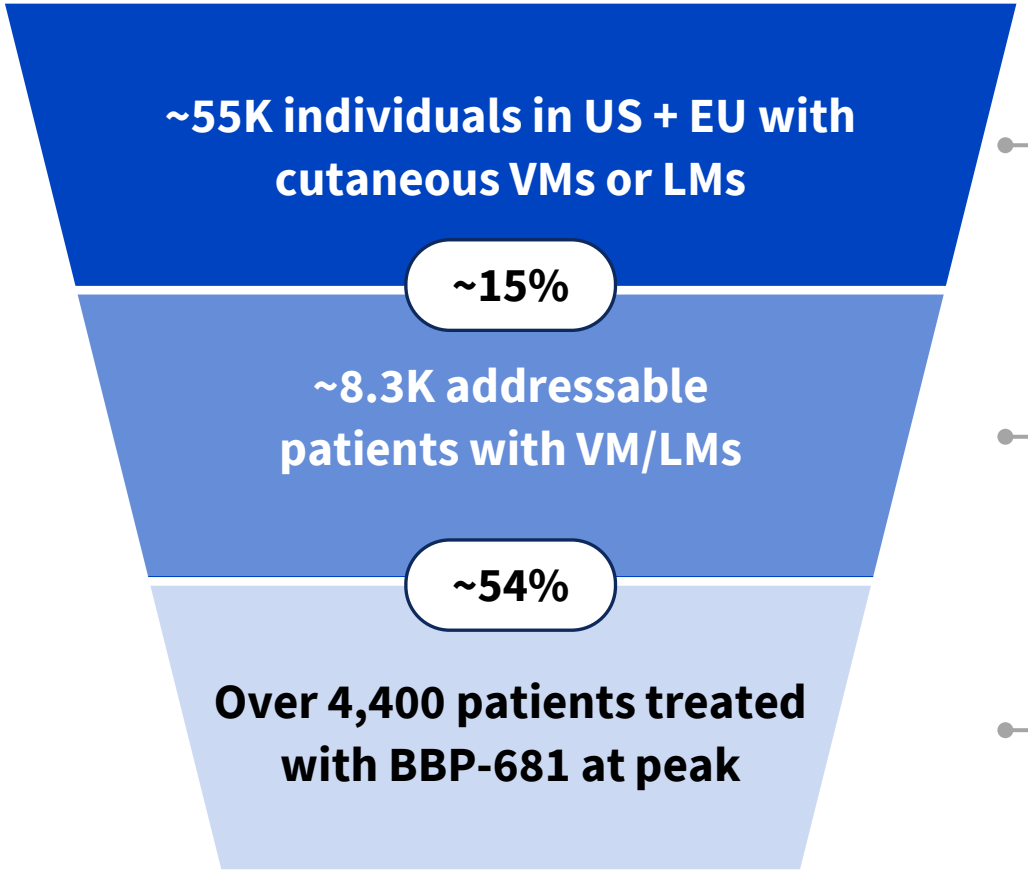
Addressable US Market Share



Description

- **Incidence of ~2/10K for VMs and ~2/10K for LMs**
- Assumes 3.9M live birth rate and 75yr life expectancy
- ~47% of patients with VMs and LMs have cutaneous lesions based on literature and KOL estimates

- **Assumes ~20% of patients with VMs/LMs are accurately diagnosed and suitable for treatment with a topical** at peak
- ~75+% of VMs are either TEK2 or PIK3CA mutated, while ~75+% of LMs are PIK3CA mutated, and thus addressable by a PI3Kai

- **Assumes a ~60% preference share for topical PI3Kai and 90% brand share within PI3Kai class given no competitors**
  - Assumes topical mTORi takes away significant share despite targeting further downstream
  - Assumes maintenance use of topical

Potential peak sales >$450M in US and over $1.1B globally by mid 2030's

Source: BBIO Internal estimates; Physician interviews; Boon, Vikkula [UpToDate]; Castel 2016; Brouillard 2021; Orphanet; Garcia-Montero 2018.

Venthera is well-positioned to address several Vascular Anomalies with druggable, genetically-defined targets and high unmet medical need

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Indication	Genetic GOF	Modality	Preclinical		Clinical	
			Discovery	IND-Enabling	Phase 1	Phase 2
Cutaneous VM/LM	*PIK3CA/TEK*	Topical gel				
Deep VM/LM	*PIK3CA/TEK*	Long Acting Injectable				
Port Wine Stains (PWS)	*GNAQ*	Topical gel				
Arteriovenous Malformations (AVM)	*MAP2K1*	Long Acting Injectable				

Venthera has the expertise and technology to develop meaningful targeted therapies in this disease space

BBP-681 is a differentiated topical PI3Kα inhibitor for VM / LM

- **VM / LM is a disease with significant morbidity**
  - Driven largely by mutations in the Tie2/PI3K/AKT pathway
  - Inadequate standard of care highlights the need for a targeted therapeutic
- **Wealth of data suggests PI3Kα inhibition is a logical therapeutic approach for VM / LM**
  - PI3Kα inhibition leads to rapid regression of VM lesions in murine model
  - Treatment with PI3Kα inhibitor meaningfully reduces VM burden in PROS patients
- **BBP-681 is a potent, topical inhibitor of PI3Kα**
  - Significant *in vitro* inhibition of PI3K signaling
  - Topical formulation allows for avoidance of systemic side effects
- **FIH Phase 1/2 study was initiated in 2021 with interim readout in 2022**
- With differentiated target and route of administration, **BBP-681 has the potential to achieve peak worldwide sales of $1B+ if approved**