Altasciences, 562 State Road DD, Auxvasse, MO 65231, United States
Altasciences.com | contact@altasciences.com

A 13-Week Dermal Toxicity Study of VIM-004 Gel, a STAR Particles Based Formulation in Göttingen Minipigs®

Ahmed Abdalla[1], Claire Bouix-Peter[2], Carine Blanchard[2], Yann Dean[2], Sylvia Furst[3],
[1]Altasciences Preclinical Columbia, Auxvasse, MO, United States, [2]Aldena Therapeutics, CH, Switzerland, [3]Certara, United States

Click here to listen to the recorded poster

ABSTRACT

Vitiligo is a skin disorder that affects melanocytes, leading to depigmented patches on the skin and mucosa[1,2] (**Figure 1**). Studies have indicated that melanocortin system defects, notably decreased levels of α–melanocyte-stimulating hormone (α-MSH), contribute to the disease mechanism[3] (**Figure 1**). Despite various therapeutic options targeting melanocytes, treating vitiligo remains challenging due to the complexity of achieving safe and effective drug delivery to get the desired degree of re-pigmentation in the lesioned skin areas[4]. This study explores VIM-004 Gel, an innovative gel formulation containing an α-MSH analog (alpha-melanocyte-stimulating hormone analog, VIM-004) combined with star-shaped particles (STAR particles) (**Figure 2**). The STAR particles in the gel, when applied and rubbed on the skin, create microscopic pores through the stratum corneum. This approach temporarily increases skin permeability and allows for the delivery of the therapeutic agent, VIM-004, in the epidermis and dermis layers to produce effective vitiligo treatment and reduce systemic toxicity.

This study evaluated the potential local and systemic toxicity of VIM-004 administered to Göttingen Minipigs® by topical application of VIM-004 Gel once daily for 90 days. In addition, the toxicokinetic characteristics of VIM-004 were also determined.

Nine Göttingen Minipigs® were randomly assigned to 3 groups - placebo, low (0.033 mg/cm²/day), and high (0.066 mg/cm²/day) dose. The placebo and test articles were applied daily for 90 days to cover at least 5% of the body surface area (BSA). The following endpoints and parameters were evaluated: mortality, clinical observations (including dose site reactions, as well as local skin indications of irritation [erythema and edema]), food consumption, body weights, transepidermal water loss (TEWL) measurements, skin puncture, ophthalmology, electrocardiography, and clinical pathology parameters. Blood and skin biopsies were collected at multiple time points to characterize VIM-004 concentrations, both systemic and local, respectively, over time.

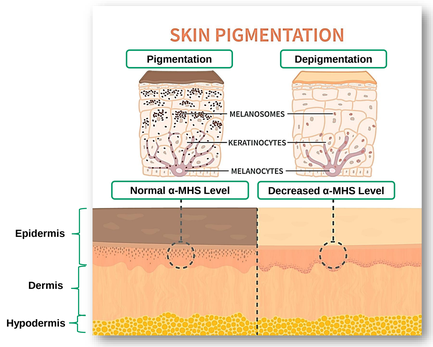

Figure 1. Role of α-MSH in the Mechanism of Vitiligo

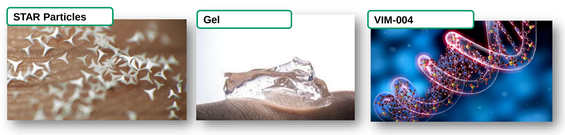

Figure 2. VIM-004 Gel Technology

MATERIALS AND METHOD

Out of the nine/sex Göttingen Minipigs®, nine/sex were randomly assigned to three groups (n=3): placebo, low (0.033 mg/cm2/day), and high (0.066 mg/cm2/day) dose. The placebo and test articles were applied daily for 90 days to cover at least 5% of the body surface area (BSA). The target BSA was divided into six minizones over the dorsal surface of the animals (3 minizones/side) that were used for the test article application, **Figure 3**. The STAR particles in the VIM-004 Gel create microscopic pores through the stratum corneum, increasing skin permeability to allow delivery of the VIM-004, when applied and rubbed on the skin.

Table 1. Test System

Description	
Species	Sus scrofa
Strain	Göttingen Minipigs®
Origin	United States of America
Condition	Naïve
Body weight range	4.0 to 7.0 kg (by initiation of dosing)
Age range	2.5 to 3 months (at initiation of dosing)
Number of animals	9 males and 9 females

Table 2. Experimental Design

Group	Test material	Dose level[a] (mg/cm²/day)	Dose conc.[b] (mg/g)	Dose amount[c] (mg/cm²)	Number of animals	
					M	F
1	Placebo	0	0	20	3	3
2	Low dose	0.022	1.1	20	3	3
3	High dose	0.066	3.3	20	3	3

Conc.= Concentration; M=Males; F=Females
[a]VIM-004 peptide amount applied (mg/cm²)
[b]VIM-004 peptide concentration in mg/g of the formulation
[c]Applied formulation amount in (mg/site)

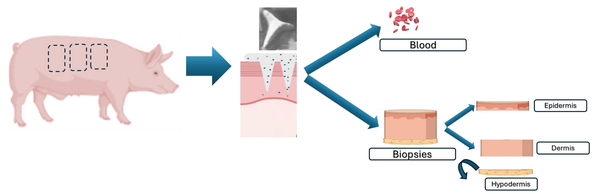

Figure 3. VIM-004 Gel Application and Samples Collection

Endpoints and Parameters Evaluations

Mortality, clinical observations (including dose site reactions, as well as local skin indications of irritation [erythema and edema]), food consumption, body weights, TEWL measurements, skin puncture, ophthalmology, electrocardiography, and clinical pathology parameters. Blood and skin biopsies were collected at multiple time points to characterize VIM-004 concentrations, both systemic and local, respectively, over time.

RESULTS

There were no unscheduled deaths. There were no VIM-004 Gel related clinical observations, Draize scores (remained between 0 and 1 across the groups with 0 being the most common), or ophthalmic findings, and no VIM-004 Gel related effects on body weight, food consumption, ECG, and clinical pathology parameters. Scheduled necropsies were conducted, and organ weights and macroscopic and microscopic (including skin biopsies) findings were evaluated. No macroscopic, microscopic, or organ weight changes were associated with the topical administration of VIM-004 Gel at any dose.

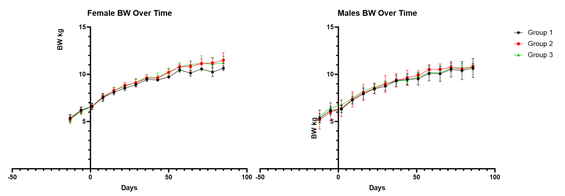

Figure 4. Body Weight

Trans Epidermal Water Loss Measurements

This parameter was used to evaluate skin permeability post-dose. Dose application with Placebo and test articles (gel formulations with suspended STAR Particles with or without VIM-004) resulted in an increase in TEWL values post-dose represented by delta TEWL (calculated average difference in TEWL measurements between post-dose and pre-dose)

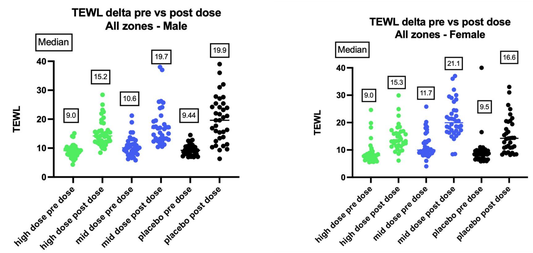

Figure 5. TWEL Measurements Pre and Post Application of VIM-004 Gel

Bioanalysis and Toxicokinetic Evaluation

Following 90 days of once-daily topical administration of VIM-004 Gel to female and male swine, the plasma concentrations of VIM-004 were not quantifiable in all plasma samples from low and high dose groups, indicating no systemic exposure of VIM-004 peptide above 0.500 ng/mL.

All TK parameters were derived using VIM-004 concentrations at 2.5 hours post-dose on Days 1, 42, and 90 using data from skin biopsies collected from treatment sites only. In general, females had lower dermis and epidermis concentrations of VIM-004 than males. Mean epidermal VIM-004 concentrations were notably higher than dermis, corroborating with higher mean % absorption in epidermis over dermis in both sexes. Mean VIM-004 concentration accumulation ratios were generally higher (>2-fold) in both matrices in low and high dose levels on Days 42 and 90 compared to Day 1 at 2.5 hours post-dose.

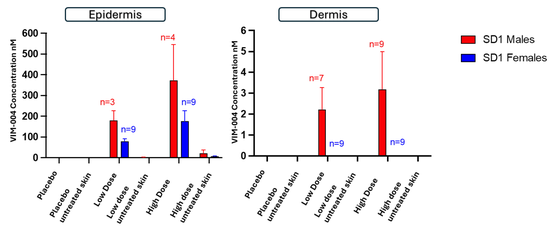

Figure 6. VIM-004 Concentrations in the Dose Site Skin of Minipigs on Day 1

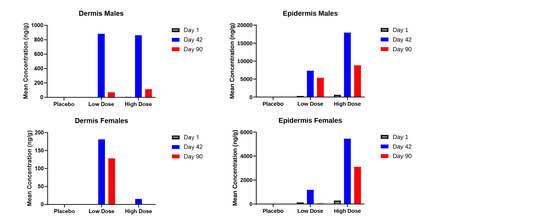

Figure 7. Summary of VIM-004 Concentrations in the Dose Site Skin of Minipigs. Data obtained from 3 Animals/Sex /Group with 3 samples taken from each animal.

Table 3. Summary of VIM-004 absorption in the Dose Site Skin of Minipigs

Parameter	Period Day	VIM-004 Gel Dose					
		Placebo		Low Dose		High Dose	
		Male	Female	Male	Female	Male	Female
Epidermis Mean % Absorption	1	0	0	27.10	11.80	18.6	8.76
	42	0	0	666	107	541	165
	90	0	0	486	4.56	267	93.9
Dermis Mean % Absorption	1	0	0	0.33	0	0.16	0
	42	0	0	80.4	16.4	26.1	0.47
	90	0	0	6.23	11.7	3.45	0.00

CONCLUSION

VIM-004 Gel applied topically to Göttingen Minipigs daily for 90 days was well tolerated and resulted in no adverse findings. Based on the absence of adverse VIM-004 Gel related findings, the No-Observed-Adverse-Effect Level (NOAEL) was considered to be 0.066 mg/cm²/day, the highest dose tested. At the NOAEL, the mean VIM-004 concentrations in the epidermis were notably higher than dermis, corroborating with higher mean % absorption in epidermis over dermis in both sexes. This confirms successful delivery of VIM-004 at pharmacologically relevant concentrations.

REFERENCES

1. Cha YC, Lee HJ, Lee SJ, Na GY, Chung SL. The Expression of the Alpha-Melanocyte Stimulating Hormone (alpha-MSH) and Melanocortin-1 Receptor (MC1R) in the Epidermis of the Vitiligo. Korean J Dermatol. 2003;41(6):690-695.
2. Bishnoi, A.; Parsad, D. Clinical and Molecular Aspects of Vitiligo Treatments. Int. J. Mol. Sci. 2018, 19, 1509. https://doi.org/10.3390/ijms19051509.
3. Grimes PE, Hamzavi I, Lebwohl M, Ortonne JP, Lim HW. The Efficacy of Afamelanotide and Narrowband UV-B Phototherapy for Repigmentation of Vitiligo. JAMA Dermatol. 2013;149(1):68–73. doi:10.1001/2013.jamadermatol.386.
4. Li R, Qiao M, Wang X, Zhao X, Sun Q. Effect of narrow band ultraviolet B phototherapy as monotherapy or combination therapy for vitiligo: a meta-analysis. Photodermatol Photoimmunol Photomed. 2017 Jan;33(1):22-31. doi: 10.1111/phpp.12277. Epub 2016 Nov 23. PMID: 27696531.
5. iStock, https://www.istockphoto.com/faq/basics