CLINUVEL

Afamelanotide for vitiligo

CLINUVEL's Phase III program: setting a new standard of care

9 November 2023

ASX	CUV
Börse Frankfurt	UR9
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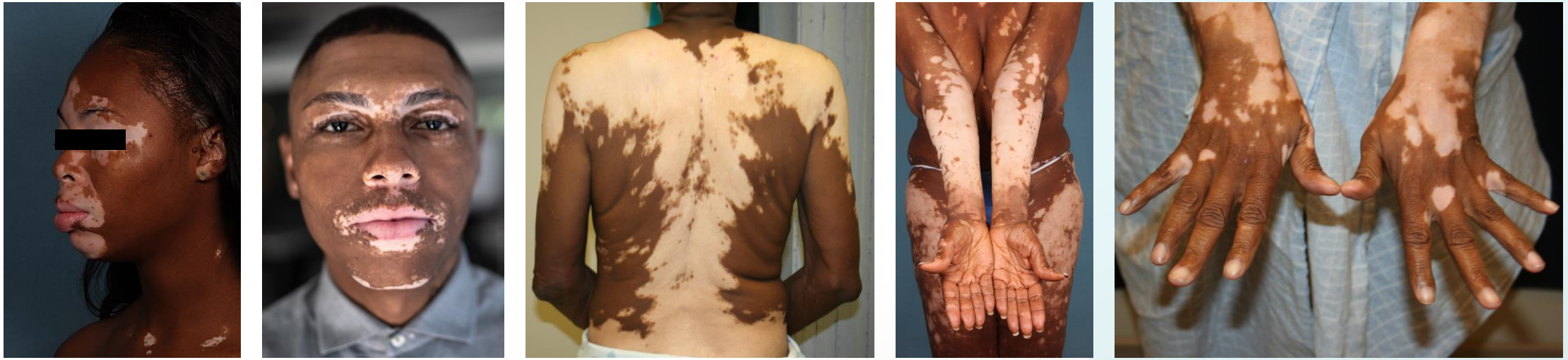
Forward-looking statement

This release contains forward-looking statements, which reflect the current beliefs and expectations of CLINUVEL's management. Statements may involve a number of known and unknown risks that could cause our future results, performance, or achievements to differ significantly from those expressed or implied by such forward-looking statements. Important factors that could cause or contribute to such differences include risks relating to: our ability to develop and commercialise pharmaceutical products; the COVID-19 pandemic and/or other world, regional or national events affecting the supply chain for a protracted period of time, including our ability to develop, manufacture, market and sell biopharmaceutical products; competition for our products, especially SCENESSE® (afamelanotide 16mg), CYACÊLLE, PRÉNUMBRA® or NEURACTHEL®; our ability to achieve expected safety and efficacy results in a timely manner through our innovative R&D efforts; the effectiveness of our patents and other protections for innovative products, particularly in view of national and regional variations in patent laws; our potential exposure to product liability claims to the extent not covered by insurance; increased government scrutiny in either Australia, the U.S., Europe, Israel, China and Japan of our agreements with third parties and suppliers; our exposure to currency fluctuations and restrictions as well as credit risks; the effects of reforms in healthcare regulation and pharmaceutical pricing and reimbursement; that the Company may incur unexpected delays in the outsourced manufacturing of SCENESSE®, CYACÊLLE, PRÉNUMBRA® or NEURACTHEL® which may lead to it being unable to supply its commercial markets and/or clinical trial programs; any failures to comply with any government payment system (i.e. Medicare) reporting and payment obligations; uncertainties surrounding the legislative and regulatory pathways for the registration and approval of biotechnology and consumer based products; decisions by regulatory authorities regarding approval of our products as well as their decisions regarding label claims; our ability to retain or attract key personnel and managerial talent; the impact of broader change within the pharmaceutical industry and related industries; potential changes to tax liabilities or legislation; environmental risks; and other factors that have been discussed in our 2023 Annual Report. Forward-looking statements speak only as of the date on which they are made, and the Company undertakes no obligation, outside of those required under applicable laws or relevant listing rules of the Australian Securities Exchange, to update or revise any forward-looking statement, whether as a result of new information, future events or otherwise. More information on preliminary and uncertain forecasts and estimates is available on request, whereby it is stated that past performance is not an indicator of future performance.

Vitiligo



Autoimmune disorder leads to loss of melanocytes

Severe impact on patient quality of life, highest impact in skin of colour

Lack of effective therapies, no pharmaceutical therapy >10% BSA

"They think it's cosmetic, but it's more for me. I am a lifelong colored person. I feel like I lost my identity."

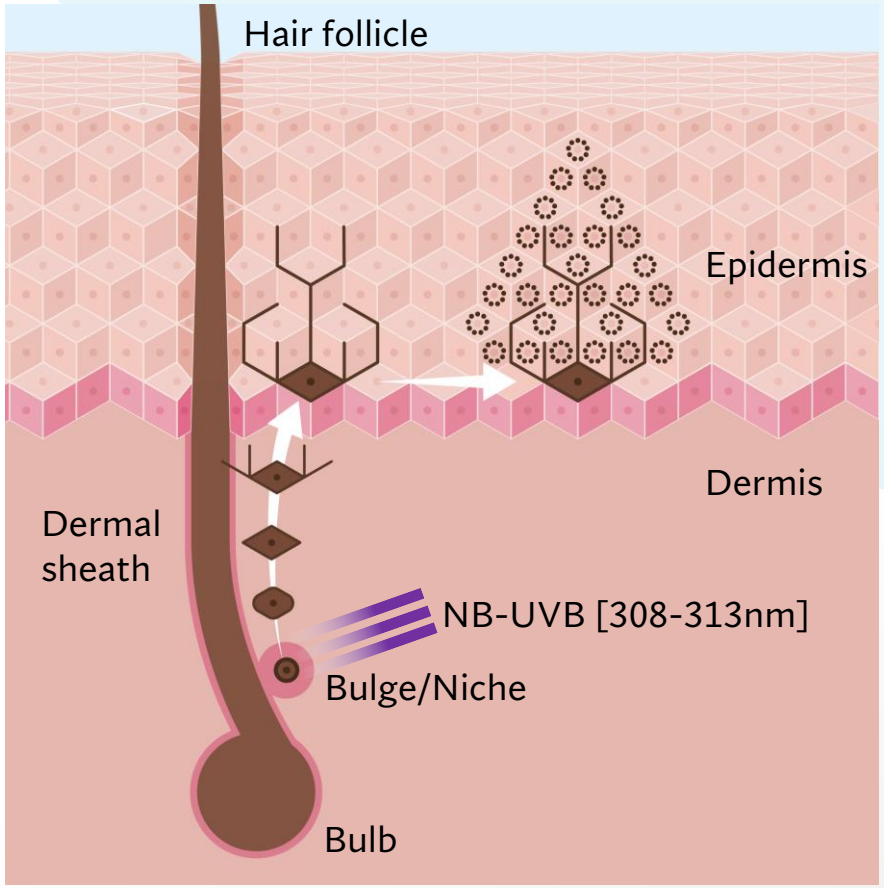
Patient testimony from FDA vitiligo workshop, March 2021

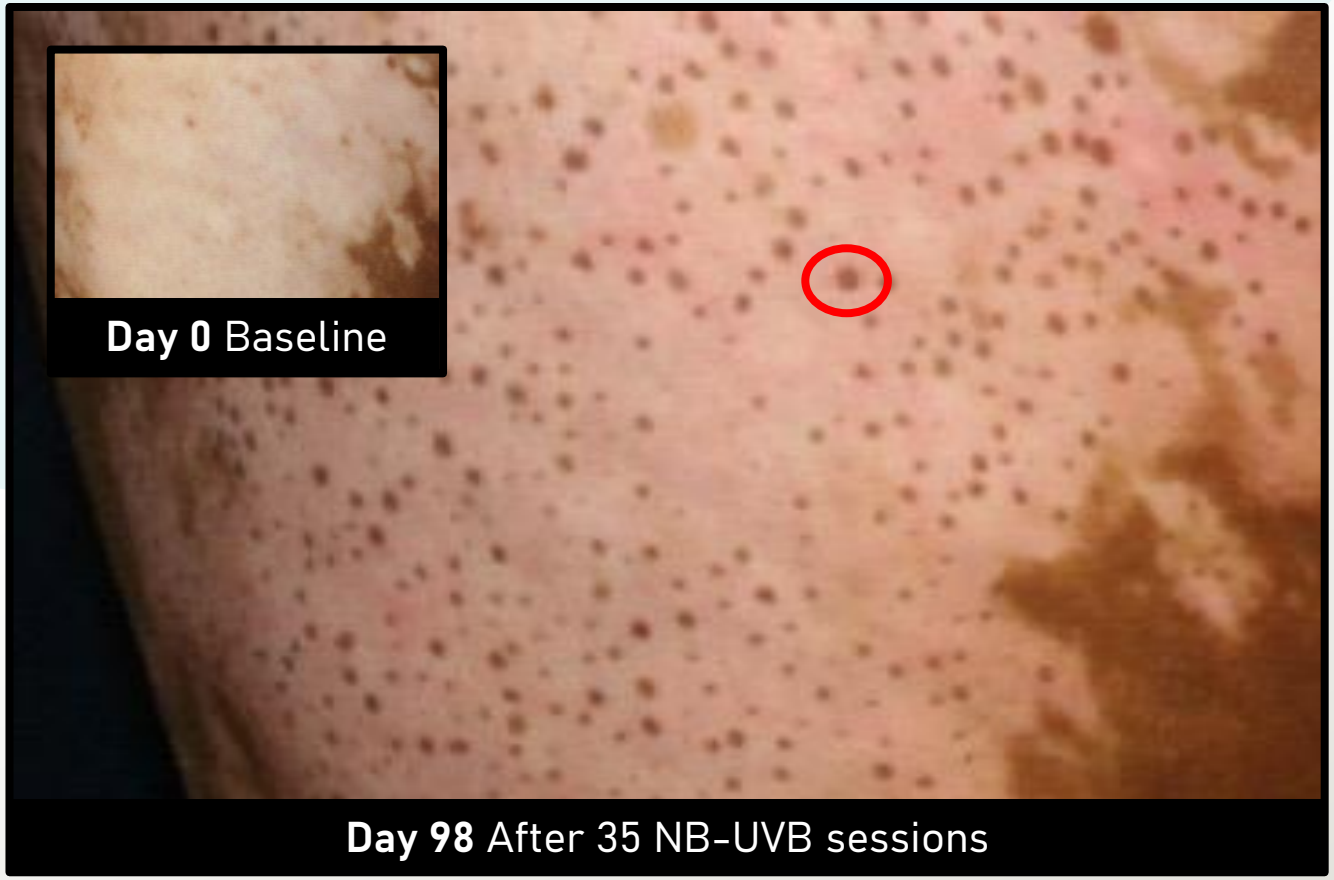
Clinical images courtesy of CUV102 investigators | BSA: Body surface area

NB-UVB – follicular repigmentation

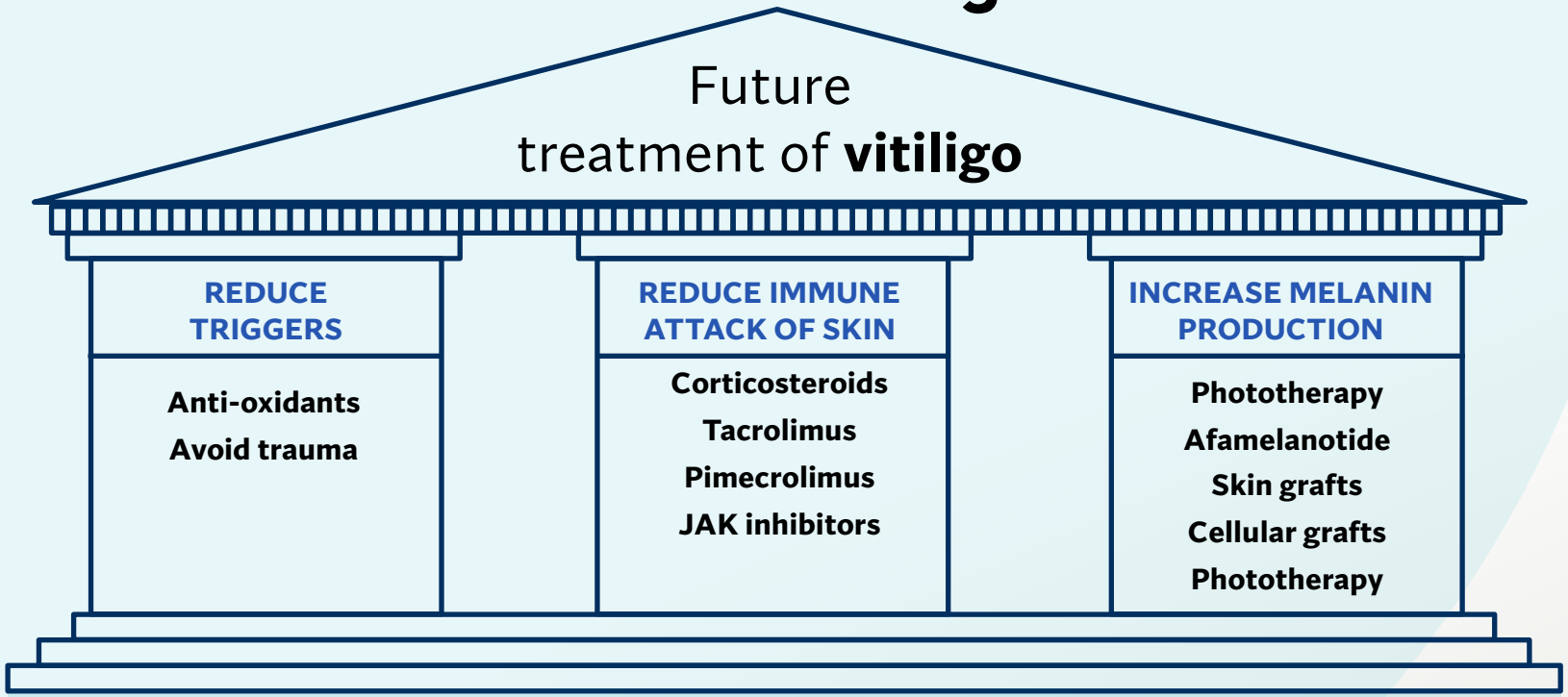
NB-UVB differentiates stem cells in the “niche” of the hair follicle to become melanoblasts.

Melanoblasts differentiate and become fully functioning melanocytes, capable of producing melanin once activated by alpha-melanocyte-stimulating-hormone (α-MSH).





Presented at AAD 2023 – Vitiligo Future Treatment



Afamelanotide

1. **non-immune suppressant**
2. physiological response
3. activates eumelanin
4. icw NB-UVB differentiates stem cells
5. stabilises eumelanin
6. **< 4 weeks to 1st response**
7. **systemic = total body**

JAK inhibitor(s)

1. **immune-suppressant**
2. non-physiological
3. not activating eumelanin
4. no effect on stem cells
5. repetitive use
6. **long time to response**
7. **topical = area-specific (≤10%) BSA**

Vitiligo – active R&D landscape

Active and ongoing clinical development programs

COMPANY	TREATMENT	PHASE II	PHASE III	APPROVED
JAK inhibitors = immune suppression				
Incyte	Ruxolitinib (topical JAK 1/2)	n=157 n=30* (subset)	n=674 (2 trials)	patients 12 years and older
	Povorcitinib (oral JAK 1)	n=171	n=888 (2 planned)*	
Pfizer	Ritlecitinib (oral JAK 3)	n=364	n=600*	
Abbvie	Upadacitinib (oral JAK 1)	n=160*		
Eli Lilly	Baricitinib (oral JAK 1/2)	n=48*		
Other approaches				
CLINUVEL	Afamelanotide +/- NB-UVB	n=58 (combination) n=6* (monotherapy)	n=200* (combination) n=200 (planned)	
AstraZeneca	Anifrolumab (monoclonal antibody) + NB-UVB	n=48*		
Pfizer	Crisaborole & PF-07038124 (phosphodiesterase-4 inhibitors; PDE-4i) +/- NB-UVB	n=64*		
Celgene[1]	Apremilast (PDE-4i)	n=77		
UH Bordeaux	Methotrexate[2]	n=44*		
Almirall[1]	Undisclosed WnT			
Avita	Autologous Cell Harvesting Device	n=100*		Adults

* Study in planning/recruiting/ongoing | [1] Program status undisclosed | [2] Immunosuppressant | Early-stage programs excluded | Sources: ClinicalTrials.gov, EUDRACT/CITIS

CUV102 study results

Results: CUV102 (Phase IIa n=56)		
Treatment (6 months)	SCENESSE®+NB-UVB vs. NB-UVB	
Repigmentation	VASI	p=0.025
Median time to repigmentation (trunk)	41 days vs 59.5 days	p=0.082
Fitzpatrick Skin Types IV-VI subset analyses (n=34)		
Repigmentation Days 56-168	VASI	p<0.001
Maintenance of repigmentation Baseline vs day 336	VASI	p=0.047

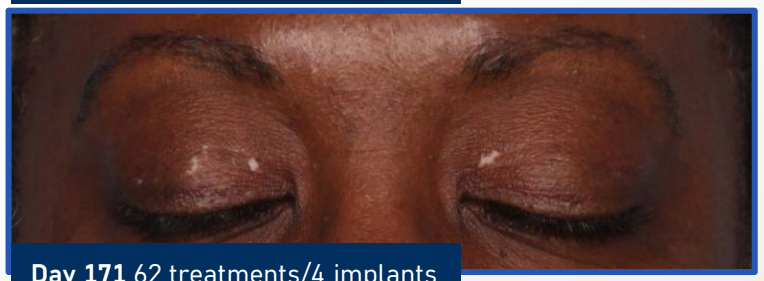
CI: Confidence Index | FST: Fitzpatrick Skin Type | VASI: Vitiligo Area Scoring Index | VETF: Vitiligo European Task Force

CUV102 Phase II study results

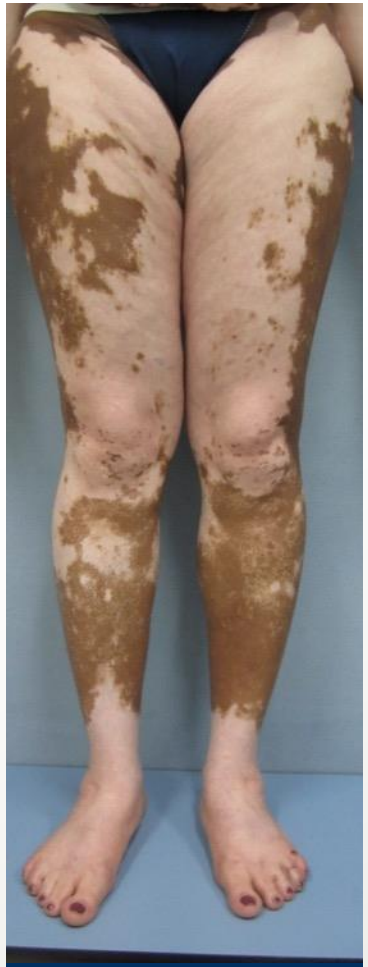
Day 0 Baseline

Day 35 15 treatments/1 implant

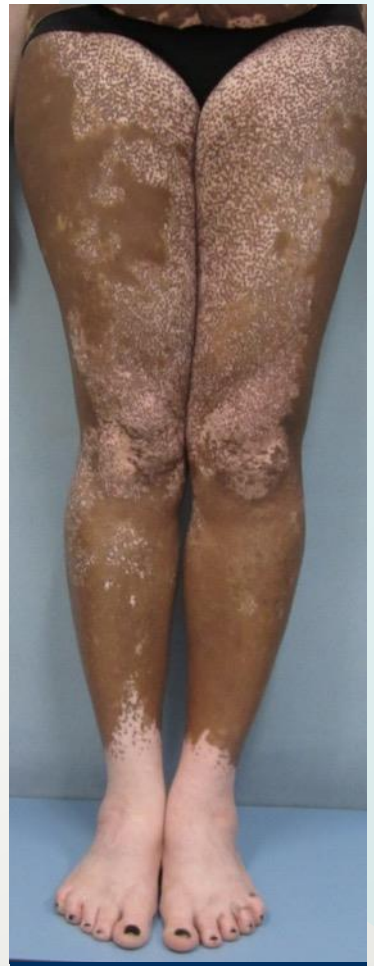
Day 66 29 treatments/2 implants



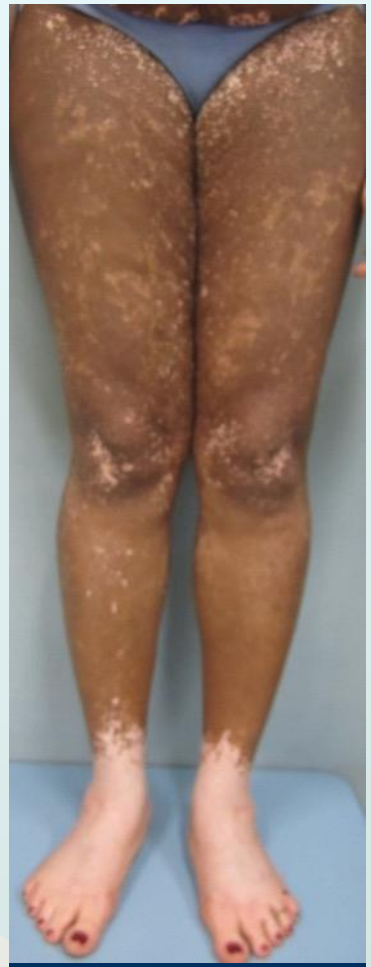
Day 171 62 treatments/4 implants



Day 0
Baseline



Day 111
After 27 NB-UVB treatments,
3 implants



Day 176
After 40 NB-UVB treatments,
4 implants

Vitiligo – global Phase III study (CUV105)

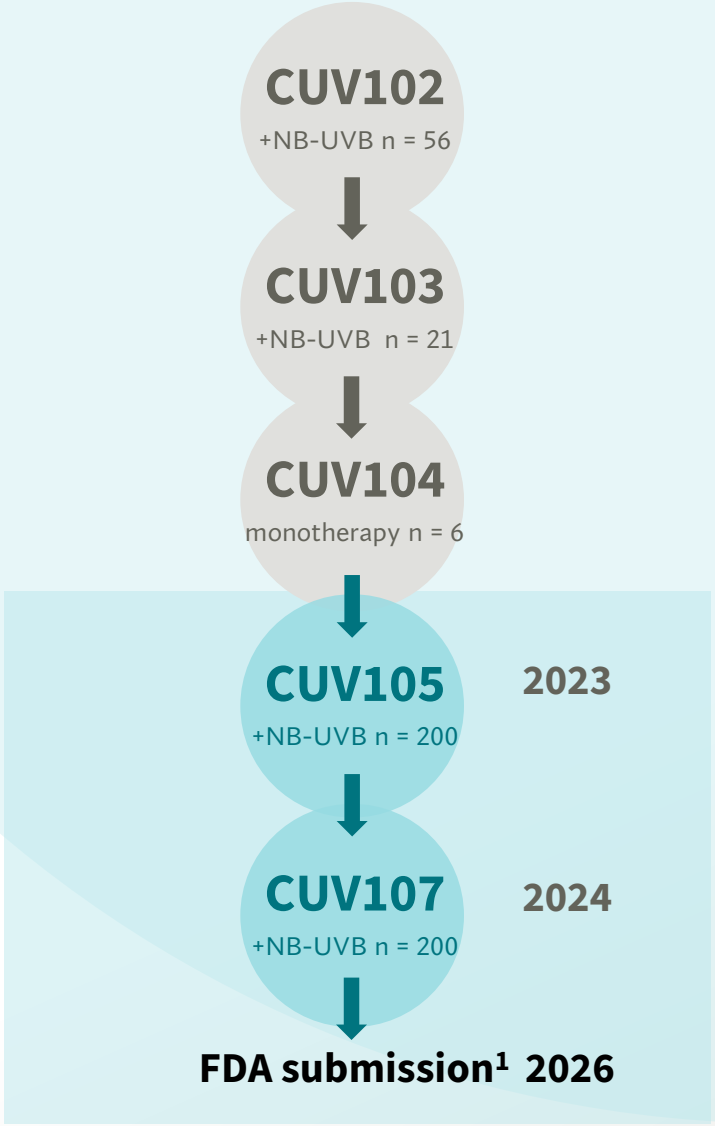
	CLINUVEL CUV105 Phase III	Incyte Phase III program[1]	Pfizer pivotal Phase III oral JAK inhibitor[2]
Study population	N=200, adults and adolescents (≥12 years) highest unmet need: darker skin (Fitzpatrick IV-VI)	N=647, adults and adolescents (≥12 years)	
Inclusion	≥0.3% BSA with facial vitiligo: T-VASI ≥0.3 & F-VASI ≥0.3	≥0.5% facial vitiligo, ≥3% BSA: T-VASI ≥3 & F-VASI ≥0.5. Total BSA ≤10	
Primary endpoint	rate of repigmentation of total body surface (T-VASI50)	F-VASI response at week 24	proportion of participants achieving F-VASI75
Secondary endpoint/s	evaluate repigmentation of the face, maintenance of repigmentation	evaluate repigmentation of the face, total repigmentation (T-VASI), noticeability	proportion of participants achieving T-VASI50
Randomisation	1:1 to SCENESSE® + NB-UVB vs NB-UVB monotherapy	2:1 to 1.5% topical ruxolitinib vs placebo, twice daily	
Treatment duration	20-week treatment phase, six-month follow up	24-week treatment phase, followed by up to 28 weeks of open label active treatment	
Sites	expert treatment centres globally	132 North America & Europe	
Status	12-month recruitment (to October 2024)	Product approved (FDA priority review)	

"Once on the market, SCENESSE® will clinically become the pigment booster"

Vitiligo Expert Panel member

[1] Rosmarin et al (2021) [2] Source: ClinicalTrials.gov

Path to market – afamelanotide



Step 1 **>15,200 doses afamelanotide administered[2]**
- Safety profile accepted

Step 2 **NB-UVB combination**
- program planning resulted in savings US$75 – $145M

Step 3 **2022** **FDA – precedent for NB-UVB as combination therapy**

Step 4 **2022** **Insurers providing reimbursement codes**

Step 5 **Project finance - clinical trials A$77m**

Step 6 **2023** **Vitiligo Expert Panel**

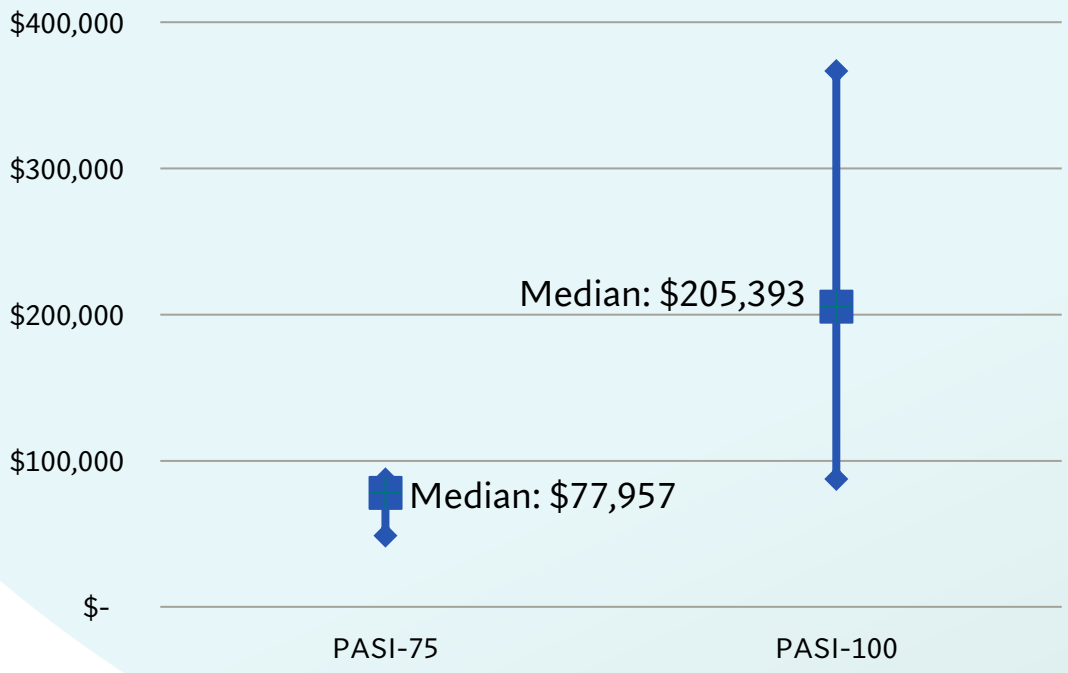
Step 7 **Train & accredit 120 US centres pre-marketing**

[1] Regulatory timelines are dictating timings and progress of filings | [2] All indications

Pricing & reimbursement

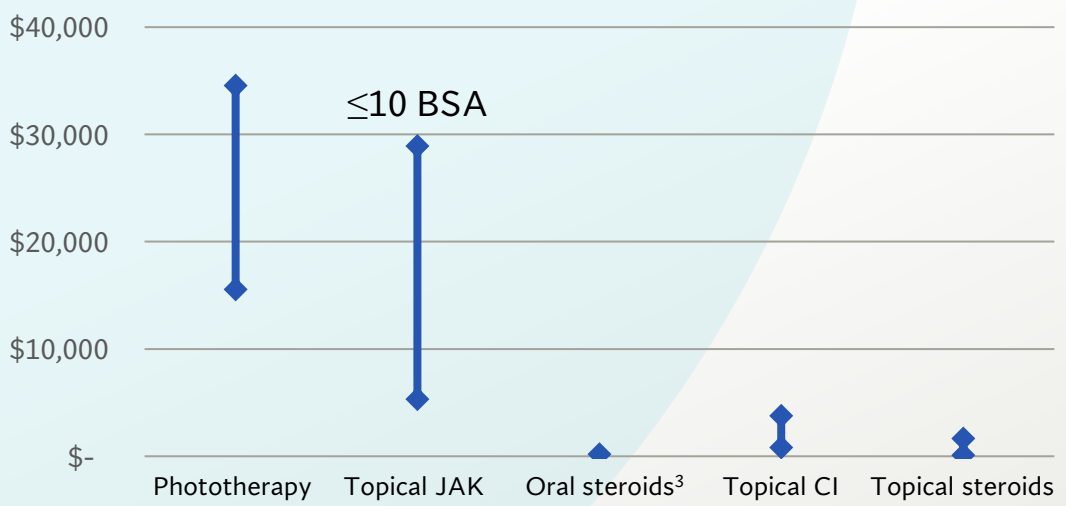
Evolving landscape in dermatology

Annual costs of successful moderate-severe psoriasis biologic treatment ($US, Feldman et al, 2019)



- Annual Medicare out of pocket costs range from $4,423-6,590[1]
- >90% of US insurance plans require PA for psoriasis biologics

Annual costs for vitiligo therapies (US$)[2]



Review of 25 US insurers' policies for vitiligo, 2023			
Treatment	Enable access	Expressly deny	No policy/ other
NB-UVB	11	3	11
Excimer laser	6	8	11
JAK inhibitor	17*	1	7

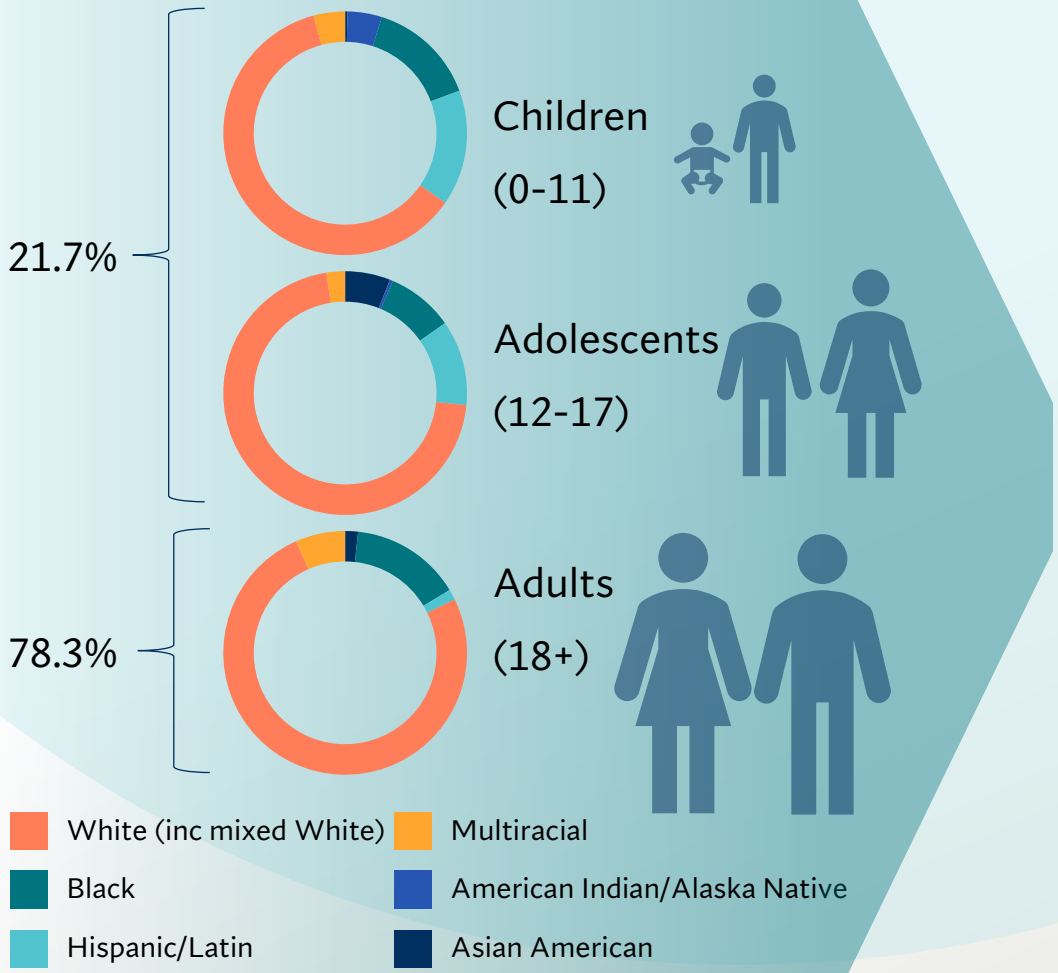
*All require Prior Authorization/ specialty drug. "Step therapy", quantity limits and ≤10% BSA restrictions common.

[1] Pourali et al (2021). [2] CLINUVEL research. Treatment costs vary according to frequency and intensive of treatment. [3] Oral steroids are only used in low doses over a 4-month dosing window. CI: calcineurin inhibitors

North American vitiligo population

2022 population: 333,287,557 (USA), 39,566,248 (Canada)

Demographics (USA)



Adapted from US Census data

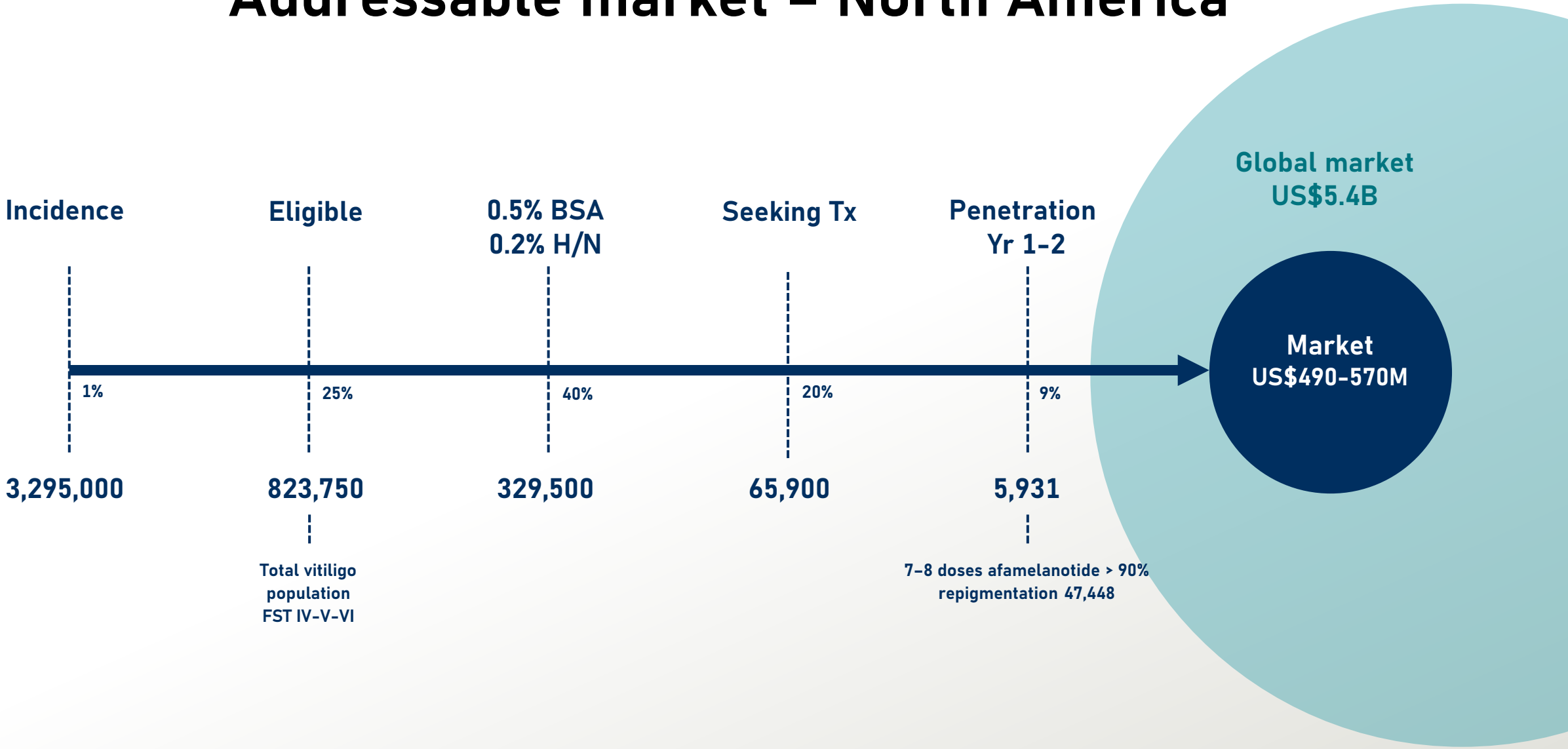
Estimated population Fitzpatrick Skin Types IV-VI

~22%

Vitiligo prevalence 1%

823,750 patients

Addressable market – North America



Conclusions

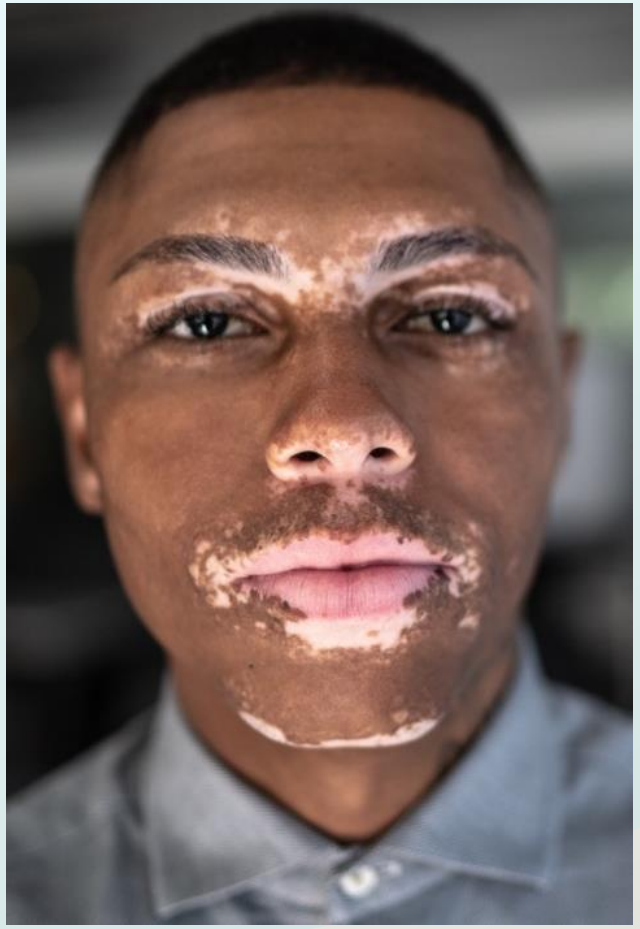
I. Vitiligo has a severe impact on patients' quality of life

II. Current treatment options limited, partially effective, clinically frustrating

III. SCENESSE® offers a systemic "pigmentary booster" effect without suppressing the immune system

IV. Phase III CUV105 study – SCENESSE® + NB-UVB vs NB-UVB monotherapy
   a. FST IV-VI, adolescents and adults
   b. repigmentation of body (T-VASI), facial lesions (F-VASI)
   c. n=200, **first patient treated (October 2023)**
   d. global recruitment at expert treatment centres

V. Path to highest unmet need = North-American addressable market US$490M p/a



References and further reading

Further details on the CUV105 study are available on CLINUVEL's website, www.clinuvel.com.

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