# Vitiligine

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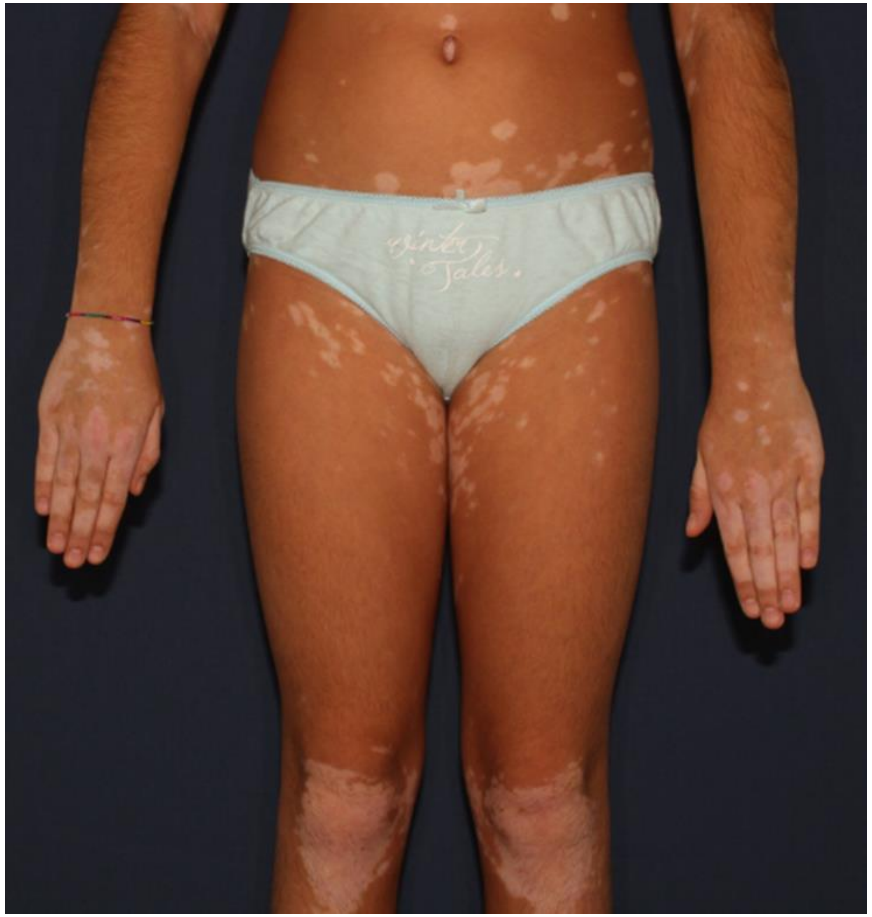
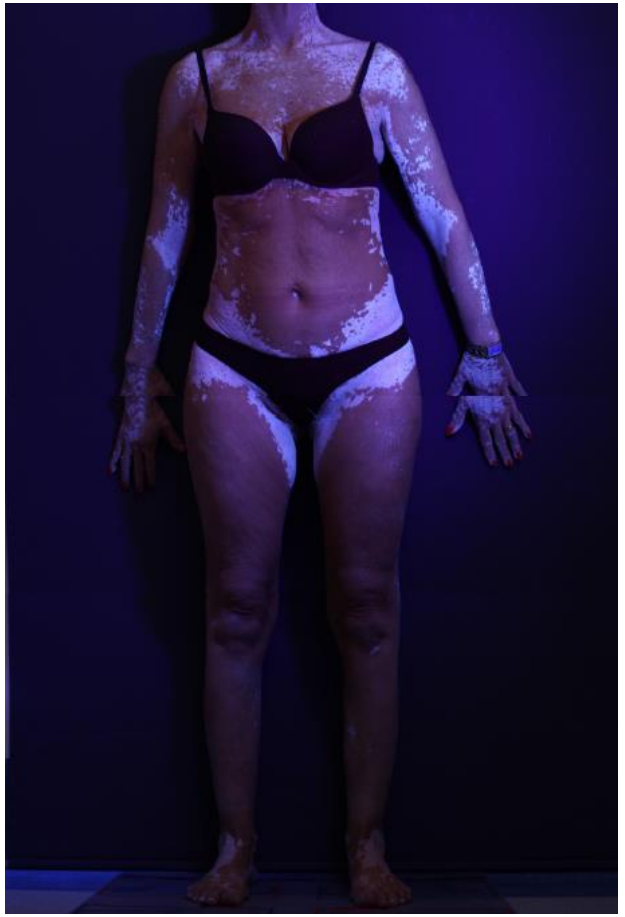
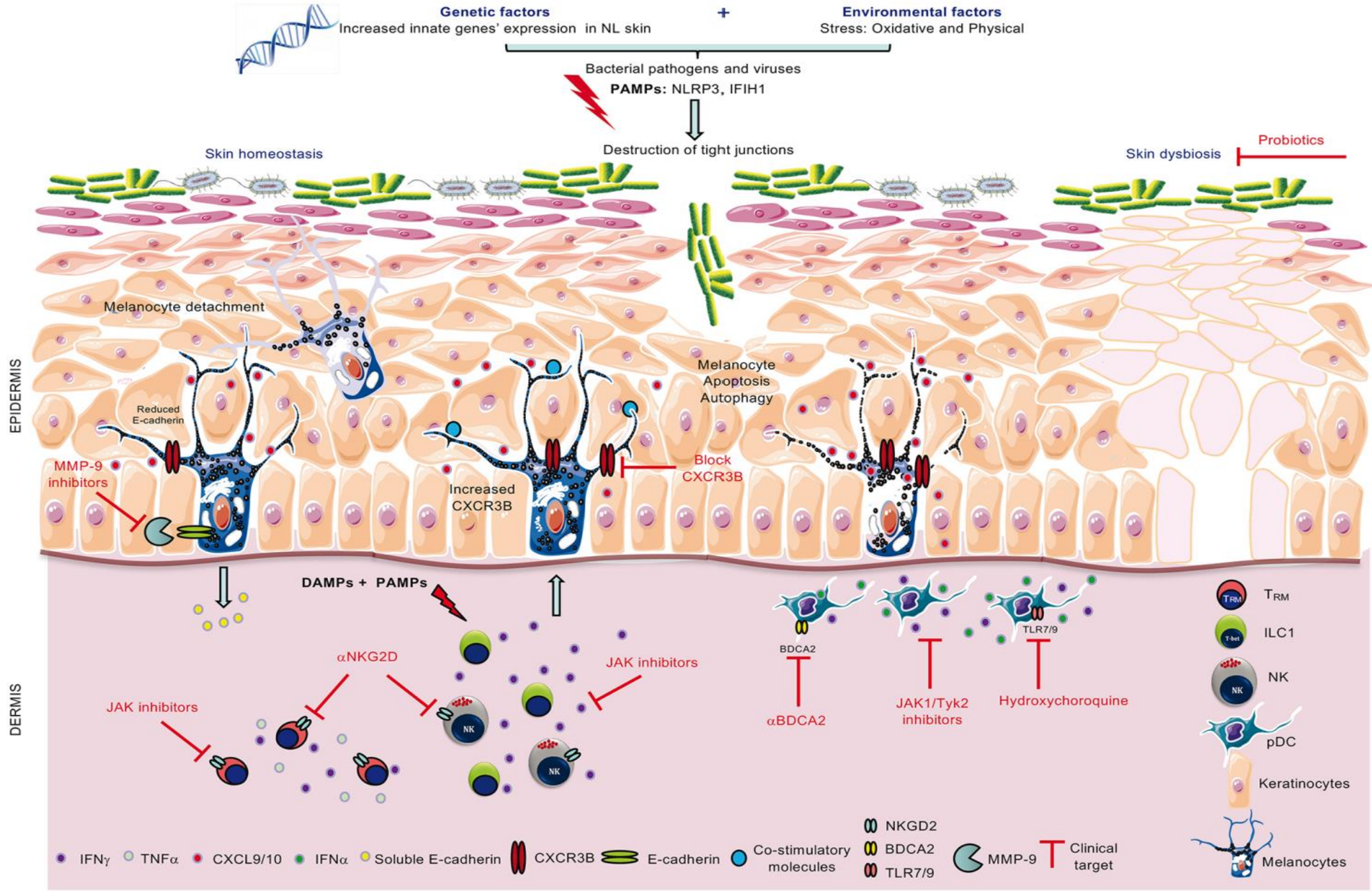
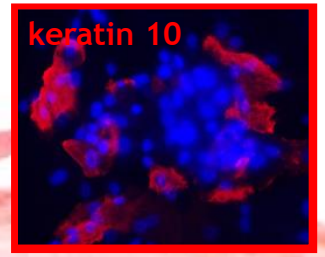
Roma

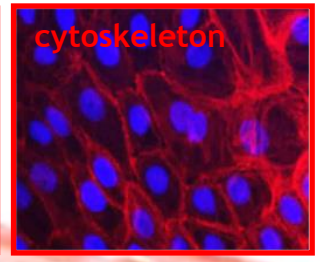




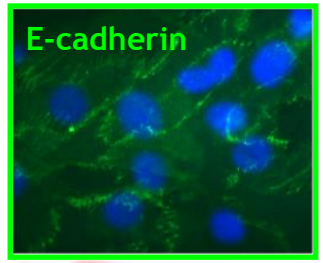
# Vitiligo


Genetic factors
Increased innate genes' expression in NL skin
+
Environmental factors
Stress: Oxidative and Physical
Bacterial pathogens and viruses
PAMPs: NLRP3, IFIH1
Destruction of tight junctions
Skin homeostasis
Skin dysbiosis
Probiotics
EPIDERMIS
DERMIS
Melanocyte detachment
Reduced E-cadherin
MMP-9 inhibitors
Increased CXCR3B
Block CXCR3B
Melanocyte Apoptosis Autophagy
DAMPs + PAMPs
αNKG2D
JAK inhibitors
JAK inhibitors
NK
NK
BDCA2
αBDCA2
JAK1/Tyk2 inhibitors
TLR7/9
Hydroxychoroquine
TRM
ILC1
NK
pDC
Keratinocytes
Melanocytes
IFNγ
TNFα
CXCL9/10
IFNα
Soluble E-cadherin
CXCR3B
E-cadherin
Co-stimulatory molecules
NKGD2
BDCA2
TLR7/9
MMP-9
Clinical target

differentiation integrity/stability adhesion




increased epidermal thickness

**ATP defects**

vitiligo keratinocytes display a deregulated/delayed differentiation associated with disomogeneous organization of actin cytoskeleton and of E-cadherin adhesion molecule

**inflammatory related profile**

**pro-senescent phenotype**

**FIBROBLASTS**

- α-SMA
- ECM protein release
- Cell size enlarged, ↑stress fibers, ↑ROS, ↑p53
- SASP secretion

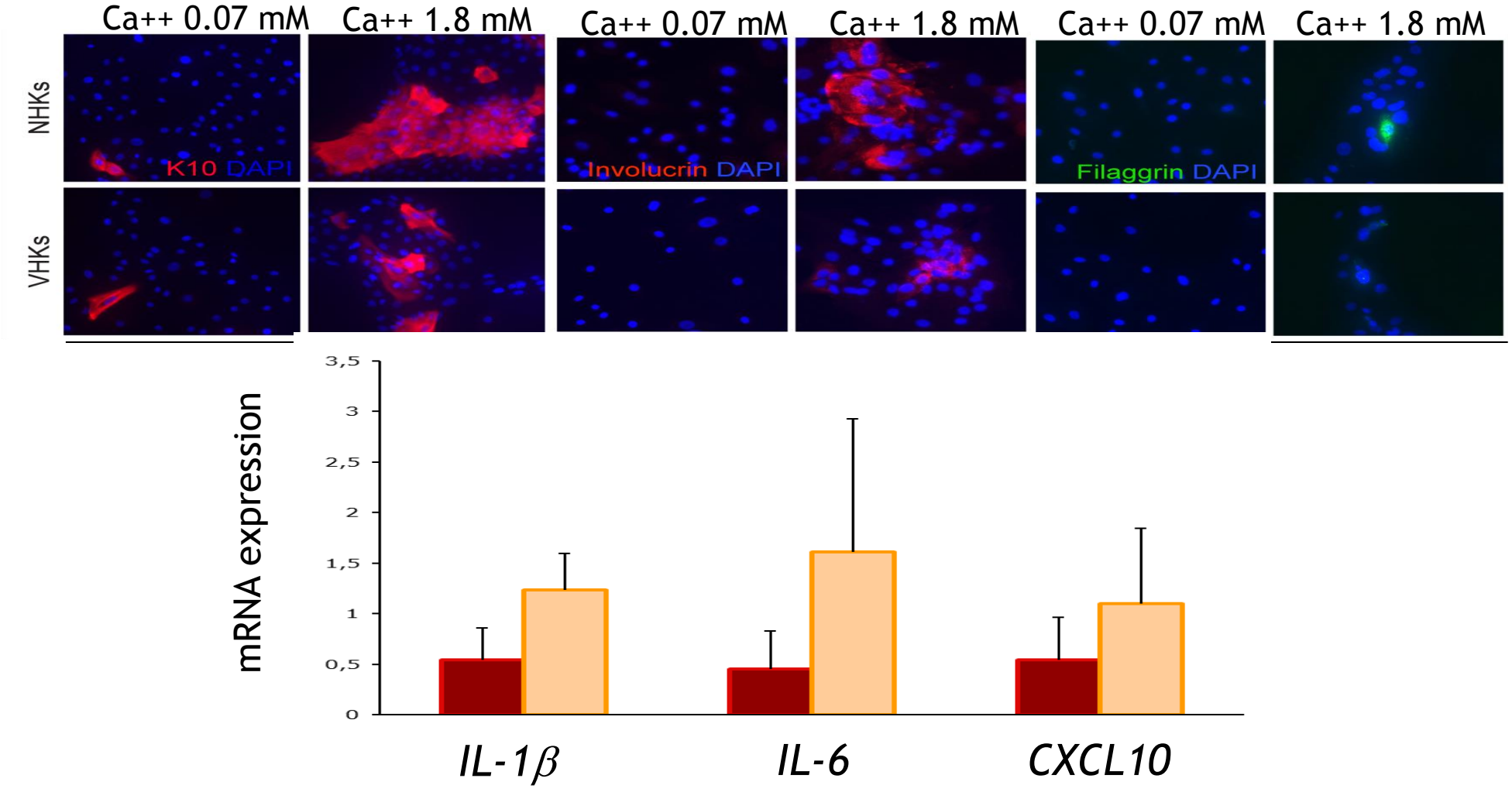
**MELANOCYTES**

- ↑ ROS generation
- ↓ antioxidant mechanisms
- Mitochondrial alterations
- SASP secretion

**KERATINOCYTES**

- ↑TNF-α and IIL-1
- ↓SCF
- Swollen Mitochondria
- Increased ROS, reduced antixodants,
- inflammosome activation

# Vitiligo: a skin barrier disease?

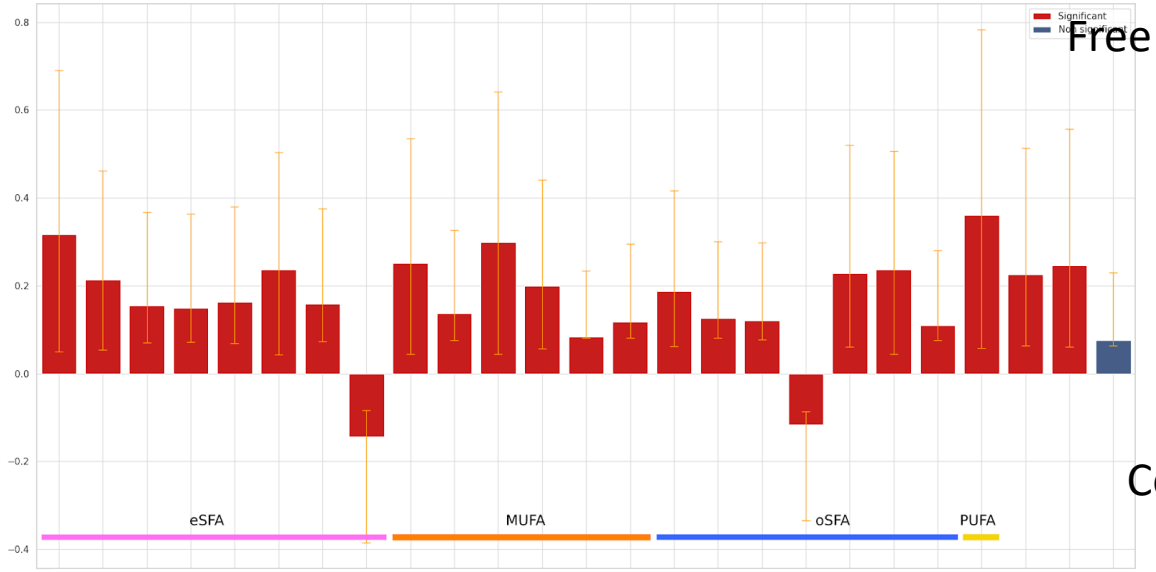


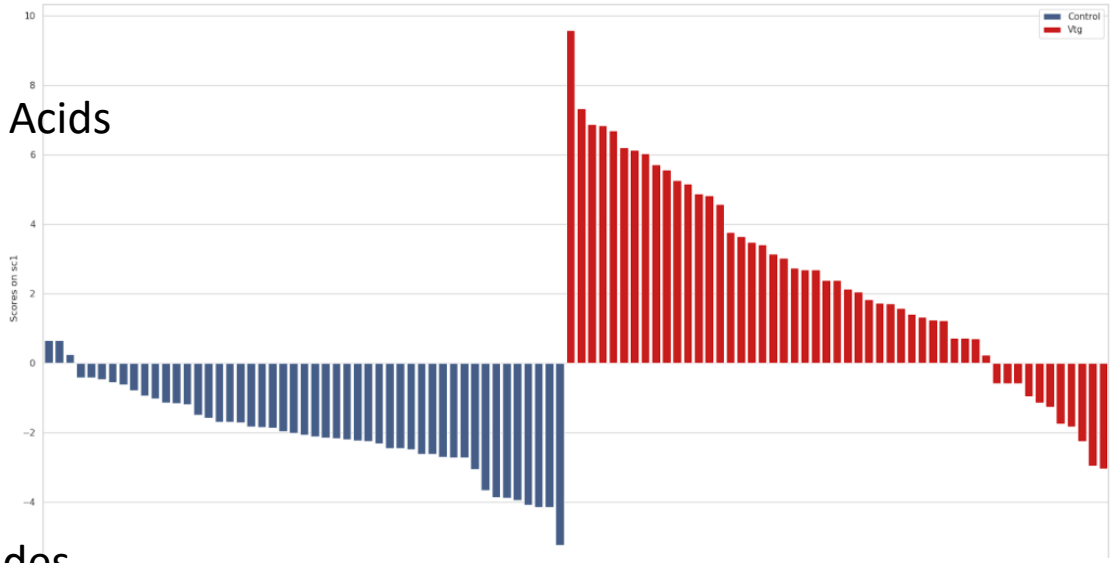

deregulated differentiation process are in non lesional vitiligo keratinocytes is associated with a spontaneous release of pro inflammatory mediators

Kovacs et al Science ADV 2022

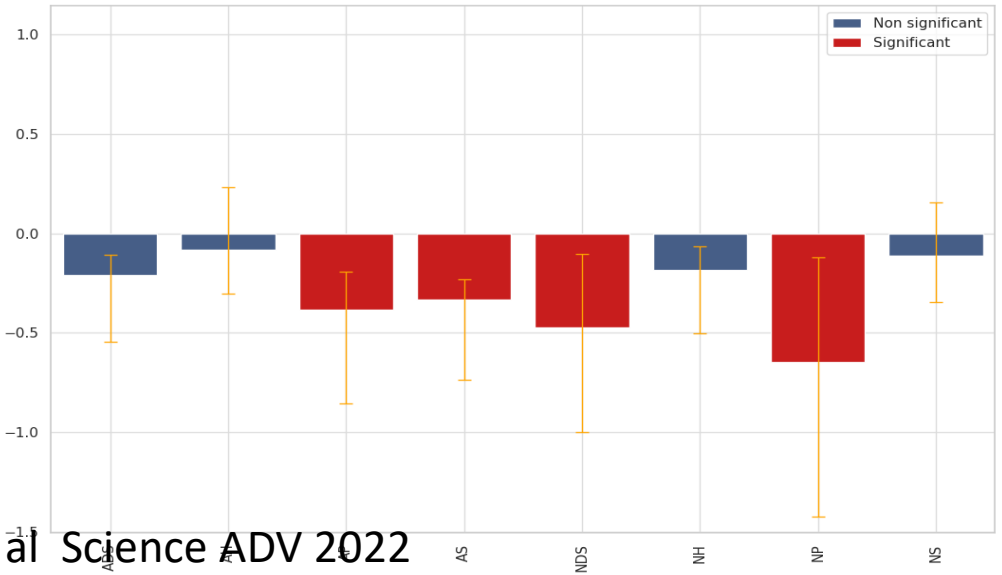
# Barrier Lipids alterations

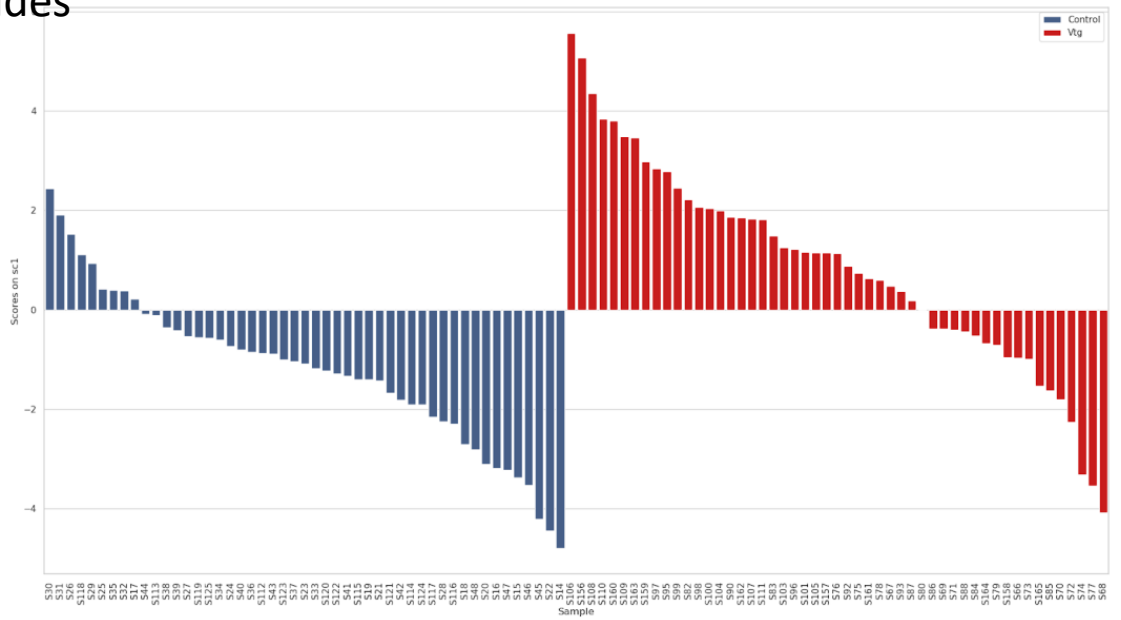
Free Fatty Acids




Ceramides




Kovacs et al Science ADV 2022

Controls and VTG patients, *p-value* < 0.0001

# Increased sensitivity of vitiligo keratinocytes to HDM

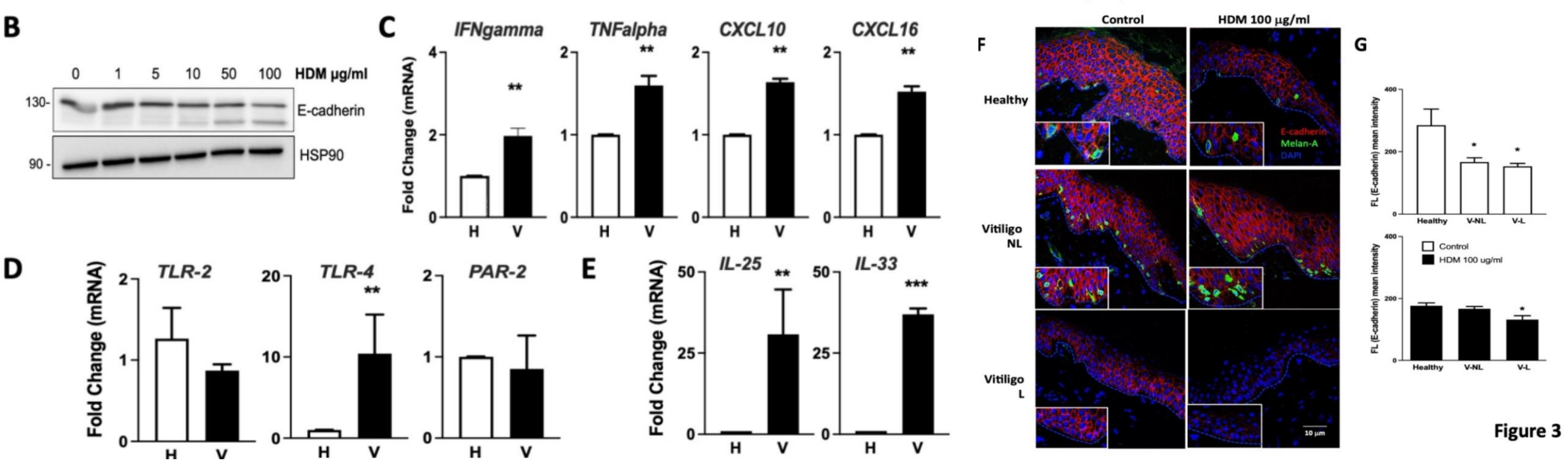
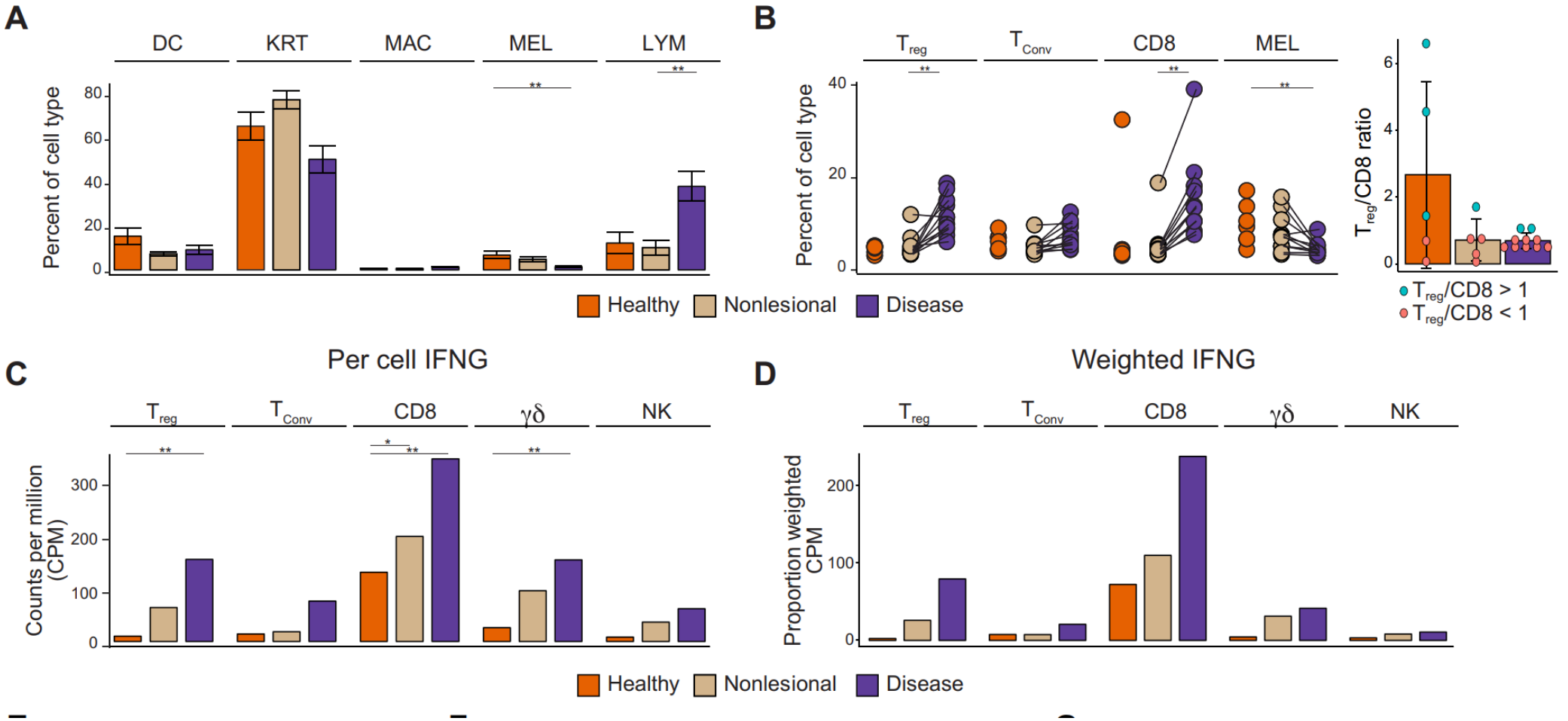



Figure 3

Bzioueche et al BJD 2023

# Activation of immune cells reveals subclinical inflammation in nonlesional vitiligo skin




Gellatly et al., Sci. Transl. Med 2021

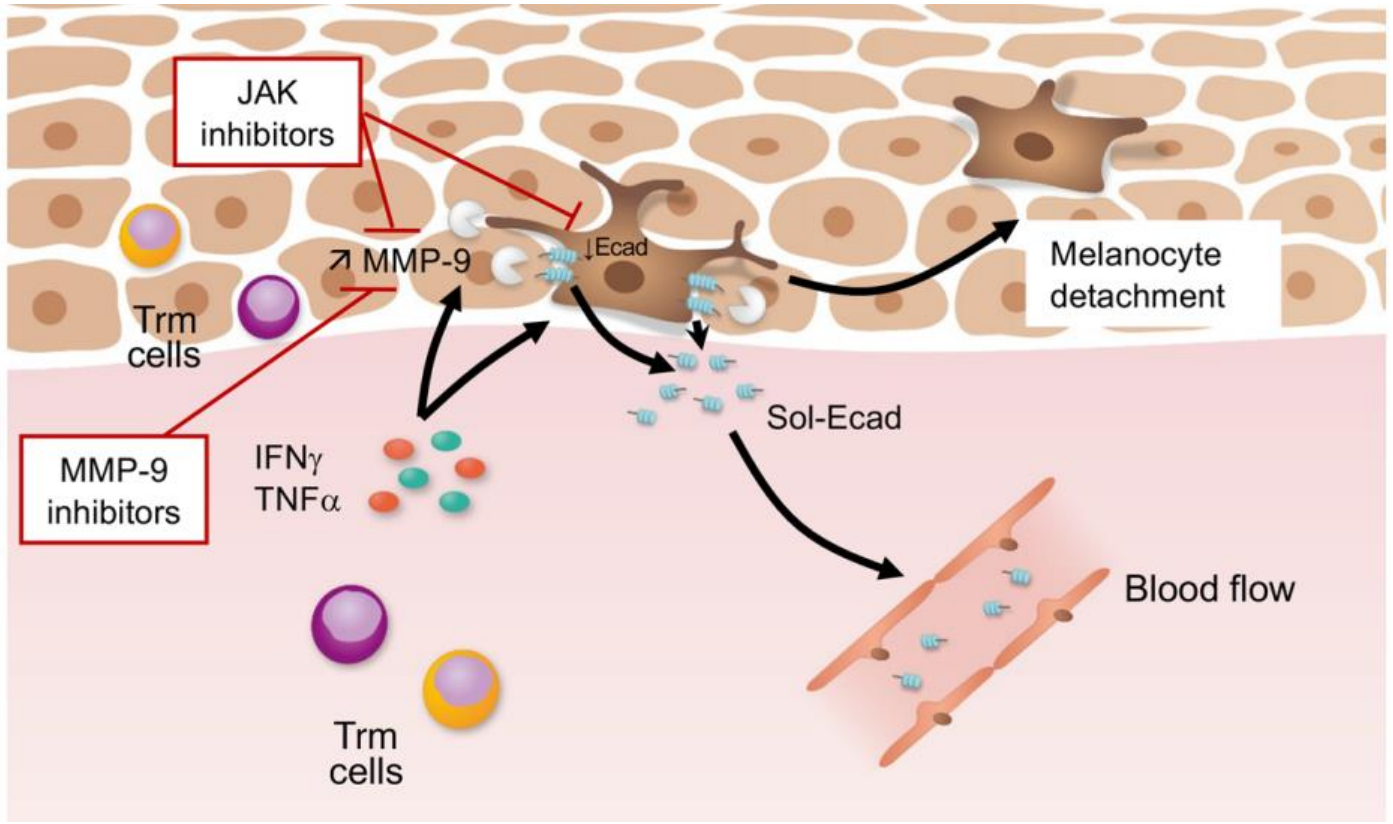
# Putative model of primary event leading to loss of melanocytes in depigmenting disorders

melanocyte destruction by cytotoxic CD8 T cells has been observed in vitro but this hypothesis lacks clear confirmation in patients.

the death of melanocytes could occur after their detachment from the basal layer of perilesional skin

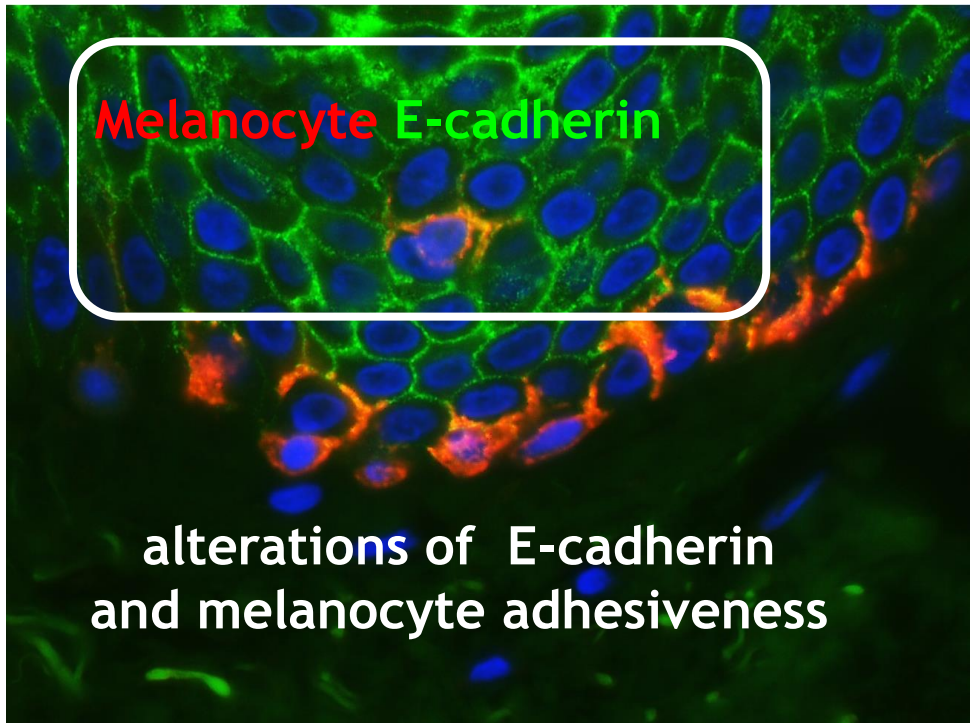
The vitiligo skin T-cell secretome did not induce melanocyte death in vitro.

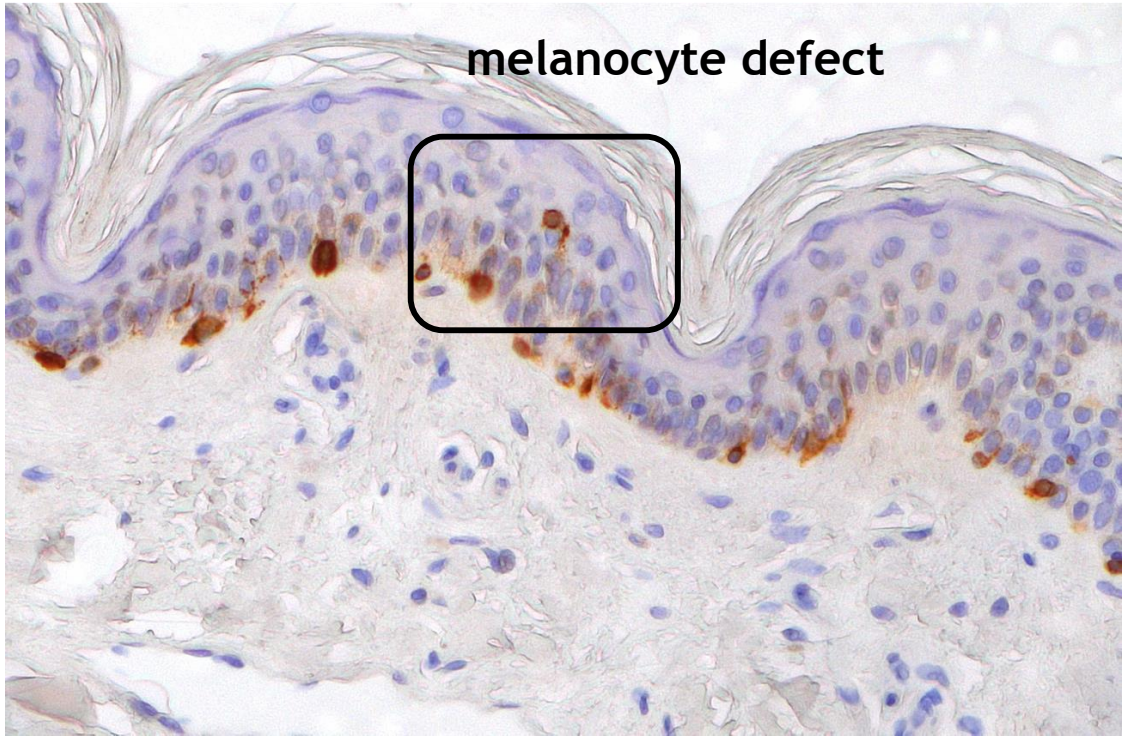
our data do not reflect the potential cytotoxic activity of activated T cells located close to remaining melanocytes in perilesional vitiligo skin




Boukhedouniet al JCI insight 2020

# Deregulated Interaction between Epidermal and Dermal Compartments in normal appearing Skin



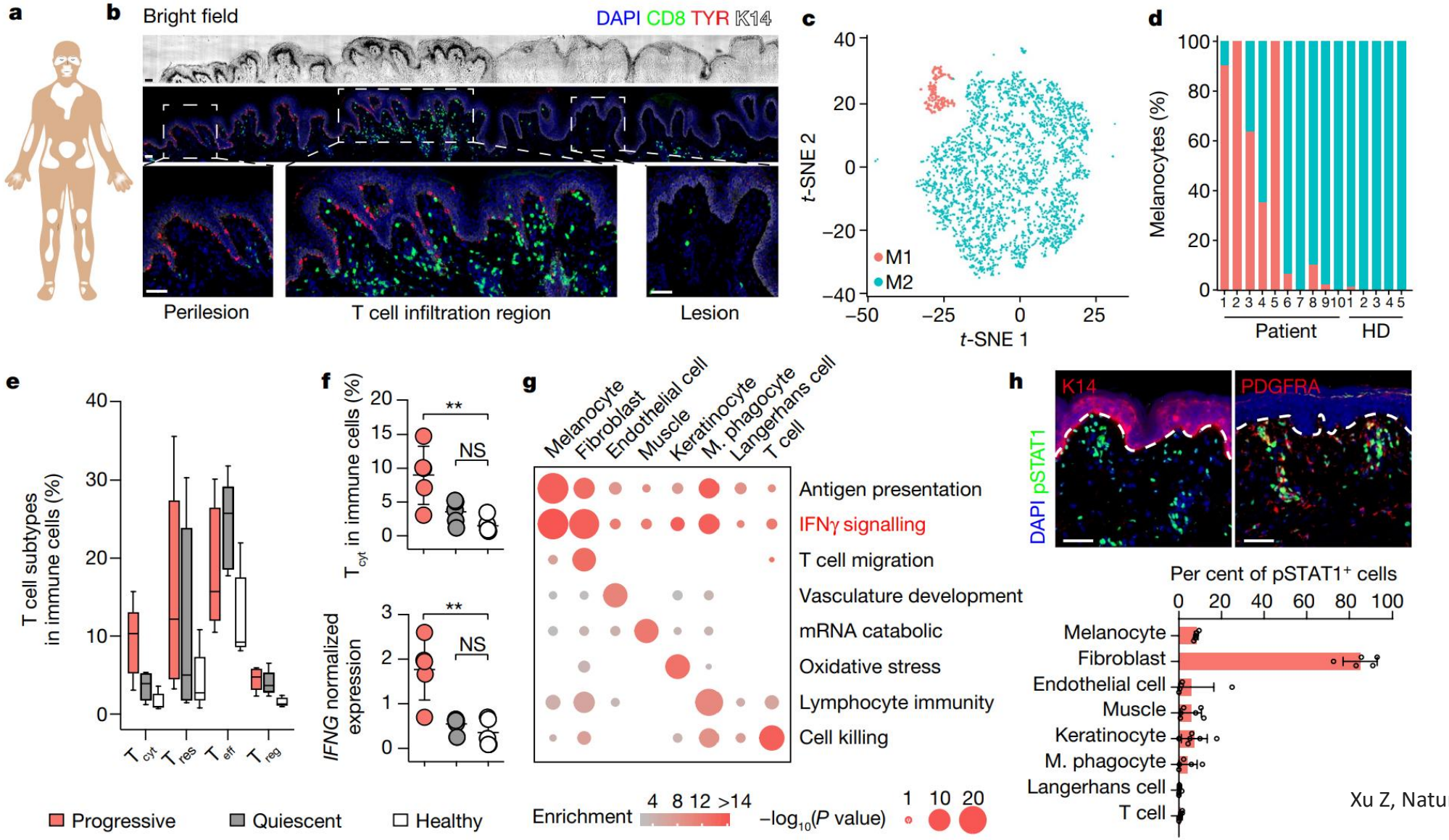



**SASP proteins (HGF, IL-1β, IL-6)**

Non-lesional vitiligo fibroblasts display metabolic alterations associated to a premature senescent phenotype and through the production of aging-associated secreted proteins they can affect melanocyte function and favor their loss

Bourdeau et al. JCI insight 2020

# Distinct IFNγ-responsive cell types in the skin of patients with vitiligo

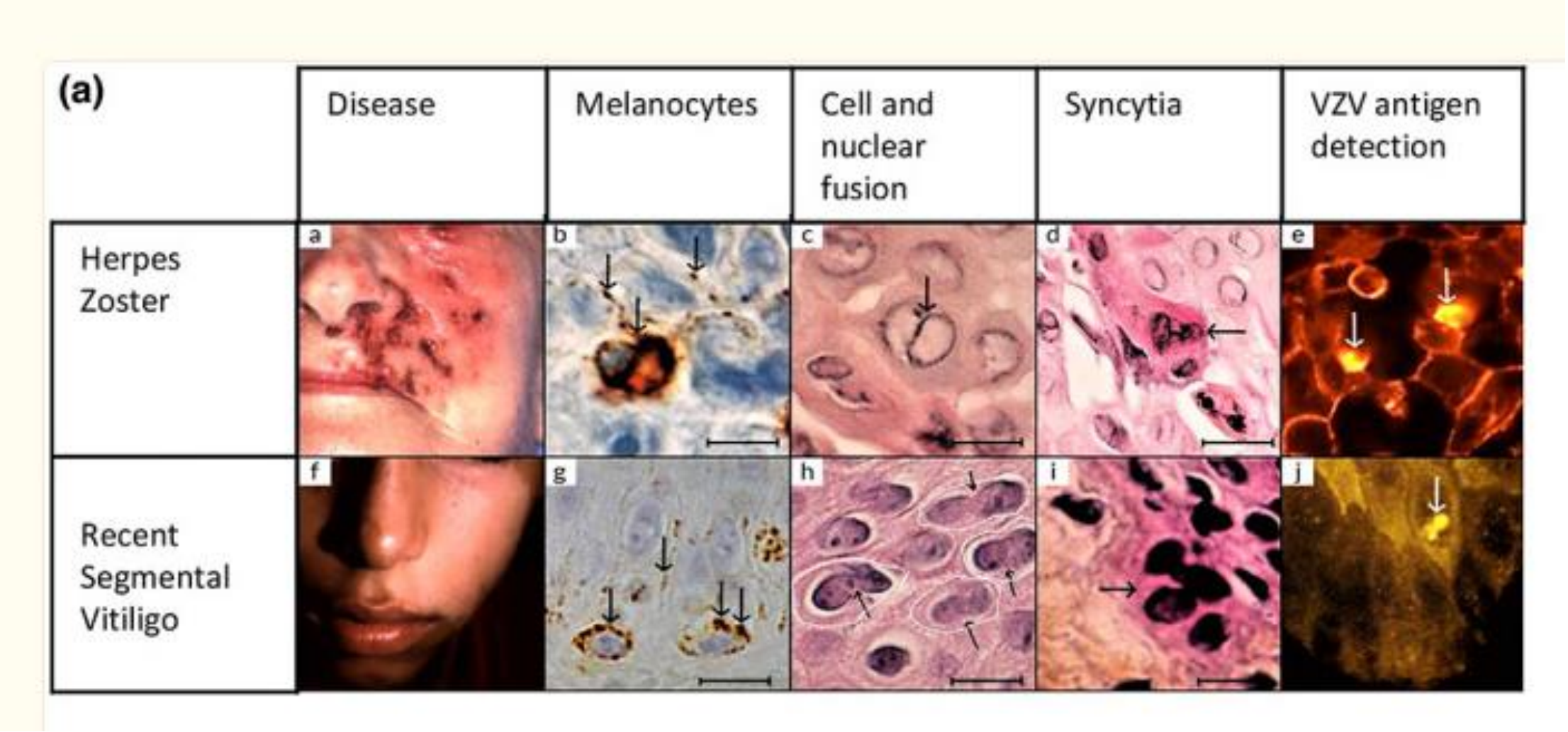



Xu Z, Nature. 2022 .

# Vitiligo and metabolic syndrome

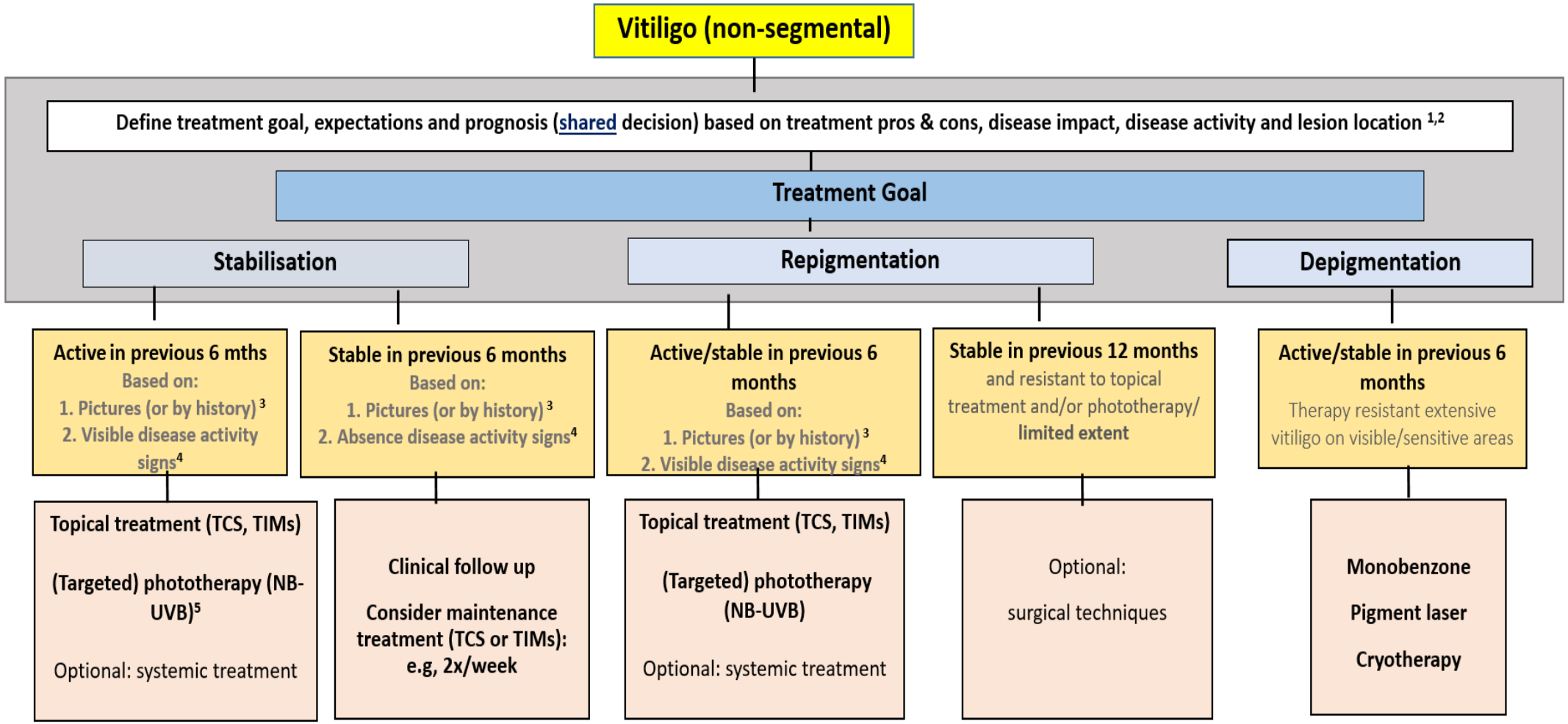
- Higher incidence of the metabolic syndrome classified according to the ATP III criteria with higher levels of fasting blood glucose especially in patients with a higher VASI in a Turkish study.
- Sharma al. have confirmed the increased rates of metabolic syndrome, hypertriglyceridemia, low HDL levels, and impaired glucose tolerance
- Azzazi et al. has shown that a subset of patients is at a higher risk of developing dyslipidemia and atherosclerosis, which might increase their future risk for the development of cardiovascular disease
- D'Arino reported lower levels of total cholesterol with LDL cholesterol and triglycerides values higher than in the controls, as well as lower HDL levels. Fast Blood Glucose PG levels significantly higher
- Possible role of gut microbioma

# Possible HZV in Segmental Vitiligo




Gauthier Y,et al PCMR 2023

# Recommendations for the management

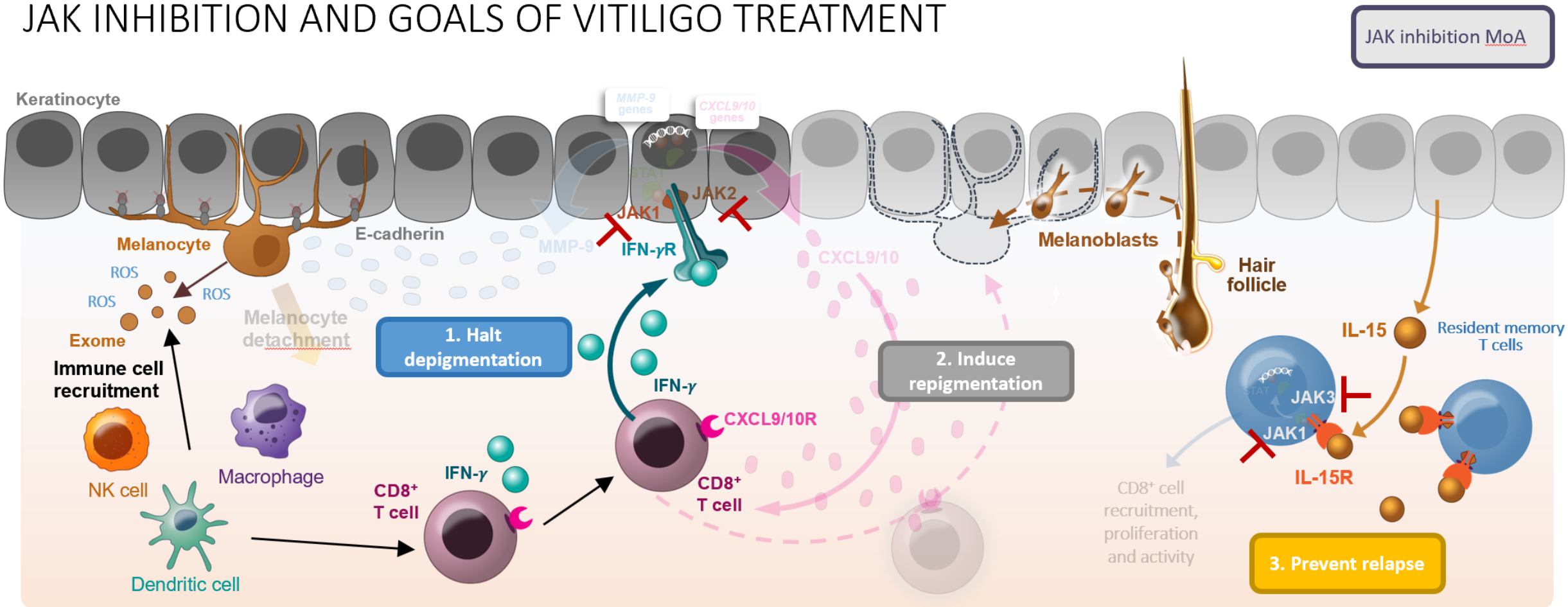



**General remarks:**

- Use algorithm in combination with information/recommendations provided in the text.
- Provide information : avoidance Koebner's phenomon, cosmetic skin camouflage, use of sunscreens (consider information leaflet)
- Consider and discuss the risk-benefit ratio in particular for systemtic treatments, combination therapies (e.g., TIMs/systemic treatment + UV) and prolonged treatment

Van Geel et al JEADV 2023

# JAK INHIBITION AND GOALS OF VITILIGO TREATMENT

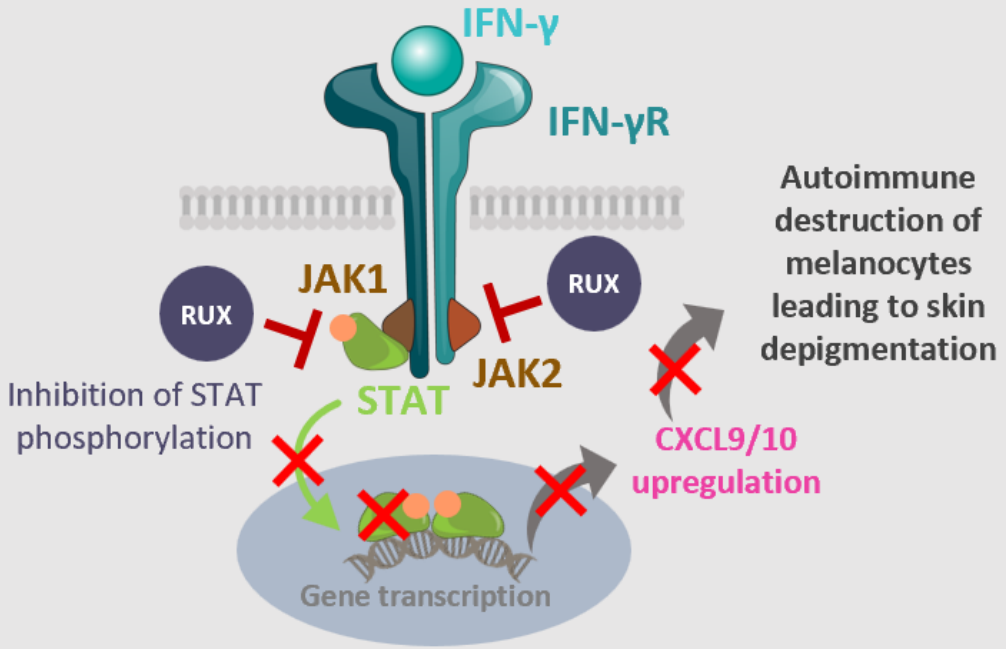


# Ruxolitinib cream mechanism of action

- **Ruxolitinib** is a non-steroidal, anti-inflammatory, selective and potent **JAK1** and **JAK2** inhibitor[1–5]
- **Ruxolitinib cream** is a topical formulation of **ruxolitinib**, which was found to have physicochemical properties suitable for delivery through the skin of patients with inflammatory skin conditions[4,6]
- Ruxolitinib binds **JAK1** and **JAK2**, preventing phosphorylation and activation of **STAT** proteins[1]

**Enzymatic potency of ruxolitinib[5]**

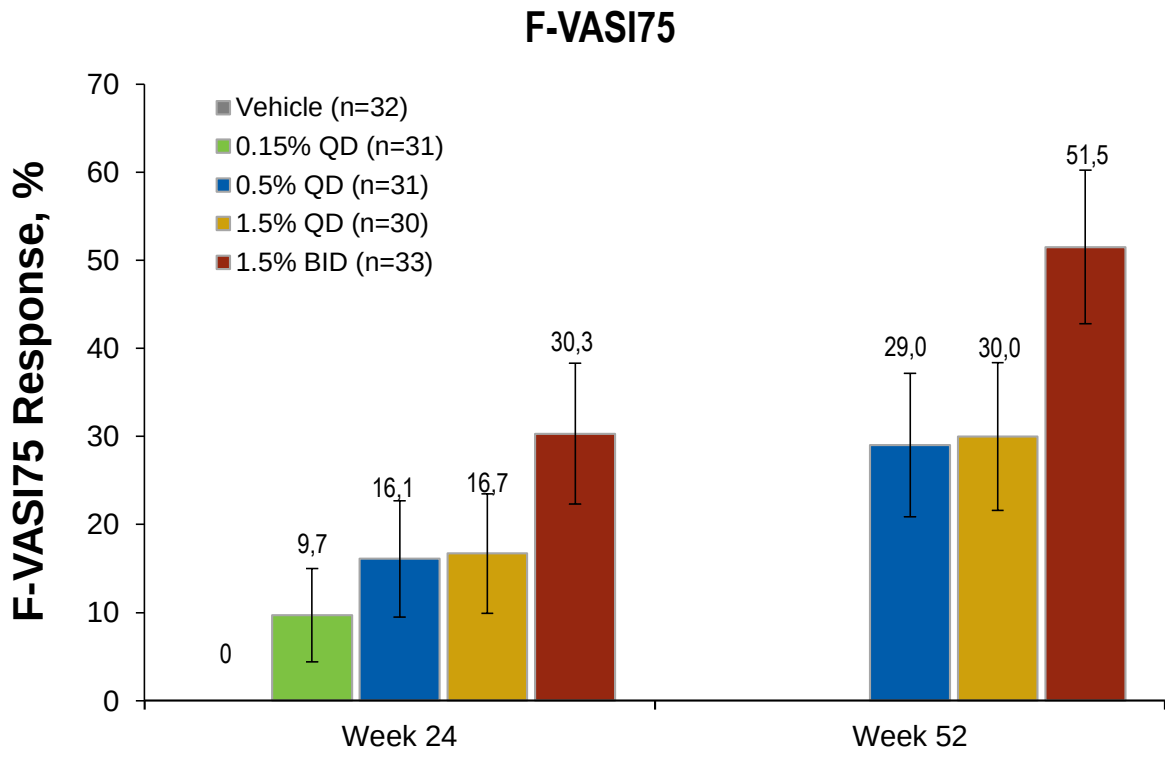
| Enzyme | $IC_{50}$ |
|---|---|
| JAK1 | 3.3±1.2 nM |
| JAK2 | 2.8±1.2 nM |
| JAK3 | 428±243 nM |
| TYK2 | 19±3.2 nM |

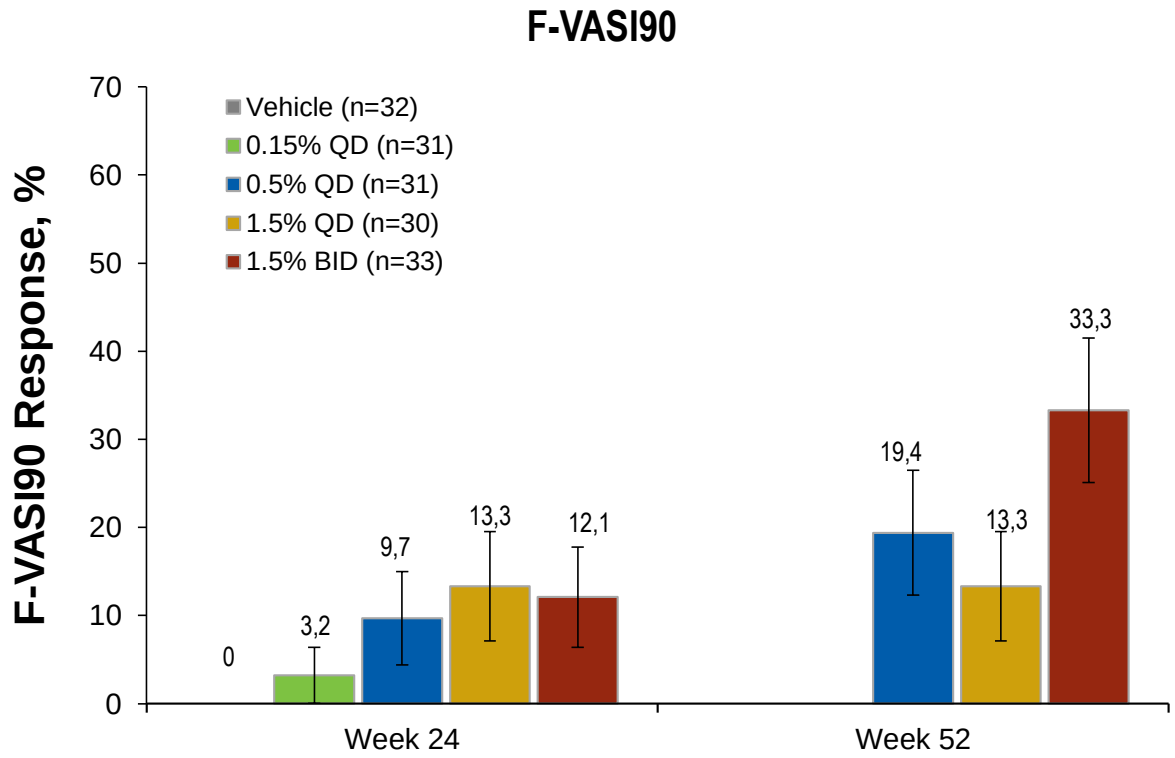



CXCL9/10, C-X-C motif chemokine ligand 9/10; $IC_{50}$, 50% inhibitory concentration; IFN, interferon; JAK, Janus kinase; RUX, ruxolitinib; STAT, signal transducer and activator of transcription; TYK2, tyrosine kinase protein 2. 1. Howell M, et a *Front Immunol.* 2019;10:2342. 2. Howell M, et al. *Ann Allergy Asthma Immunol*. 2018;120:367-375. 3. Lee H, et al. *J Invest Dermatol*. 2016;136:2427-2435. 4. Kim BS, et al. *J Allergy Clin Immunol*. 2020;145:572-582. 5. Covington M, et al. *E J Pharmacol*. 2020;885:173505. 6. Smith, P. et al. *Pharmaceutics*. 2021;13:1044.

Howell MD, et al. *Front Immunol*. 2019;10:2342. 5. Rashighi M, Harris JE. *Dermatol Clin*. 2017;35:257–265. 6. Rosmarin D, et al. *Lancet*. 2020;396:110–120. 7. Chen X, et al. *Free Radical*

# F-VASI75 and F-VASI90 Responses to Topical Ruxolitinb




Error bars indicate standard error.

# Efficacy of 52 weeks' treatment twice daily 1,5% Ruxolitinib cream

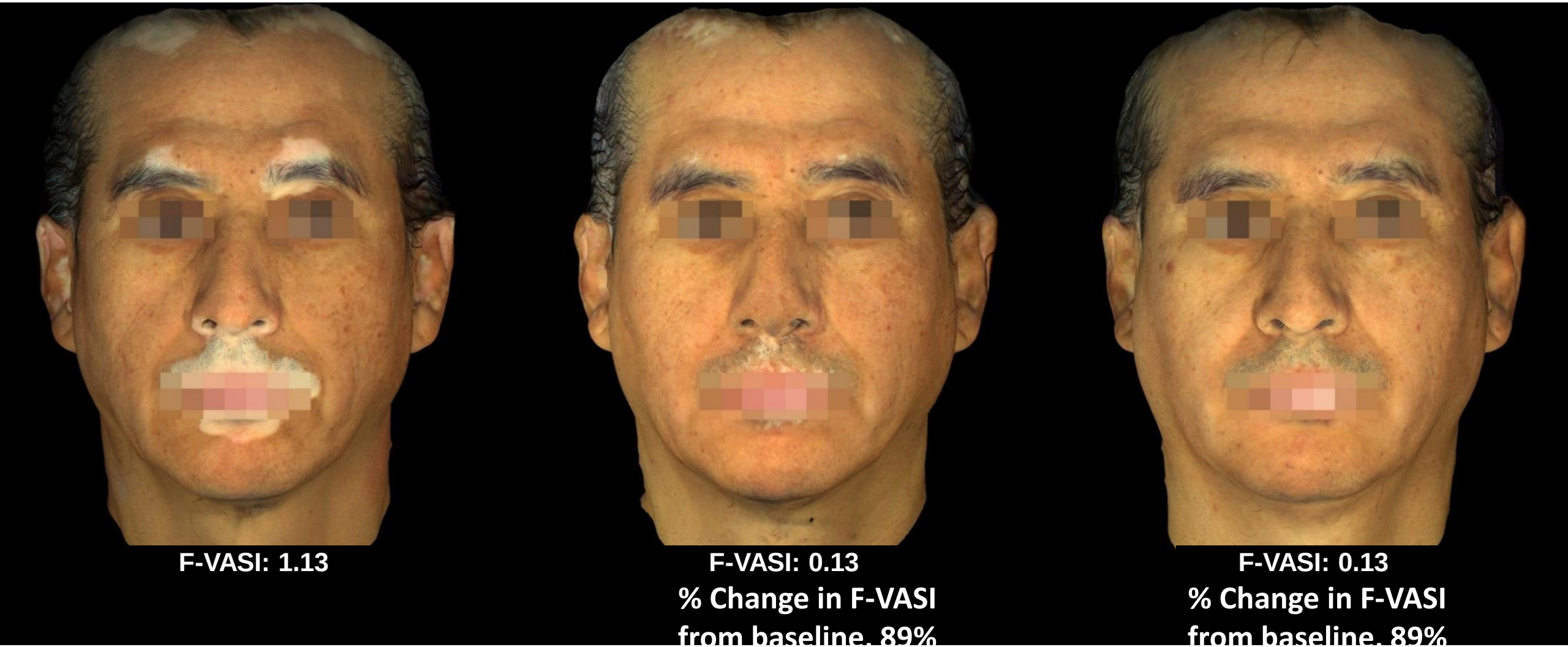
| | TRuE-V1 | | TRuE-V2 | |
|---|---|---|---|---|
| VASI | 1.5% ruxolitinib cream b.i.d. *n* = 173 (variability) | Vehicle to week 24 weeks/1.5% Ruxolitinib cream b.i.d. after Week 24 *n* = 82 (variability) | 1.5% ruxolitinib cream b.i.d. *n* = 177 (variability) | Vehicle (up to Week 24 weeks)/1.5% ruxolitinib cream b.i.d. after Week 24 *n* = 82 (variability) |
| F-VASI25 (Week 52) | 89.6 (84.1, 93.7) | 74.4 (63.6, 83.4) | 82.5 (76.1, 87.8) | 71.6 (60.5, 81.1) |
| F-VASI50 (Week 52) | 75.1 (68.0, 81.4) | 56.1 (44.7, 67.0) | 74.0 (66.9, 80.3) | 49.4 (38.1, 60.7) |
| F-VASI75 (Week 52) | 52.6 (44.9, 60.2) | 26.8 (17.6, 37.8) | 48.0 (40.5, 55.6) | 29.6 (20.0, 40.8) |
| F-VASI90 (Week 52) | 32.9 (26.0, 40.5) | 12.2 (6.0, 21.3) | 27.7 (21.2, 34.9) | 16.0 (8.8, 25.9) |
| T-VASI25 (Week 52) | 77.5 (70.5, 83.5) | 56.1 (44.7, 67.0) | 76.8 (69.9, 82.8) | 53.1 (41.7, 64.3) |
| T-VASI50 (Week 52) | 53.2 (45.5, 60.8) | 31.7 (21.9, 42.9) | 49.2 (41.6, 56.8) | 22.2 (13.7, 32.8) |
| T-VASI75 (Week 52) | 20.2 (14.5, 27.0) | 9.8 (4.3, 18.3) | 20.9 (15.2, 27.6) | 8.6 (3.5, 17.0) |
| T-VASI90 (Week 52) | 3.5 (1.3, 7.4) | 2.4 (0.3, 8.5) | 6.8 (3.6. 11.5) | 1.2 (0, 6.7) |

Abbreviations: F-VASI, facial vitiligo area scoring index; T-VASI, total body vitiligo area scoring index; VASI, vitiligo area scoring index.

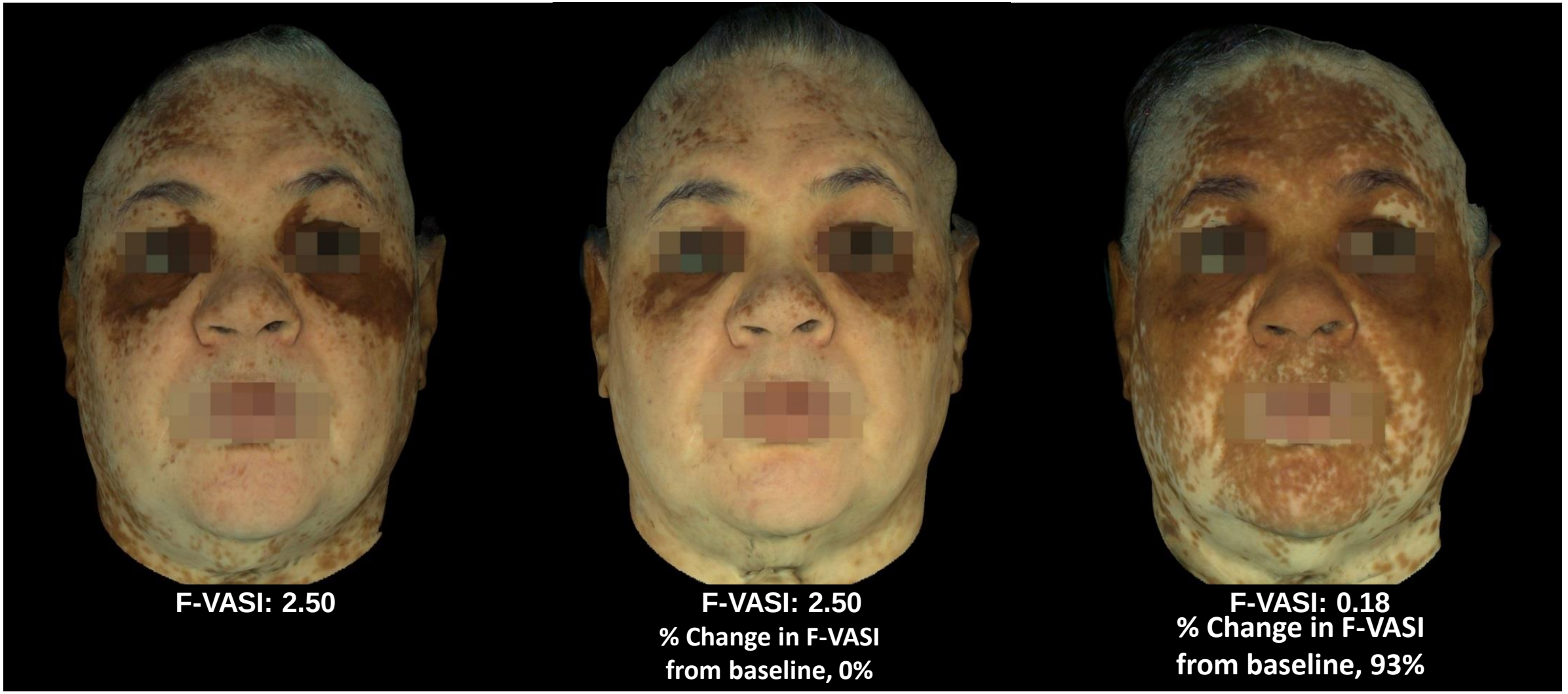
Tavoletti et al JEADV 23

# F-VASI Response

*Ruxolitinib Cream 1.5% BID*



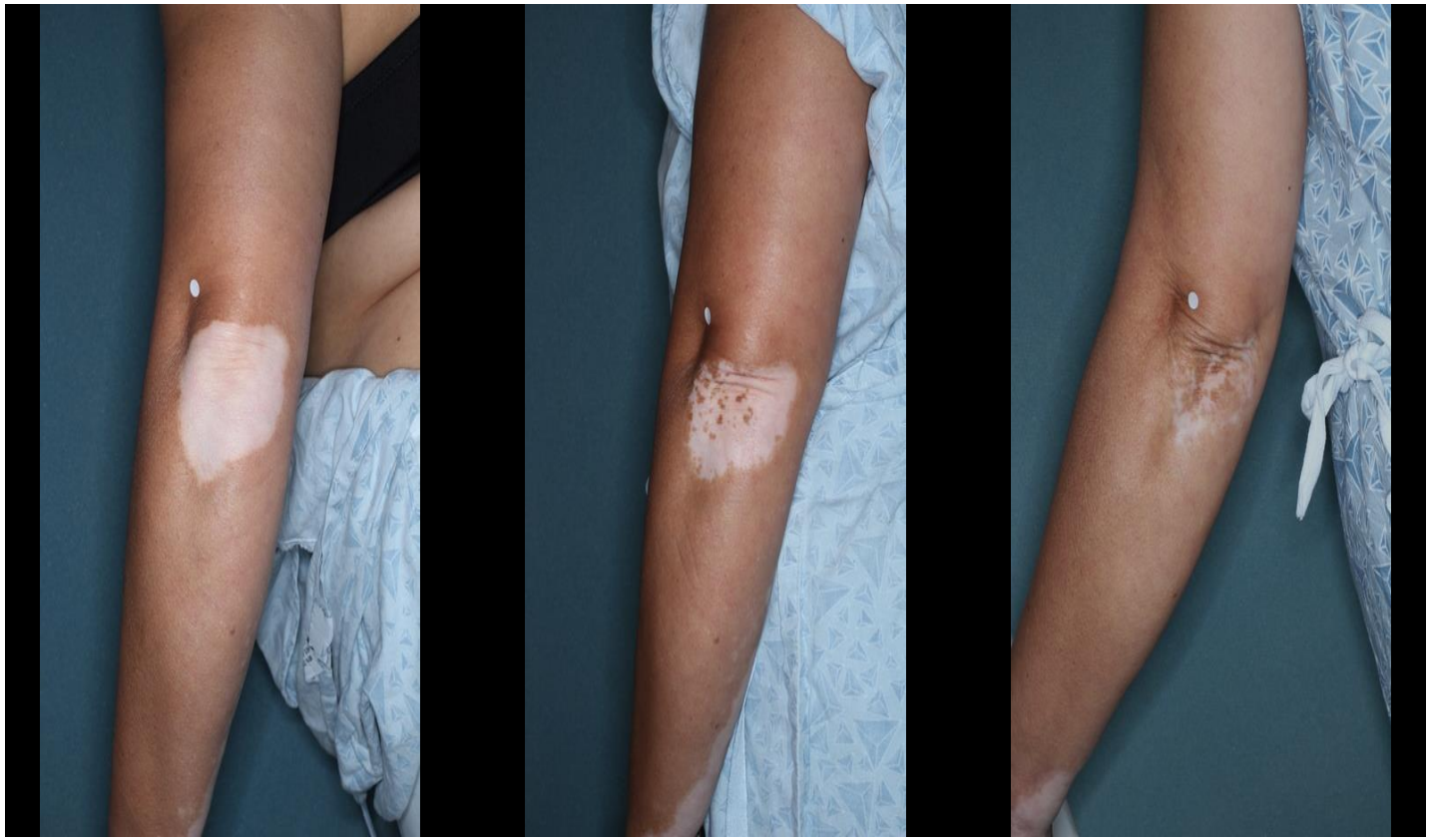
# F-VASI Response



# Clinical Images Showing T-VASI Response

*Ruxolitinib Cream 1.5% QD*

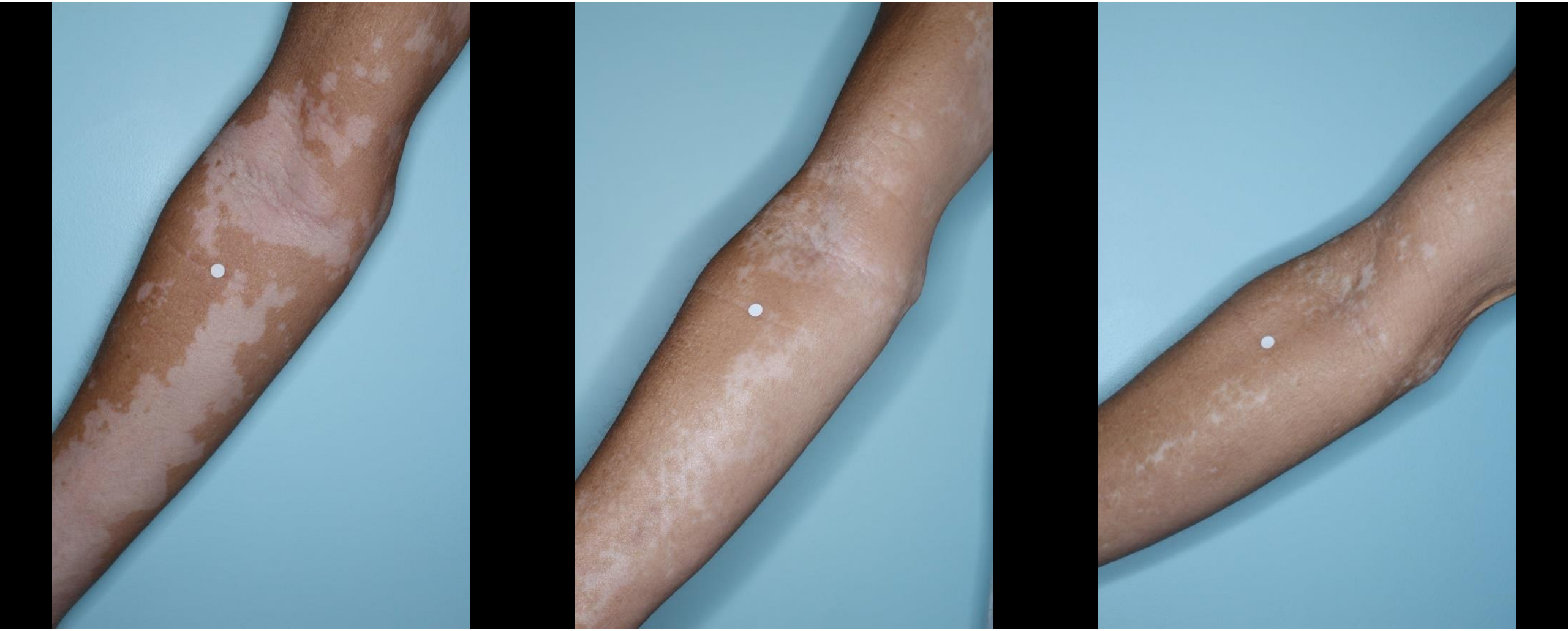
**Day 1** **Week 24** **Week 52**



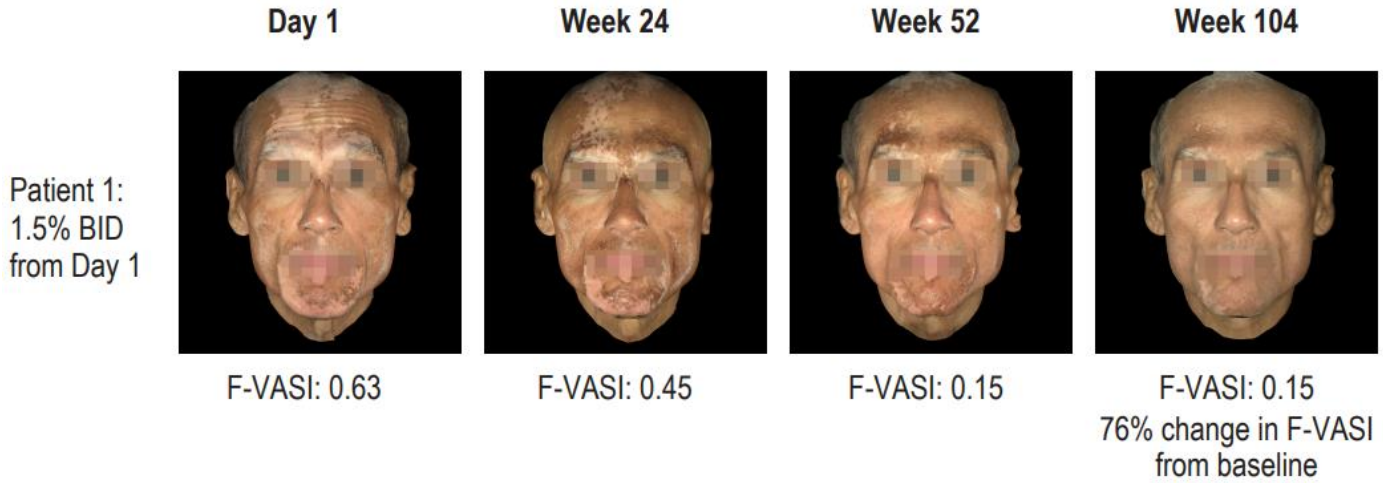
# Clinical Images Showing T-VASI Response

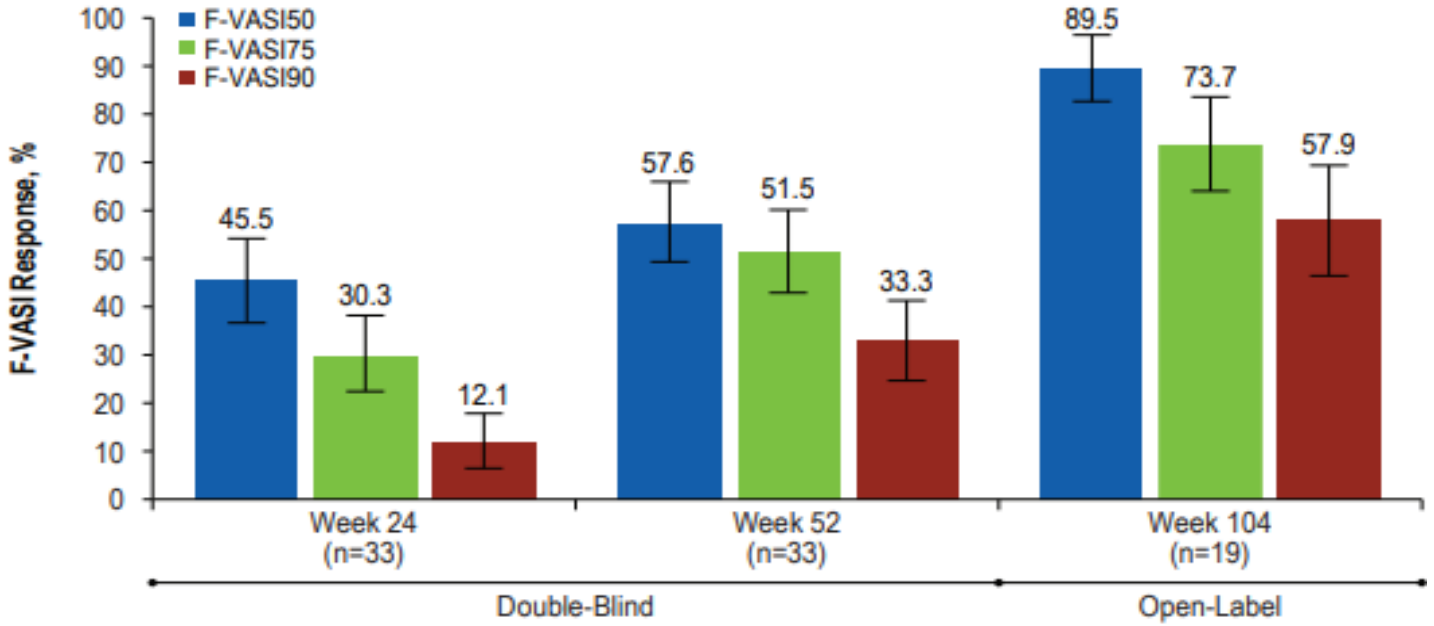
*Ruxolitinib Cream 1.5% BID*

**Day 1** **Week 24** **Week 52**



# Safety and Efficacy of Ruxolitinib Cream for the Treatment of Vitiligo: 104-Week Data From a Phase 2 Study



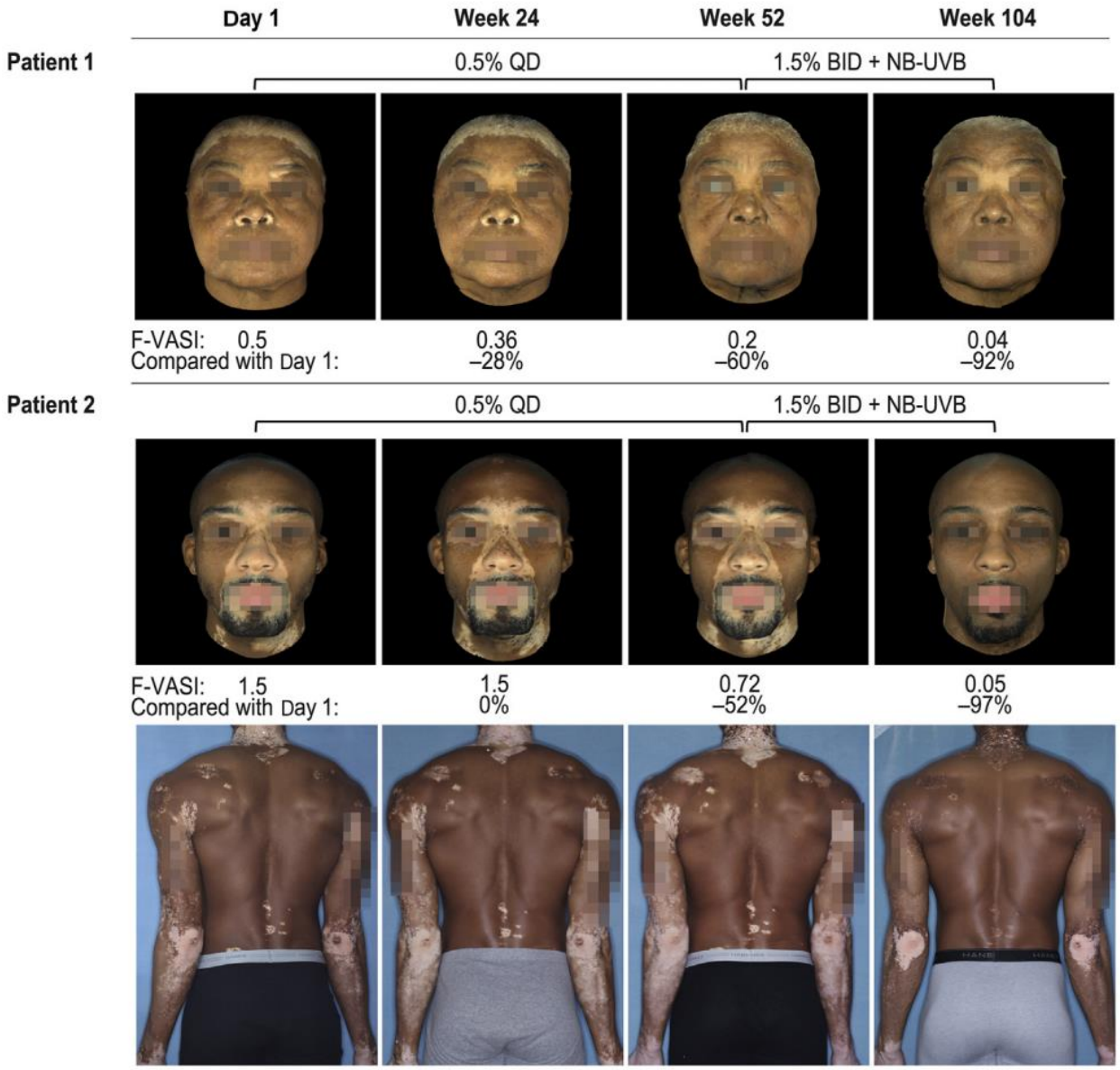



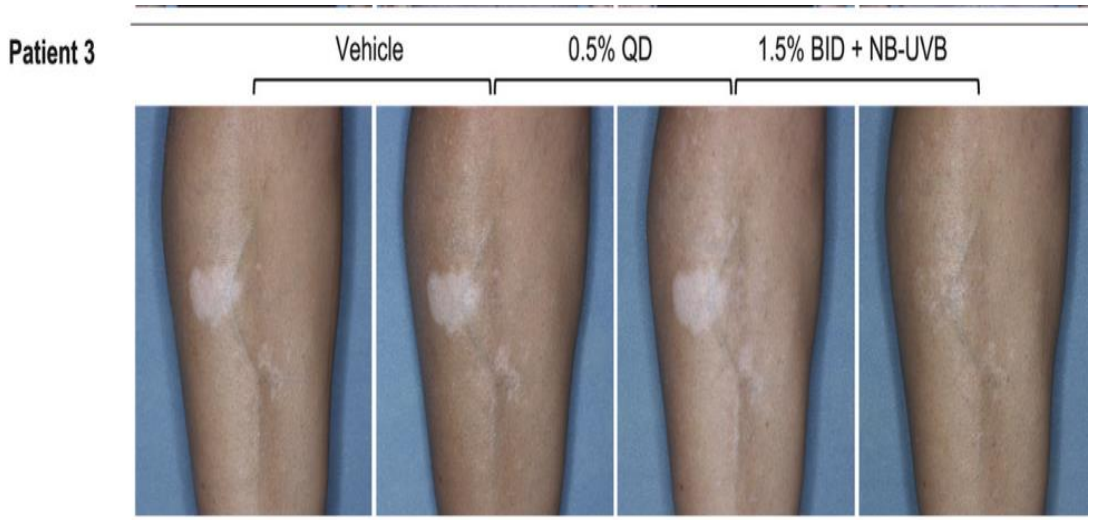

Substantial facial and total body Repigmentation through 104 weeks treatment

Longer therapy associated with greater repigmentation well tollerated over a 2-year

*Harris J et al.*

# Facial and total body vitiligo lesions of patients treated with ruxolitinib cream 1,5% BID and NB-UVB phototherapy




AG Pandya et al. JID 2022

American Academy of Dermatology (AAD), March 25–29, 2022, Boston, MA, USA

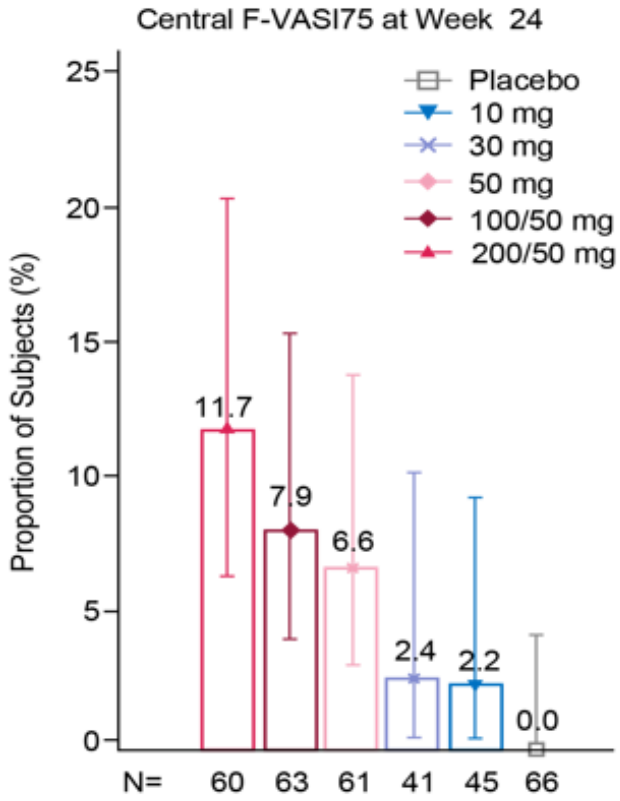
# Ritlecitinib (PF-06651600), an oral JAK3/TEC inhibitor, shows efficacy in patients with active non-segmental vitiligo across Fitzpatrick skin types: results from a Phase 2b, randomized, dose-ranging study with an extension period

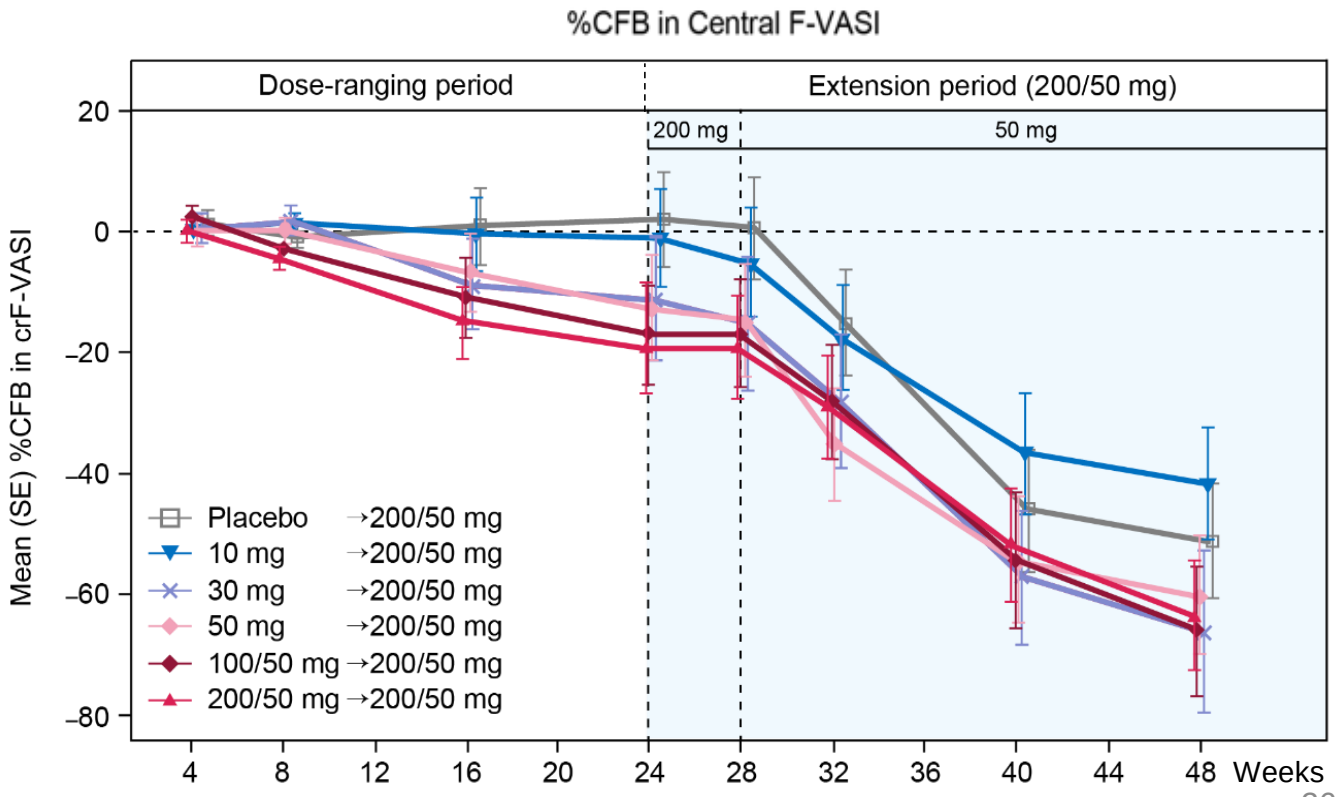
Elena Peeva[1], Yuji Yamaguchi[2], Brett King[3], George Han[4], Lori Ann Cox[2], Anindita Banerjee[5], Mauro Picardo[6], Jung Min Bae[7], Abigail Sloan[5], Rodney Sinclair[8], Khaled Ezzedine[9]

[1]Inflammation & Immunology Research Unit, Pfizer, Cambridge, MA, USA; [2]Inflammation & Immunology Research Unit, Pfizer, Collegeville, PA, USA; [3]Department of Dermatology, Yale School of Medicine, New Haven, CT, USA; [4]Department of Dermatology, Zucker School of Medicine at Hofstra/Northwell, New Hyde Park, NY, USA; [5]Clinical Statistics, Pfizer, Cambridge, MA, USA; [6]Cutaneous Physiopathology Laboratory, San Gallicano Dermatological Institute IRCCS, Rome, Italy; [7]Department of Dermatology, The Catholic University of Korea, Seoul, Korea; [8]Clinical Trials, Sinclair Dermatology, Melbourne, Australia; [9]Department of Dermatology, Hôpital Henri Mondor, Créteil, France

# Efficacy of Ritlecitinib at 24 Weeks & ~ 48 Weeks

%CFB in **crF-VASI** = −60% ~ −66%;
Proportion of **crF-VASI75** = 30% ~ 37%






%CFB=percent change from baseline; crF-VASI= centrally read facial-vitiligo scoring index; F-VASI75= proportion of patients achieving ≥75% improvement in F-VASI; SE=standard error

# Patient Photographs, Fitzpatrick Skin Type II

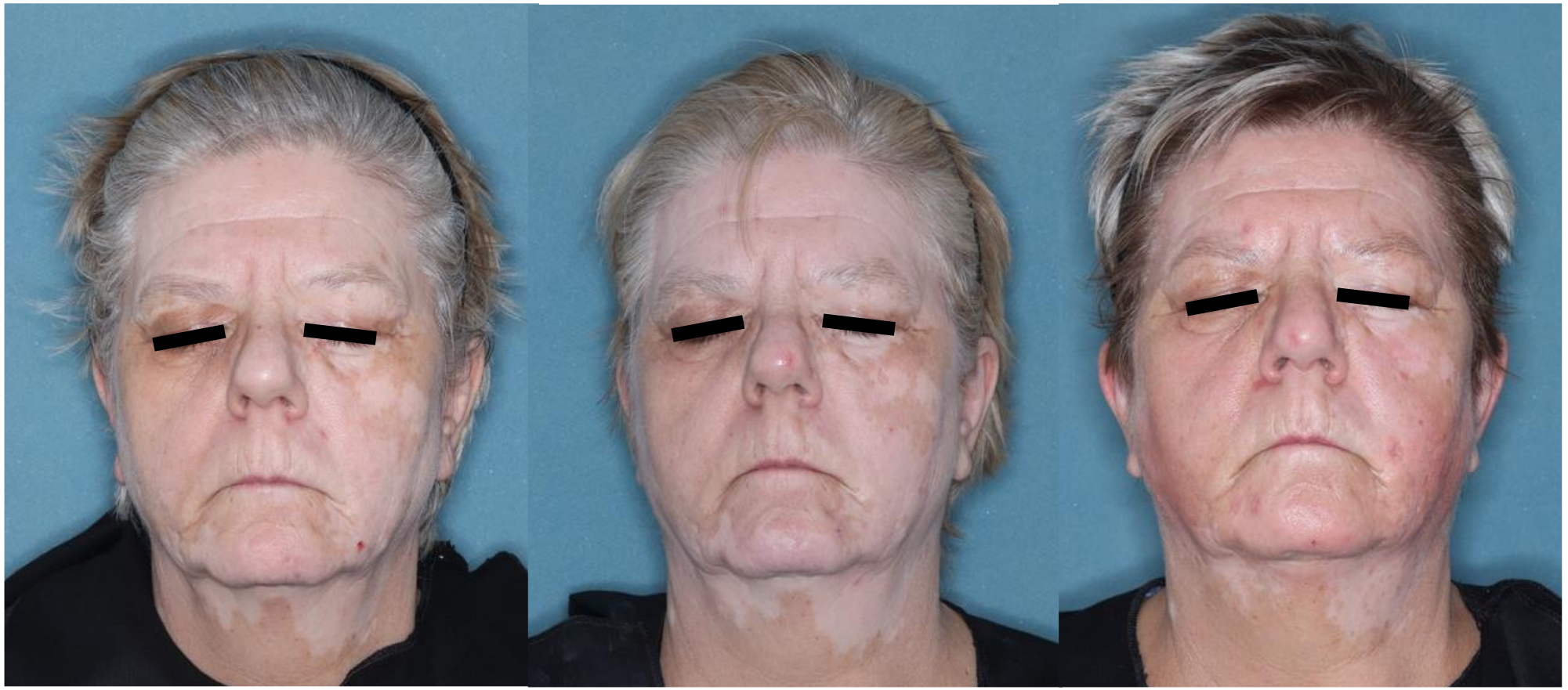
**Day 1**
crF-VASI: 2.60

Ritlecitinib
50 mg

**Week 24**
crF-VASI: 2.60
%CFB: 0

Ritlecitinib
200/50 mg

**Week 48**
crF-VASI: 0.90
% CFB: −65



%CFB=percent change from baseline; crF-VASI=centrally read facial-vitiligo area scoring index

# Patient Photographs, Fitzpatrick Skin Type V

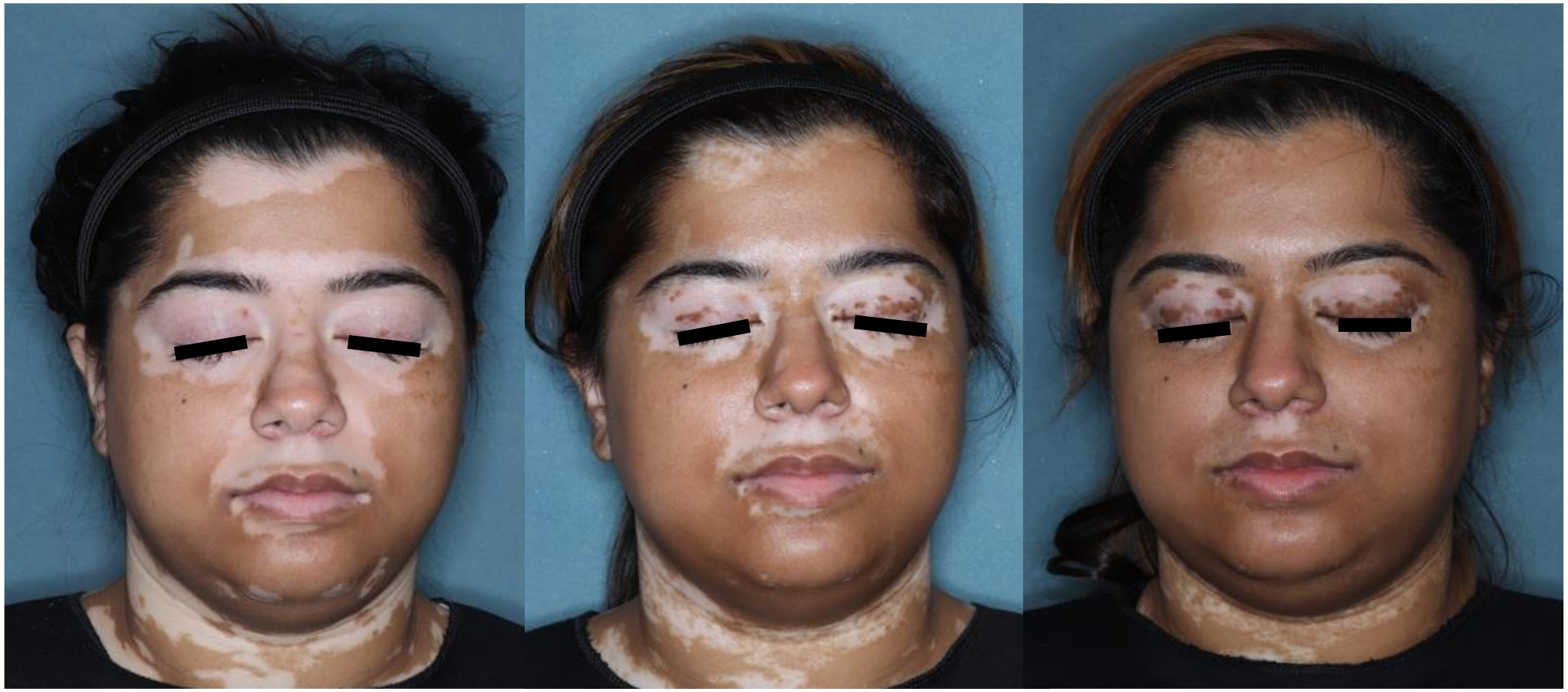
**Day 1**
crF-VASI: 1.04

Ritlecitinib
50 mg

**Week 24**
crF-VASI: 0.54
%CFB: −48

Ritlecitinib
200/50 mg

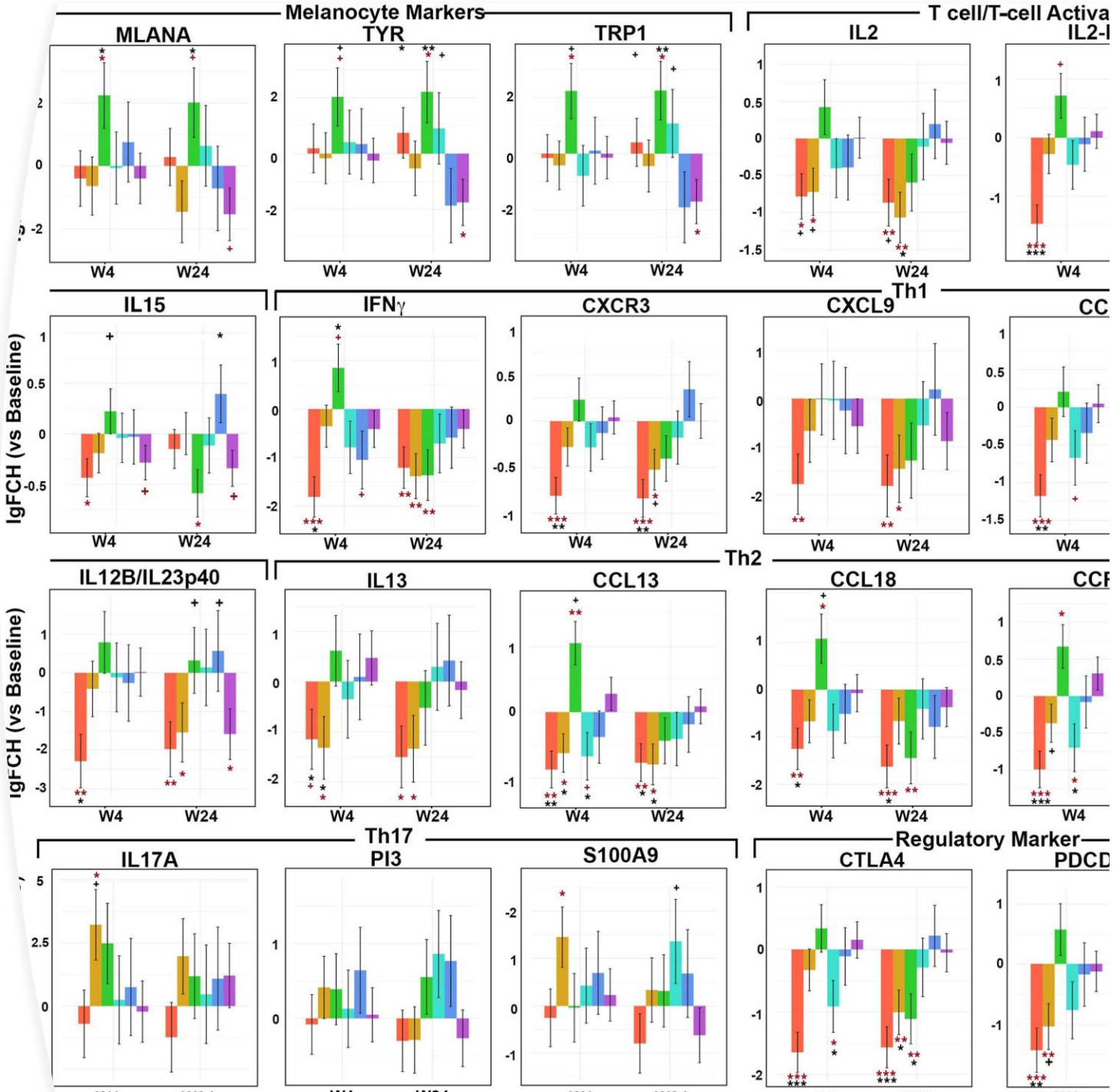
**Week 48**
crF-VASI: 0.13
% CFB: − 88



%CFB=percent change from baseline; crF-VASI=centrally read facial-vitiligo area scoring index

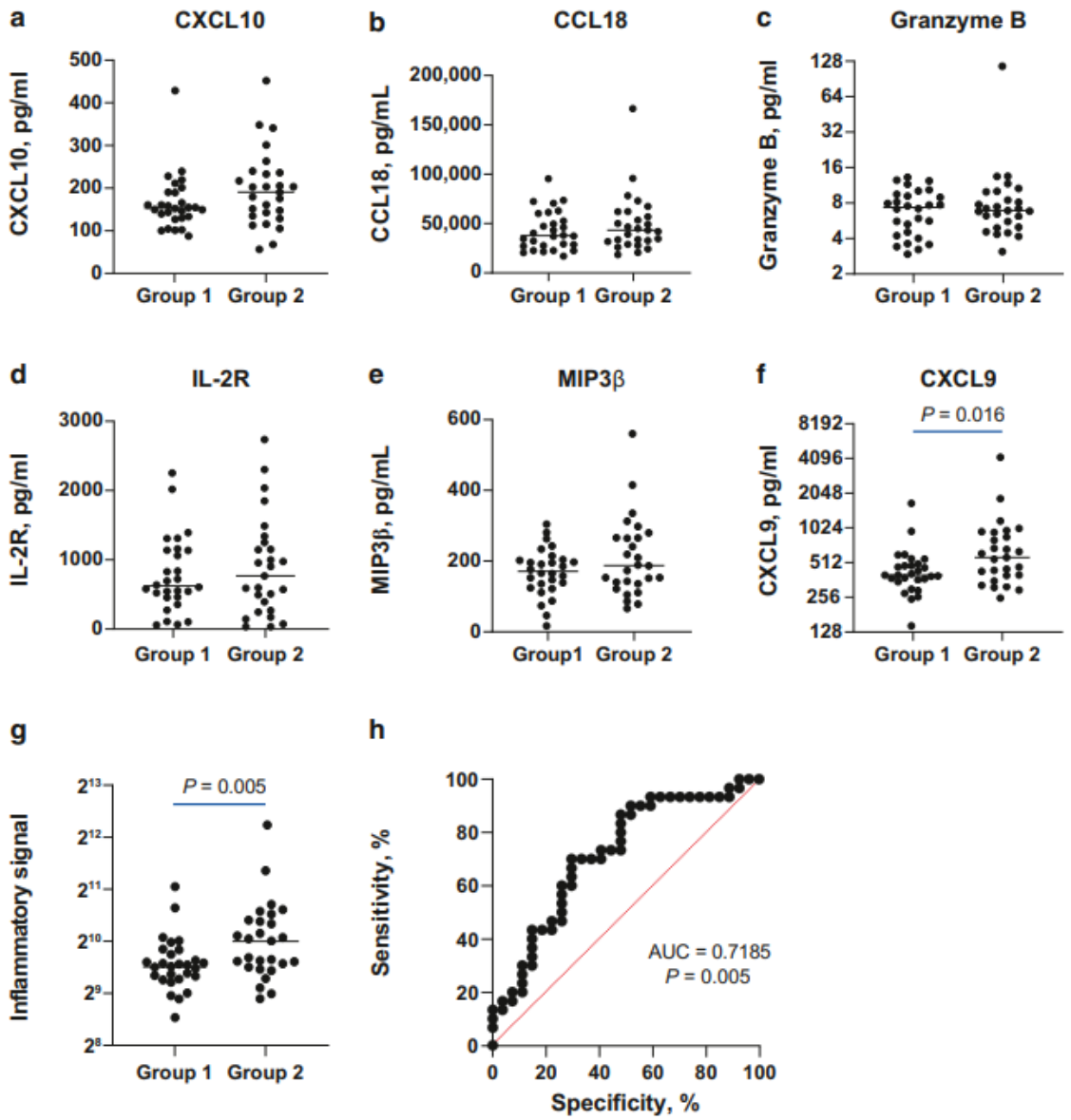
# Melanocyte and Immune cells markers modification in lesional skin of patients treated with Ritlecitinib for 24 weeks

- significant increase in melanocyte markers
- Decreases in markers of T-cell infiltrates, T-cell activation, and NK activation.
- significant decrease in markers associated with the innate immune response at weeks 4 and 24 compared to placebo and baseline



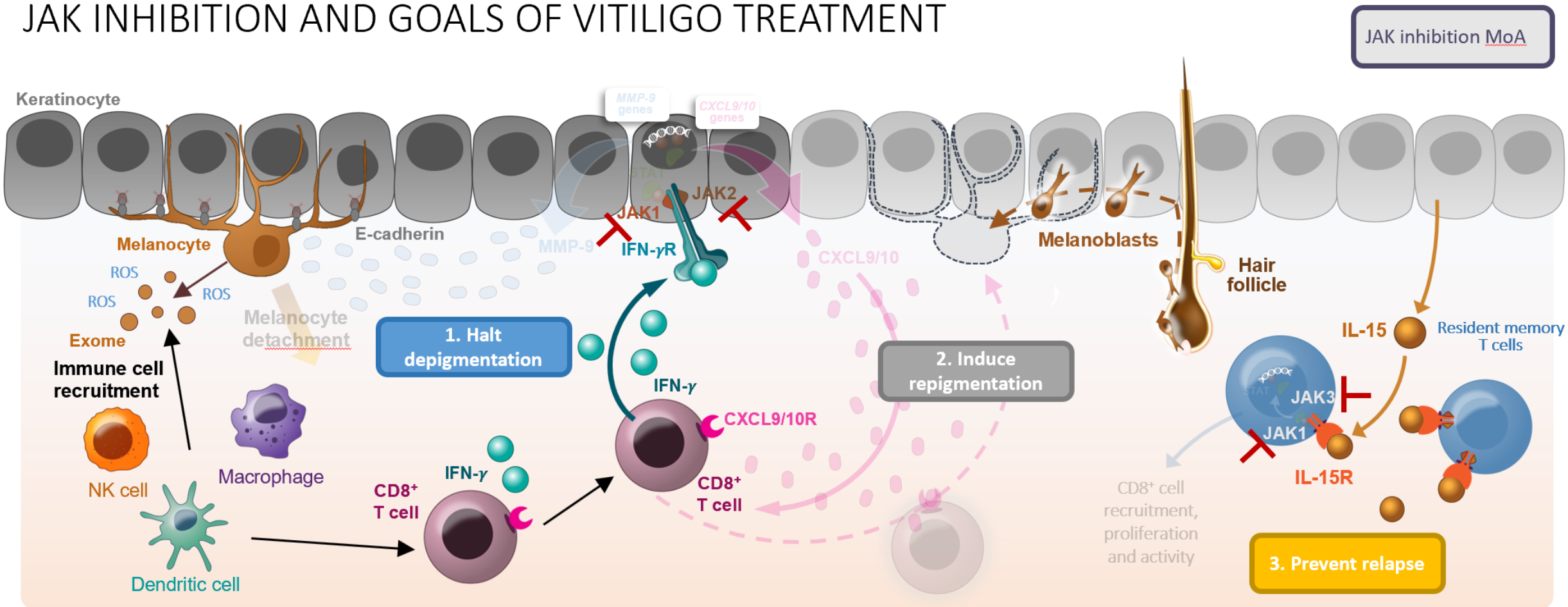
# Stratification by baseline inflammatory signal

The analysis identified potential differences between patients who achieved ≥50% improvement in facial Vitiligo Area Scoring Index at 24 weeks and those who did not that require deeper scientific interrogation and may be important in stratifying therapeutic benefit for patients with vitiligo.



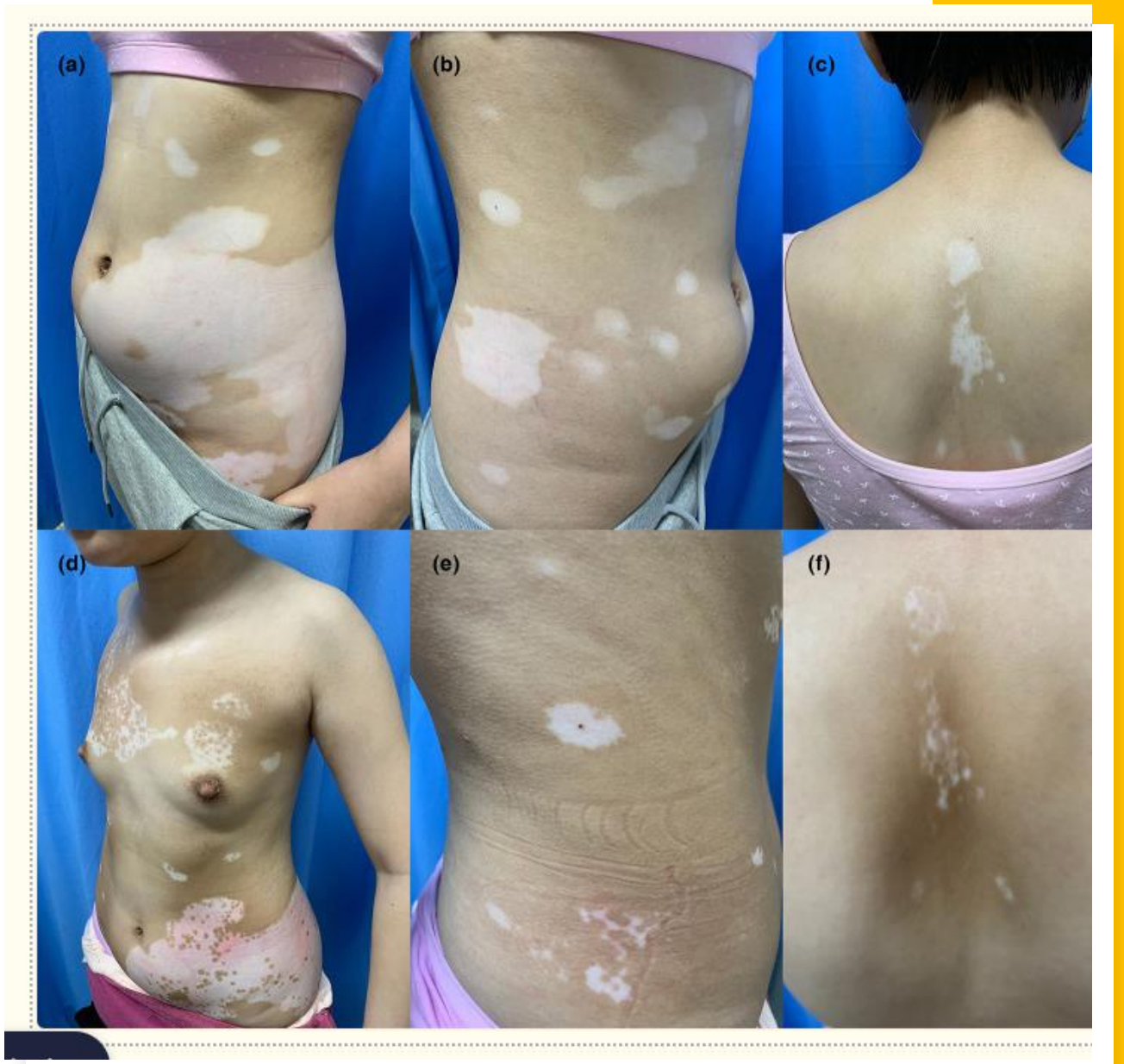

Howell MD, et al JID Innov. 2023 Sep

# JAK INHIBITION AND GOALS OF VITILIGO TREATMENT



# Baricitinib in Vitiligo

Significant repigmentation on the trunk after twice-daily oral baricitinib application for 8 months



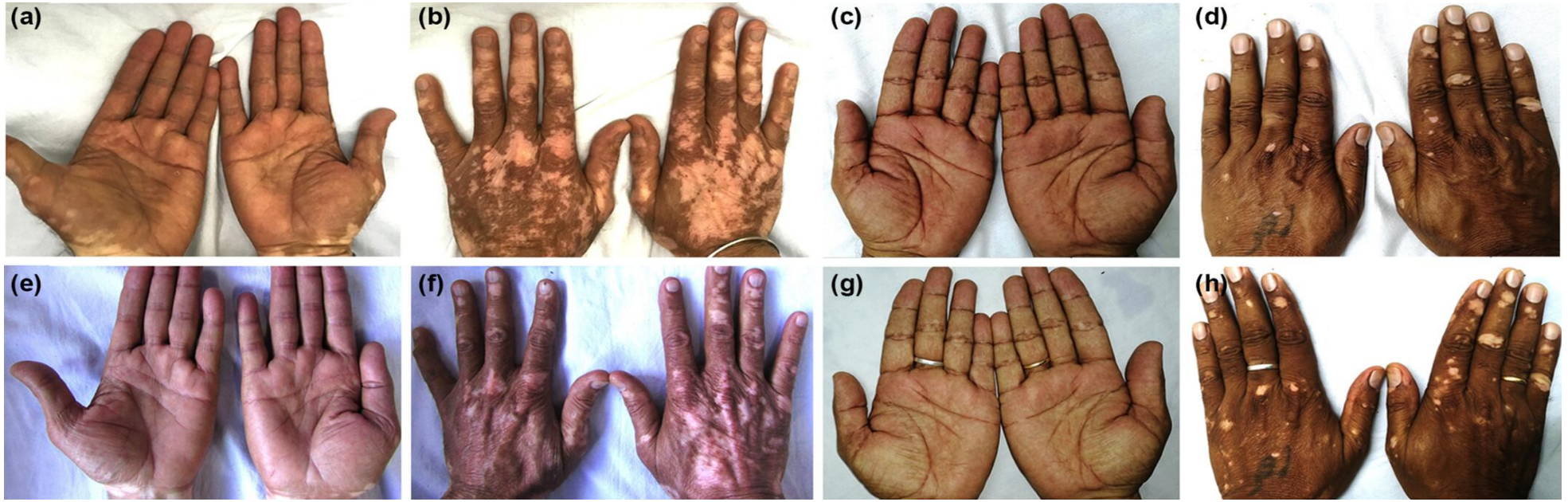

Li X, Sun Y, et al. Clin Cosmet Investig Dermatol. 2023

# AHR and Vitiligo


A 19-year-old female patient with vitiligo on the left cheek before receiving the treatment, 1 month after using tapinarof 1% cream, and 6 months after using tapinarof 1% cream.

Liu L JAAD Case Rep. 2023 Jul 26;39:150-151.

# A randomized prospective study to assess the role of topical tacrolimus as preventive therapy in unstable acral vitiligo




Clinical images showing lesion of acral vitiligo at baseline in group A (a, b) and group B (c, d) and repigmentation in group A (e, f) and group B (g, h) at 24 weeks.

Acad Dermatol Venereol, First published: 19 July 2023, DOI: (10.1111/jdv.19362)

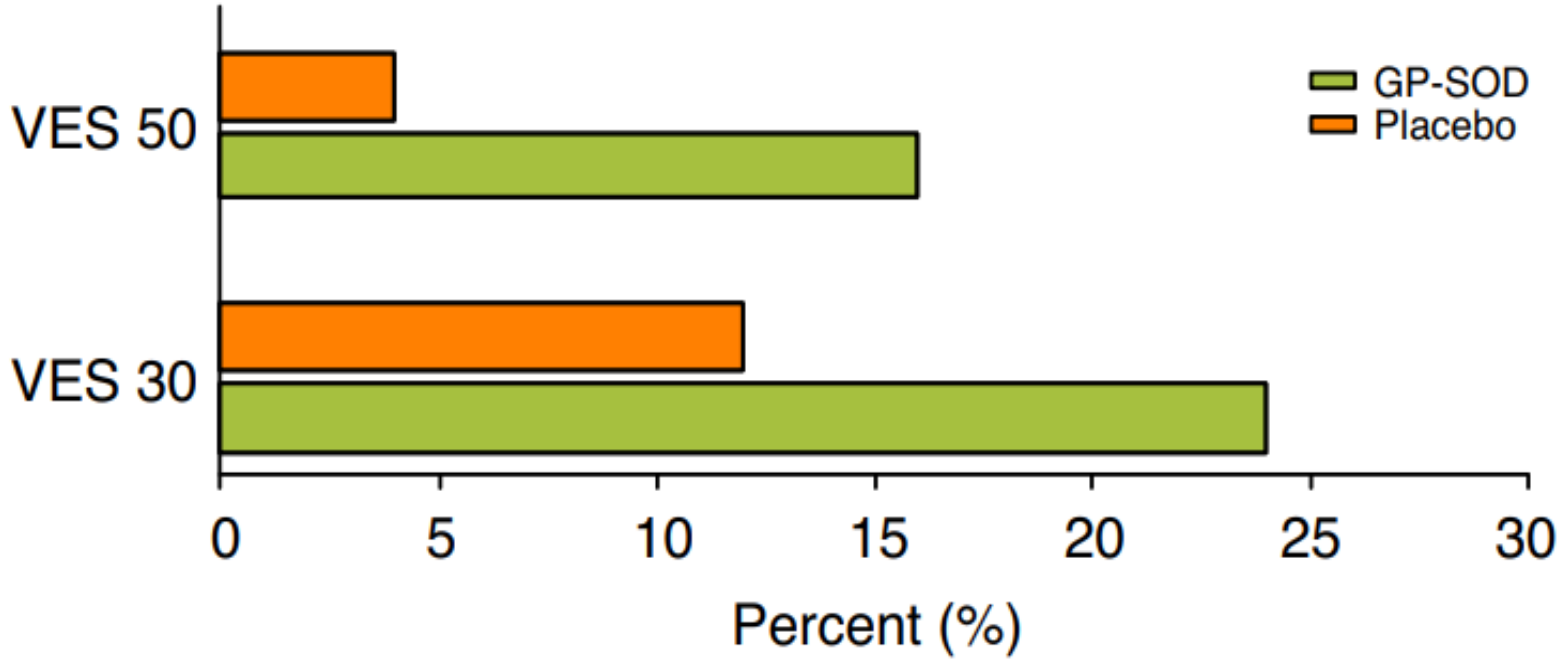
# Antioxidants in Vitiligo treatment

- Evidences that antioxidant supplementation alone or in combination with other conventional therapies may serve as a promising strategy for vitiligo patients (Wang et al 2019)
- oral antioxidant supplements may serve as a convenient approach with a good safety profile (J. Baek and M. G. Lee, 2016)
- the antioxidant supplement by phyllanthus emblica, khellin, Ginkgo biloba, Glycyrrhizin, polyunsaturated fatty acid, or carotenoids also increased the therapeutic efficacy of topic or phototherapy for vitiligo patients (P. E. Grimes and R. Nashawati,2017, Bishnoi and D. Parsad, 2018, F. Guarneri 2021)
- antioxidant agents alone are unable to elicit significant repigmentation in most of the studies, but they are likely to provide additional benefits as adjunctive approaches to conventional treatments.

# Gliadin protected SOD in Vitiligo

Proportion of patients achieving 30% and 50% improvement in Vitiligo Extent Score treated with Gliadin protected –SOD or placebo plus UVB

The subjects received gliadin-protected SOD
1 g/day for 12 weeks followed by 0.5 g/day for 12 weeks) or placebo in combination with twice-weekly sessions of NB-UVB.
The primary endpoint was the total repigmentation rate at 24 weeks,




Fontas et al JEADV 2021

# conclusioni

Meccanismi immunologici e non immunologici sono coinvolti nella patogenesi con la partecipazione di più popolazioni cellulari cutanee

La migliore comprensione dei meccanismi coinvolti ha portato alla individuazione di diversi target terapeutici e lo sviluppo di terapie analoghe a quelle per altre MIC

Lunghi periodi di trattamento sono necessari per ottenere una repigmentazione