Inmunoterapia en dermatología

V EDICIÓN

25 de abril de 2024

Casa de Convalescència, Barcelona

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Psoriasis: lo mejor de 2023 y pipeline

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Declaración de Conflictos de Interés

He recibido honorarios por participar en consultorías, como ponente y en ensayos clínicos patrocinados por AbbVie, Almirall, Amgen, Boehringer Ingelheim, Eli Lilly, Janssen, LEO Pharma, MSD, Novartis, Pfizer y UCB Pharma.

No tengo conflictos de interés en la elaboración de esta presentación

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Contenido

- Patogenia
- Clínica
- Comorbilidades y recomendaciones
- Terapéutica actual y pipeline

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Contenido

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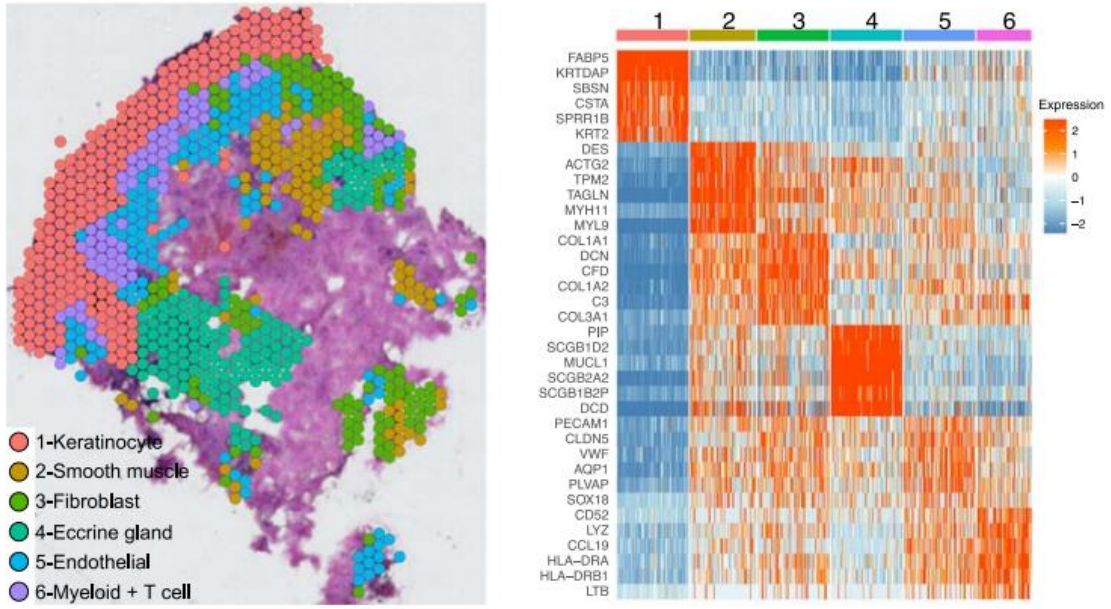
- Clínica
- Comorbilidades y recomendaciones
- Terapéutica actual y pipeline

nature communications

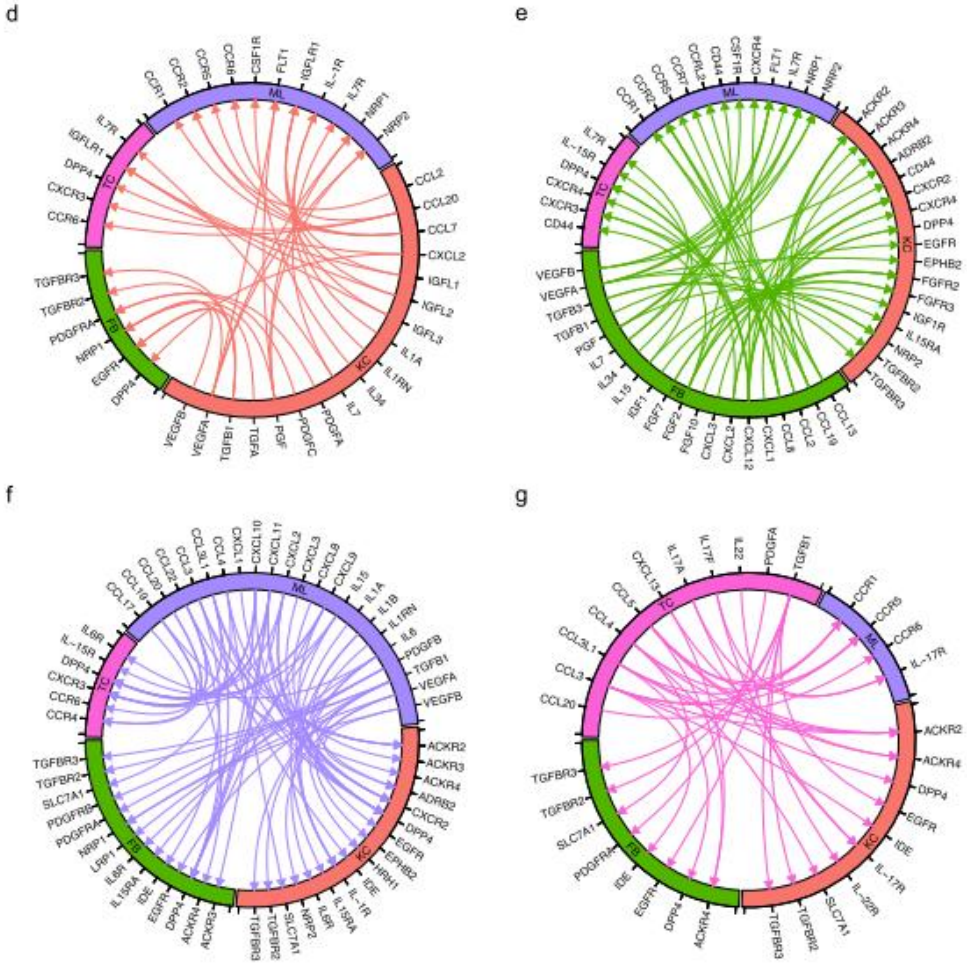
Article

https://doi.org/10.1038/s41467-023-39020-4

Single cell and spatial sequencing define processes by which keratinocytes and fibroblasts amplify inflammatory responses in psoriasis



NS healthy normal skin,
PN psoriatic non-lesional skin,
PP psoriasis skin



Circos plot showing the cytokine and growth factor ligand–receptor interactions with a higher score in PP compared to NS

Participación activa de fibroblastos más allá de su función estructural

Na et al. Nature Communications. 2023; 14:3455

A single-cell atlas of IL-23 inhibition in cutaneous psoriasis distinguishes clinical response

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DAVID WU, ASHLEY A. HAILER, SIJIA WANG, MICHELLE YUAN, JAMIE CHAN, ABDULLAH EL KURDI, DAVID HAN, HIRA ALI, BLAIZE D'ANGIO, [...], AND RAYMOND J. CHO +14 authors Authors Info & Affiliations

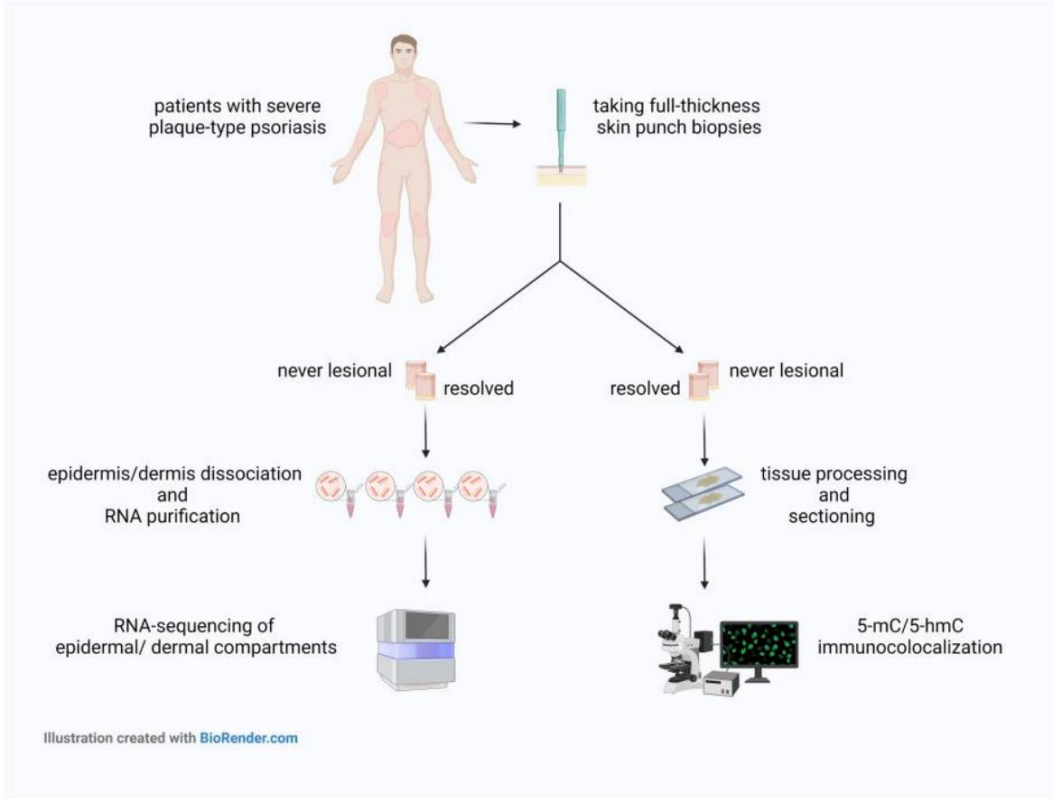
Science Immunology

Psoriasis vulgaris and other chronic inflammatory diseases improve markedly with therapeutic blockade of interleukin-23 (IL-23) signaling, but the genetic mechanisms underlying clinical responses remain poorly understood. Using single-cell transcriptomics, we profiled immune cells isolated from lesional psoriatic skin before and during IL-23 blockade. In clinically responsive patients, a psoriatic transcriptional signature in skin-resident memory T cells was strongly attenuated. In contrast, poorly responsive patients were distinguished by persistent activation of IL-17–producing T (T17) cells, a mechanism distinct from alternative cytokine signaling or resistance isolated to epidermal keratinocytes. Even in IL-23 blockade–responsive patients, we detected a recurring set of recalcitrant, disease-specific transcriptional abnormalities. This irreversible immunological state may necessitate ongoing IL-23 inhibition. Spatial transcriptomic analyses also suggested that successful IL-23 blockade requires dampening of >90% of IL-17–induced response in lymphocyte-adjacent keratinocytes, an unexpectedly high threshold.
Collectively, our data establish a patient-level paradigm for dissecting responses to immunomodulatory treatments.

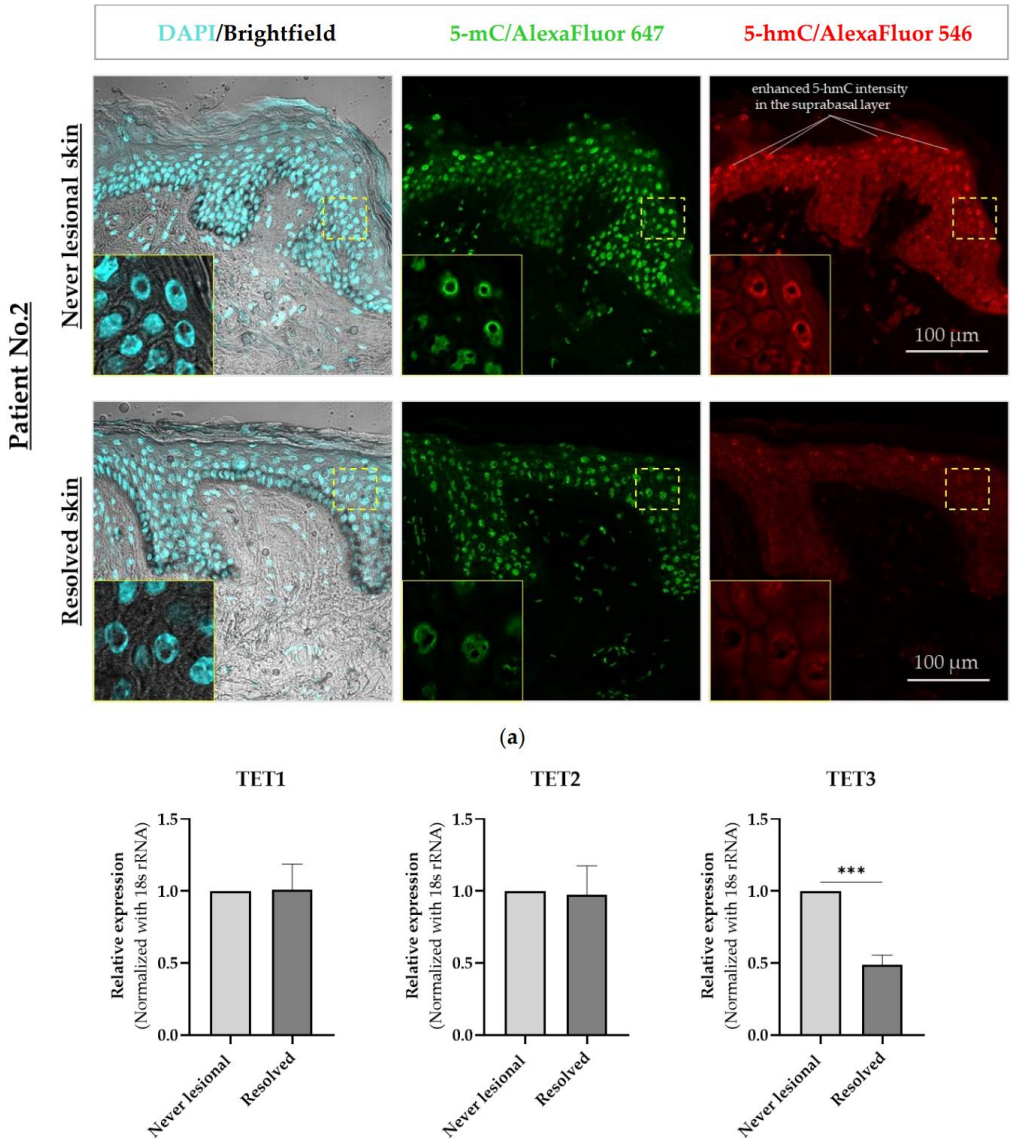
Wu et al. Sci Immunol. 2024 Jan 26;9(91):eadi2848.

Article

Psoriatic Resolved Skin Epidermal Keratinocytes Retain Disease-Residual Transcriptomic and Epigenomic Profiles

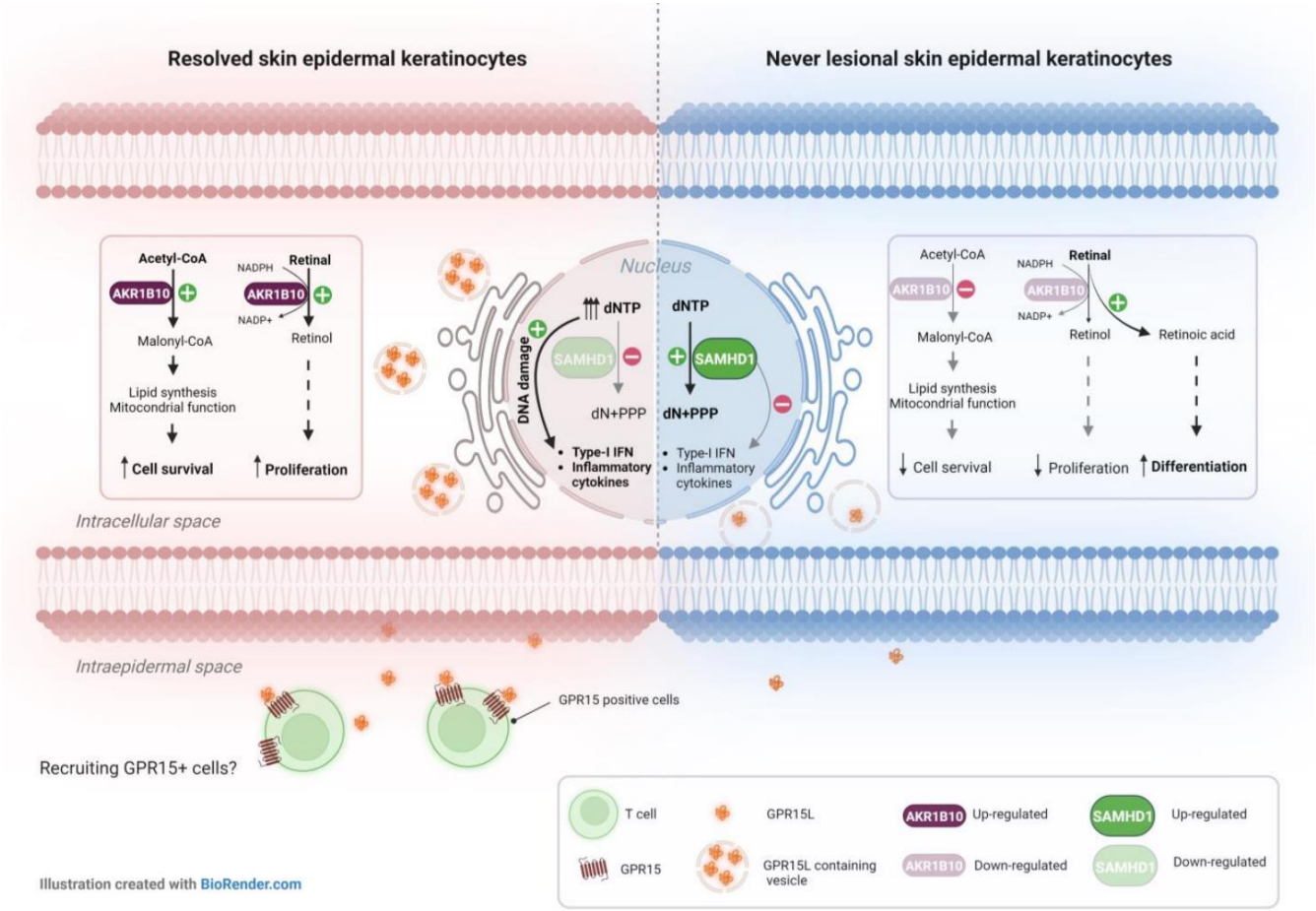


5-mC (5-methylcytosine)
5-hmC (5-hydroxymethylcytosine)



TET3: ten-eleven translocation (TET)3

Ghaffarinia et al. Int. J. Mol. Sci. 2023, 24, 4556



DEGs: differentially expressed genes

Ghaffarinia et al. Int. J. Mol. Sci. 2023, 24, 4556

Mechanism of action of the three DEGs:

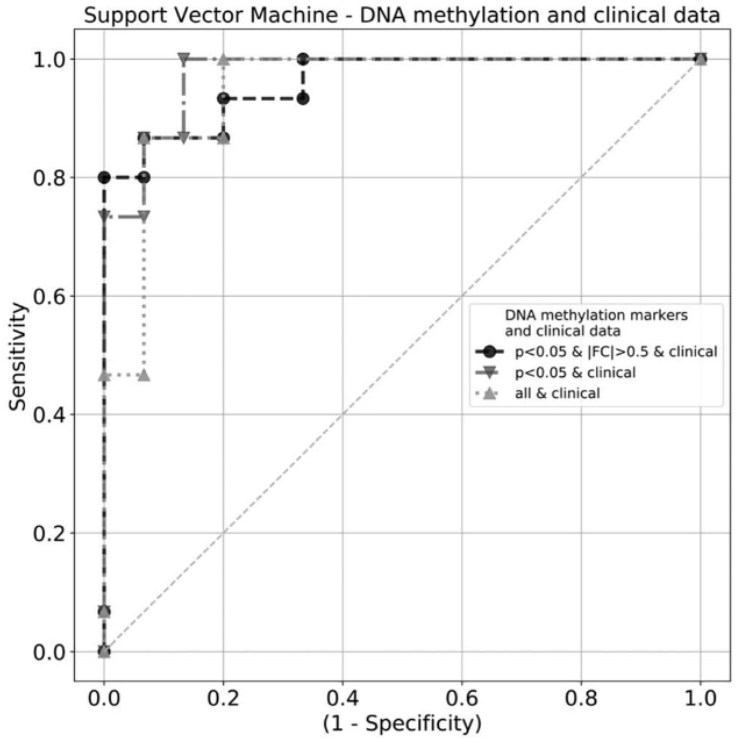
Significantly lower levels of the **SAMHD1** gene in resolved epidermal keratinocytes might be accompanied by abnormal dNTP accumulation, which can induce DNA damage. It is established that damaged DNA species can trigger type-I IFN and innate immune responses.

Strong up-regulation of **GPR15L** in resolved epidermal keratinocytes may lead to the recruitment of GPR15+ cells, such as T-cells, into the epidermal compartment.

The strong up-regulation of **AKR1B10** gene may result in reduced RA and consequently increased keratinocytes survival and proliferation.

Metilación ADN como predictor APs

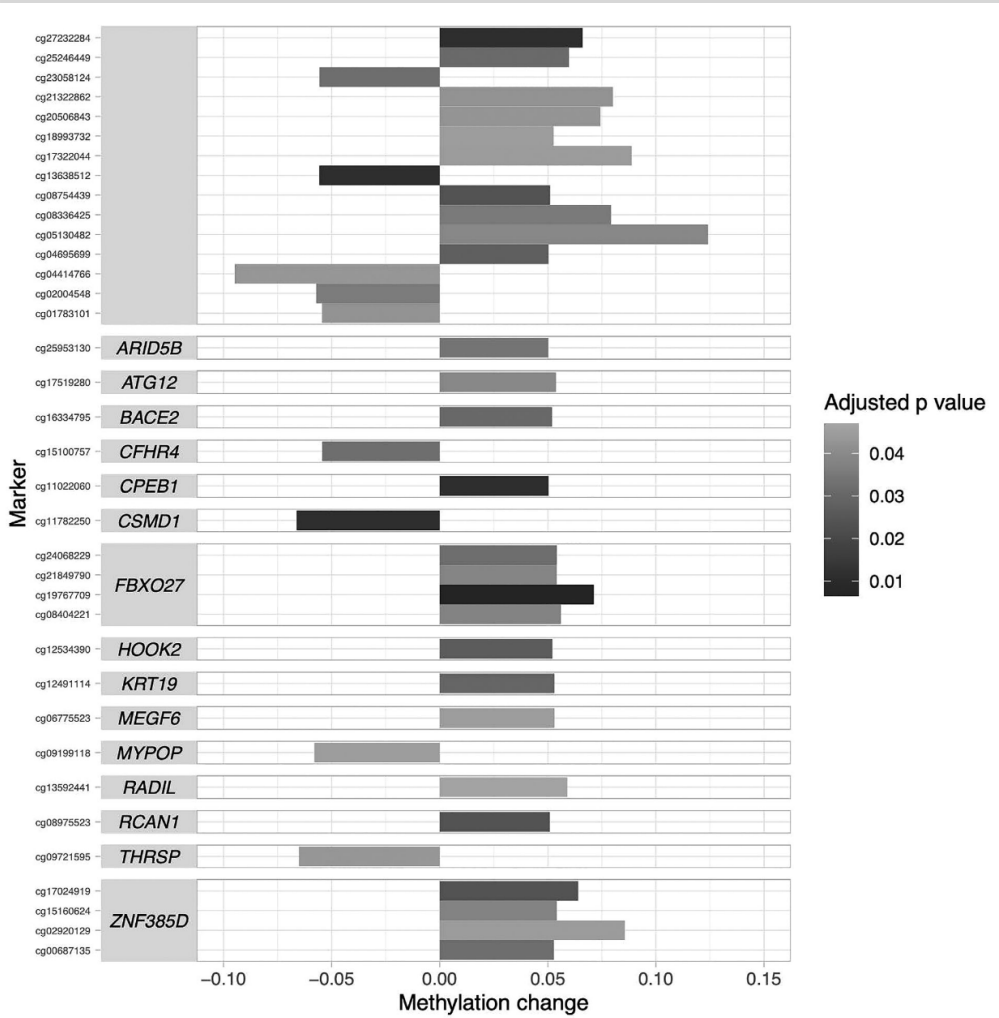
- 60 pacientes con PsO que desarrollaron PsA – 60 PsO sin PsA
- Estudio de metilación del genoma completo
- 36 zonas de metilación relevantes en 15 genes y varias zonas intrónicas.



American College of Rheumatology
Empowering Rheumatology Professionals

Arthritis & Rheumatology
Vol. 75, No. 12, December 2023, pp 2178–2184
DOI 10.1002/art.42654

Prediction of Psoriatic Arthritis in Patients With Psoriasis Using DNA Methylation Profiles



Cruz-Correa et al. Arthritis Rheumatol. 2023 Dec;75(12):2178-2184.

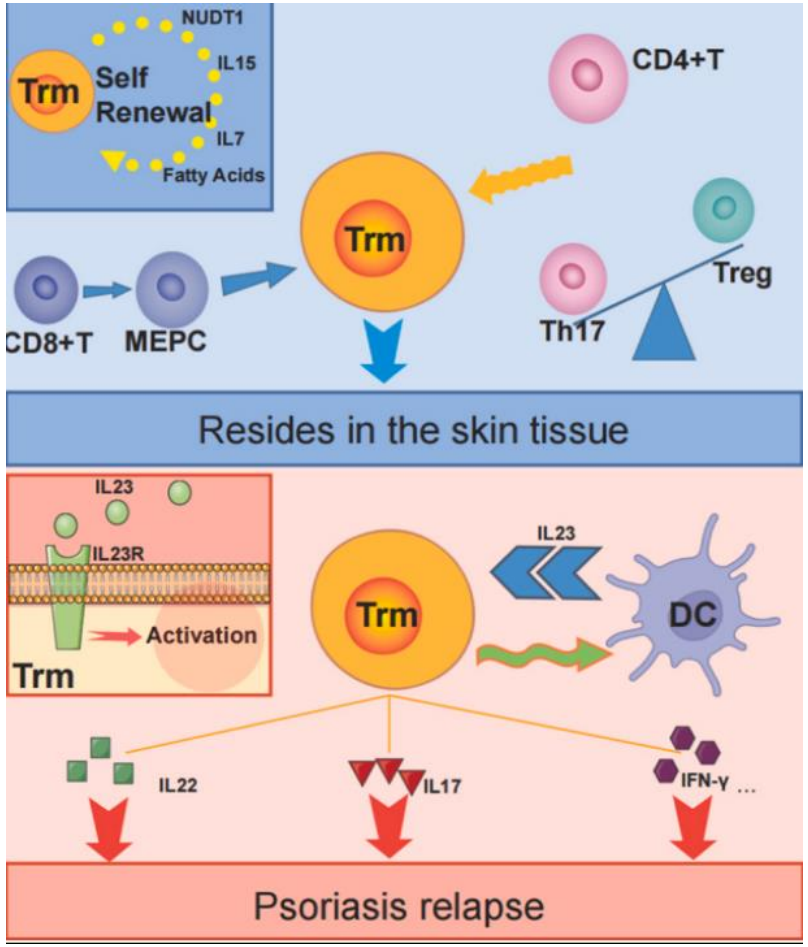
Contenido

- Patogenia
- **Clínica: modificación de la enfermedad**
- Comorbilidades y recomendaciones
- Terapéutica actual y pipeline

Modificación de la enfermedad

Characteristics and sources of tissue-resident memory T cells in psoriasis relapse

Canbin Dong [1], Lanmei Lin [1], Juan Du [*]



Received: 14 June 2023 | Accepted: 13 November 2023
DOI: 10.1111/jdv.19652

LETTER TO THE EDITOR

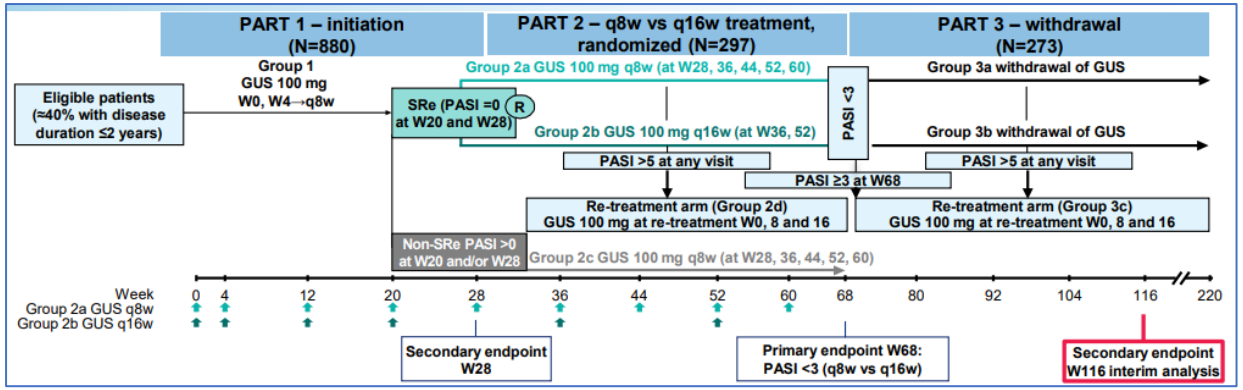
JEADV

An international Delphi consensus to define a clinically appropriate definition of disease modification for plaque psoriasis

In patients with moderate-to-severe plaque psoriasis, in the absence of precise biomarkers, disease modification may be evaluated by sustained **BSA<1% / PGA <0/1** for **>12 months** following **treatment cessation**.

Eyerich et al. . J Eur Acad Dermatol Venereol. 2023 Dec 10. doi: 10.1111/jdv.19652.
Dong et al. Curr Res Immunol. 2023 Sep 6;4:100067.

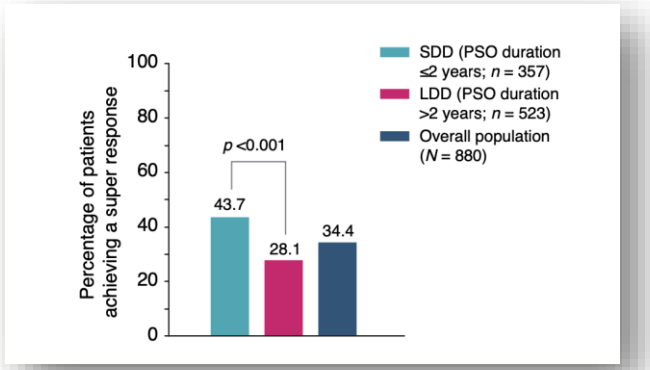
Early disease intervention with guselkumab in psoriasis leads to a higher rate of stable complete skin clearance ('clinical super response'): Week 28 results from the ongoing phase IIIb randomized, double-blind, parallel-group, GUIDE study



1ª etapa

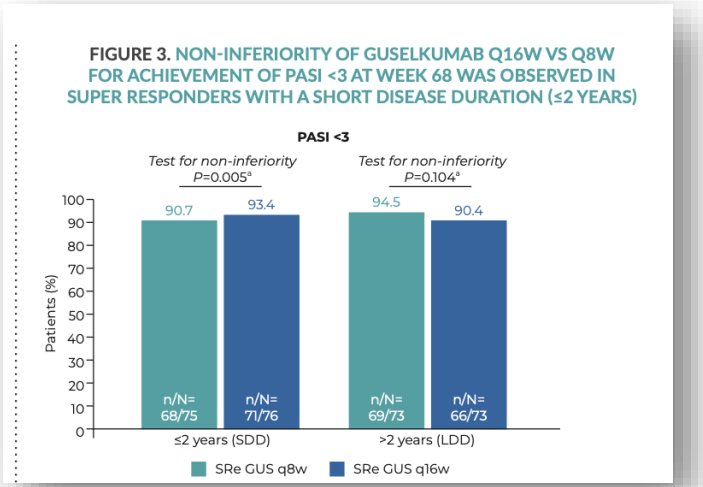
Superrespondedores (SR) :

PASI 0 w24-28 43% SR vs 28%



- Impacto de la **intervención temprana** de la o con guselkumab en pacientes con psoriasis en placas de moderada a grave.
- **Ps < 2 años vs Ps > 2 años.**

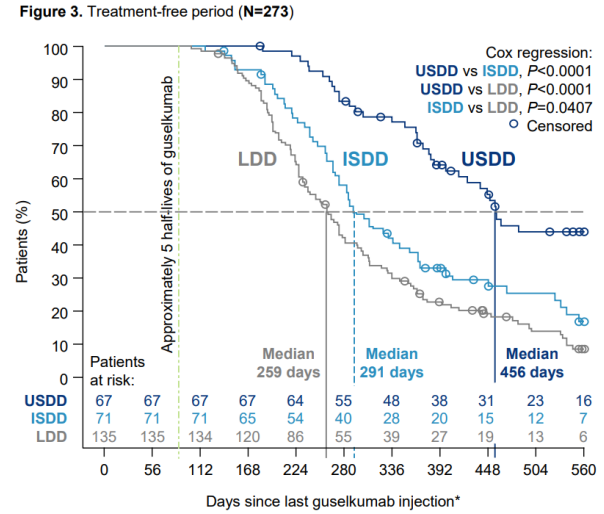
2ª etapa Q16 semanas no inferior a Q8



No inferioridad de guselkumab 100 mg **cada 16 semanas** frente a cada 8 semanas para el mantenimiento del control de la enfermedad (PASI <3) **en SRes en la semana 68**

3ª etapa

Mantenimiento respuesta sin tratamiento



El mantenimiento de respuesta es mayor cuanto más corto es el tiempo de evolución de la enfermedad

Journal of the European Academy of Dermatology and Venereology April 2023

AAD San Diego 2024

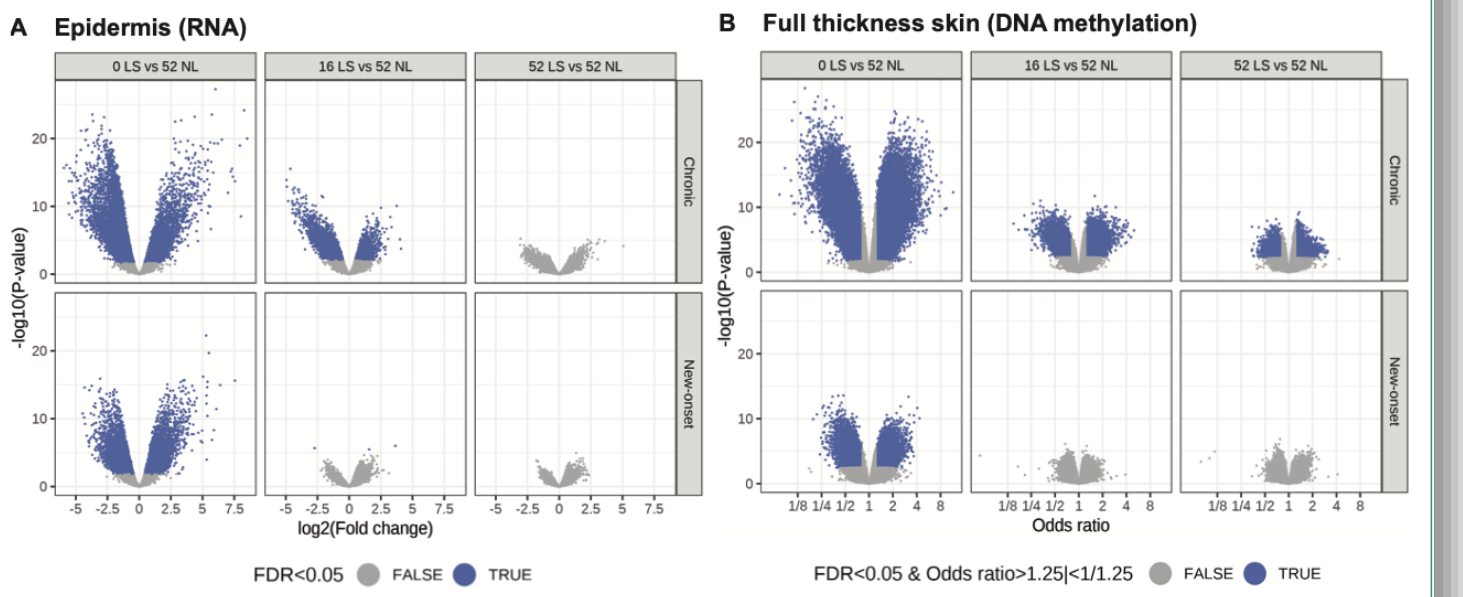
Secukinumab demonstrates superiority over narrow-band ultraviolet B phototherapy in new-onset moderate to severe plaque psoriasis patients: Week 52 results from the STEPIn study

Lars Iversen, Curdin Conrad, Liv Eidsmo, Antonio Costanzo, Joanna Narbutt, Andreas Pinter, Külli Kingo, Raquel Rivera Diaz, Frank Kolbinger, ManikPrabhu Nanna, Jennifer Annika Frueh, Piotr Jagiello

Intervención precoz Secu Ps < 12 meses

Impacto del tratamiento con secukinumab en las firmas moleculares subyacentes en Pso de nueva aparición
(<12 meses la PsO crónica (≥ 5años)

Figure 2. Differences in resolution of gene expression (A) and DNA methylation (B) in lesional skin of new-onset and chronic PsO over time



Differential analysis of LS to NL biopsy samples.
FDR, false discovery rate; LS, lesional; NL, non-lesional.

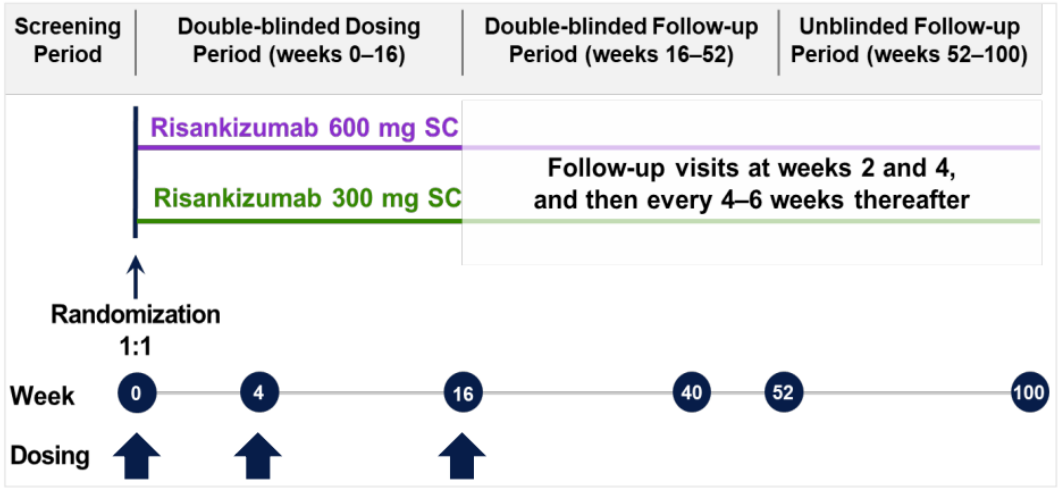
Las diferencias en la metilación del ADN " cicatriz molecular**" se normalizaron en la piel de Ps de nueva aparicion en la semana 16**

ISID 2023; Tokyo, Japan; 10–13 May 2023.
Clin Exp Dermatol 2023; **00**:1–8

High Induction Dosing of Risankizumab in Patients With Moderate-To-Severe Plaque Psoriasis: 52 Week Results From the Phase 2 KNOCKOUT Study

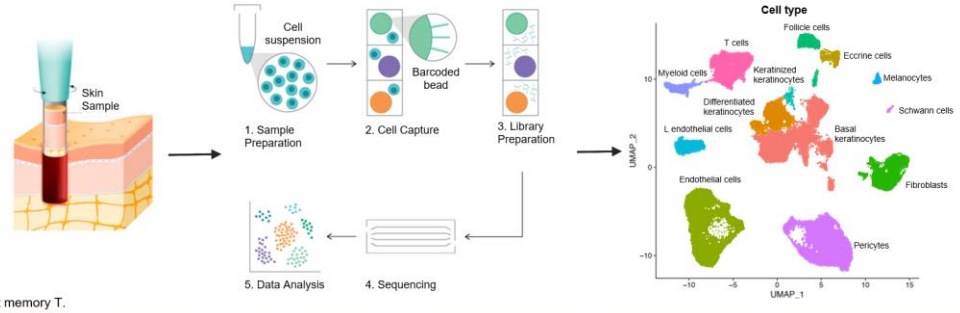
Hipótesis: las **dosis iniciales más altas de risankizumab pueden suprimir de manera más efectiva las cTRM ,** y si esto da como **resultado ausencia de lesiones** durante **períodos de tiempo más prolongados <u>después de la suspensión del fármaco.</u>**

Study design of KNOCKOUT (NCT05283135)



T_{RM} Cell Detection and Quantification

- **Skin biopsies of lesional and non-lesional skin will be collected at Weeks 0 and 52 and processed for RNA seq analysis**
- **RNA seq will be used to evaluate change from baseline to Week 52 in T_{RM} cell number and effector function**



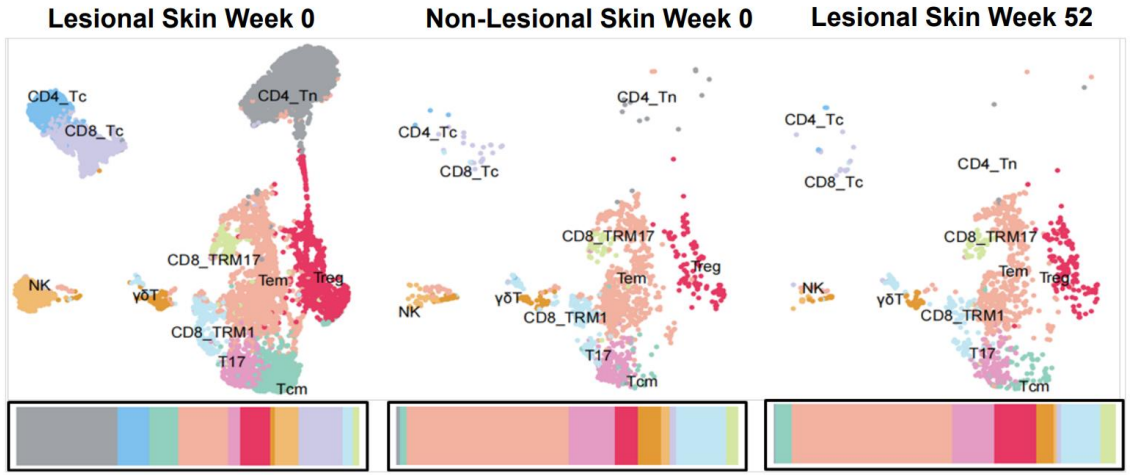
T_{RM}, resident memory T.

Key endpoints

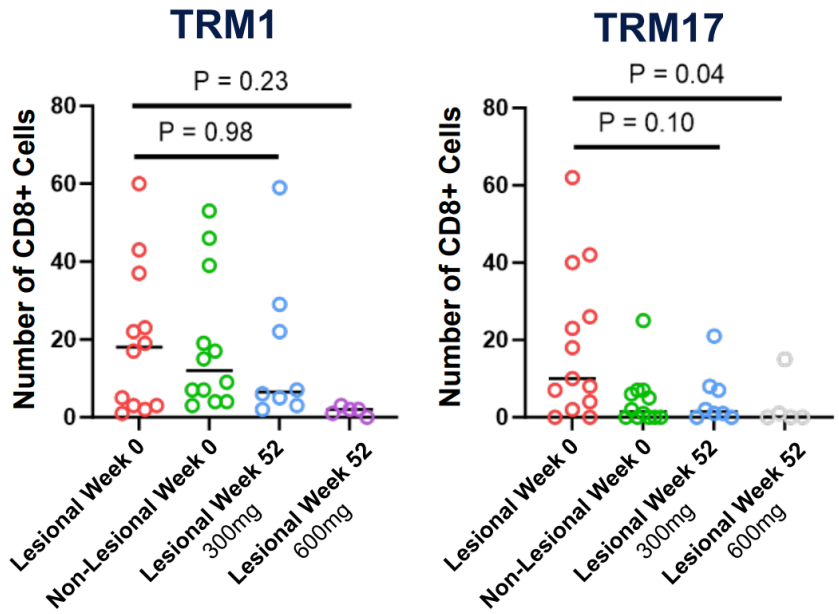
- *Primary*: Change in T_{RM} cell number from baseline to Week 52
- *Secondary*: PASI 100 at Weeks 28, 40, and 52; safety at Week 52

Blauvelt. Late breaking research. AAD 2024, San Diego, CA

Single-cell RNA seq Analysis of Lesional and Non-lesional Cells

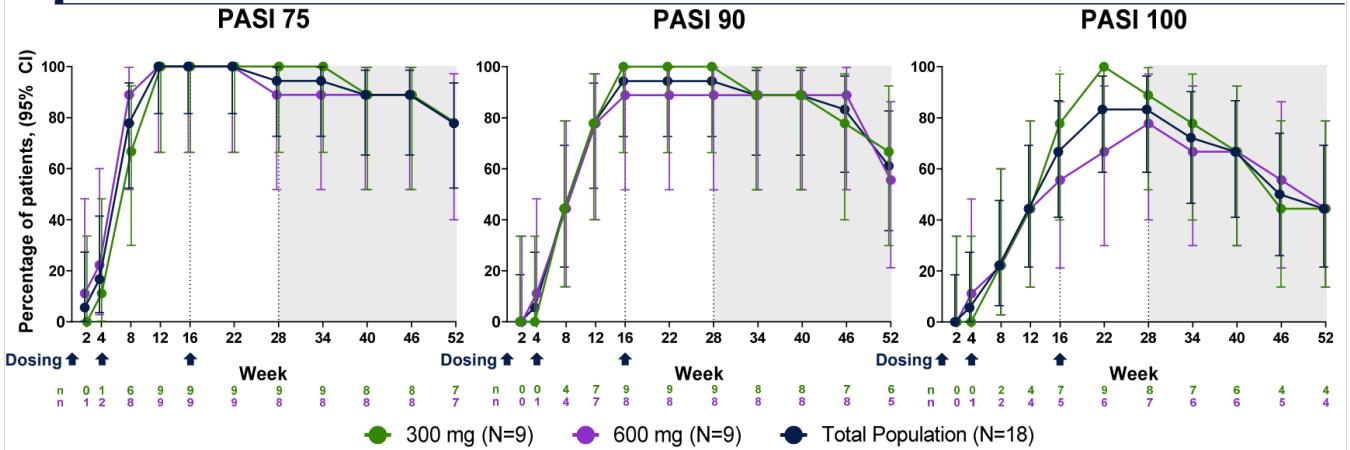


Differential distribution of T cell sub-clusters from baseline lesional skin, non-lesional skin, and post-treatment lesional skin



*Lesional baseline (n = 13), non-lesional baseline (n = 12), and post-treatment low-dose (n = 8) and high-dose risankizumab (n = 5) groups (one-way ANOVA)

PASI 75, 90, and 100 Responses from Baseline to Week 52 (mNRI)



- Rapid and high improvements in skin responses were observed with high doses of risankizumab induction

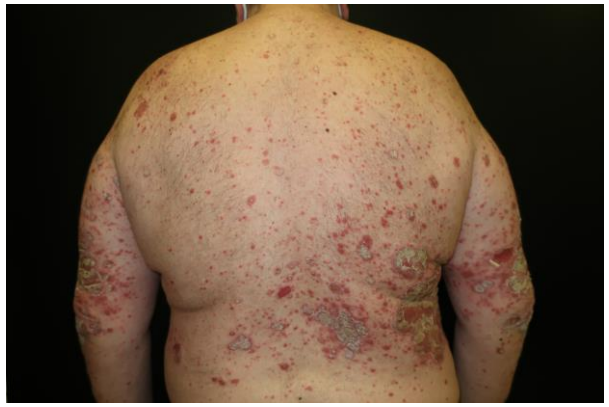
Blauvelt. Late breaking research. AAD 2024, San Diego, CA

Contenido

- Patogenia
- Clínica
- **Comorbilidades y recomendaciones**
- Terapéutica actual y pipeline

Relación entre psoriasis y comorbilidades:
Randomización mendeliana

Psoriasis



DM tipo 2

Causal relationship and shared genetic loci between psoriasis and type 2 diabetes through trans-disease meta-analysis

Matthew T Patrick, PhD[1], Philip E Stuart[1], Haihan Zhang[1,2], Qingyuan Zhao, PhD[3], Xianyong Yin, PhD[2], Kevin He, PhD[2], Xu-jie Zhou, MD PhD[4], Nehal N. Mehta, MD[5], John J Voorhees, MD[1], Michael Boehnke, PhD[2], Johann E Gudjonsson, MD PhD[1], Rajan P Nair, PhD[1], Samuel K. Handelman, PhD[6], James T Elder, MD PhD[1,7], Dajiang J Liu, PhD[8], Lam C Tsoi, PhD[1,2,9,*]

Obesidad

Evidence of a causal relationship between body mass index and psoriasis: A mendelian randomization study

Ashley Budu-Aggrey[1,2*], Ben Brumpton[1,3,4*], Jess Tyrrell[5,6*], Sarah Watkins[1,2*], Ellen H. Modalsli[7,8], Carlos Celis-Morales[9], Lyn D. Ferguson[9], Gunnhild Åberge Vie[7], Tom Palmer[10], Lars G. Fritsche[3], Mari Løset[3,8], Jonas Bille Nielsen[11], Wei Zhou[12], Lam C. Tsoi[13,14], Andrew R. Wood[5], Samuel E. Jones[5], Robin Beaumont[9], Marit Saunes[8,15], Pål Richard Romundstad[7], Stefan Siebert[16], Iain B. McInnes[16], James T. Elder[13,17], George Davey Smith[1,2], Timothy M. Frayling[5‡], Bjørn Olav Åsvold[3,18‡], Sara J. Brown[19,20‡], Naveed Sattar[9‡], Lavinia Paternoster[1,2‡]

Esclerosis múltiple

Shared Genetic Risk Factors for Multiple Sclerosis/Psoriasis Suggest Involvement of Interleukin-17 and Janus Kinase–Signal Transducers and Activators of Transcription Signaling

Matthew T. Patrick, PhD, Rajan P. Nair, PhD, Kevin He, PhD, Philip E. Stuart, MS, Allison C. Billi, MD, PhD, Xiang Zhou, PhD, Johann E. Gudjonsson, MD, PhD, Jorge R. Oksenberg, PhD, James T. Elder, MD, PhD, and Lam C. Tsoi, PhD

Riesgo Cardiovascular

Psoriasis and cardiovascular disease risk in European and East Asian populations: evidence from meta-analysis and Mendelian randomization analysis

Liming Zhang[1*], Yuxiang Wang[2], Li Qiu[1] and Jian Wu[1]

Dislipemia

Elevated plasma triglycerides increase risk of psoriasis: A cohort and Mendelian randomization study Get access

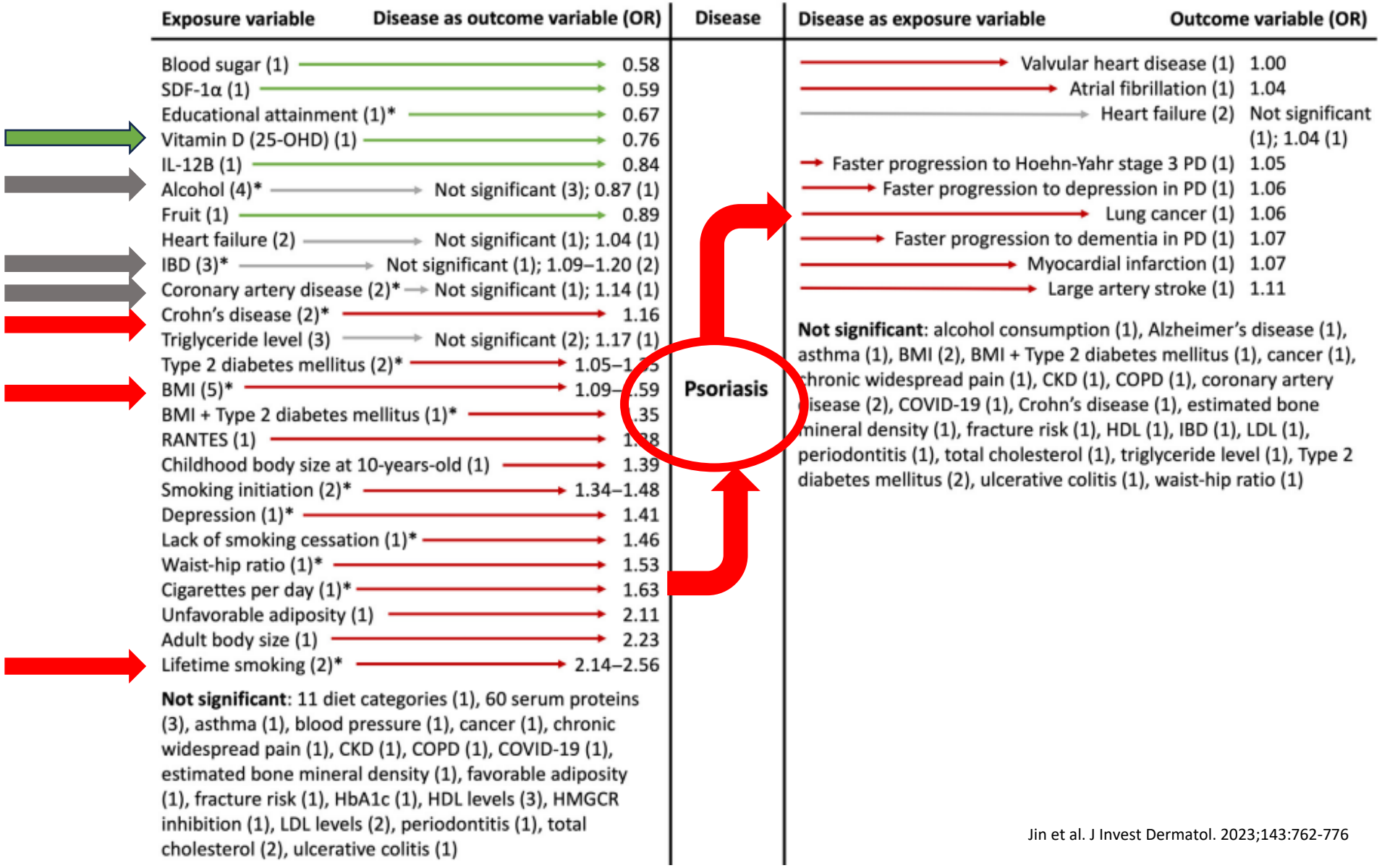
Serum Lipids and Risk of Incident Psoriasis: A Prospective Cohort Study from the UK Biobank Study and Mendelian Randomization Analysis

Disease consequences of higher adiposity uncoupled from its adverse metabolic effects using Mendelian randomisation

Susan Martin[1], Jessica Tyrrell[1], E Louise Thomas[2], Matthew J Bown[3,4], Andrew R Wood[1], Robin N Beaumont[1], Lam C Tsoi[5], Philip E Stuart[5], James T Elder[5,6], Philip Law[7], Richard Houlston[7], Christopher Kabrhel[8,9], Nikos Papadimitriou[10], Marc J Gunter[10], Caroline J Bull[11,12,13], Joshua A Bell[11,12], Emma E Vincent[11,12,13], Naveed Sattar[14], Malcolm G Dunlop[15,16], Ian PM Tomlinson[17], Sara Lindström[18,19], INVENT consortium , Jimmy D Bell[2], Timothy M Frayling[1*], Hanieh Yaghootkar[1,2,20*]

Patrick et al. Ann Neurol. 2023 Aug;94(2):384-397.
Patrick et al. J Invest Dermatol. 2021 Jun;141(6):1493-1502.
Xiao et al. J Invest Dermatol. 2022 Dec;142(12):3192-3199.e12.
Zhang et al. BMC Med. 2022 Nov 1;20(1):421. doi: 10.1186/s12916-022-02617-5.
Martin et al. Elife. 2022 Jan 25;11:e72452.
Budu-Aggrey et al.PLoS Med. 2019 Jan 31;16(1):e1002739.
Greve et al. Br J Dermatol. 2024 Feb 27:ljae089.

Mendelian Randomization Studies in Psoriasis and Psoriatic Arthritis: A Systematic Review



Jin et al. J Invest Dermatol. 2023;143:762-776

Cardiovascular Screening Practices and Statin Prescription Habits in Patients with Psoriasis among Dermatologists, Rheumatologists and Primary Care Physicians

Journal of Investigative Dermatology
Volume 142, Issue 6, June 2022, Pages 1519-1522

Commentary

Is It Prime Time for Statin Therapy in Psoriasis?

Nehal N. Mehta [1], Joel M. Gelfand [2]

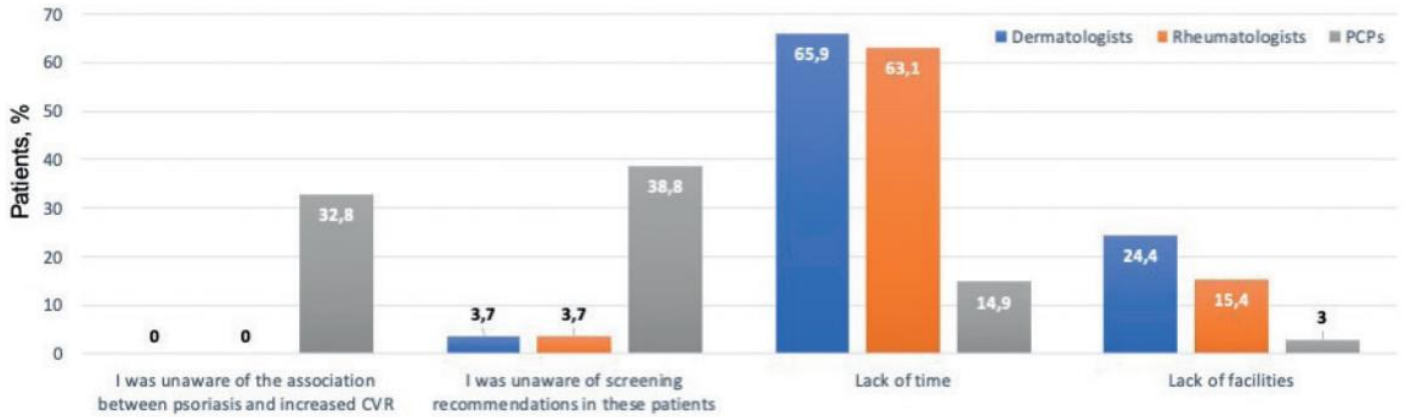


Fig. 2. Reasons for not screening for cardiovascular risk factors (CVRFs). *Bars* indicate percentage of physicians within each specialty that marked every option. PCP: primary care physician.

Más del 60% de los médicos de atención primaria declararon que desconocían la relación entre la psoriasis y las enfermedades cardiovasculares.

El 50% de los dermatólogos y reumatólogos que no prescriben estatinas estarían dispuestos a empezar a recetarlas.

Table IV. Statin prescription habits and predisposition to start prescribing them

	Dermatologists ($n = 103$)	Rheumatologists ($n = 94$)	OR (95% CI)
Current prescription of statins, *n* (%)	13 (12.6)	35 (37.2)	*OR 0.24 (0.12–0.50) **OR 0.04 (0.01–0.16)
Would you be willing to start prescribing statins?[a]			
Yes (%)	47 (52.2)	27 (45.8)	
I would start prescribing after attending specific training courses for dermatologists or rheumatologists	43 (91.5)	27 (100)	
Others motives[b]	4 (8.5)	0 (0.0)	
No (%)	43 (47.8)	32 (54.2)	
This exceeds the role of a dermatologists	15 (35.0)	9 (28.1)	
I do not have enough time to determine the need for statins	23 (53.5)	19 (59.4)	
I do not have the necessary material means to determine the need for statins	14 (32.6)	4 (12.5)	

Berna-Rico et al. Acta Derm Venereol. 2023 Mar28;103:adv5087.

Statins and psoriasis: Position statement by the Psoriasis Task Force of the European Academy of Dermatology and Venerology

A. Gonzalez-Cantero[1,2] | W. H. Boehncke[3] | J. De Sutter[4] | J. L. Zamorano[5] | J. Lambert[6] | L. Puig[7,8,9]

ELSEVIER

Journal of Investigative Dermatology
Volume 142, Issue 6, June 2022, Pages 1519-1522

Commentary

Is It Prime Time for Statin Therapy in Psoriasis?

Nehal N. Mehta[1], Joel M. Gelfand[2]

LDLc treatment goal

Cardiovascular risk

100 mg/dl (2.6 mmol/l)

Low to Moderate risk
- Low to moderate risk according to **SCORE 2/SCORE 2-OP***

70 mg/dl (1.8 mmol/l) and a ≥50% reduction of LDL-C vs baseline

High risk
- Total cholesterol >8mmol/l (310 mg/dl) or LDL-c >4.9 mmol/l (>190 mg/dl) or blood pressure ≥180/100 mmHg
- DM without organ damage, or duration ≥10 years or another additional risk factor
- Moderate chronic kidney disease
- High risk according to **SCORE 2/SCORE 2-OP***

HIGH INTENSITY TREATMENT with statins should be prescribed when the treatment aim is at least a 50% LDL-C reduction

55 mg/dl (1.4 mmol/l) and a ≥50% reduction of LDL-C vs baseline

Very high risk
- Documented (clinical or imaging) ASCVD
- DM with target organ damaged, or severe chronic kidney disease
- Familiar hypercholesterolemia with ASCVD or another major risk factor
- Very high risk according to **SCORE 2/SCORE 2-OP***

cLDL< 100
cLDL <70
cLDL<50

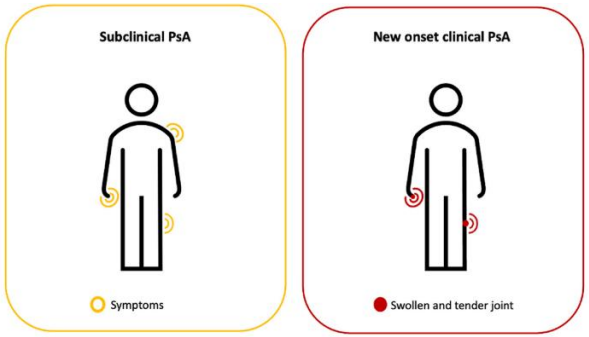
González-Cantero et al. J Eur Acad Dermatol Venereol. 2023 Sep

Transición

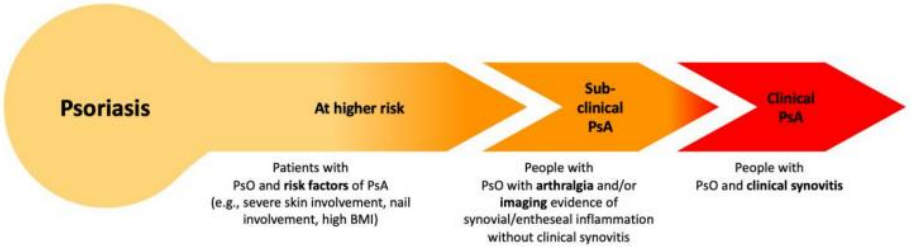
RMD Open — Rheumatic & Musculoskeletal Diseases

ORIGINAL RESEARCH

Characterisation of prodromal and very early psoriatic arthritis: a systematic literature review informing a EULAR taskforce



Subclinical PsA	New onset clinical PsA
Pain	Peripheral pattern[1]
Joint tenderness	Oligoarthritis[2]
Arthralgia	Articular erosions [3]
Imaging determined enthesopathy	



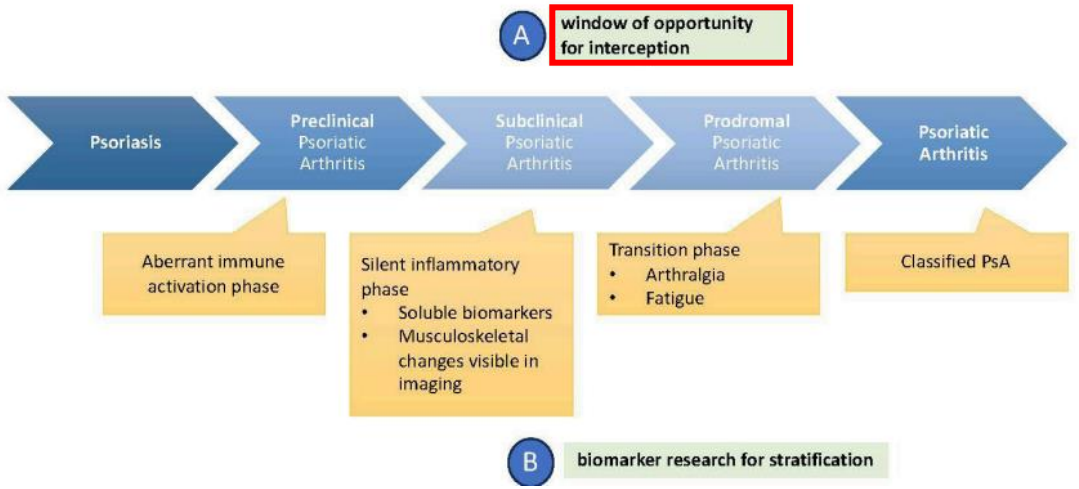
Nomenclature for research and prevention/interception trials in people with PsO at risk of PsA	
Phase	*Definition*
A. At higher risk	People with PsO at higher risk of PsA (i.e., severe skin involvement, nail involvement, obesity, familial history) of PsA.*
B. Sub-clinical	People with PsO with arthralgia and/or imaging evidence of synovial/entheseal inflammation without clinical synovitis
C. Clinical	People with PsO and clinical synovitis

Intercepción

RMD Open — Rheumatic & Musculoskeletal Diseases

VIEWPOINT

Association between biological immunotherapy for psoriasis and time to incident inflammatory arthritis: limitations and opportunities



De Marco G, et al. RMD Open 2023;9:e003143
Zabotti et al. Ann Rheum Dis. 2023 Sep;82(9):1162-1170.
Koehm M, Behrens F. RMD Open 2023;9:e003166

¿Tienen menos riesgo de desarrollar artritis psoriásica los pacientes con psoriasis tratados con biológicos?

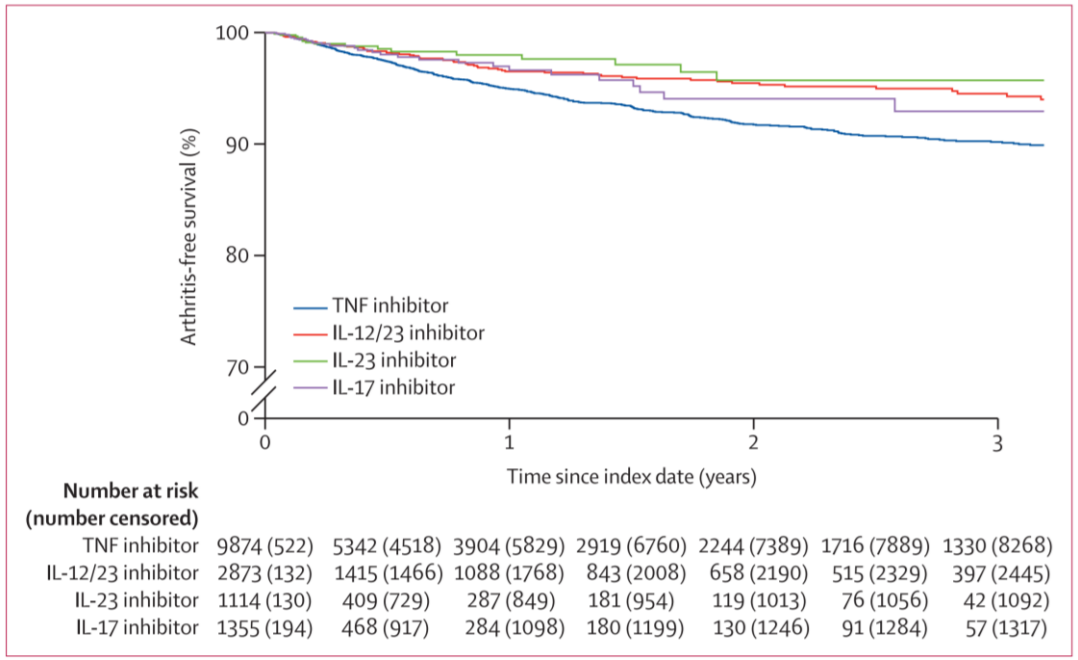
	Study	Study Design	No of Patients	Treatment	Findings
🟢	Gisondi et al. [68]	Retrospective non-randomized study	464	NB-UVB phototherapy vs. bDMARDs (TNFi, IL-17i, IL-12/23i)	Lower risk of PsA development in patients on bDMARDs compared with phototherapy
🟢	Acosta Felquer et al. [69]	Retrospective cohort study	1719	Topicals (topical treatment, phototherapy, no treatment) vs. cDMARDs (MTX, CsA) vs. bDMARDs (TNFi, IL-17i, IL-12/23i).	Lower risk of PsA development in patients on bDMARDs compared with topicals but not compared with cDMARDs
🟢	Rosenthal et al. [70]	Retrospective cohort study	1326	bDMARDs (TNFi, IL-12/23i, IL-17i, IL/23i) vs. other treatment	Lower risk of PsA development in patients on bDMARDs
🟢	Solmaz et al. [71]	Retrospective chart review	203	bDMARDs (TNFi, IL-17i, IL-12/23i) vs. cDMARDs vs. other/no treatment	Lower risk of PsA development in patients on bDMARDs and cDMARDs
🟢	Acquacalda et al. [72]	Prospective study	34	cDMARDs (MTX, CsA, Aci) vs. bDMARDs (TNFi, IL-12/23i)	cDMARDs and bDMARDs improve enthesitis
🟢	Kampylafka et al. [73]	Prospective study	20	Secukinumab (IL-17i)	Secukinumab improves subclinical inflammatory joint changes
	Savage et al. [74]	Prospective study	23	Ustekinumab (IL-12/23i)	Ustekinumab improves subclinical enthesopathy
	Haberman et al. [75]	Randomized, double-blind, placebo-controlled, trial	200	Guselkumab (IL-23i) vs. placebo	Ongoing study
🔴	Meer et al. [76]	Retrospective cohort study	193,709	bDMARDs (TNFi, IL-17i, IL-12/23i, IL-23i) vs. cDMARDs/phototherapy	Higher risk of PsA development in patients on bDMARDs compared with cDMARDs/phototherapy
🟡	Napolitano et al. [82]	Retrospective study	434	bDMARDs (TNFi, IL-12/23i)	In some patients bDMARDs may not prevent PsA development
	Balato et al. [83]	Retrospective study	326	phototherapy	Phototherapy is not able to prevent or delay PsA development

Kimak et al. J. Clin. Med. 2023, 12, 3850. https://doi.org/10.3390/jcm12113850

¿Es posible la intercepción farmacológica?

Association between biological immunotherapy for psoriasis and time to incident inflammatory arthritis: a retrospective cohort study

THE LANCET
Rheumatology



Number at risk (number censored)							
TNF inhibitor	9874 (522)	5342 (4518)	3904 (5829)	2919 (6760)	2244 (7389)	1716 (7889)	1330 (8268)
IL-12/23 inhibitor	2873 (132)	1415 (1466)	1088 (1768)	843 (2008)	658 (2190)	515 (2329)	397 (2445)
IL-23 inhibitor	1114 (130)	409 (729)	287 (849)	181 (954)	119 (1013)	76 (1056)	42 (1092)
IL-17 inhibitor	1355 (194)	468 (917)	284 (1098)	180 (1199)	130 (1246)	91 (1284)	57 (1317)

Figure 2: **Time to inflammatory arthritis among patients initiating biological therapies for psoriasis (n=15 501)**
TNF=tumour necrosis factor. IL=interleukin.

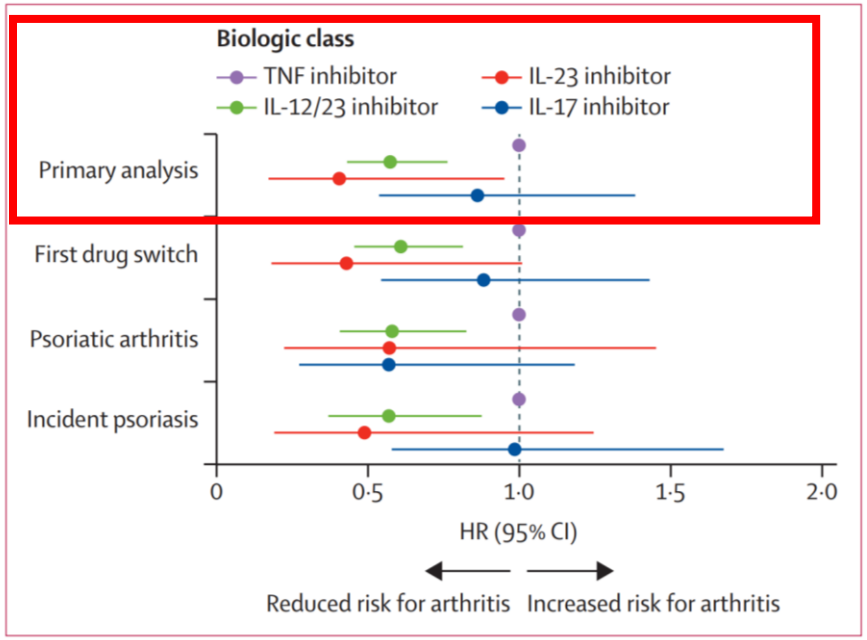


Figure 3: **Forest plot depicting adjusted HRs for time to inflammatory arthritis for the primary model and three sensitivity analyses**

- The most common **first biologic class prescribed were TNF inhibitors (10 037 [64·8%] patients)** followed by IL-12/23 inhibitors (2914 [18·8%]), IL-17 inhibitors (1401 [9·0%]), and IL-23 inhibitors (1149 [7·4%])
- Among 3148 patients who switched biologic class, **the most common second biologic prescribed was IL-12/23 inhibitor (1189 [37·8%] patients)** followed by IL-17 inhibitor (818 [26·0%]), TNF inhibitor (603 [19·2%]), and IL-23 inhibitor (538 [17·1%]).

Singla et al. Lancet Rheumatol 2023; 5: e200–07

Comorbilidades Psoriasis: impacto en el tratamiento

Comorbidities and Biologic Treatment Selection for Psoriasis		PsA	IBD	Hepatitis B		Hepatitis C	CHF (NYHA III/IV)	MS	HIV	Malignancy
				Anti HBc+	HBsAg+					
TNFα Inhibitors	Etanercept									
	Adalimumab									
	Certolizumab Pegol									
IL-12/23 Inhibitor	Ustekinumab									
IL-23 Inhibitors	Guselkumab									
	Tildrakizumab									
	Risankizumab									
IL-17 Inhibitors	Secukinumab									
	Ixekizumab									
	Brodalumab									
	Bimekizumab									

Safe/Preferred | Avoid | Data is limited but can be safe; collaboration needed | Use caution; collaboration needed | Data lacking

March 11, 2024

Jeffrey M. Cohen, M.D.; Department of Dermatology, Yale School of Medicine

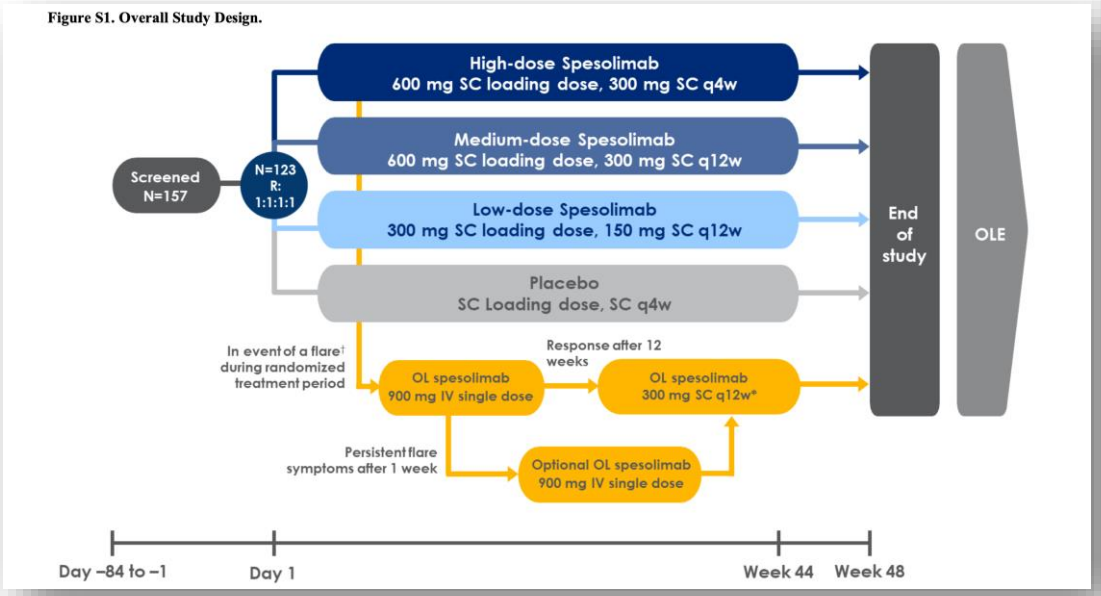
Contenido

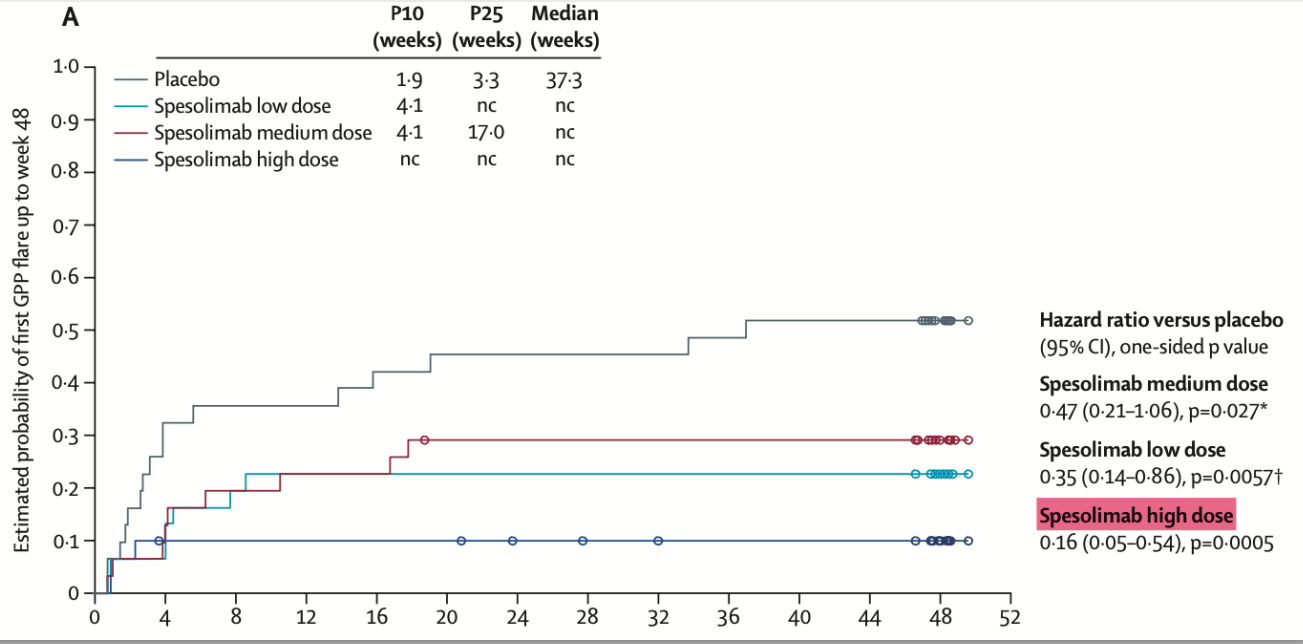
- Patogenia
- Clínica
- Comorbilidades y recomendaciones
- **Terapéutica actual y futura**

Psoriasis pustulosa generalizada
Spesolimab

Efficacy and safety of subcutaneous spesolimab for the prevention of generalised pustular psoriasis flares (Effisayil 2): an international, multicentre, randomised, placebo-controlled trial

- **Objetivo: Tiempo de brote hasta semana 48**



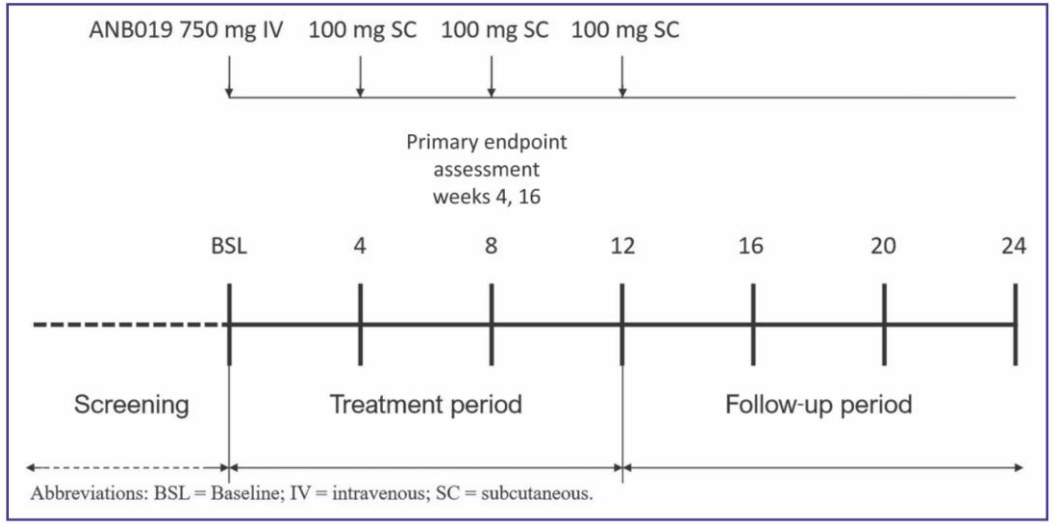


Dosis elevadas spesolimab cada 4 semanas **reducen el riesgo de brotes de PPG.**

Lancet. 2023 Oct 28;402(10412):1541-1551.

Imsidolimab

Imsidolimab: Ac monoclonal humanizado anti-IL36R
1ª dosis iv + tres dosis sc los días 27,57,85
Reclutan 8 paciente s: 6 finalizan estudio



Br J Dermatol. 2023 Jul

Imsidolimab, an anti-interleukin-36 receptor monoclonal antibody, for the treatment of generalized pustular psoriasis: results from the phase II GALLOP trial

Objetivo 1º : % de pacientes que alcanzan respuesta clínica medida por" *Clinical global impression scale*" (CGS) a las semanas 4 y 16

- ✓ **50%** a las semanas 4 y 16 consiguen y mantienen
- ✓ " mucha mejoría"(*CGS*)

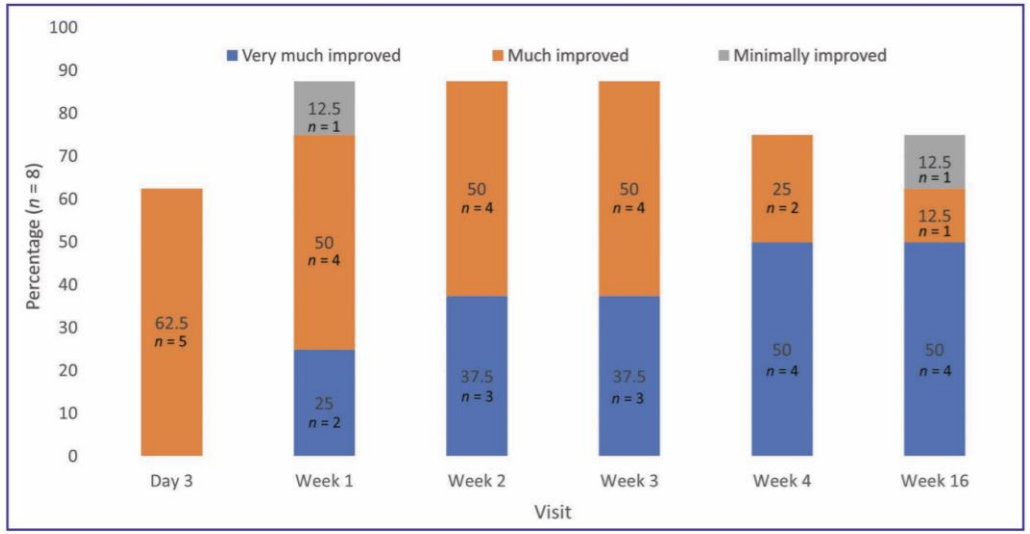
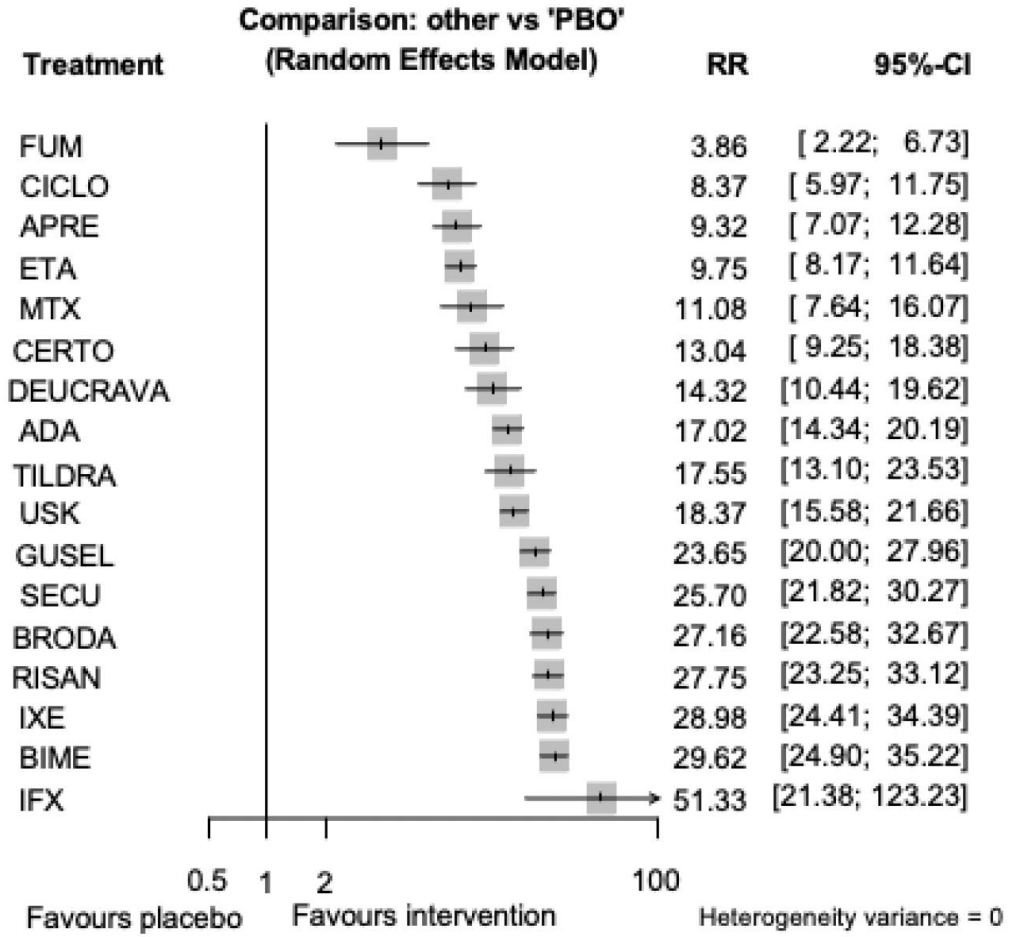
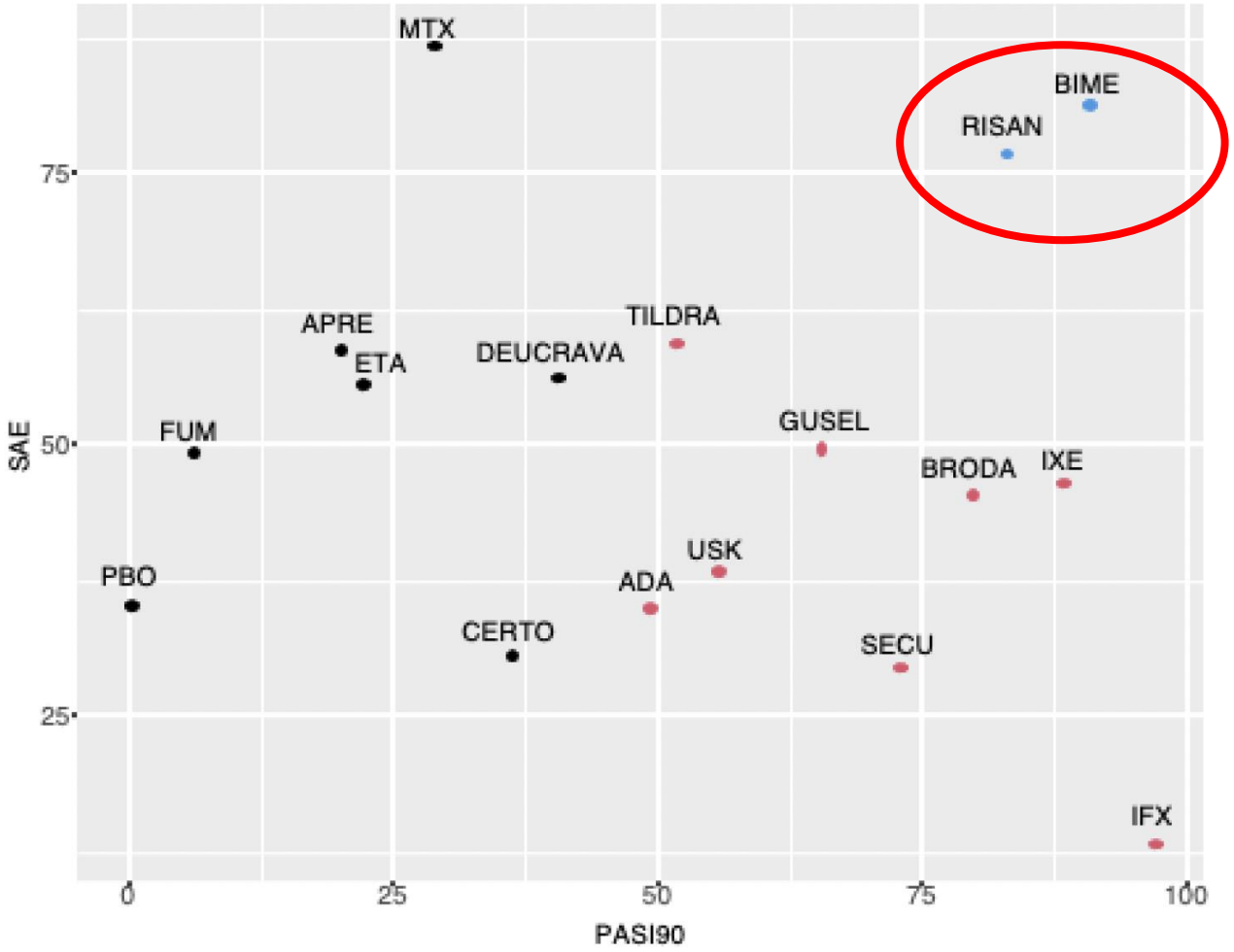


Figure 2 Primary efficacy endpoint: proportion and number of patients who achieved a clinical response, according to the Clinical Global Impression scale, by study visit (full analysis set).

Estudio para evaluar la eficacia y seguridad de imsidolimab (ANB019) en el tratamiento de sujetos con GPP (GEMINI1) fase III: fin del reclutamiento Agosto 23

Panorama actual en el tratamiento de la psoriasis

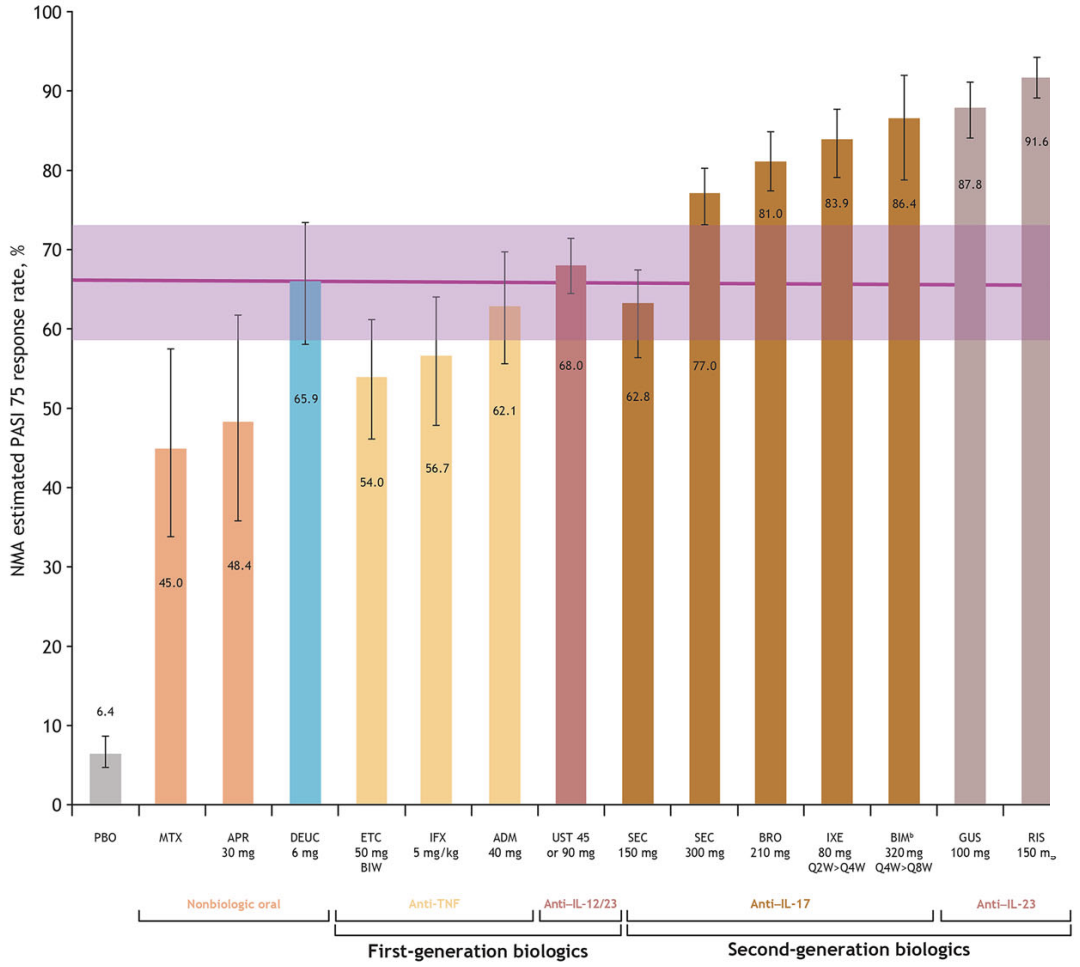




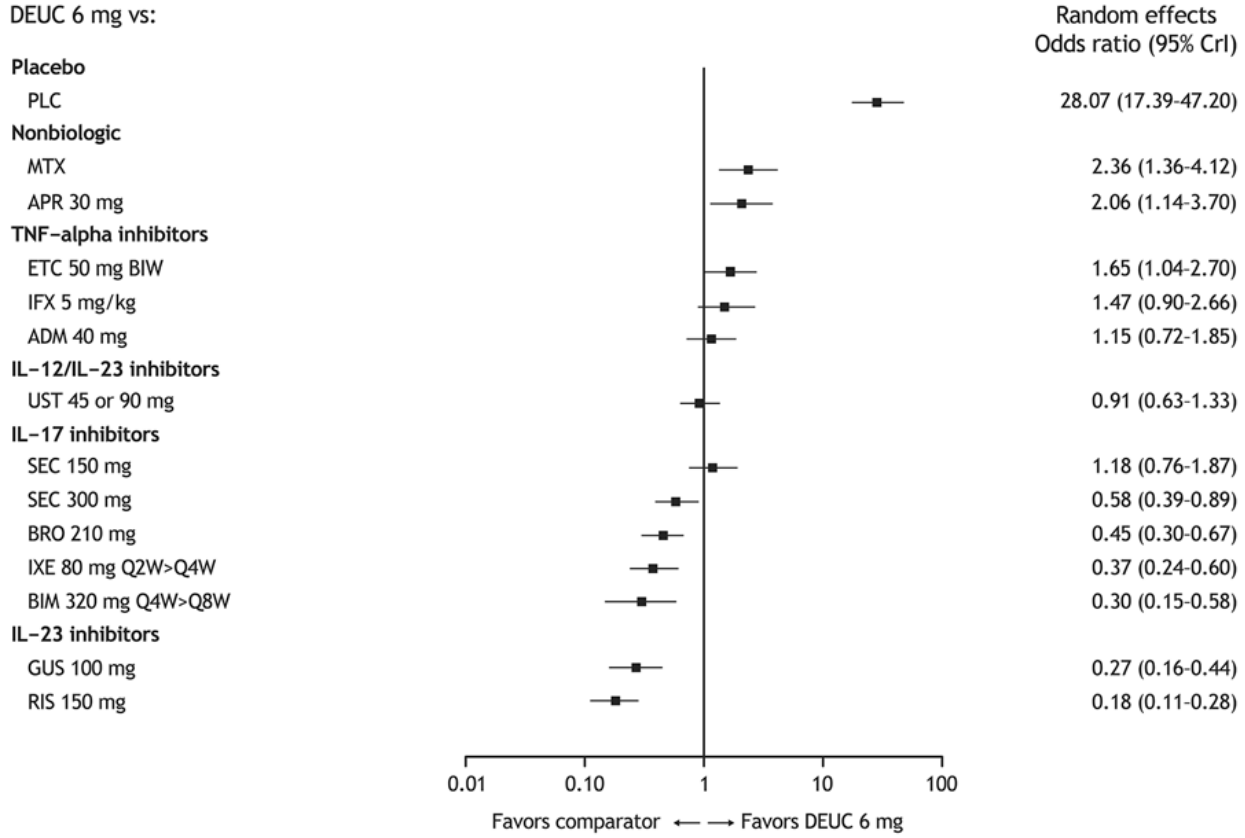
Sbidian E, et al. Cochrane Database Syst Rev. 2023 Jul 12;7(7):CD011535.

Panorama actual en el tratamiento de la psoriasis

(b) Long-term (44–60 weeks) estimated PASI 75 response

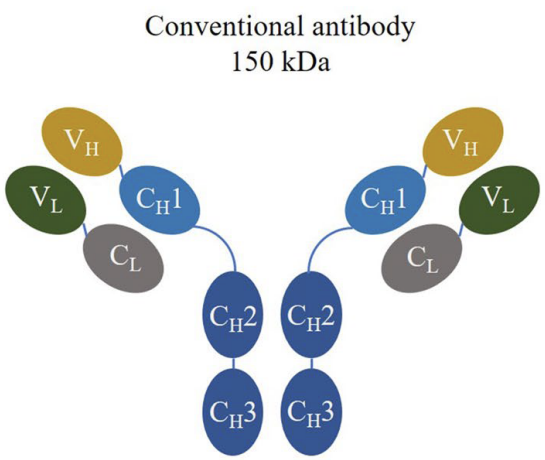


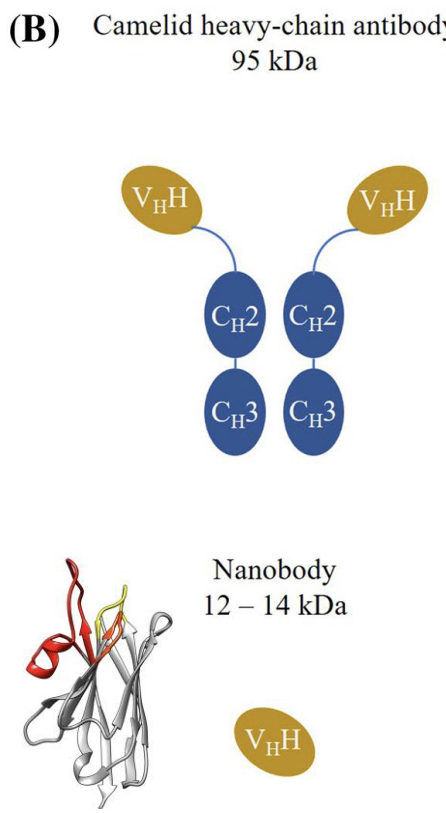
(c) Long-term (44–60 weeks) PASI 75 response

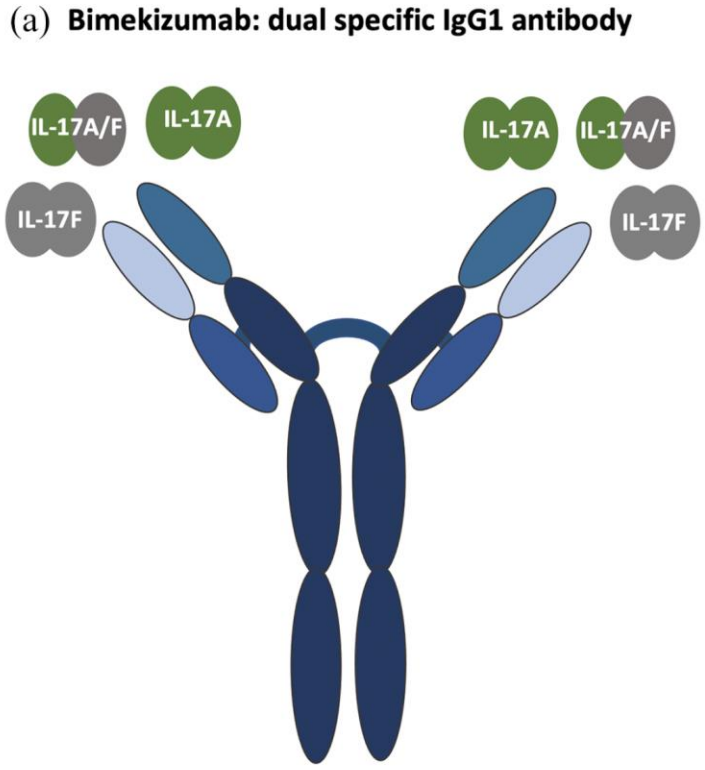


Armstrong AW, et al. Dermatol Ther (Heidelb). 2023 Oct 6. doi: 10.1007/s13555-023-01034-7.

Nuevas estructuras moleculares en el arsenal terapéutico







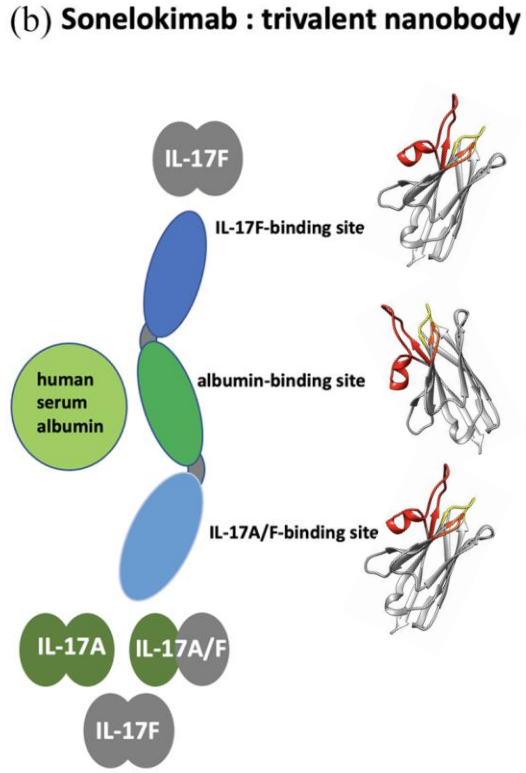
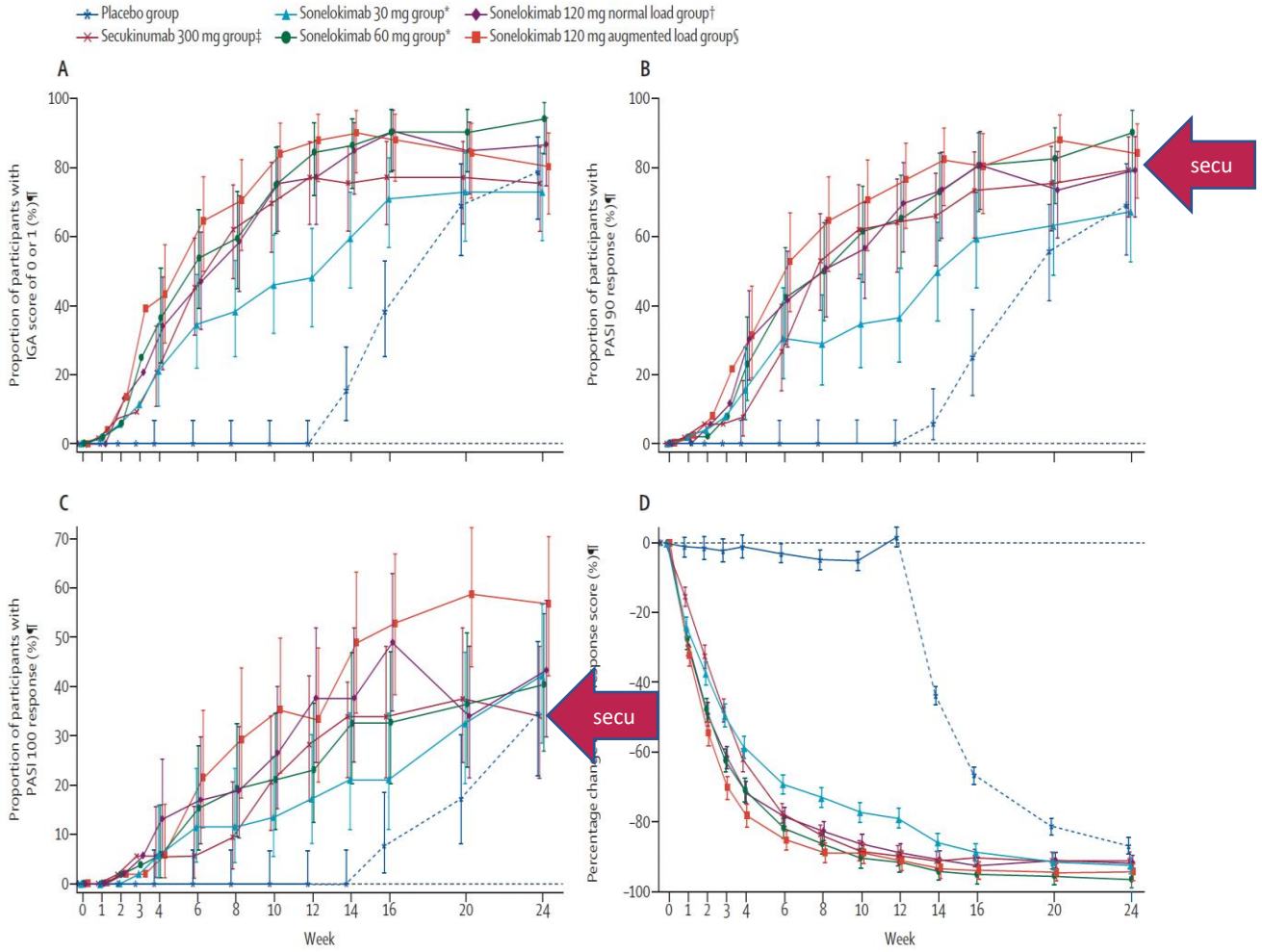


Figure 1. Schematic representation of bimekizumab and sonelokimab's molecular structures. (a) Bimekizumab has an antigen-binding site that neutralizes interleukin (IL)-17A, IL-17F and their heterodimers (dual specificity). (b) Sonelokimab is a trivalent camelid nanobody comprised of an *N*-terminal moiety that binds specifically to IL-17F, a central moiety binding to serum albumin for stabilization and a C-terminal moiety binding IL-17A and IL-17F (bispecific inhibitor).

Jovčevska I, Muyldermans S. BioDrugs. 2020 Feb;34(1):11-26.

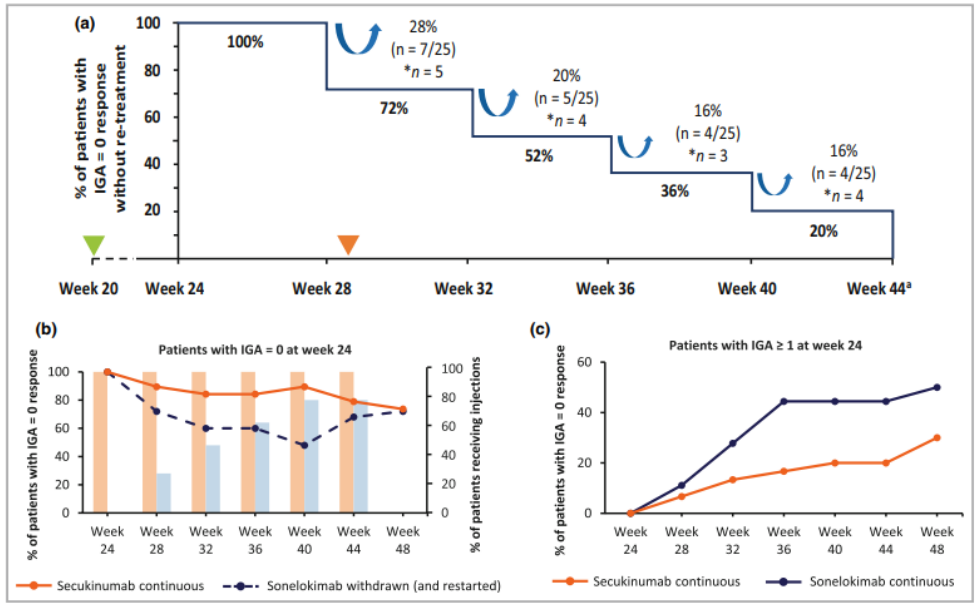
Iznardo H, Puig L. Ther Adv Chronic Dis. 2021 Aug 12;12:20406223211037846.

Sonelokimab (Merck Serono/MoonLake) phase 2b



Papp K, et al. *Lancet* 2021; 397: 1564–75

Maintenance of response in moderate-to-severe psoriasis after withdrawal of the interleukin (IL)-17A and IL-17F nanobody sonelokimab: is there a role for IL-17F in disease reoccurrence?

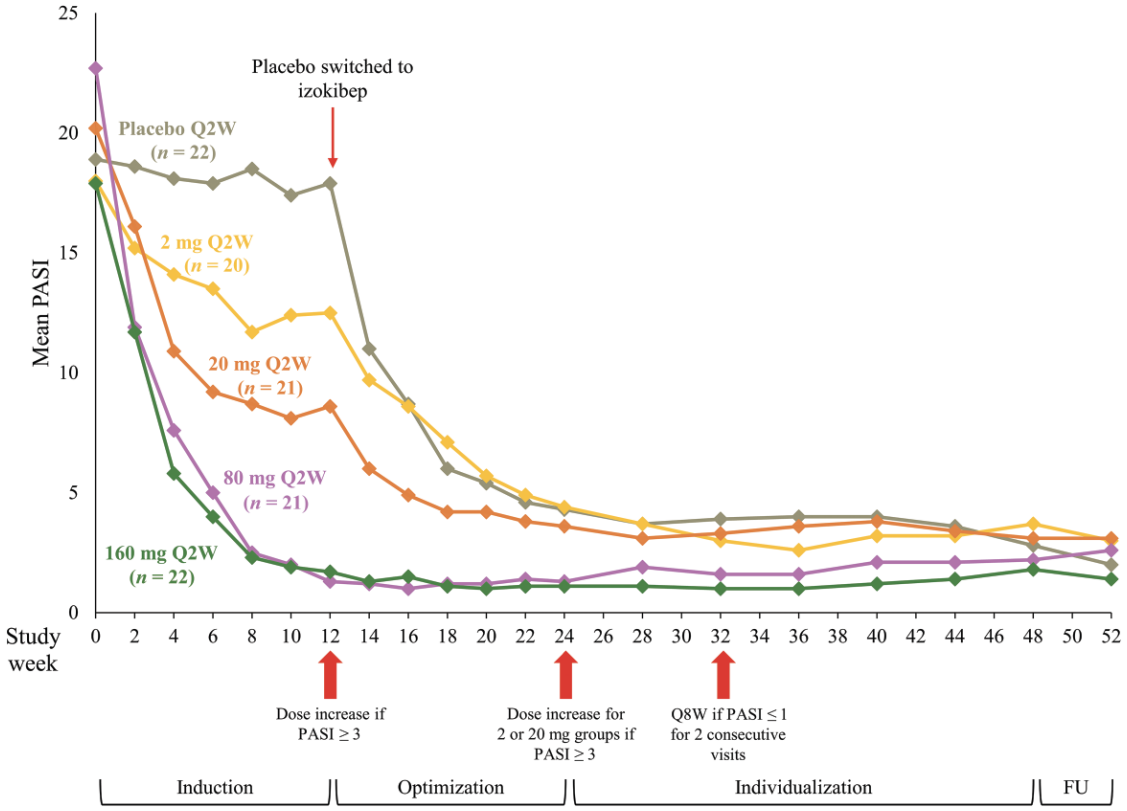


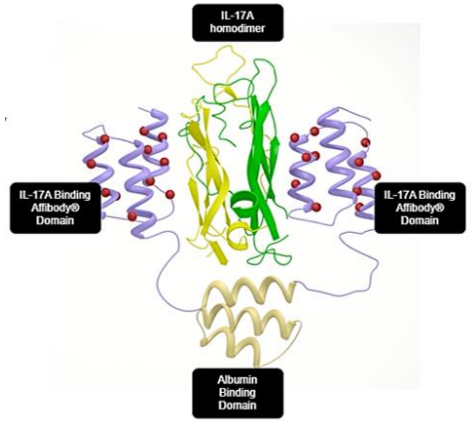
Retention of skin clearance after 7 half-lives following randomized withdrawal:

- Risankizumab 70% (7x28 days)
- Guselkumab 67% (7x18 days))
- Bimekizumab 40% (7x26 days)
- **Sonelokimab 50% (7x12 days)**

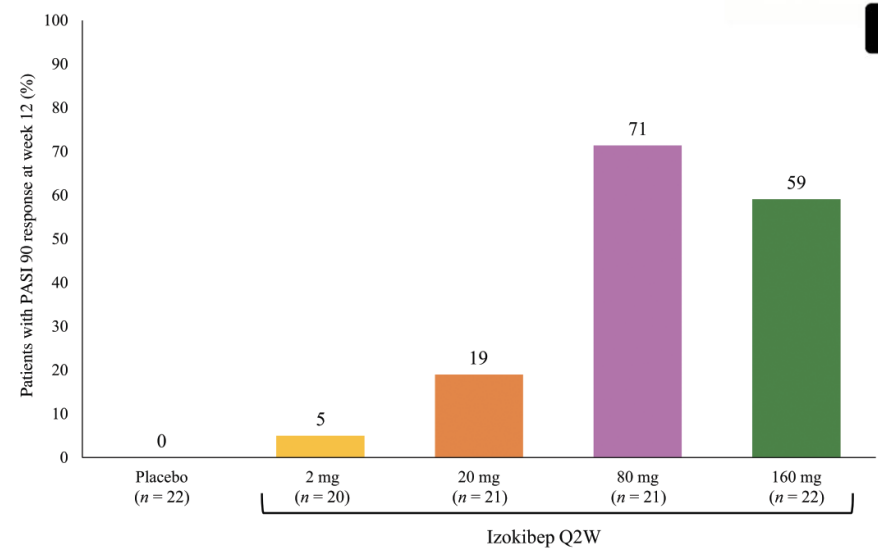
Reich K, Cullen E, Weinberg M. Br J Dermatol. 2022 Oct;187(4):591-593.

Izokibep for the treatment of moderate-to-severe plaque psoriasis: a phase II, randomized, placebo-controlled, double-blind, dose-finding multicentre study including long-term treatment





PASI 90

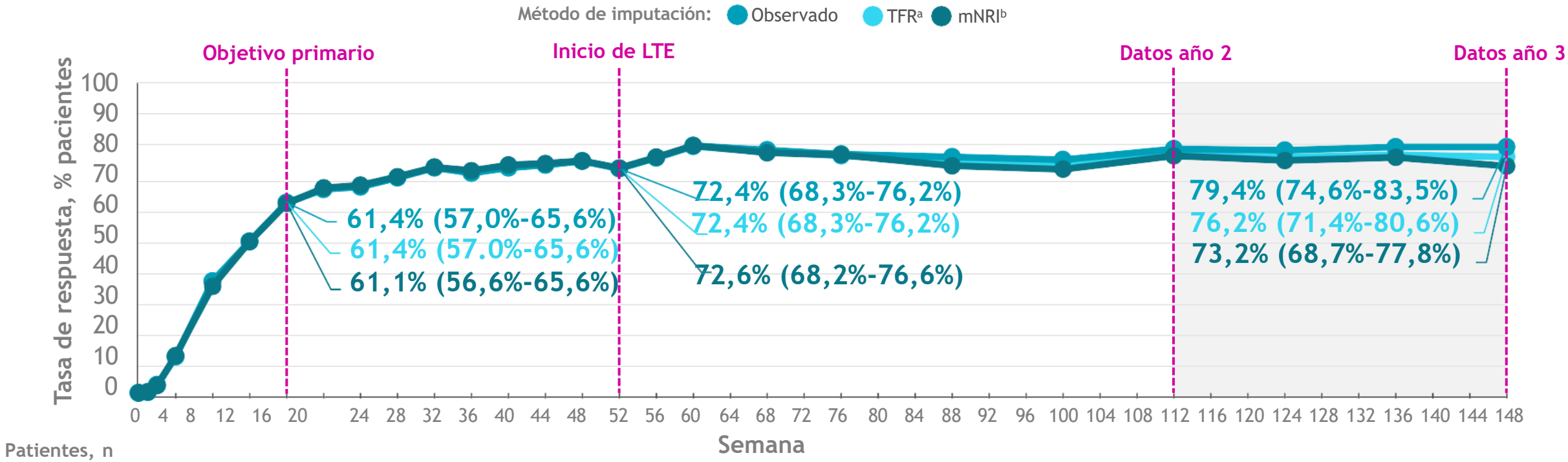


Yes	0	1	4	15	13
No	22	18	16	2	8
Missing	0	1	1	4	1

The safety profile of izokibep was generally comparable to placebo at week 12 except for **injection site reactions and diarrhoea**. These AEs **decreased after the first 12 weeks of the study**. There were **no cases of IBD** and a **very low incidence of *Candida* spp**. infection, comparable to placebo.

Gerdes S, et al. Br J Dermatol. 2023 Sep 15;189(4):381-391.

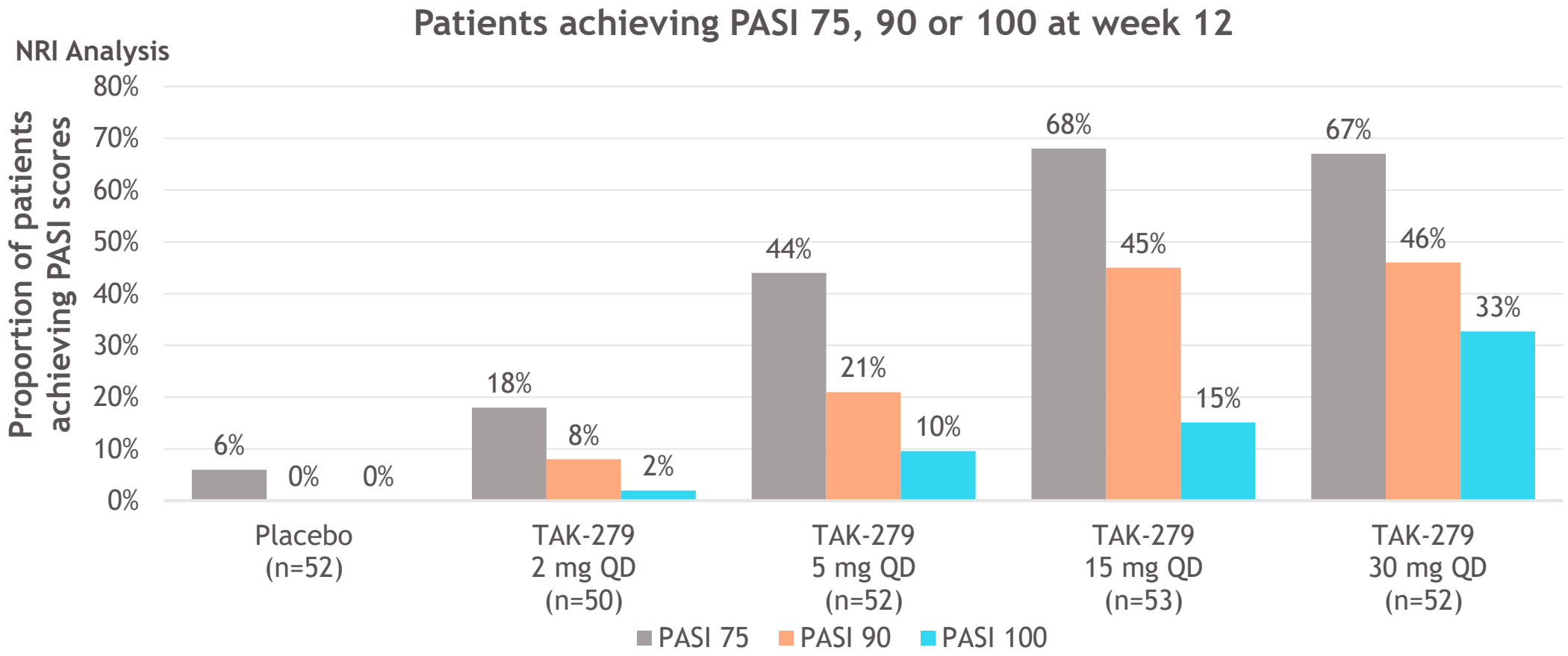
Tasas de respuesta PASI 75 con tratamiento continuo con deucravacitinib desde el día 1 hasta los 3 años



Patientes, n																								
Observado	513	511	509	507	510	507	505	495	506	500	495	496	500	511	477	489	482	485	463	449	438	428	407	339
TFR	513	511	509	507	510	507	505	495	506	500	495	496	500	511	477	490	485	489	469	457	449	439	420	353
mNRI	456	456	456	456	456	456	456	456	456	456	456	456	456	456	456	456	456	456	456	456	456	456	456	456

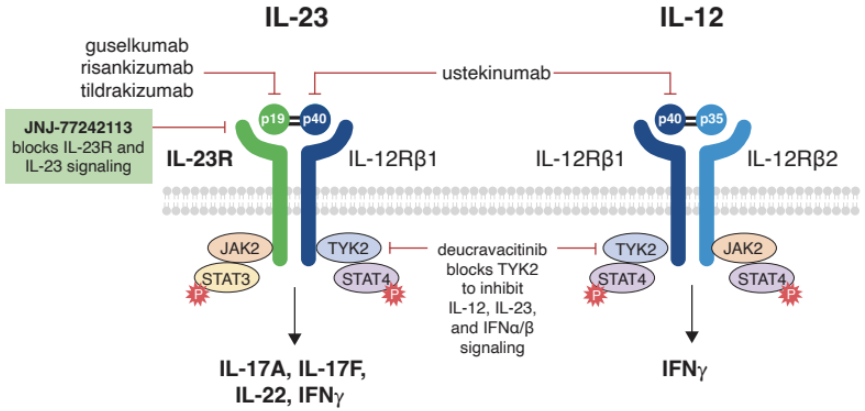
Armstrong AW, et al. Presented at the 32nd European Academy of Dermatology & Venereology Congress; 11—14 October 2023; Berlin, Germany

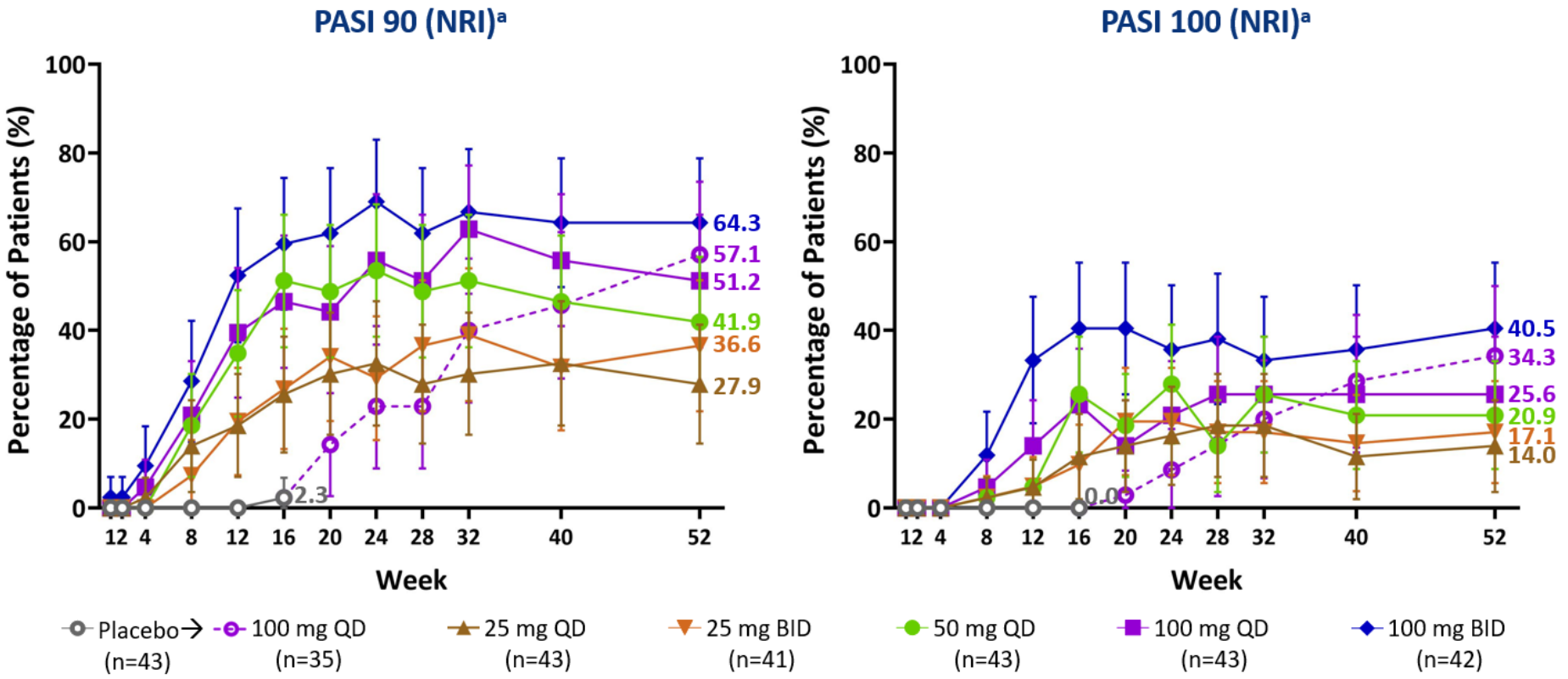
Zasocitinib (TAK-279) Phase 2b efficacy results: Patients achieving PASI 75, 90, or 100 at Week 12

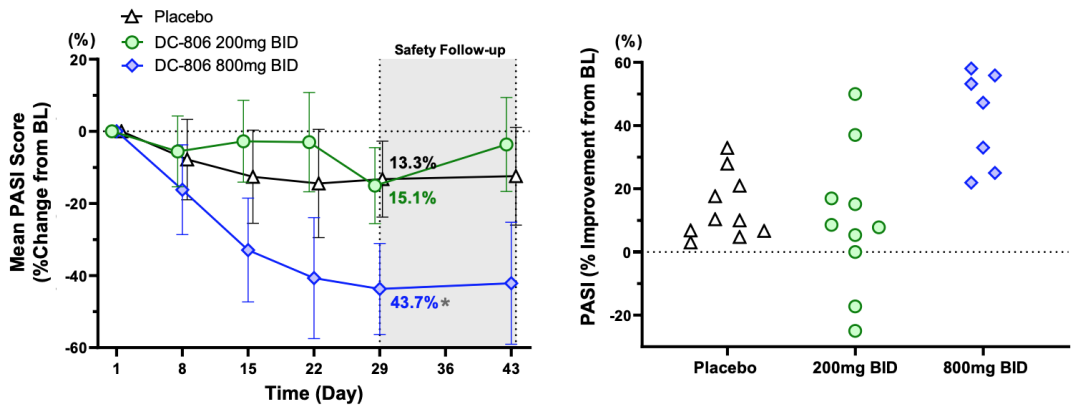


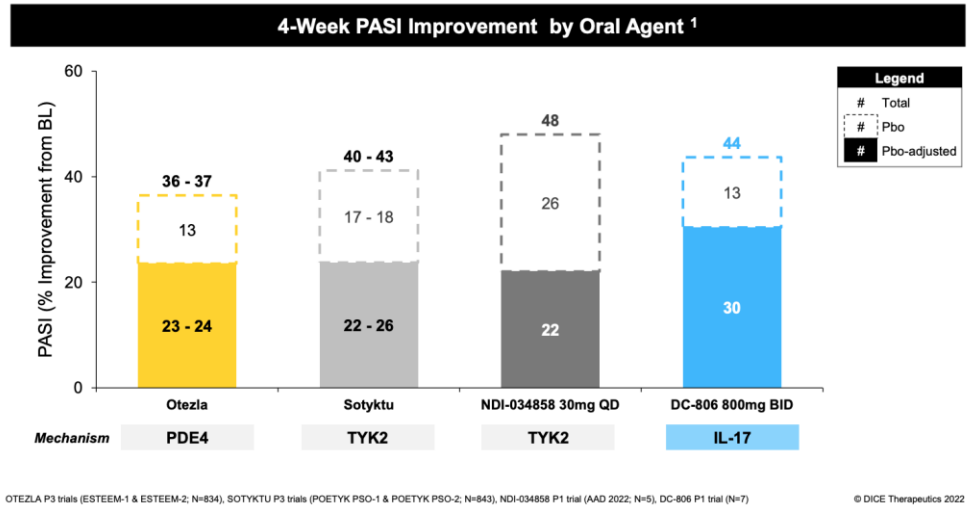
p values from a Cochran-Mantel-Haenazel test, with prior biologic treatment included as a stratification factor, comparing the proportion of patients in the treatment group versus placebo. For secondary endpoints (PASI 90 and PASI 100). P values are nominal: *p<0.05; **p<0.005, p<0.001
Modified intent-to-treat (miTT) analysis set: all patients who were randomized and received at least one dose of study treatment
CI, confidence interval; NRI, non-responder imputation, PASI, Psoriasis Area and Severity Index; QD, once daily.
Takeda. Accessed March 2023. https://www.takeda.com/newsroom/newsreleases/2023/takeda-announces-positive-results-in-phase-2b-study-of-investigational-tak-279.

Ferris, *et al*. A Phase 2b, Long-term Extension, Dose-ranging Study of Oral JNJ-77242113 for the Treatment of Moderate-to-Severe Plaque Psoriasis: FRONTIER 2. Presented at AAD 2024









https://investors.dicetherapeutics.com/static-files/97510404-4b85-43f6-b1de-aa58dbb7c375

DICE Therapeutics Announces Positive Topline Data from Phase 1 Clinical Trial of Lead Oral IL-17 Antagonist, DC-806, for Psoriasis

Oct 11, 2022

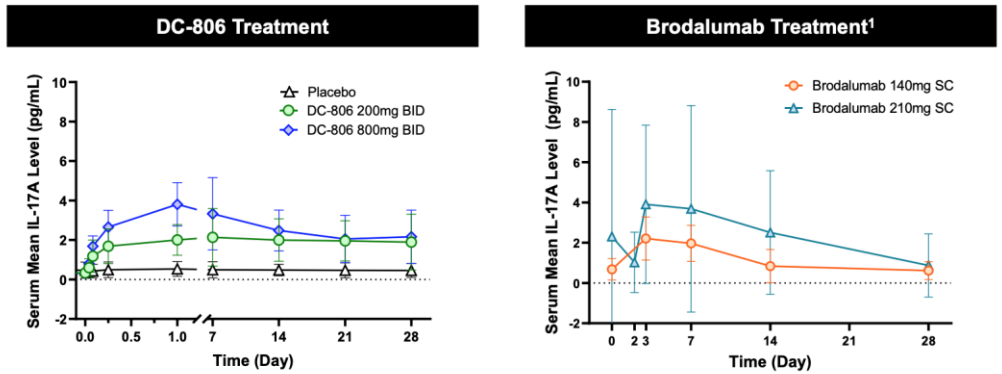
PDF Version

Clinical proof-of-concept in psoriasis patients achieved with a mean percentage reduction in PASI from baseline at 4 weeks of 43.7% in the high dose group compared to 13.3% in the placebo group, with an exploratory p-value of 0.0008

DC-806 was well tolerated with an excellent safety profile across all dose groups in healthy volunteers and psoriasis

DC-806 increased serum IL-17A to levels comparable to brodalumab

DICE



A Study to Evaluate the Efficacy and Safety of DC-806 in Participants With Moderate to Severe Plaque Psoriasis (Illuminate)

The safety and scientific validity of this study is the responsibility of the study sponsor and investigators. Listing a study does not mean it has been evaluated by the U.S. Federal Government. Know the risks and potential benefits of clinical studies and talk to your health care provider before participating. Read our disclaimer for details.

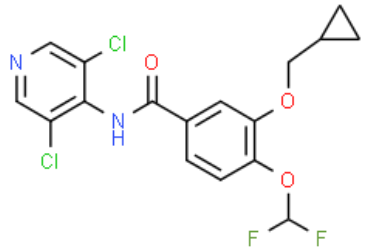
ClinicalTrials.gov Identifier: NCT05896527

Recruitment Status : Recruiting
First Posted : June 9, 2023
Last Update Posted : June 9, 2023

See Contacts and Locations

Roflumilast

COPD: 0.5mg/d
34.7€/month (Daxas®, generics)



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Full English text available at
www.actasdermo.org

REVISIÓN

Roflumilast tópico y oral en dermatología. Una revisión narrativa

M. Mansilla-Polo[a,b], E. Gimeno[c] y D. Morgado-Carrasco[c,d,*]

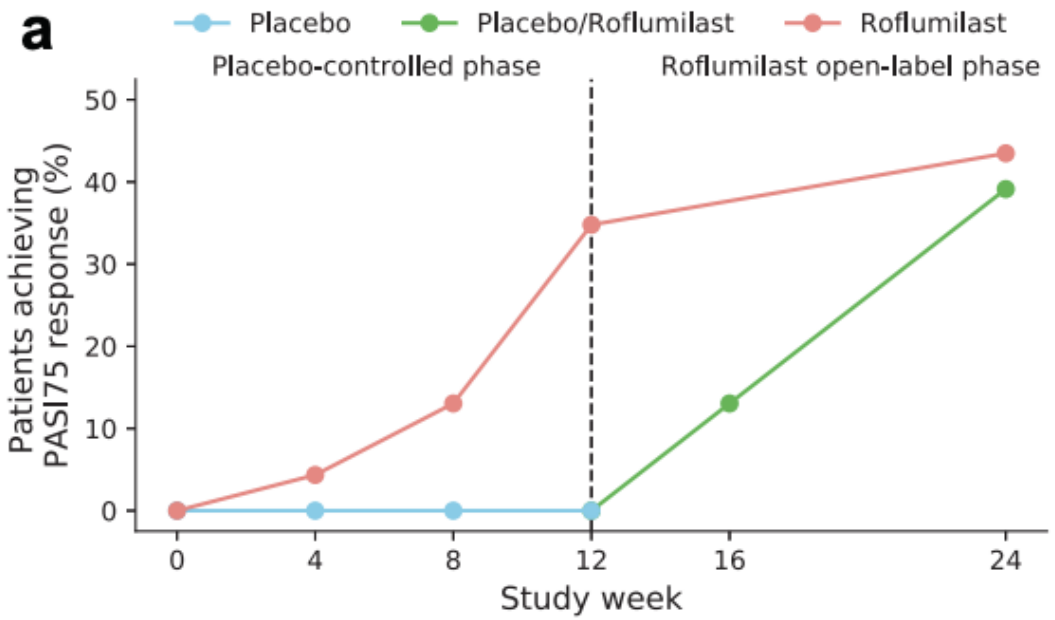
Efficacy and safety of oral roflumilast for moderate-to-severe psoriasis—a randomized controlled trial (PSORRO)

Mette Gyldenløve,[a,g] Howraman Meteran,[b,c] Jennifer A. Sørensen,[d] Simon Fage,[e] Yiqiu Yao,[d] Jesper Lindhardsen,[f] Christoffer V. Nissen,[d] Tanja Todberg,[a] Simon F. Thomsen,[d] Lone Skov,[a,g] Claus Zachariae,[a,g] Lars Iversen,[e] Mia-Louise Nielsen,[d] and Alexander Egeberg[d,g,]*

A company-independent, multicenter, randomized, double-blind, placebo-controlled trial (ClinicalTrials.gov NCT04549870). Patients were randomized 1:1 to receive monotherapy with oral roflumilast 500 µg once daily (n=23) or placebo (=23). At week 12, placebo patients were switched to open-label roflumilast through week 24.

The most prevalent, drug-related adverse events in both treatment groups were transient **gastrointestinal symptoms, weight-loss, headache, and insomnia**. A total of three patients (roflumilast n = 2; placebo, n = 1) discontinued therapy due to adverse events.

Gyldenløve M, et al. Lancet Reg Health Eur. 2023 Apr 21;30:100639.



NNT wk 12 roflumilast: 2.86

NNT wk 16 apremilast (NMA): 3.71

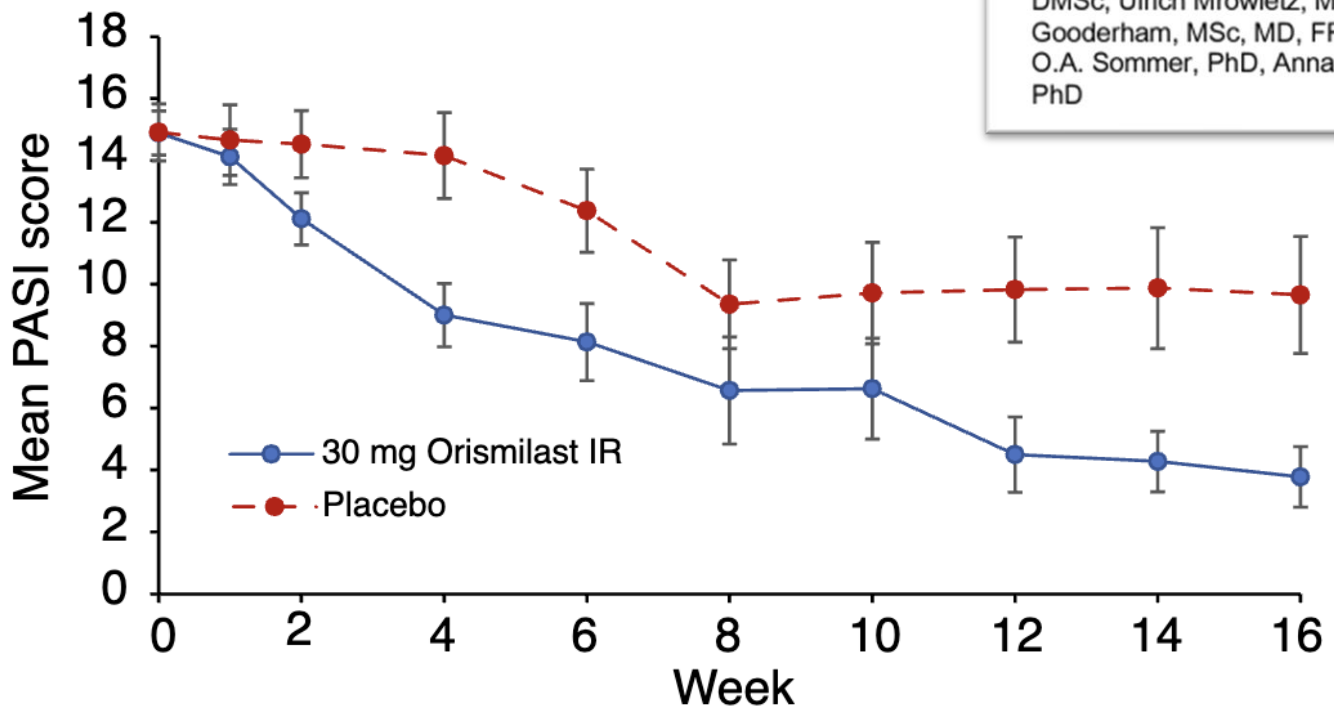
Armstrong AW, et al. Med Res Opin. 2018 Jul;34(7):1325-1333.

Orismilast

Journal Pre-proof

Orismilast in moderate-to-severe psoriasis: Efficacy and safety from a 16-week, randomized, double-blinded, placebo-controlled, dose-finding, phase 2b trial (IASOS)

Richard B. Warren, BSc, MBChB (Hons), PhD, FRCP, Lars E. French, MD, Andrew Blauvelt, MD, MBA, Richard G. Langley, MD, FRCPC, Alexander Egeberg, MD, PhD, DMSc, Ulrich Mrowietz, MD, Hamish J.A. Hunter, BSc (Hons), PhD, MRCP, Melinda Gooderham, MSc, MD, FRCPC, Per Soerensen, MSc, Philippe Andres, MD, Morten O.A. Sommer, PhD, Anna Carlsson, MSc, Kim D. Kjøller, MD, Bruce E. Strober, MD, PhD



PASI-75 at week 16 was 44.4% compared to 5.6% for patients on placebo (odds ratio [OR]: 15.7, p = 0.019)

NNT wk 16 orismilast: 2.58

NNT wk 16 apremilast (NMA): 3.71

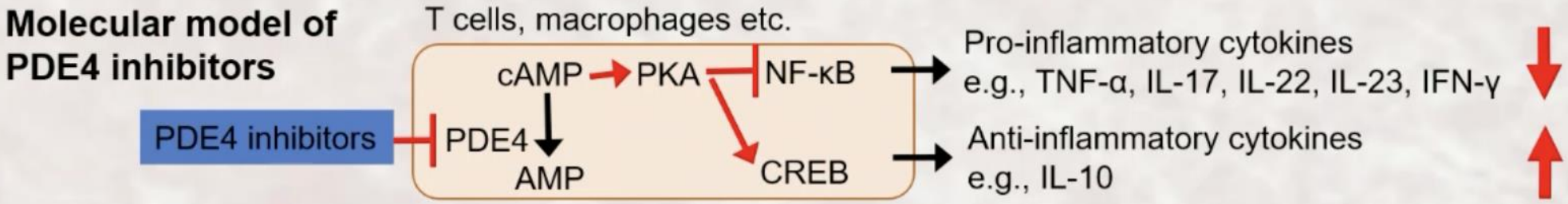
Warren RB, et al. J Eur Acad Dermatol Venereol. 2023 Apr;37(4):711-720.

Armstrong AW, et al. Med Res Opin. 2018 Jul;34(7):1325-1333.

ME3183

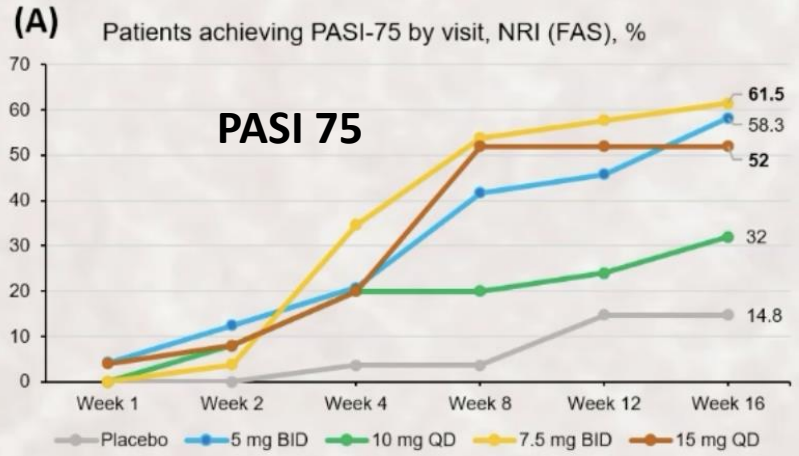
- Apremilast, an oral phosphodiesterase 4 (PDE4) inhibitor, and deucravacitinib, an oral tyrosine kinase 2 inhibitor, are new oral medications that have been introduced to treat psoriasis in the last decade.
- However, there is still an unmet need for additional oral treatments for psoriasis that are highly effective, safe, and tolerable.
- In an in vitro non-clinical study, the oral selective PDE4 inhibitor ME3183 inhibited PDE4B more strongly than existing marketed PDE4 inhibitors.

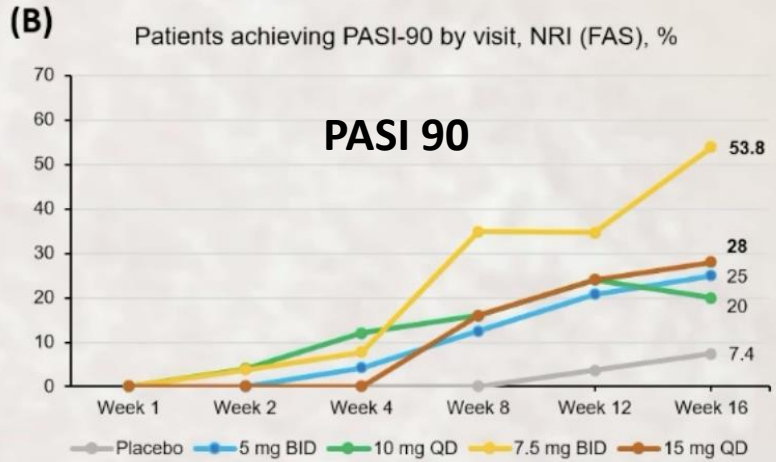
In vitro inhibitory activity against PDE4B1				
Compound	**ME3183**	**Apremilast**	Roflumilast	Crisaborole
IC_{50} nM	**2.3**	**42**	4.3	237

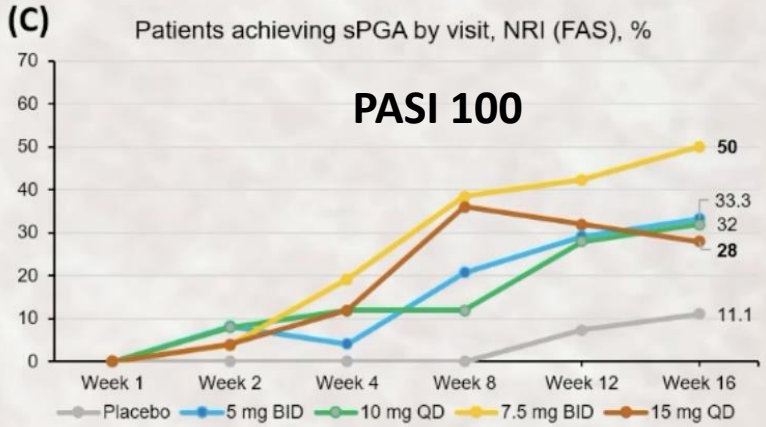


ME3183

Figure 4. Proportion of patients achieving PASI-75 (**A**), PASI-90 (**B**), and sPGA 0/1 (**C**) throughout the study period (FAS)







- Early improvement after administration was observed in PASI-75/90 (**Figure 4A** and **4B**) up to 16 weeks.
- A greater proportion of patients on ME3183 active doses achieved PASI-90 and sPGA 0/1 vs placebo throughout the study period (**Figure 4B** and **4C**).

Abbreviations: BID, twice daily; FAS, full analysis set; NRI, non-responder imputation; PASI-75/90, ≥75%/90% reduction from baseline in the Psoriasis Area and Severity Index score; QD, once daily; sPGA, Static Physician's Global Assessment.

Name	Target	Route of administration	Overall stage	Ongoing trials in psoriasis	Primary endpoint
IBI112	IL-23p19	SQ	Phase 2	NCT05003531	PASI 90 at 16 weeks
PN-235	IL-23 Receptor	Oral	Phase 2	NCT05357755 NCT05223868 NCT05364554	PASI 75 at 16 weeks / 36 wk
Netakimab	IL-17A	SQ	Phase 3	NCT03390101	PASI 75 at 12 weeks
Vunakizumab	IL-17A	SQ		NCT04839016	PASI 90 or sPGA of 0/1 at 12 weeks
SSGJ-608	IL-17A	SQ	Phase 3	NCT05536726	PASI 75 at 12 weeks
Izokibep	IL-17A	SQ	Phase 2	-	PASI 90 at 12 weeks
Gumokimab	IL-17A	SQ	Phase 2	NCT05096364	PASI 90 at 12 weeks
Spesolimab	IL-36 Receptor	IV, SQ maintenance	Phase 3	NCT03886246 NCT05239039 NCT05200247 NCT04399837 NCT04493424	TEAEs up to 252 weeks TEAEs up to 17 weeks TEAEs up to 17 weeks Time to first flare (up to 48 weeks) TEAEs up to 260 weeks
Imsidolimab	IL-36 Receptor	IV, SQ maintenance	Phase 3	NCT05352893 NCT05366855	GPPPGA score of 0/1 at 4 weeks Incidence of AEs up to 24 weeks

Modificado de Dragos and Vender. Dermatol Ther (Heidelb) (2022) 12:2715–2730

Name	Target	Route of administration	Overall stage	Ongoing trials in psoriasis	Primary endpoint
Mufemilast	PDE4	Oral	Phase 3	NCT04839328	PASI 75 at 16 weeks
ME3183	PDE4	Oral	Phase 2	NCT05268016	PASI 75 at 16 weeks
Orismilast	PDE4	Oral	Phase 2	NCT05190419	% change in PASI score from baseline to 16 weeks
Jaktinib	JAK1/2	Oral	Phase 2	NCT04612699	PASI 75 at 12 weeks
Deucravacitinib	TYK2	Oral	Phase 3	NCT04036435 NCT04167462 NCT05478499 NCT05124080 NCT04772079	
NDI-034858	TYK2	Oral	Phase 2	NCT04999839	PASI 75 at 12 weeks
AUR101	RORct	Oral	Phase 2	NCT04855721	PASI 75 at 12 weeks
Cedirogant	RORct	Oral	Phase 2	NCT05044234	PASI 75 at 16 weeks
BI 730,357	RORct	Oral	Phase 2	-	
GSK2982772	RIPK1	Oral	Phase 2	-	
Piclodenoson	A3AR	Oral	Phase 3		
RIST4721	CXCR2	Oral	Phase 2	NCT05194839	PPPASI 50 at 12 weeks
SCD-044	SIPR1	Oral	Phase 2	NCT04566666	PASI 75 at 16 week
ADX-629	RASP	Oral	Phase 2		
Rimegepant	CGRP	Oral	Phase 2	NCT04629950	Change in PASI score from baseline to 16 weeks

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Mensajes clave

- Estudios single-cell y metilación ADN pueden cambiar el manejo de la enfermedad.
- La modificación de la enfermedad pasa por la intervención precoz.
- Papel clave del dermatólogo en prevención de comorbilidades.
- El futuro pasa por las nuevas moléculas orales.