Highlights 2024 aedv

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25-28 SEPT 2024

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ACADEMIA ESPAÑOLA DE DERMATOLOGÍA Y VENEREOLOGÍA

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Psoriasis y otras enfermedades inflamatorias: novedades terapéuticas

Sergio Alique García

Hospital Virgen de la Luz de Cuenca

ser_alique

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NO TENGO CONFLICTOS DE INTERÉS

ACADEMIA ESPAÑOLA DE DERMATOLOGÍA Y VENEREOLOGÍA

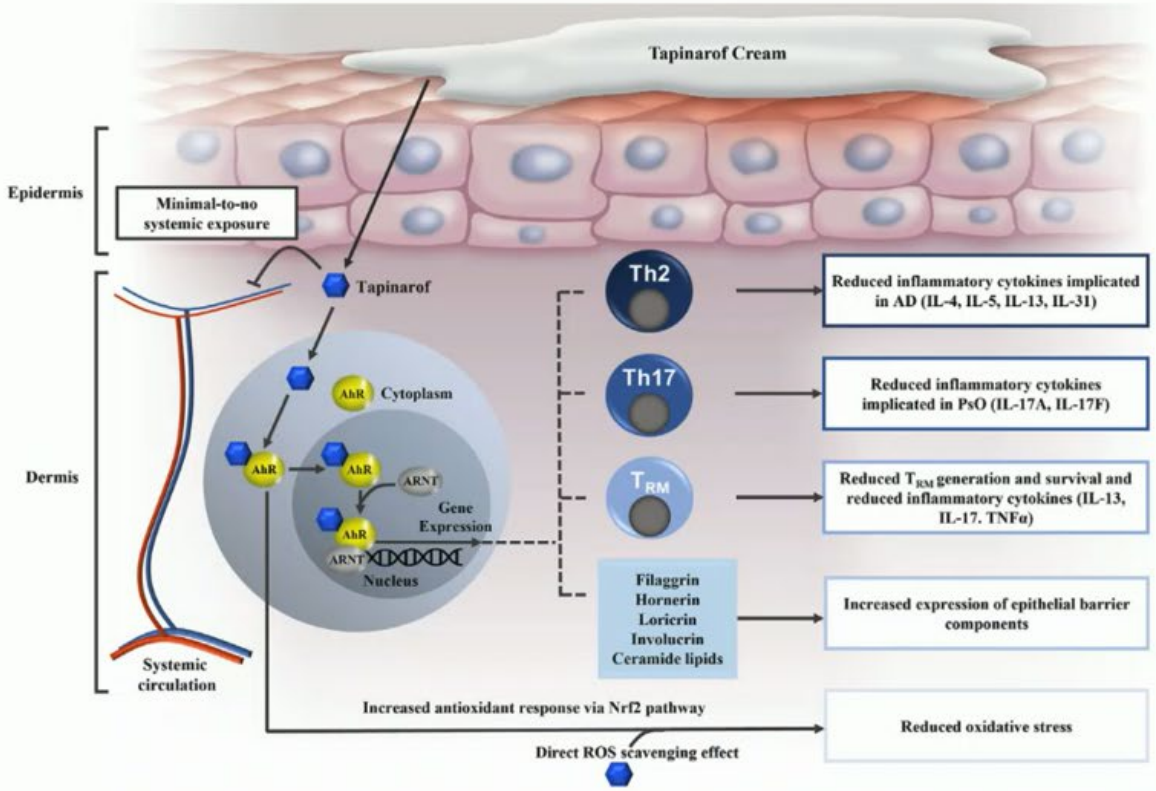
Sumario

- Tratamientos tópicos
- Pequeñas moléculas orales
- Fármacos biológicos

- **Tratamientos tópicos**
- Pequeñas moléculas orales
- Fármacos biológicos

Tapinarof

Tapinarof, an AhR agonist: Proposed mechanism of action



Tapinarof was first isolated from metabolites of Photorhabdus luminescens, a species of obligate symbiotic bioluminescent bacteria that live within the gut of insect-specific pathogenic nematodes.

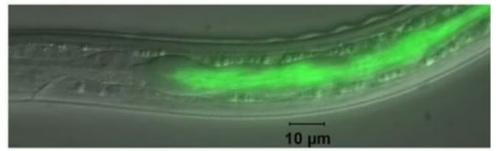
After entering host insects, the nematodes release the bacilli, whose secondary metabolites preserve insect tissue in optimal conditions for nematode growth

One of the metabolites was identified as tapinarof, a small molecule with low molecular weight (254 g/mol).

Silverberg et al. J Allergy Clin Immunol 2024;154:1-10

Diamant Thaçi

New topicals



Tapinarof

Tapinarof 1% once daily in clinical trials PSOARING

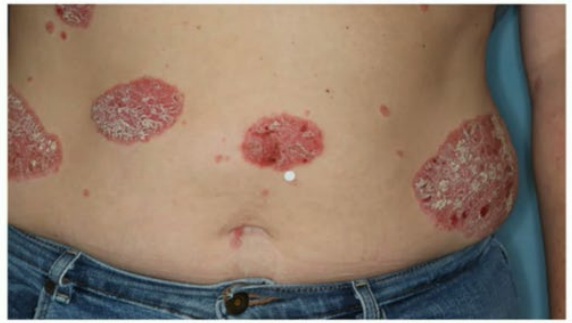
Trial name, identifier, literature citation	Trial population	Trial design	Frequency, duration of treatment	Primary and key secondary efficacy end points	Adverse events ≥5% and safety profile*
PSOARING 1, NCT03956355, Lebwohl et al, 2021[11]	Adults with mild-to-severe plaque psoriasis (N = 510)	Randomized, double-blind, vehicle-controlled	Once daily for 12 wk	• PGA response: 35.4% tapinarof cream 1% once daily vs 6.0% vehicle once daily ($P < .001$)† • PASI75: 36.1% tapinarof cream 1% once daily vs 10.2% vehicle once daily ($P < .001$)‡	• Folliculitis: 23.5% tapinarof vs 1.2% vehicle; 1 severe event • Nasopharyngitis: 7.4% tapinarof vs 5.9% vehicle • Contact dermatitis: 5.0% tapinarof vs 0.6% vehicle; none severe
PSOARING 2, NCT03983980, Lebwohl et al, 2021[11]	Adults with mild-to-severe plaque psoriasis (N = 515)	Randomized, double-blind, vehicle-controlled	Once daily for 12 wk	• PGA response: 40.2% tapinarof cream 1% once daily vs 6.3% vehicle once daily ($P < .001$)† • PASI75: 47.6% tapinarof cream 1% once daily vs 6.9% vehicle once daily ($P < .001$)‡	• Folliculitis: 17.8% tapinarof vs 0.6% vehicle; none severe • Contact dermatitis: 5.8% tapinarof vs 0% vehicle; 1 severe event
PSOARING 3, NCT04053387, Strober et al, 2022[12]	Adults with mild-to-severe plaque psoriasis (N = 763)	Long-term, open label, continuous or intermittent	Once daily for 40 wk	• Complete disease clearance (PGA score = 0): 40.9% (n = 312/763) • 58.2% (n =302/519) with PGA score ≥ 2 achieved PGA score = 0 or 1 • 130.1 (SD = 89.4) days with off-therapy remittive effect§	• Folliculitis: 22.7% • Contact dermatitis: 5.5%

Silverberg et al. J Allergy Clin Immunol 2024;154:1-10

Tapinarof

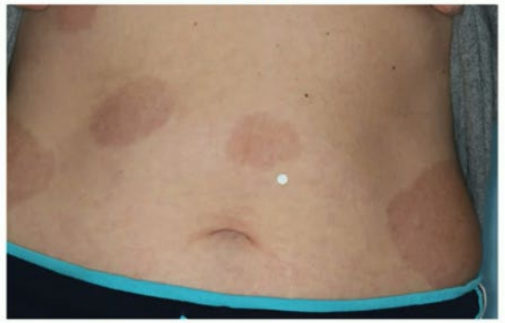
PSOARING 1

Baseline



- PGA=4
- PASI=19.8
- BSA=19.1%
- DLQI=6
- PP-NRS=10

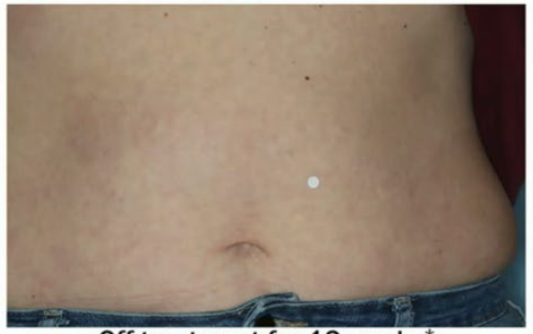
Week 12



- PGA=1
- PASI=3.8
- BSA=5.0%
- DLQI=0
- PP-NRS=0

PSOARING 3 (long-term extension trial)

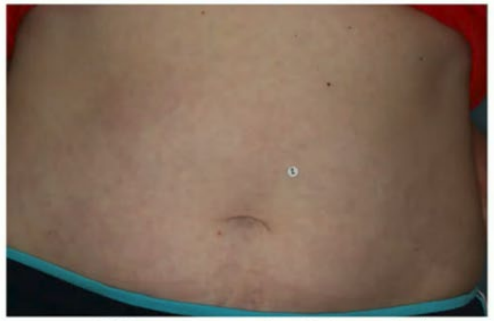
Week 36 (long-term extension Week 24)*



Off treatment for 12 weeks*

- PGA=1
- PASI=1.2
- BSA=0.2%
- DLQI=0
- PP-NRS=N/A

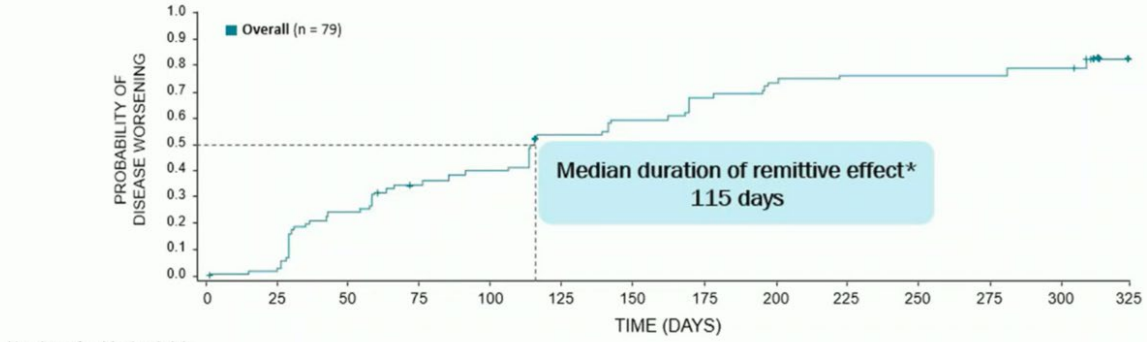
Week 48 (long-term extension Week 36)†



Off treatment for 24 weeks†

- PGA=2
- PASI=5.4
- BSA=2.5%
- DLQI=2
- PP-NRS=N/A

Tapinarof cream for the treatment of plaque psoriasis: Results from thePSOARING 3 trial



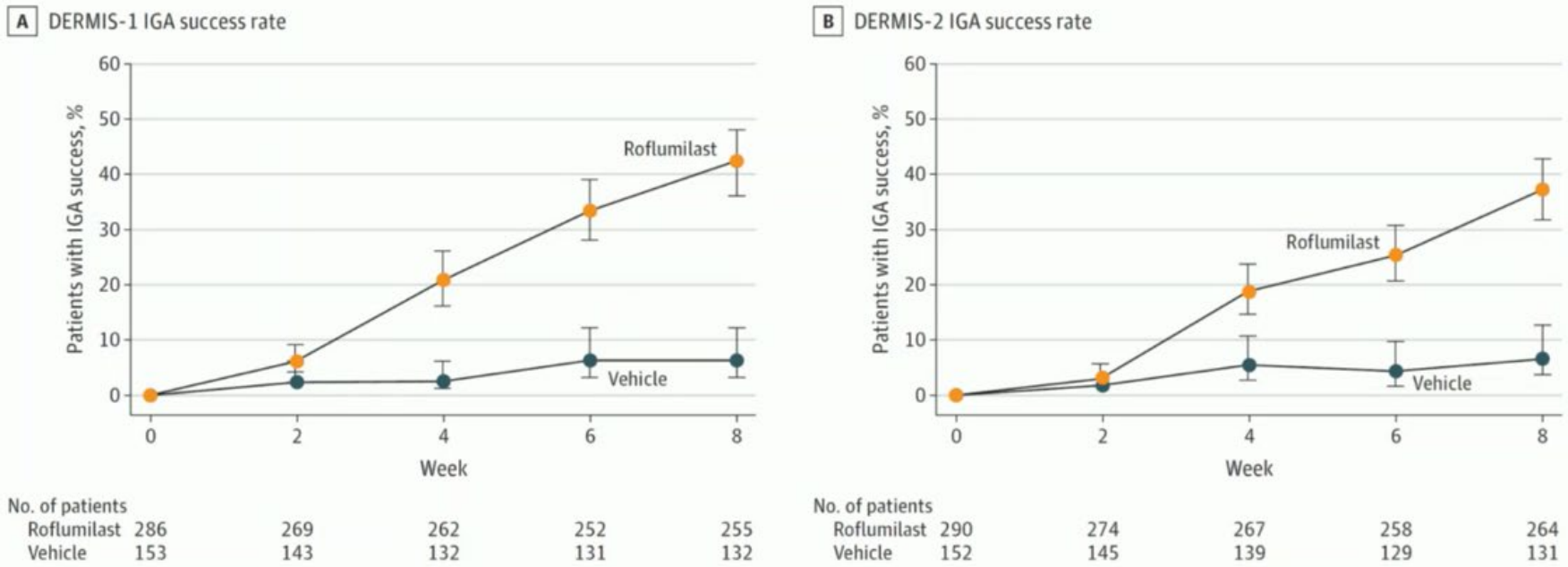
Number of subjects at risk

Tapinarof→Tapinarof†	74	71	54	45	41	30	26	20	16	14	14	14	13	0
Vehicle→Tapinarof†	5	5	4	3	3	3	3	3	3	3	3	3	2	0
Overall	79	76	58	48	44	33	29	23	19	17	17	17	15	0

Roflumilast

Effect of Roflumilast Cream vs Vehicle Cream on Chronic Plaque Psoriasis

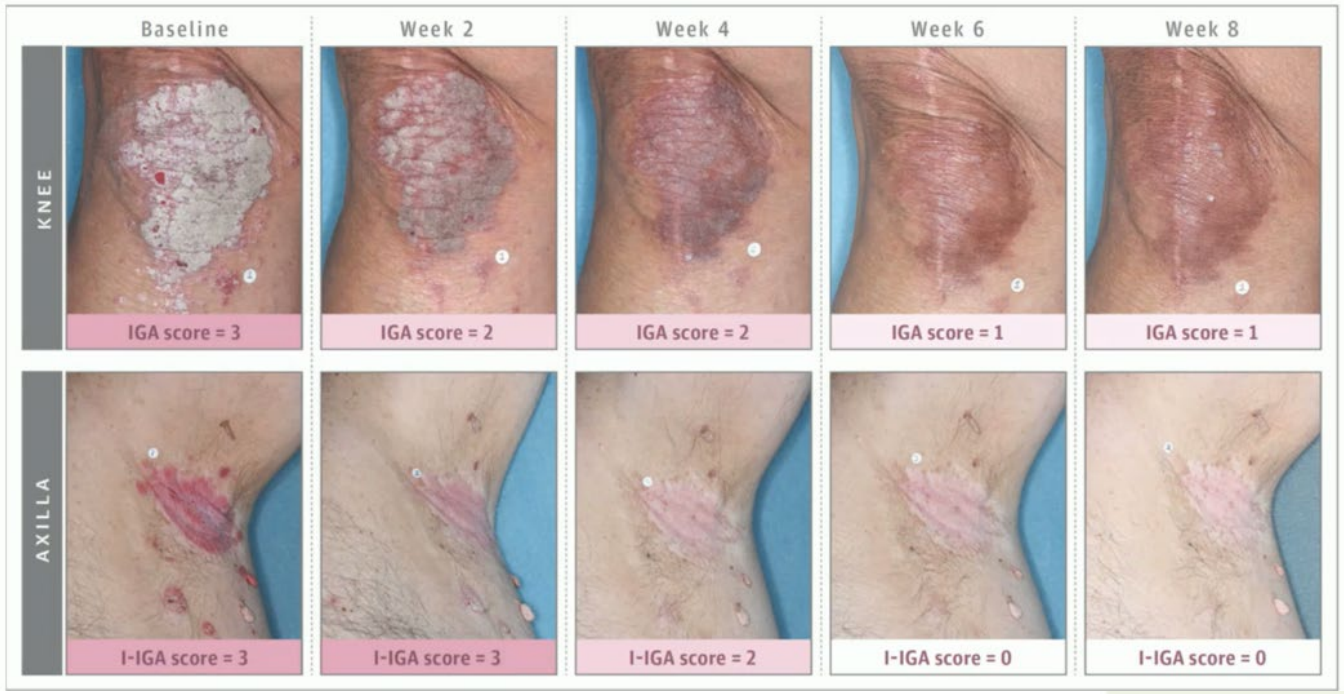
The DERMIS-1 and DERMIS-2 Randomized Clinical Trials



P < .001 for the difference at 8 weeks for both studies. P values are based on analysis with imputation of missing data and stratification by pooled study sites, baseline IGA, and baseline intertriginous IGA. Whiskers represent 95% CIs

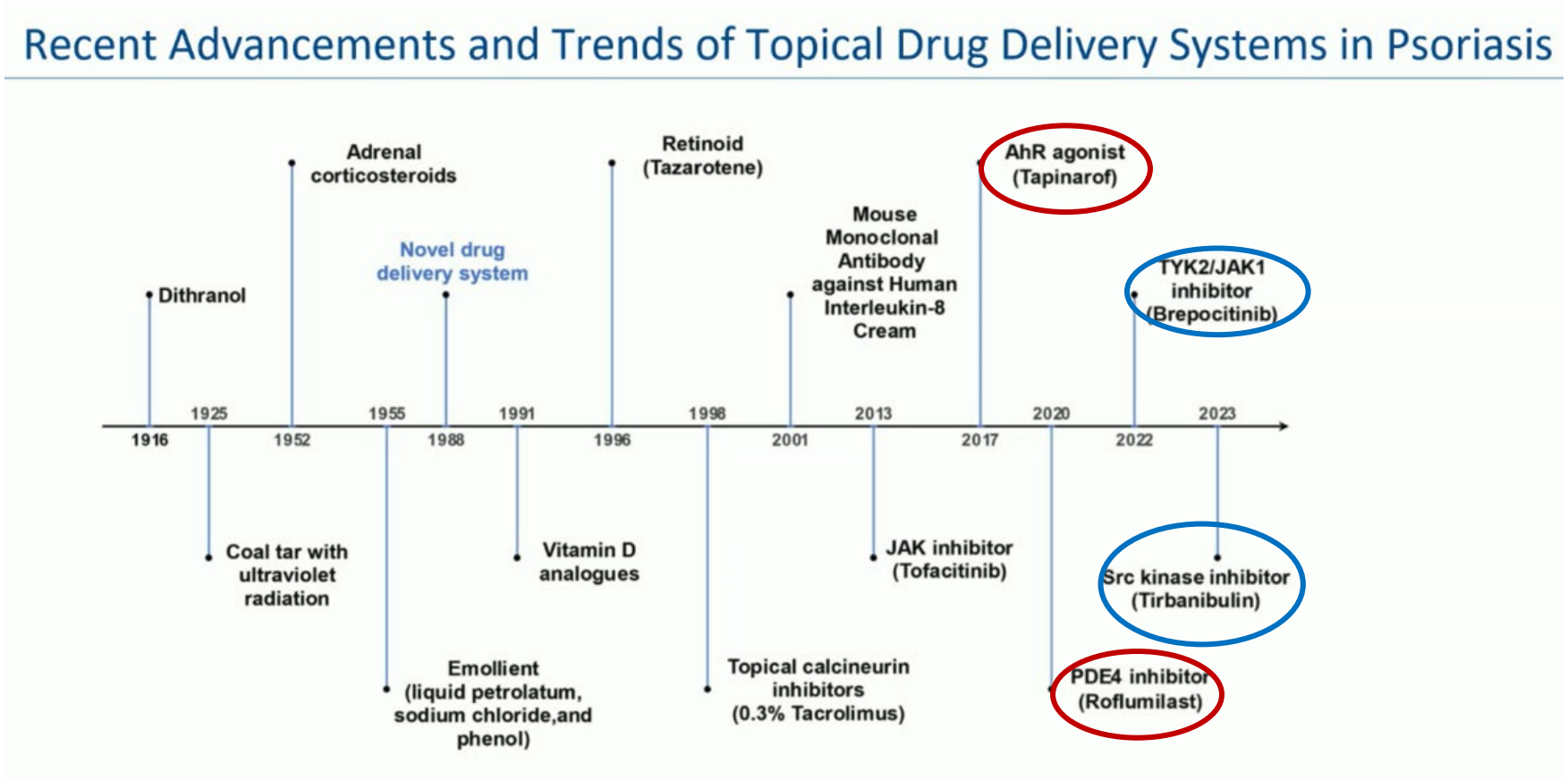
Lebwohl M et al. JAMA. 2022;328(11):1073-1084.

Roflumilast

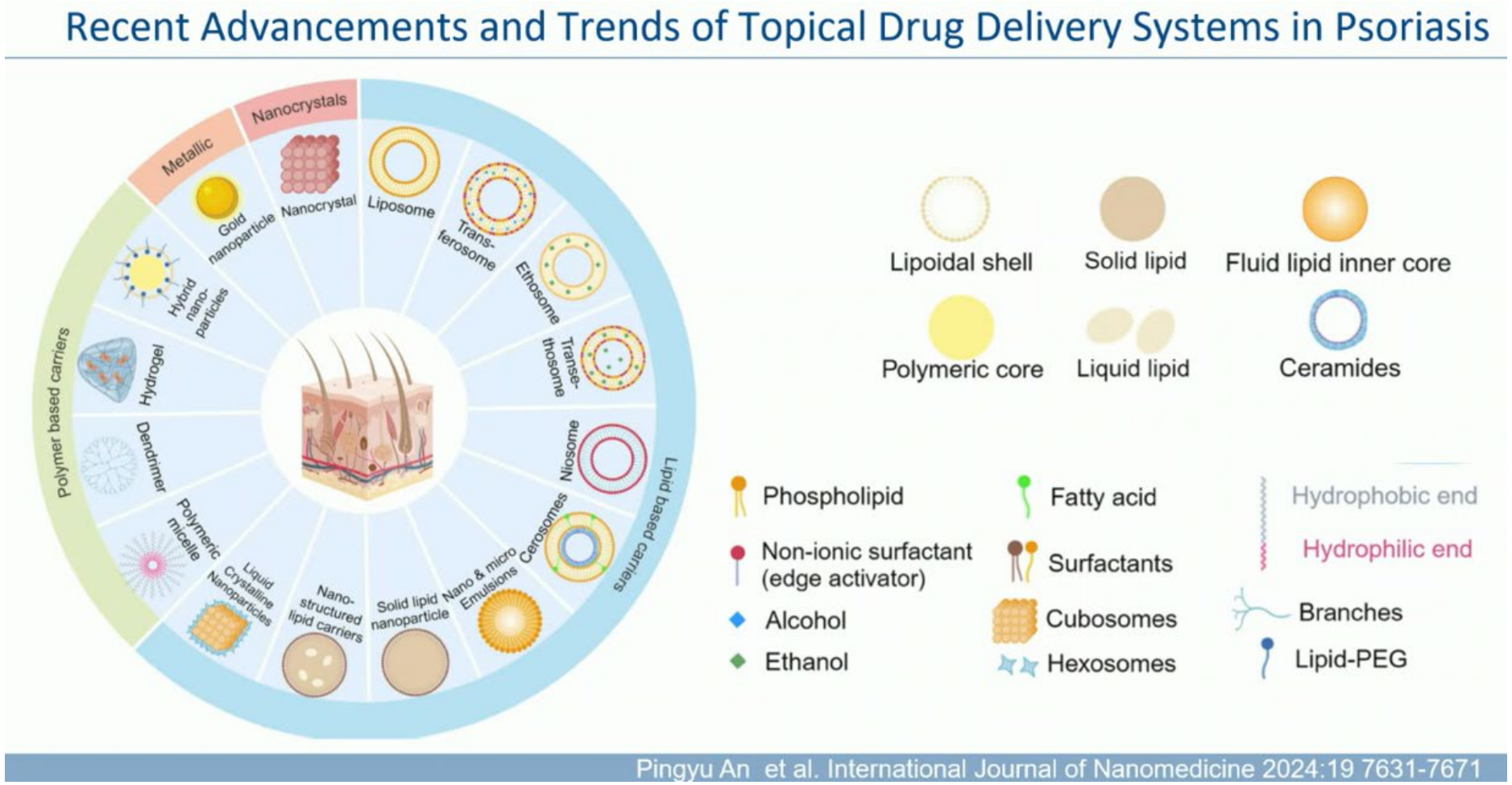


Adverse events	No. (%) DERMIS-1 trial Roflumilast (n = 286)	DERMIS-1 trial Vehicle (n = 153)	DERMIS-2 trial Roflumilast (n = 290)	DERMIS-2 trial Vehicle (n = 152)
Patients with any treatment-emergent adverse event[a]	72 (25.2)	36 (23.5)	75 (25.9)	28 (18.4)
Patients with any treatment-related treatment-emergent adverse event[b]	7 (2.4)	3 (2.0)	16 (5.5)	8 (5.3)
Patients with any serious adverse event[c]	2 (0.7)	1 (0.7)	0	1 (0.7)
Patients who discontinued study due to adverse event	5 (1.7)	2 (1.3)	1 (0.3)	2 (1.3)
Most common treatment-emergent adverse event (>2% in any treatment group)				
Diarrhea	10 (3.5)	0	8 (2.8)	0
Headache	3 (1.0)	2 (1.3)	11 (3.8)	1 (0.7)
Hypertension[d]	5 (1.7)	6 (3.9)	4 (1.4)	0
Nasopharyngitis	5 (1.7)	3 (2.0)	1 (0.3)	1 (0.7)
Psoriasis[e]	0	3 (2.0)	1 (0.3)	0

Futuras terapias tópicas

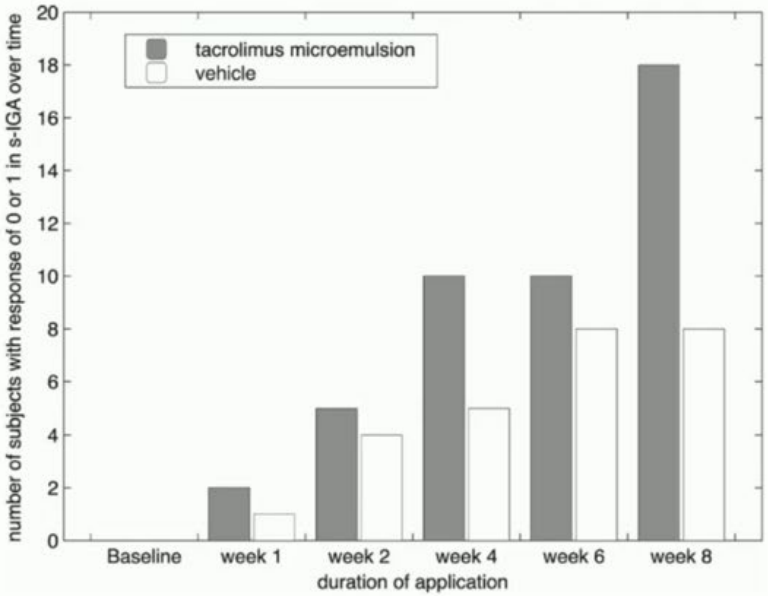


Nuevas formulaciones



Tacrolimus en microemulsión

Efficacy and Safety of Topical Tacrolimus Microemulsion Applied Twice Daily in Patients with Mild to Moderate Scalp Psoriasis



- Tacrolimus is a calcineurin inhibitor that is approved in topicals for atopic dermatitis
- Microemulsions (1 mg/ ml) are colloidal vehicles that are suitable for stably dissolving tacrolimus and transporting it into the skin
- Recently (June 2024) approved and reimbursed in Germany for scalp psoriasis

Pinter A et al. Dermatol Ther (Heidelb) (2024) 14:521–532

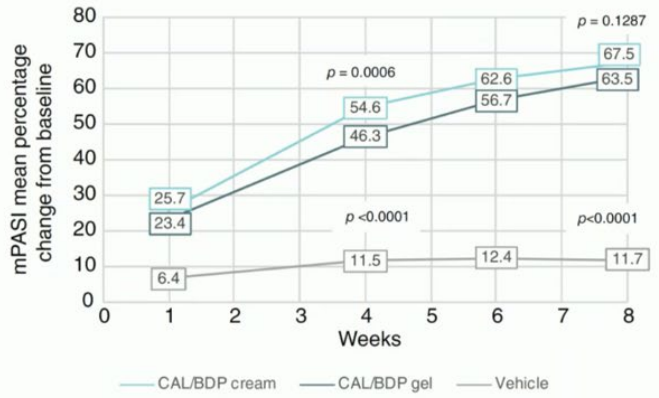
Tecnología PAD: Calcipotriol/betametasona

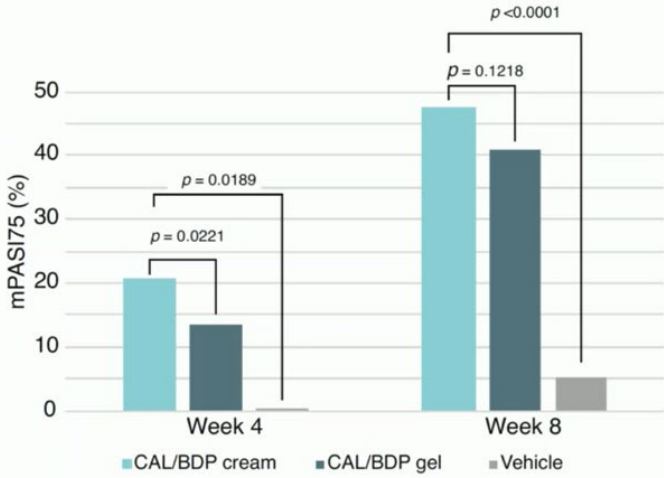
Polyaphron dispersion or PAD Technology™

- PAD Technology™: is a novel innovative and proprietary topical formulation and drug delivery system
- Nanoscale bicontinuous multi-molecular structure of oil, water and surfactants forming a robust outer shell
- PAD Technology™ formulations are manufactured in a modular process enabling integration of multiple functionalities

Praestegaard M, Steele F, Crutchley N. Dermatol Ther (Heidelb). 2022 Oct;12(10):2217-2231

Calcipotriol and Betamethasone Dipropionate Cream Based on PAD Technology for the Treatment of Plaque Psoriasis

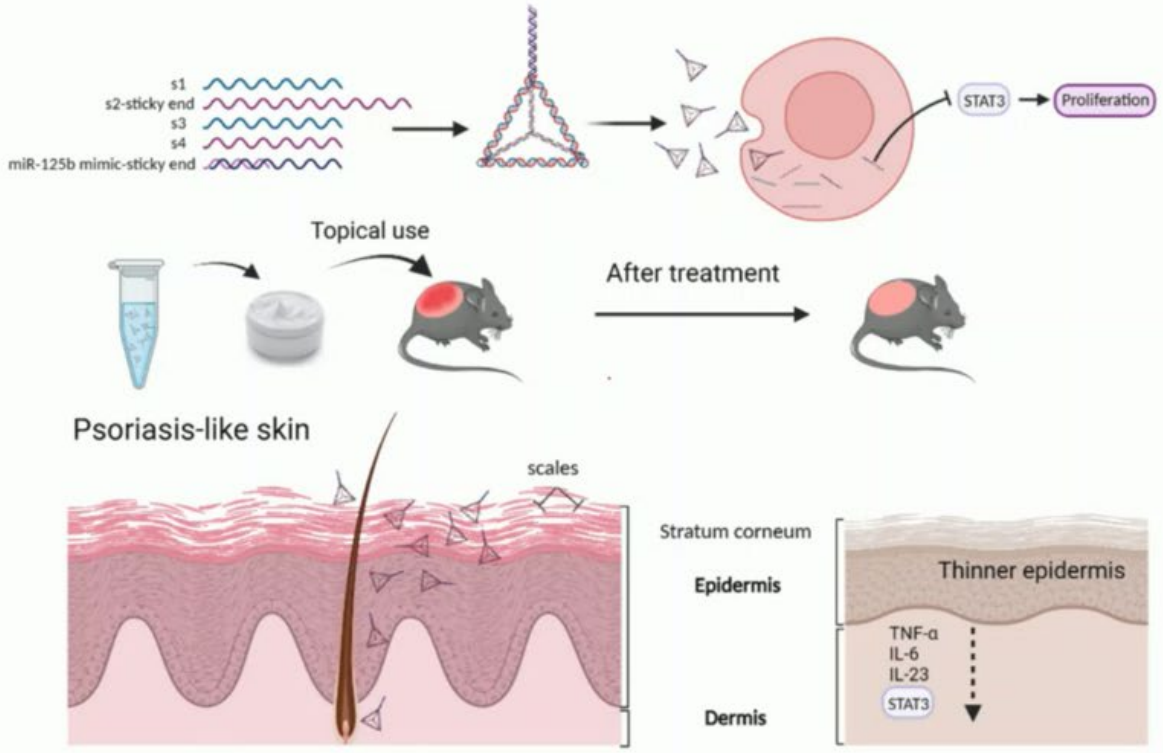




Pinter A. et al. J Eur Acad Dermatol Venereol. 2023 Nov;37(11):2327-2335

MicroRNA

Topical Delivery of microRNA-125b by Framework Nucleic Acids for Psoriasis Treatment



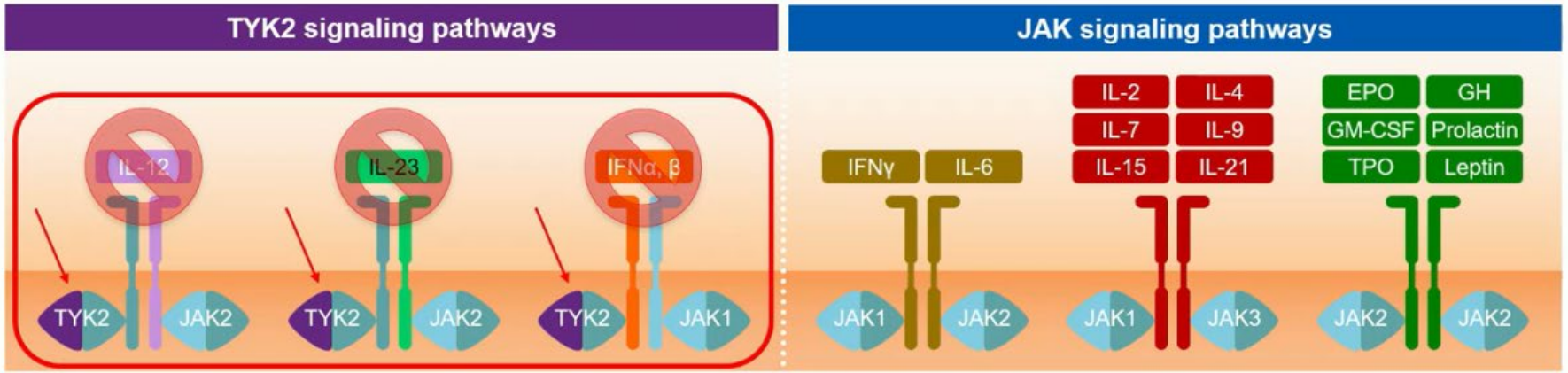
- miR-125b non-coding RNAs, play significant roles in RNA-silencing and post-transcriptional gene expression regulation
- Framework nucleic acid (FNA) is a three-dimensional DNA nanostructure (nanoparticle) with specific size and shape, capable of efficient internalization via the caveolin-mediated endocytic pathway
- miR-125b is one of the most downregulated miRNAs in psoriasis skin, and its overexpression in primary human keratinocytes would inhibit the cell proliferation and upregulates multiple markers of differentiation

Han Y et al. International Journal of Nanomedicine 2024:19 2625–2638

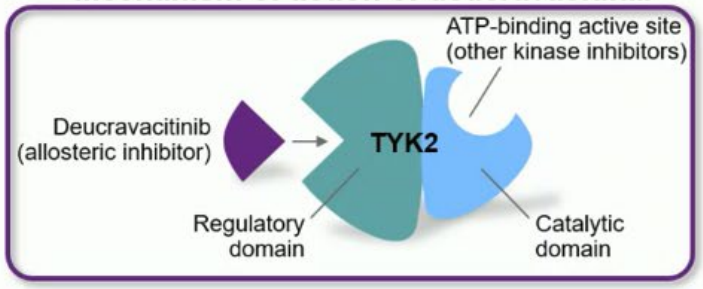
- Tratamientos tópicos
- **Pequeñas moléculas orales**
- Fármacos biológicos

Deucravacitinib

TYK2 mediates signaling of fewer cytokines compared with JAKs 1–3



Mechanism of action of deucravacitinib

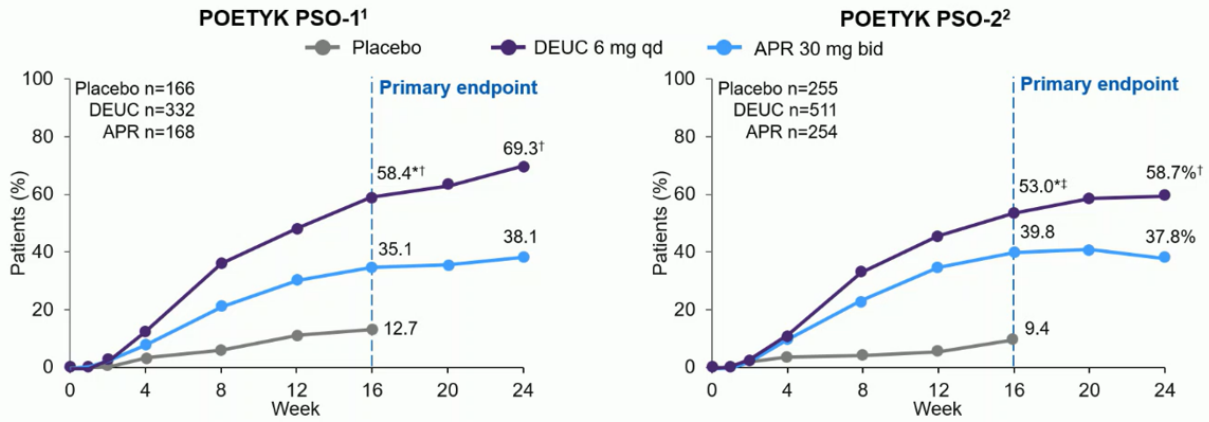


- The oral TYK2 inhibitor deucravacitinib is a molecule that binds selectively to a regulatory domain of TYK2 and changes its conformation such that the kinase activity is inactivated
- This approach has more selectivity than any previous attempt to target the kinase domain of JAKs

Deucravacitinib

POETYK PSO-1 and PSO-2: PASI 75 at Weeks 16 and 24

PASI 75 response at Week 16 (coprimary endpoint) and through Week 24 (NRI)

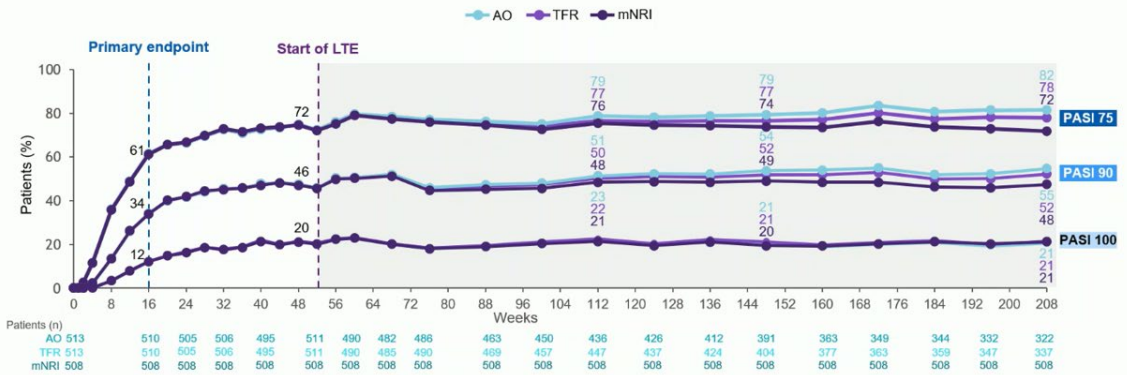


- 82.5% (PSO-1) and 80.4% (PSO-2) of deucravacitinib patients who achieved PASI 75 at Week 24, and continued treatment, maintained response at Week 52

*P<0.0001 vs placebo, †P<0.0001 vs apremilast, ‡P=0.0004 vs apremilast

1. Armstrong AW, et al. J Am Acad Dermatol 2023;88:29–39; 2. Strober B, et al. J Am Acad Dermatol 2023;88:40–51; Armstrong AW, et al. AAD VMX 2021, Late breaker. Sponsored by Bristol Myers Squibb

POETYK PSO LTE: Maintenance of PASI responses among patients with up to 4 years of deucravacitinib treatment

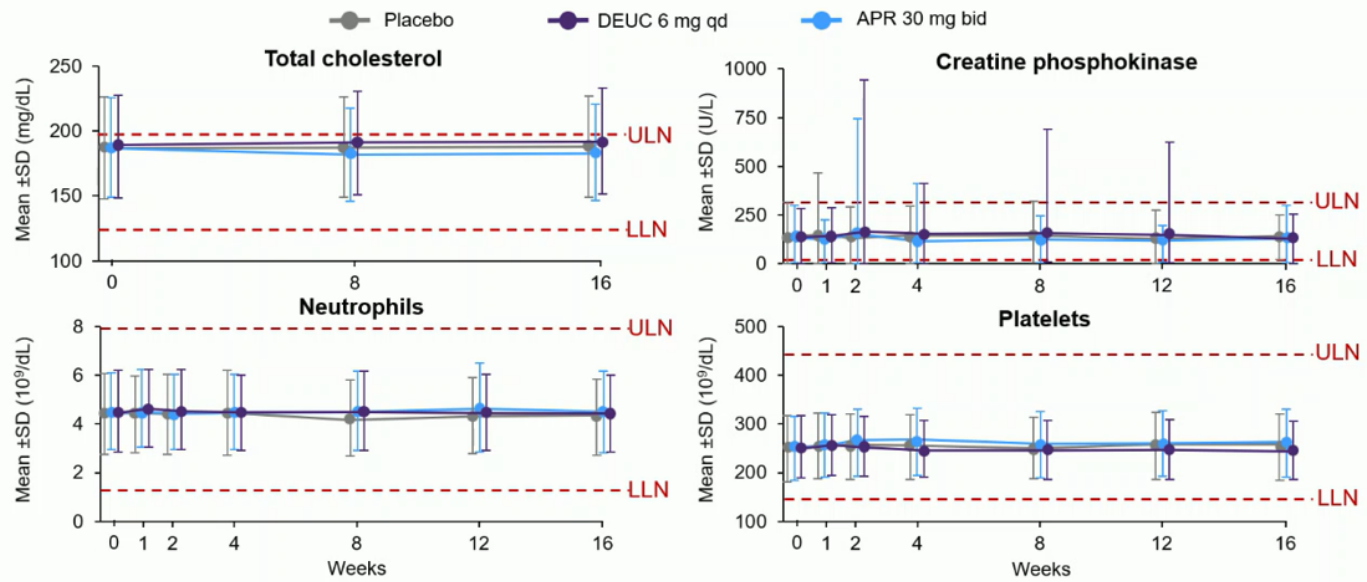


- Responses for sPGA 0/1 and sPGA 0 followed a similar trend as seen for PASI 90 and PASI 100, respectively

Vaile J, et al. EADV Symposium 2024. Sponsored by BMS

Deucravacitinib

POETYK PSO-1 and PSO-2: Laboratory parameters (integrated), Weeks 0–16

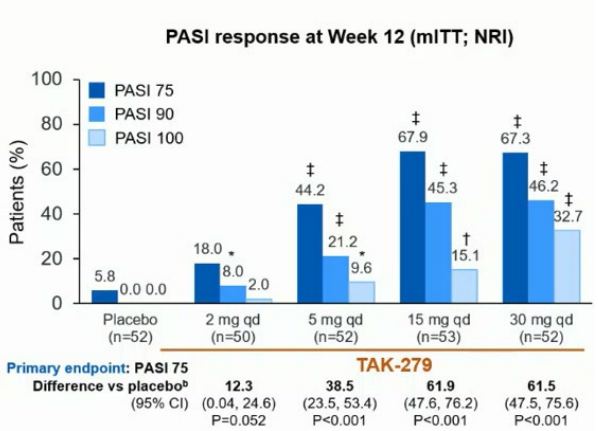


- No clinically significant trends observed for laboratory parameters; similar results were observed between Weeks 16 and 52

Strober B, et al. J Eur Acad Dermatol Venereol 2024;38:1543–54; Armstrong AW, et al. AAD VMX 2021, Late breaker. Sponsored by Bristol Myers Squibb

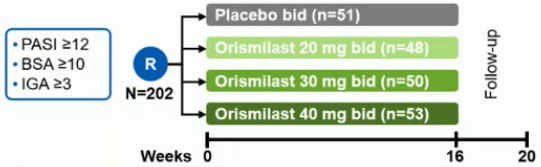
Futuro

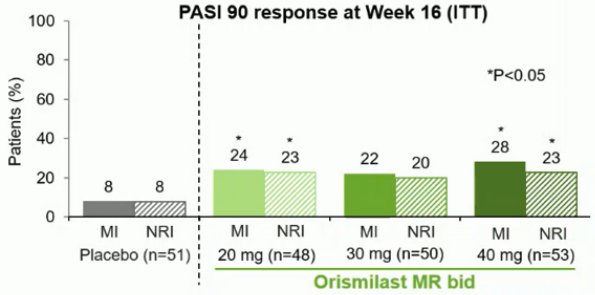
Randomized, double-blind, placebo-controlled Phase 2b trial of oral allosteric TYK2 inhibitor TAK-279 for moderate to

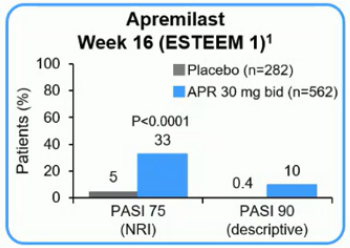


IASOS: Randomized, double-blind, placebo-controlled Phase 2b trial of oral selective PDE4-B/D inhibitor orismilast for moderate

- Second oral PDE4i to enter the psoriasis space
  - PDE4B and -D inhibitor: 2–5-fold more potent than apremilast
- Phase 2b dose-finding trial of **orismilast modified-release** (MR) tablets



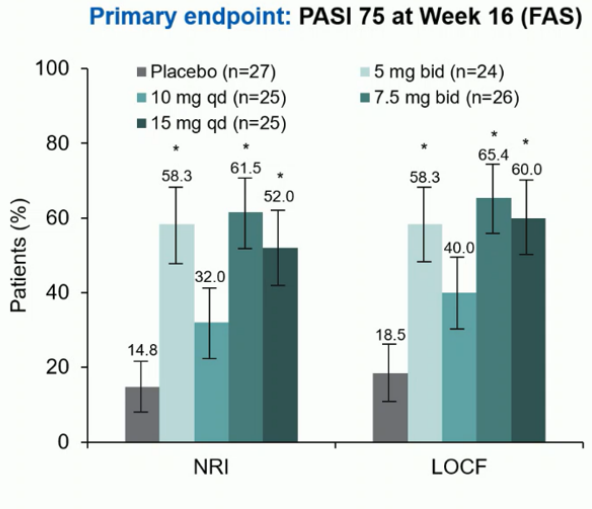


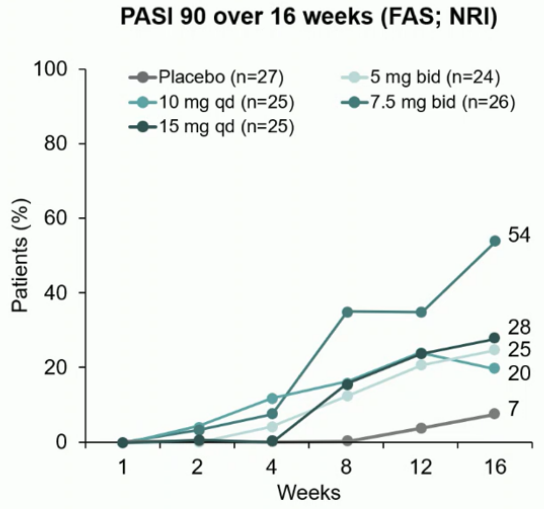


- **Safety:** No new safety signals. Infection and depression rates similar to placebo, with no suicidal ideation, malignancy or death reported. Tolerability was dose dependent; the most frequent AEs were diarrhea, nausea, and headache

Warren RB, et al. AAD 2023, Late-breaking abstract. Sponsored by Union Therapeutics; 1. Papp K, et al. J Am Acad Dermatol 2015;73:37–49

Phase 2 trial: PASI responses with oral PDE4 inhibitor ME3183 among patients with moderate to severe psoriasis



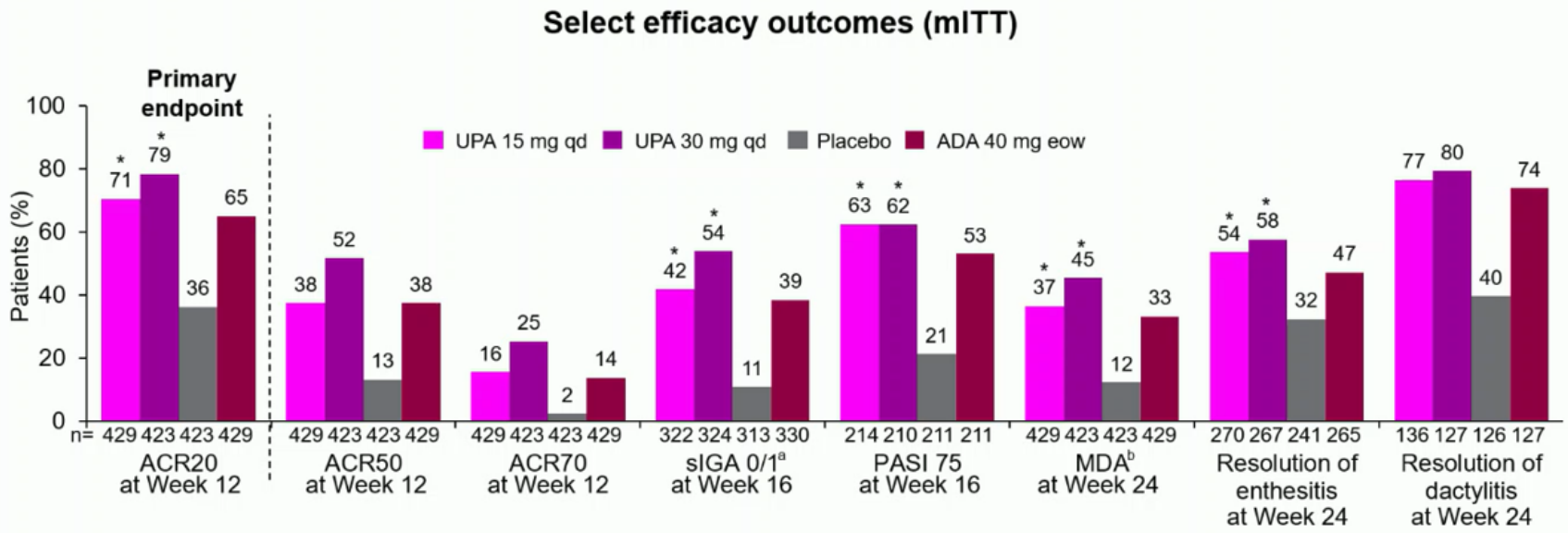


*P<0.01 vs placebo. Error bars represent standard error. FAS, final analysis set; NRI, nonresponder imputation

Papp K, et al. EADV 2023, D2T01.3K. Sponsored by Meiji Seika Pharma

Upadacitinib en APs

SELECT-PsA 1: Key outcomes after treatment with upadacitinib versus placebo and adalimumab among adults with psoriatic



*P<0.001 vs placebo (controlled for multiplicity)
For binary endpoints, NRI was used to handle missing data
[a]Plus ≥2-point decrease from baseline; [b]MDA determined as fulfilment of 5 of 7 criteria: Tender joint count ≤1, swollen joint count ≤1, PASI score ≤1 or ≤3% BSA involvement, patient pain NRS ≤1.5, PtGA-disease activity NRS ≤2.0, HAQ-DI score ≤0.5, Leeds Enthesitis Index ≤1

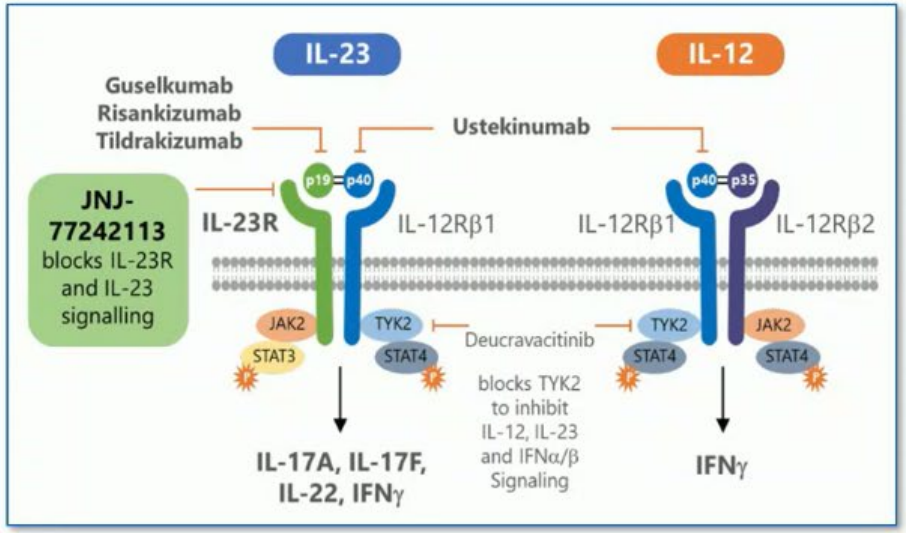
McInnes IB, et al. N Engl J Med 2021;384:1227–39.

- Tratamientos tópicos
- Pequeñas moléculas orales
- **Fármacos biológicos**

Antagonista oral IL-23R

FRONTIER 1: Phase 2, randomized, placebo-controlled, dose-ranging trial of JNJ-77242113, an oral IL-23R antagonist, for moderate to severe psoriasis

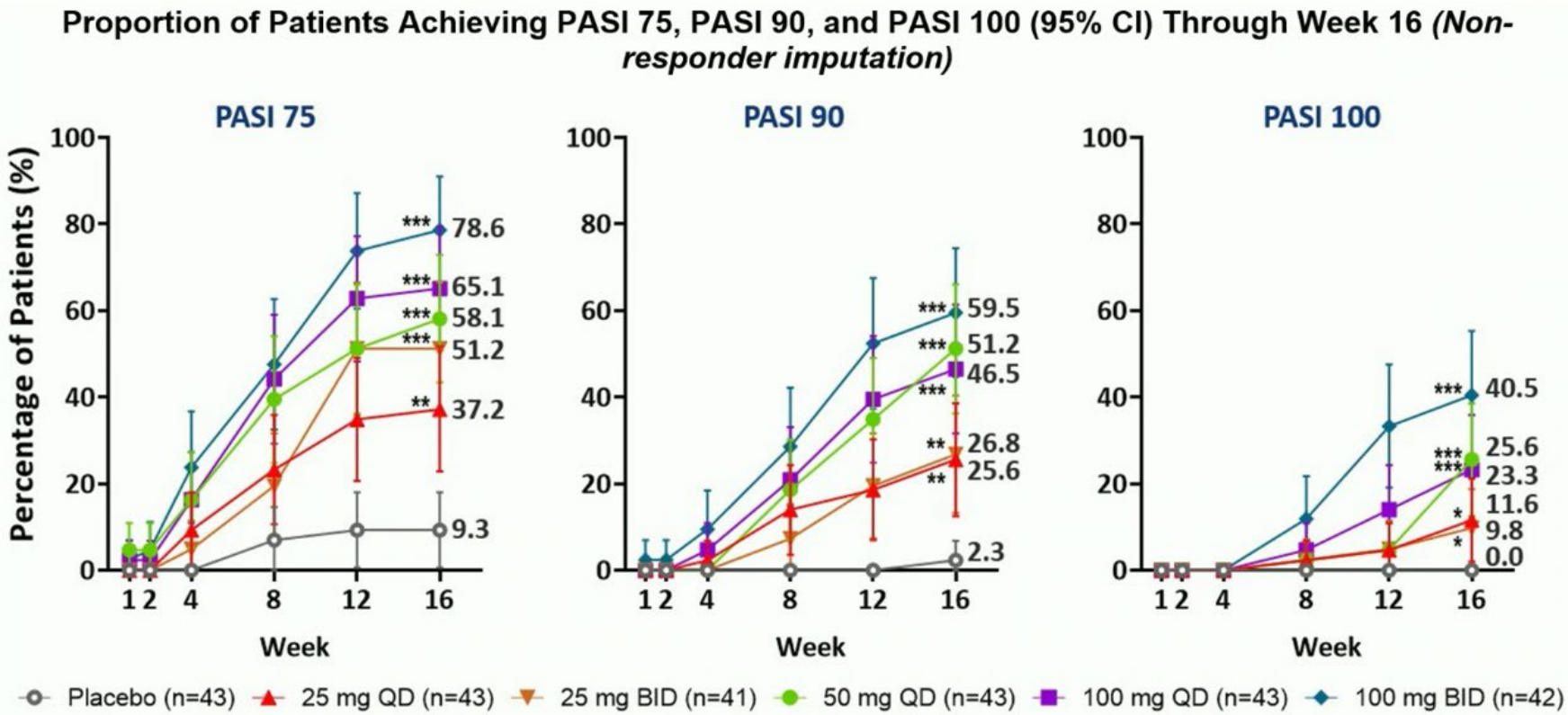
- JNJ-77242113, **a first-in-class oral IL-23R antagonist peptide**, selectively and potently blocks IL-23 signaling and downstream inflammatory cytokine production[1]
- Due to its **GI stability** and potency, JNJ-77242113 can provide systemic IL-23 pathway blockade through oral dosing[1]
- **FRONTIER 1: Dose-ranging trial** to evaluate safety and efficacy of orally administered JNJ-77242113 at 16 weeks in patients with moderate to severe psoriasis



1. Fourie A, et al. Presented at ISID 2023, May 10–13

Bissonnette R, et al. WCD 2023. Late-breaking oral. Sponsored by Janssen Research & Development, LLC

Antagonista oral IL-23R



*nominal p<0.05 vs placebo; **nominal p<0.01 vs placebo; ***nominal p<0.001 vs placebo. p-values are based on Cochran-Mantel-Haenszel (CMH) chi-square test stratified by baseline weight category (≤90 kg, >90 kg). Patients who discontinued study agent due to lack of efficacy/worsening of PsO, or who initiated a prohibited PsO treatment were considered non-responders after the occurrence. Patients with missing data were considered non-responders.

Bissonnette R, et al. WCD 2023. Late-breaking oral. Sponsored by Janssen Research & Development, LLC

Spesolimab

Response of ACH to Spesolimab

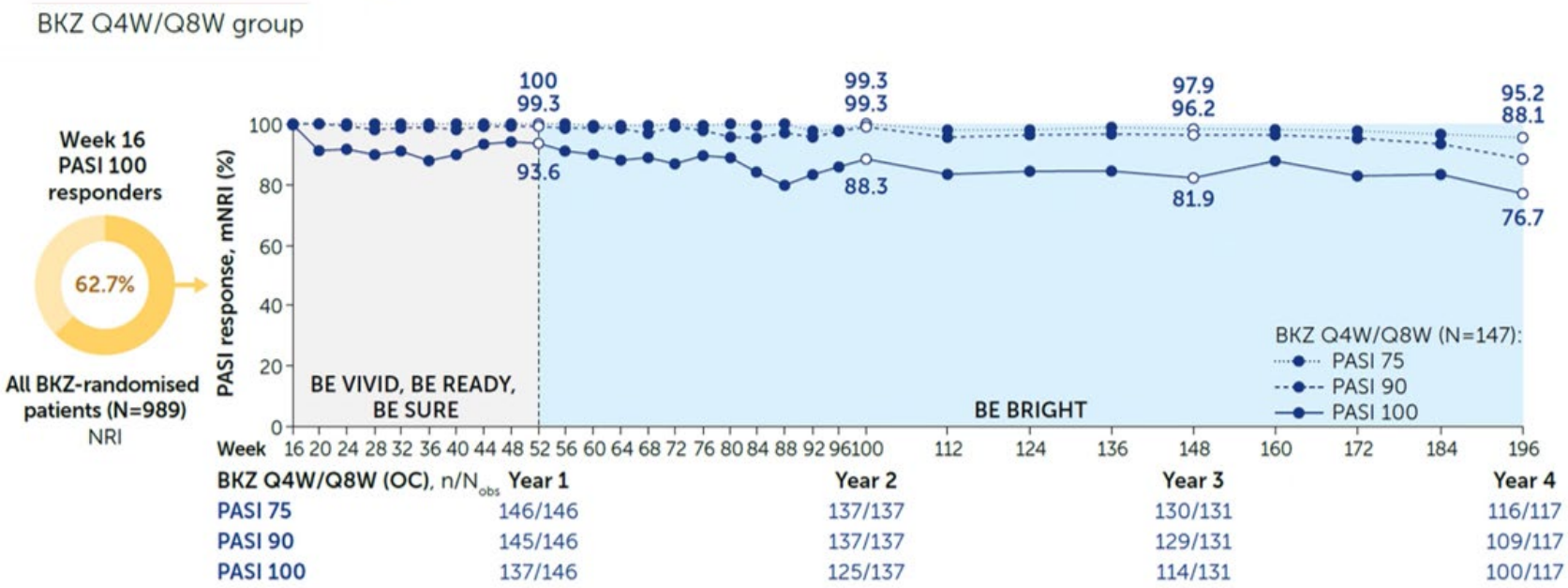
- 9 yr old girl
- IL36RN missense mutation
- Pustular nail dystrophy and scattered red, scaly plaques
- IV spesolimab (15mg/kg) at week 0 and 4
- Dramatic improvement at week 8

Wang Y et al. JAMA Dermatol 2024

A Fingernails after treatment

Bimekizumab

Bimekizumab: PASI response in week 16 PASI 100 responders to year 4 (mNRI)



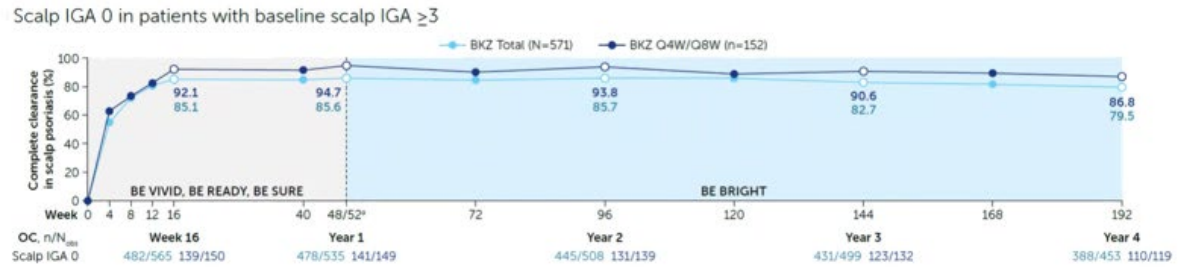
BKZ Q4W/Q8W (OC), n/N_{obs}	Year 1	Year 2	Year 3	Year 4
PASI 75	146/146	137/137	130/131	116/117
PASI 90	145/146	137/137	129/131	109/117
PASI 100	137/146	125/137	114/131	100/117

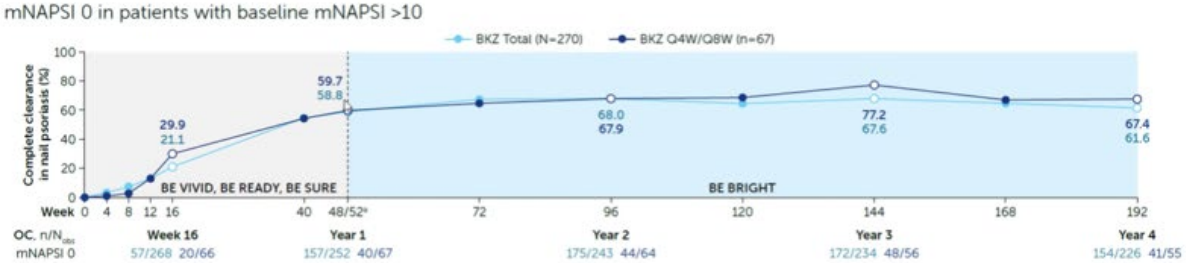
- For the BKZ Q4/8W group, PASI 100/90/75 responses were similarly high through 4 years compared to the BKZ Total group

For mNRI, patients who discontinued due to lack of efficacy/treatment-related adverse events were considered non-responders at subsequent timepoints; multiple imputation was used for all other missing data. Patients who entered the BE READY escape arm were considered as non-responders from the date of escape until the end of BE READY, after which they were considered in the same way as all other non-escape patients during the BE BRIGHT OLE.[1] BE VIVID lasted 52 weeks and BE SURE and BE READY lasted 56 weeks; to pool data across studies, Week 56 data were not included. In this figure, the period after Week 52 corresponds to the BE BRIGHT OLE. **1.** Warren RB et al. N Engl J Med 2021;385:130–41, NCT03412747.
All content on this slide is from Thaçi D et al. EADV 2024. Poster 3281.

Bimekizumab

Bimekizumab: complete clearance of scalp, palmoplantar psoriasis and nail psoriasis over 4 years (mNRI)





[a] Week 48/52 data are from Week 48 of BE SURE and BE READY, and Week 52 of BE VIVID, due to differences in assessment schedules. All content on this slide is from Merola JF et al. EADV 2024. Poster P3320.

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La Academia Española de Dermatología y Venereología expresa su agradecimiento al patrocinador UCB, por su especial apoyo y contribución con la actividad formativa Highlights 2024.

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