Hospital Universitario de La Princesa

UAM Universidad Autónoma de Madrid

IV EDICIÓN

INMUNOTERAPIA EN DERMATOLOGÍA

30 de marzo de 2023

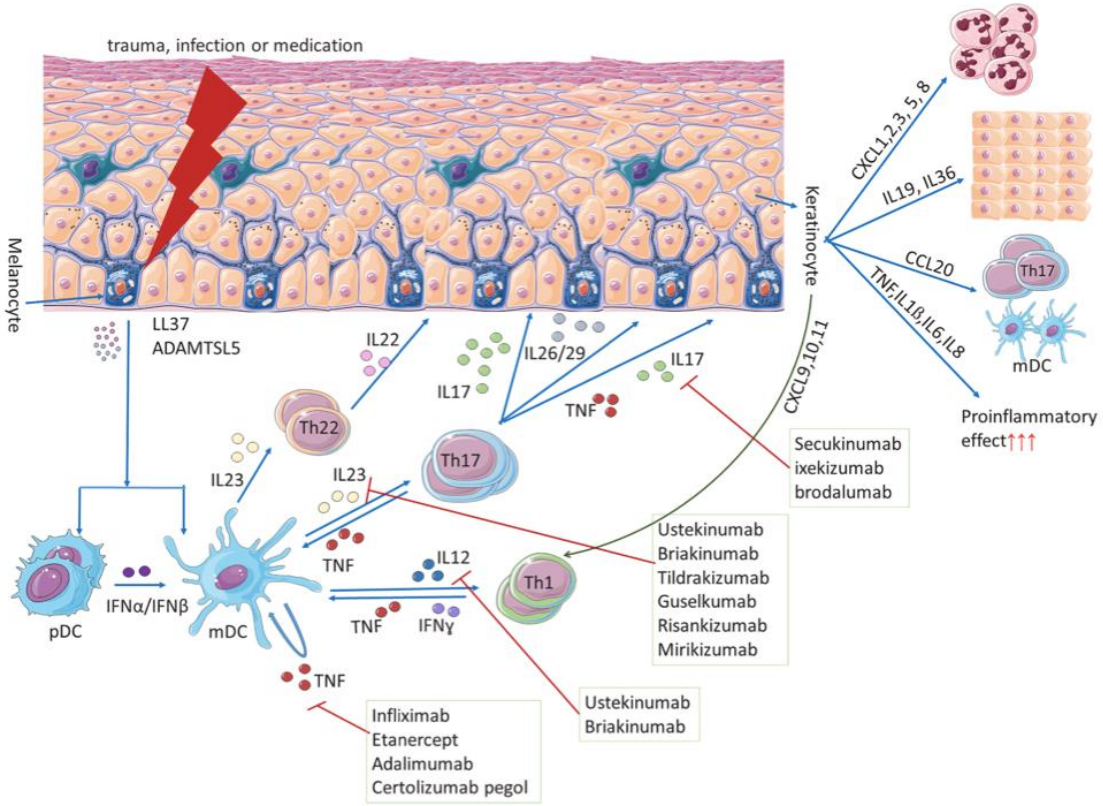
M. Llamas-Velasco, Hospital Universitario de la Princesa, Madrid

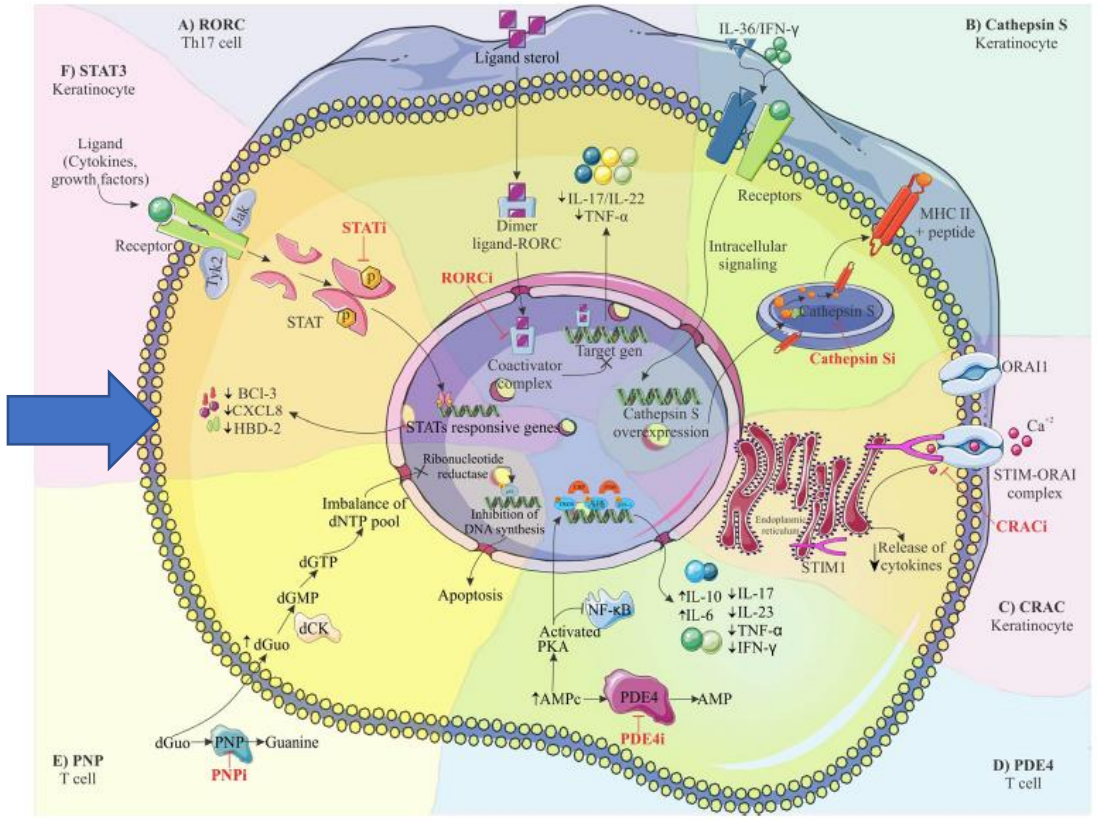
Dónde estamos en terapia biológica/moléculas pequeñas en psoriasis 2023

Conflictos de interés

- Advisory board member, consultant, research support, participation in clinical trials and honorary for speaking) with the following pharmaceutical companies: Abbvie, Almirall, Amgen, Boehringer, Celgene, Janssen, Leo,Lilly, Kyowa kirin, Novartis and UCB.

De la etiopatogenia a la terapéutica

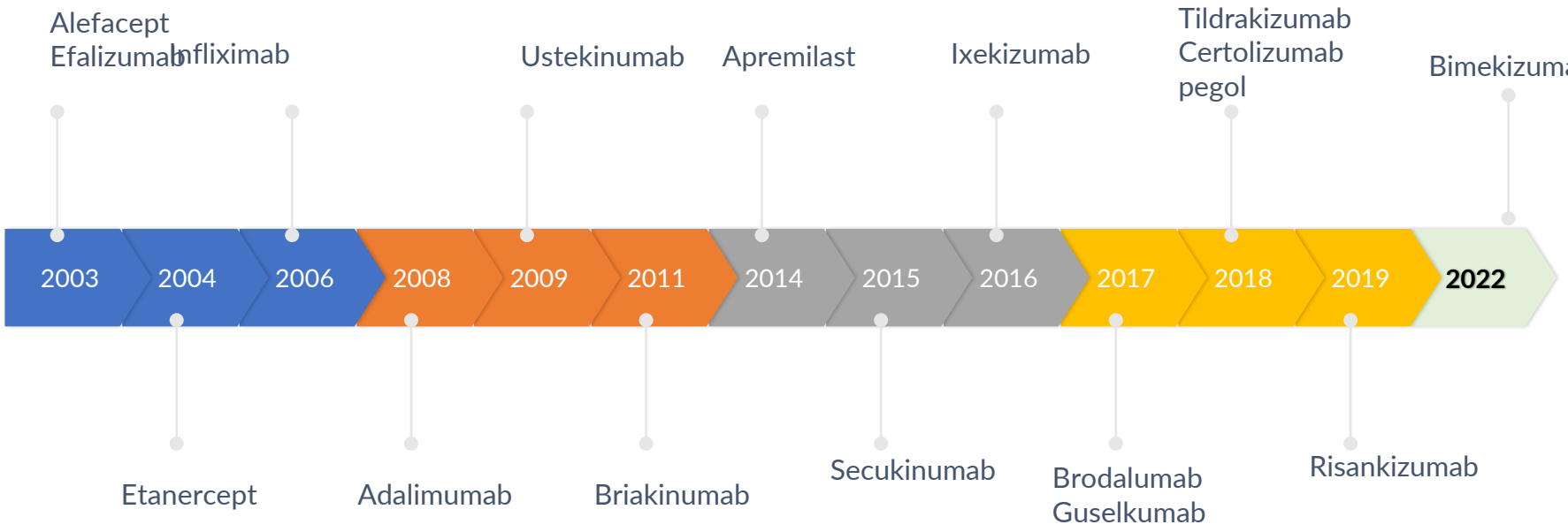




Balogh E, et al. *Expert Opin Emerg Drugs*. 2020.
Kimball A, et al. *Br J Dermatol*. 2014.
Thakur V, et al. *Front Med (Lausanne)*. 2022.

Desarrollo de nuevos medicamentos

En los últimos 15 años, nuevos tratamientos biológicos y nuevos **objetivos terapéuticos**.



¿Futuro?

Tópicos
Pequeñas moléculas
Biológicos duales

Shobeiri S, et al. *Int Immunopharmacol*. 2021

Desarrollo de nuevos medicamentos

En los últimos 15 años, nuevos tratamientos biológicos y nuevos **objetivos terapéuticos**.

¿Por qué necesitamos nuevos fármacos?

Tasas de respuesta variables

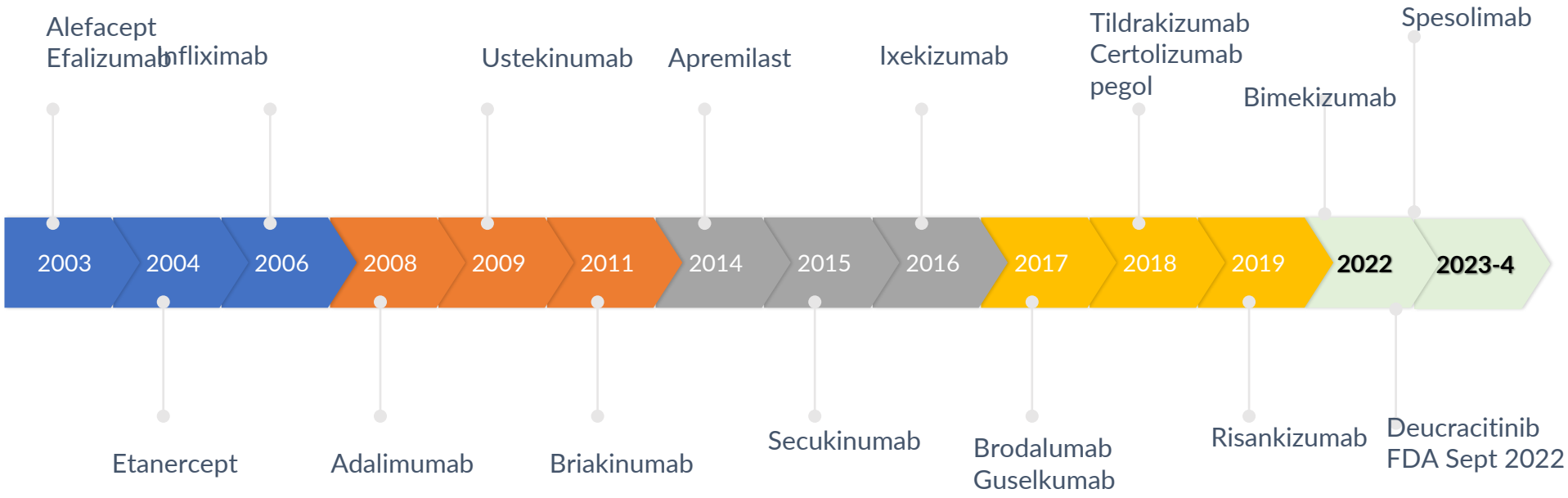
Pacientes resistentes, intolerantes o con contraindicaciones

- Etanercept
- Adalimumab
- Briakinumab
- Secukinumab
- Brodalumab
- Guselkumab
- Risankizumab

Shobeiri S, et al. *Int Immunopharmacol*. 2021

Desarrollo de nuevos medicamentos

En los últimos 15 años, nuevos tratamientos biológicos y nuevos **objetivos terapéuticos**.



¿Futuro?

Tópicos
Pequeñas moléculas
Biológicos duales
Nanobodies

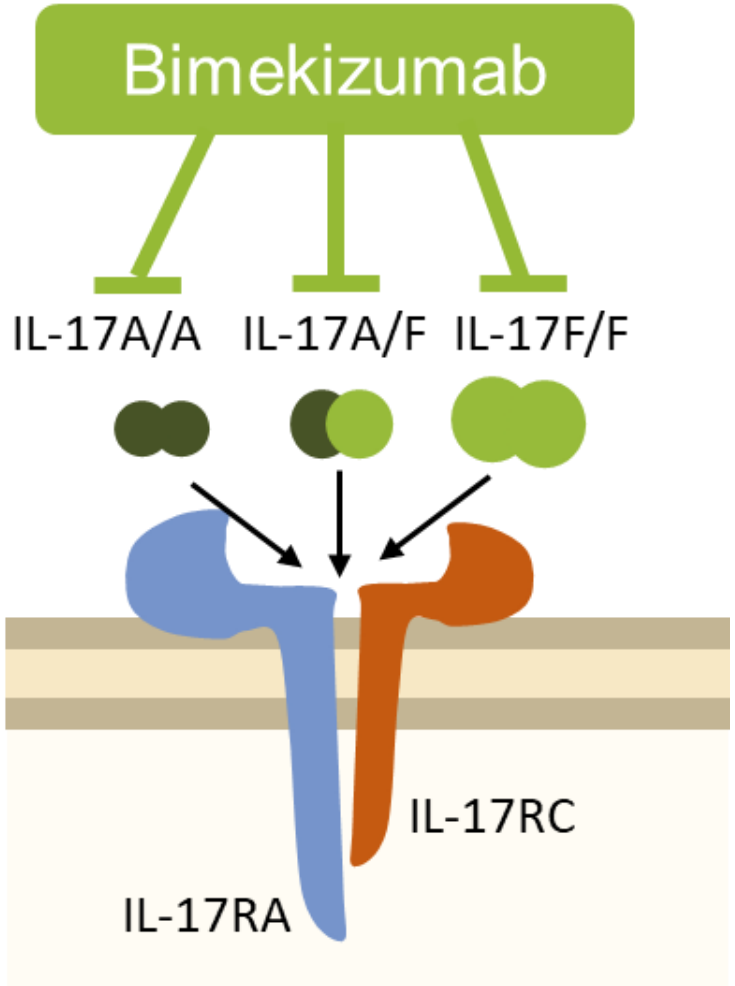
Nuevos tópicos

Tapinarof 1% crema
Roflumilast crema 0,3%

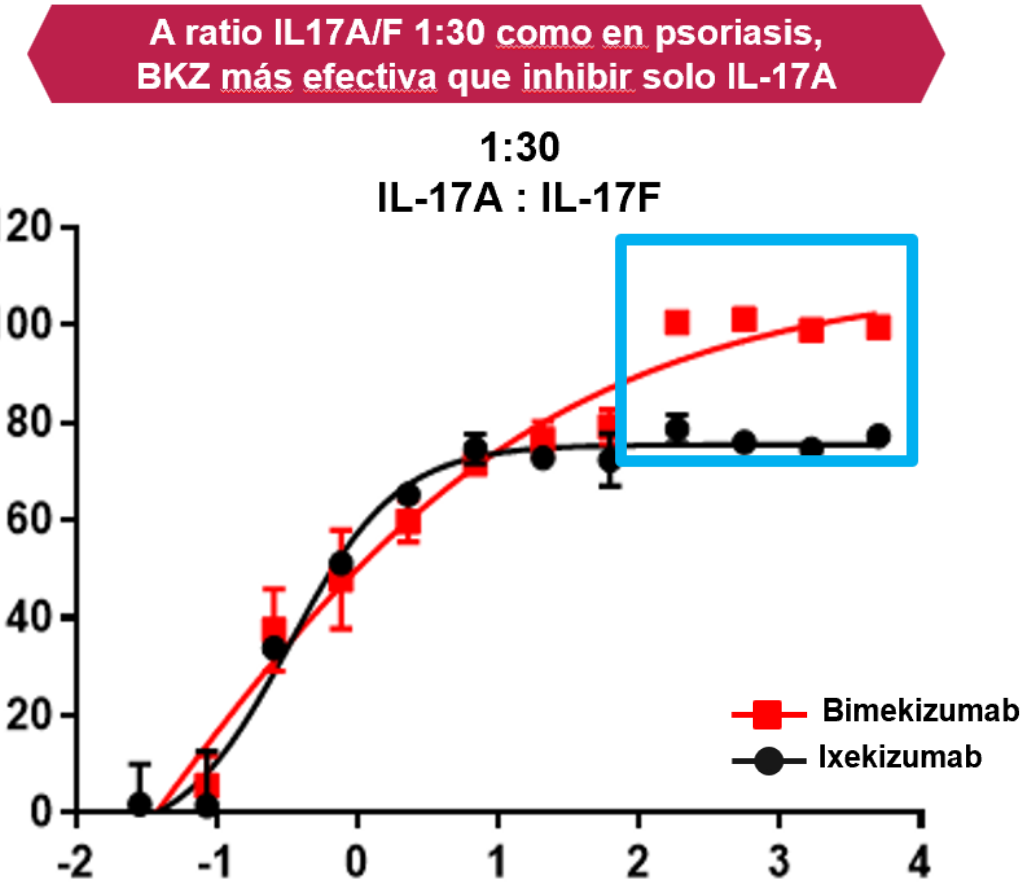
Shobeiri S, et al. *Int Immunopharmacol*. 2021

BIMEKIZUMAB (Bimzelx®)

- Inhibición dual, IL17A y F



IgG1 humanizada monoclonal



BIMEKIZUMAB

Amplio desarrollo. Potente inhibición.

Psoriasis

Hidradenitis suppurativa (HS)

Psoriatic arthritis (PsA)

Axial spondyloarthritis (axSpA)

PHASE 2B

BE ABLE 1 (PS0010)
Phase 2b double-blind, dose-ranging study in patients with moderate to severe **plaque psoriasis**

BE ABLE 2 (PS0011)
Phase 2b dose-blind, extension study (from PS0010) in patients with moderate to severe **plaque psoriasis**

HS0001
Phase 2b double-blind study in patients with moderate to severe **hidradenitis suppurativa**

BE ACTIVE 1 (PA0008)
Phase 2b double-blind, dose-ranging study in patients with active **PsA**

BE ACTIVE 2 (PA0009)
Phase 2b open-label extension study (from PA0008) in patients with active **PsA**

BE AGILE 1 (AS0008)
Phase 2b double-blind, dose-ranging study in patients with active **ankylosing spondylitis**

BE AGILE 2 (AS0009)
Phase 2b open-label extension study (from AS0008) in patients with active **ankylosing spondylitis**

PHASE 3

BE VIVID (PS0009)
Phase 3 double-blind placebo and active comparator (**ustekinumab**)-controlled study in moderate to severe **plaque psoriasis**

BE READY (PS0013)
Phase 3 double-blind **placebo**-controlled study (**Q4W and Q8W**) with randomised withdrawal period in moderate to severe **plaque psoriasis**

BE SURE (PS0008)
Phase 3 double-blind active comparator (**adalimumab**)-controlled, dose-blind study (**Q4W and Q8W**) in moderate to severe **plaque psoriasis**

BE BRIGHT (PS0014)
Phase 3 open-label extension study (from PS0009, PS0013, PS0008); **Q4W and Q8W**) in moderate to severe **plaque psoriasis**

BE RADIANT (PS0015)
Phase 3b double-blind, **secukinumab**-controlled study in moderate to severe **plaque psoriasis**

BE HEARD 1 (HS0003)
Phase 3 double-blind study in patients with moderate to severe **hidradenitis suppurativa**

BE HEARD 2 (HS0004)
Phase 3 double-blind study in patients with moderate to severe **hidradenitis suppurativa**

BE OPTIMAL (PA0010)
Phase 3 double-blind, placebo and active reference (**adalimumab**)-controlled study in active **PsA**

BE COMPLETE (PA0011)
Phase 3 double-blind, placebo-controlled study in active **PsA** with **inadequate response to TNFi**

BE VITAL (PA0012)
Phase 3 open-label extension study (from PA0010 and PA0011) in active **PsA**

BE MOBILE 1 (AS0010)
Phase 3 double-blind study in patients with active **non-radiographic axial spondyloarthritis**

BE MOBILE 2 (AS0011)
Phase 3 double-blind study in patients with active **ankylosing spondylitis**

BE MOVING (AS0014)
Phase 3 open-label extension study (from AS0010 and AS0011) in active **axSpA, ankylosing spondylitis and non-radiographic axSpA**

BE VIVID PASI 90 85% a semana 16; 81.6% a semana 52.

Risk of candidiasis associated with interleukin-17 inhibitors: A real-world observational study of multiple independent sources

Linda Davidson,[a,*] Juul M.P.A. van den Reek,[b] Mariolina Bruno,[a] Florence van Hunsel,[c] Ron M.C. Herings,[d,e] Vasiliki Matzaraki,[a,f] Collins K. Boahen,[a] Vinod Kumar,[a,f] Hans M.M. Groenewoud,[g] Frank L. van de Veerdonk,[a] Mihai G. Netea,[a,h] Elke M.G.J. de Jong,[b] and Bart Jan Kullberg,[a]

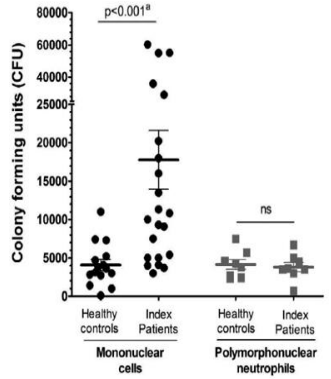
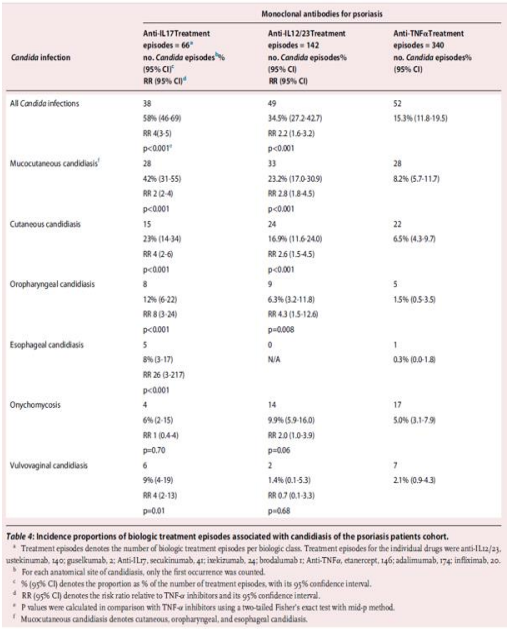


Figure 1. Immunology studies in psoriasis patients with candi-

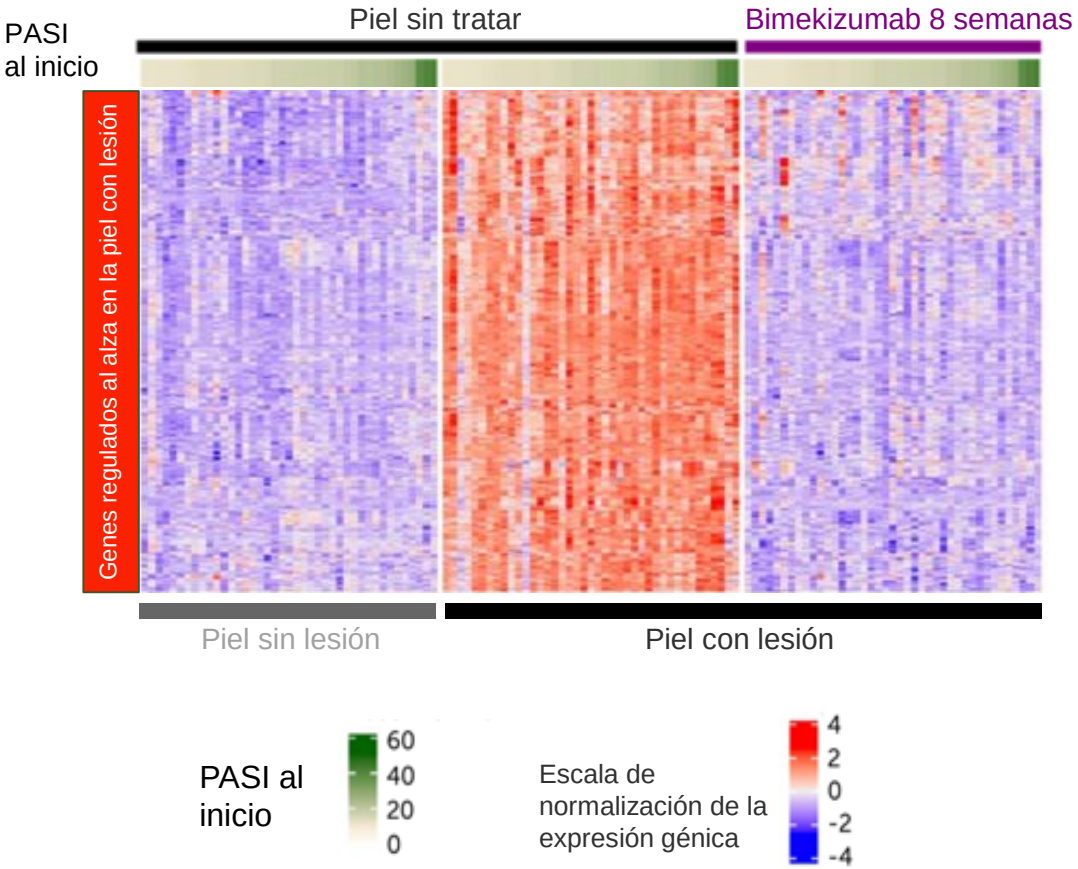


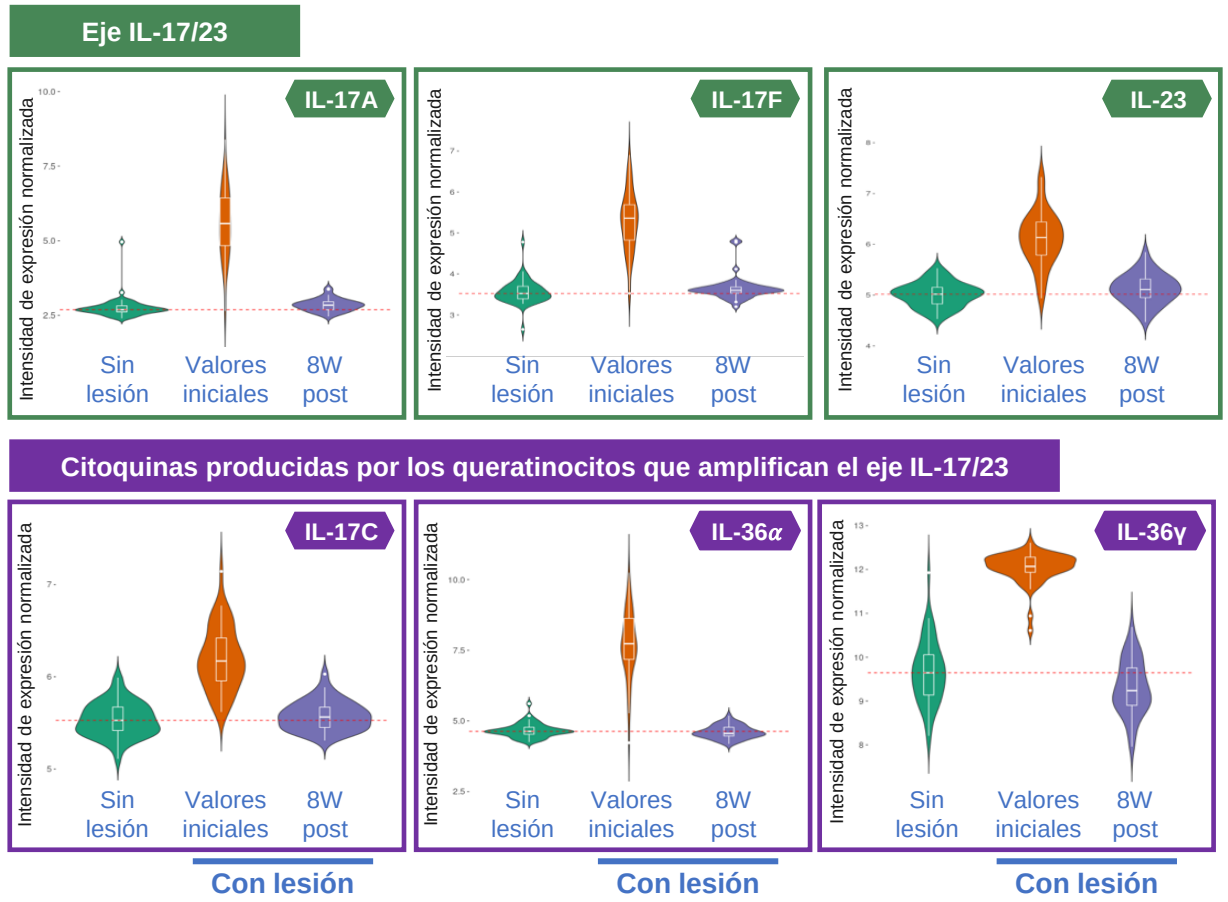
Candida infection	Monoclonal antibodies for psoriasis: Anti-IL17Treatment episodes = 66[a] no. Candida episodes[b]% (95% CI)[c] RR (95% CI)[d]	Anti-IL12/23Treatment episodes = 142 no. Candida episodes% (95% CI) RR (95% CI)	Anti-TNFαTreatment episodes = 340 no. Candida episodes% (95% CI)
All Candida infections	38	49	52
	58% (46-69)	34.5% (27.2-42.7)	15.3% (11.8-19.5)
	RR 4(3-5)	RR 2.2 (1.6-3.2)	
	p<0.001[e]	p<0.001	
Mucocutaneous candidiasis[f]	28	33	28
	42% (31-55)	23.2% (17.0-30.9)	8.2% (5.7-11.7)
	RR 2 (2-4)	RR 2.8 (1.8-4.5)	
	p<0.001	p<0.001	
Cutaneous candidiasis	15	24	22
	23% (14-34)	16.9% (11.6-24.0)	6.5% (4.3-9.7)
	RR 4 (2-6)	RR 2.6 (1.5-4.5)	
	p<0.001	p<0.001	
Oropharyngeal candidiasis	8	9	5
	12% (6-22)	6.3% (3.2-11.8)	1.5% (0.5-3.5)
	RR 8 (3-24)	RR 4.3 (1.5-12.6)	
	p<0.001	p=0.008	
Esophageal candidiasis	5	0	1
	8% (3-17)	N/A	0.3% (0.0-1.8)
	RR 26 (3-217)		
	p<0.001		
Onychomycosis	4	14	17
	6% (2-15)	9.9% (5.9-16.0)	5.0% (3.1-7.9)
	RR 1 (0.4-4)	RR 2.0 (1.0-3.9)	
	p=0.70	p=0.06	
Vulvovaginal candidiasis	6	2	7
	9% (4-19)	1.4% (0.1-5.3)	2.1% (0.9-4.3)
	RR 4 (2-13)	RR 0.7 (0.1-3.3)	
	p=0.01	p=0.68	

Table 4: **Incidence proportions of biologic treatment episodes associated with candidiasis of the psoriasis patients cohort.**
[a] Treatment episodes denotes the number of biologic treatment episodes per biologic class. Treatment episodes for the individual drugs were anti-IL12/23, ustekinumab, 140; guselkumab, 2; Anti-IL17, secukinumab, 42; ixekizumab, 24; brodalumab 1; Anti-TNFα, etanercept, 146; adalimumab, 174; infliximab, 20.
[b] For each anatomical site of candidiasis, only the first occurrence was counted.
[c] % (95% CI) denotes the proportion as % of the number of treatment episodes, with its 95% confidence interval.
[d] RR (95% CI) denotes the risk ratio relative to TNF-α inhibitors and its 95% confidence interval.
[e] P values were calculated in comparison with TNF-α inhibitors using a two-tailed Fisher's exact test with mid-p method.
[f] Mucocutaneous candidiasis denotes cutaneous, oropharyngeal, and esophageal candidiasis.

Candidiasis oral 18.2% en BEVIVID %.
10-18% según EC

El tratamiento con bimekizumab normaliza la expresión de los genes implicados en psoriasis en un estudio en fase 2





8W post: tras 8 semanas de tratamiento con bimekizumab
Bimekizumab se administró en dos dosis de 320 mg cada cuatro semanas. Se utilizó un panel de genes para medir la expresión génica. La firma de genes patógenos se muestra mediante un mapa de calor de los datos de expresión génica.
Oliver R, Krueger JG, Glatt S, et al. Br J Dermatol. 23 de octubre de 2021.

NUEVOS BIOLÓGICOS EN PIPELINE

	Agent (acronym)	Mode of action	Study phase	Clinical trial identifier	Pso severity	Study duration	Primary endpoint	Status
Biologics	ABY035/AF02 (Izokibep)	IL-17A inhibitor	Phase II	NCT03591887	Moderate-to-severe	56 weeks	PASI 90 at week 12	Completed
	M1095/ALX-0761 (Sonelokimab)	Anti-IL-17A/F Nanobody	Phase II b	NCT03384745	Moderate-to-severe	52 weeks	IGA 0/1 at week 12	Completed
	SHR-1314 (Vunakizumab)	mAb anti IL-17A	Part A: Phase I	NCT03463187	Moderate-to-severe	24 weeks	N. of participants with clinically significant events	Unknown
			Part B: Phase II	NCT03463187	Moderate-to-severe	36 weeks	PASI 75 at week 12	
	CC-90006	Anti-PD-1 agonist antibody	Phase I	NCT03337022	Mild-to moderate	20 weeks	N. of participants with clinically significant adverse events	Completed
	Namilumab	Anti-GM-CSF antibody	Phase II	NCT02129777	Moderate-to-severe	52 weeks	PASI 75 at week 12	Completed
	GSK2831781	Anti-LAG-3 antibody	Phase I	NCT02195349	Mild-to moderate	Up to 307 days	N. of participants with clinically significant adverse events	Completed

Calabrese et al. Expert opinión on investigational drugs. E pub 22/Feb/2023

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	GSK2831781	Anti-LAG-3 antibody	Phase I	NCT02195349	Mild-to moderate	Up to 307 days	N. of participants with clinically significant adverse events	Completed

Bloqueo útil en AR. No parece buena diana en psoriasis

Calabrese et al. Expert opinión on investigational drugs. E pub 22/Feb/2023

Anti IL23 R oral NCT05357755
Gumokimab fase II antiIL17A
Imsilodimab IL36 R fase 3

NUEVOS BIOLÓGICOS EN PIPELINE

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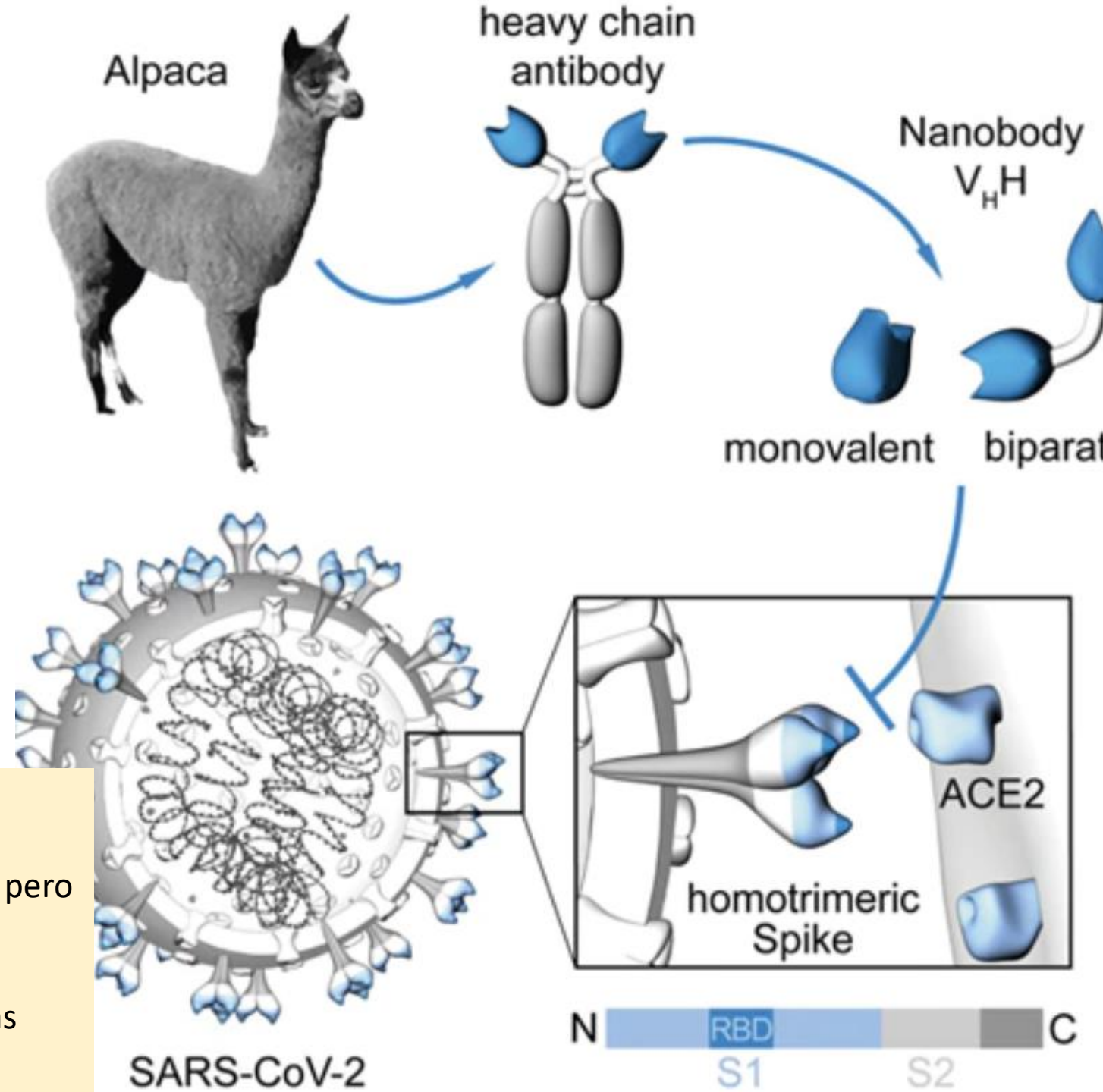
Calabrese et al. Expert opinión on investigational drugs. E pub 22/Feb/2023. Drakos Derm Ther 2022



NANOBODY TECHNOLOGY

Son moléculas que bloquean las dianas que conocemos pero sin estructura de inmunoglobulina

Sonelokimab es nanobody que bloquea mismas citocinas que bimekizumab

SPESOLIMAB: SPEVIGO® 450 MG

RESEARCH SUMMARY

Trial of Spesolimab for Generalized Pustular Psoriasis

Bachelez H et al. DOI: 10.1056/NEJMoa2111563

CLINICAL PROBLEM

Generalized pustular psoriasis (GPP) is a rare, life-threatening inflammatory skin disease characterized by widespread eruption of sterile pustules. Interleukin-36 is implicated in the pathogenesis of GPP. Accordingly, spesolimab — a humanized anti–interleukin-36 receptor monoclonal antibody — could be a potential treatment option for patients with GPP.

CLINICAL TRIAL

Design: A phase 2, multicenter, randomized, double-blind, placebo-controlled trial examined the efficacy and safety of spesolimab in adults presenting with a moderate-to-severe GPP flare.

Intervention: 53 patients were randomly assigned in a 2:1 ratio to receive either a single 900-mg intravenous dose of spesolimab or placebo. The primary end point was a Generalized Pustular Psoriasis Physician Global Assessment (GPPGA) pustulation subscore of 0 (range, 0 [no visible pustules] to 4 [severe pustulation]) at the end of week 1.

RESULTS

Efficacy: Patients in the spesolimab group were significantly more likely to have clearance of pustular lesions at 1 week than those in the placebo group.

Safety: Through 1 week, serious adverse events and infections were more common in the spesolimab group than in the placebo group. In addition, through 12 weeks that included an open-label extension of the trial, two patients in the spesolimab group had a drug reaction with eosinophilia and systemic symptoms; one of the two patients also had a drug-induced hepatic injury.

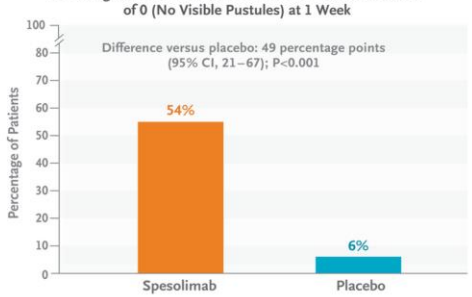
LIMITATIONS AND REMAINING QUESTIONS

- The size and duration of the trial were limited.
- At day 8, many patients, including most patients in the placebo group, were given open-label spesolimab and were followed for 12 weeks; comparisons could not be drawn between the groups during this portion of the trial.

Links: Full Article | NEJM Quick Take

Primary End Point

Percentage of Patients with a GPPGA Pustulation Subscore of 0 (No Visible Pustules) at 1 Week



Summary of Adverse Events

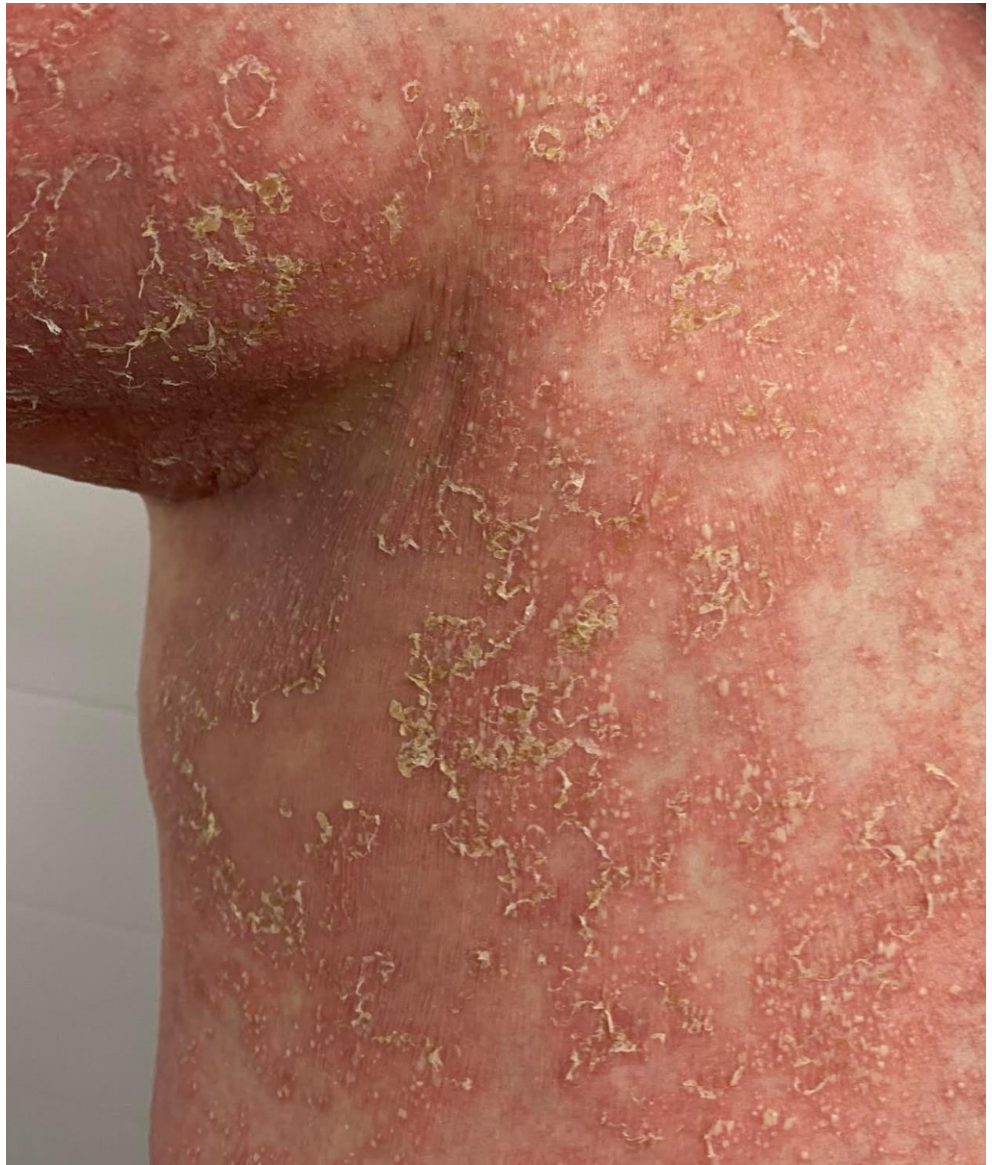
Serious Adverse Events at 1 Week	
Spesolimab (N=35)	Placebo (N=18)
6%	0%

Infections at 1 Week	
Spesolimab (N=35)	Placebo (N=18)
17%	6%

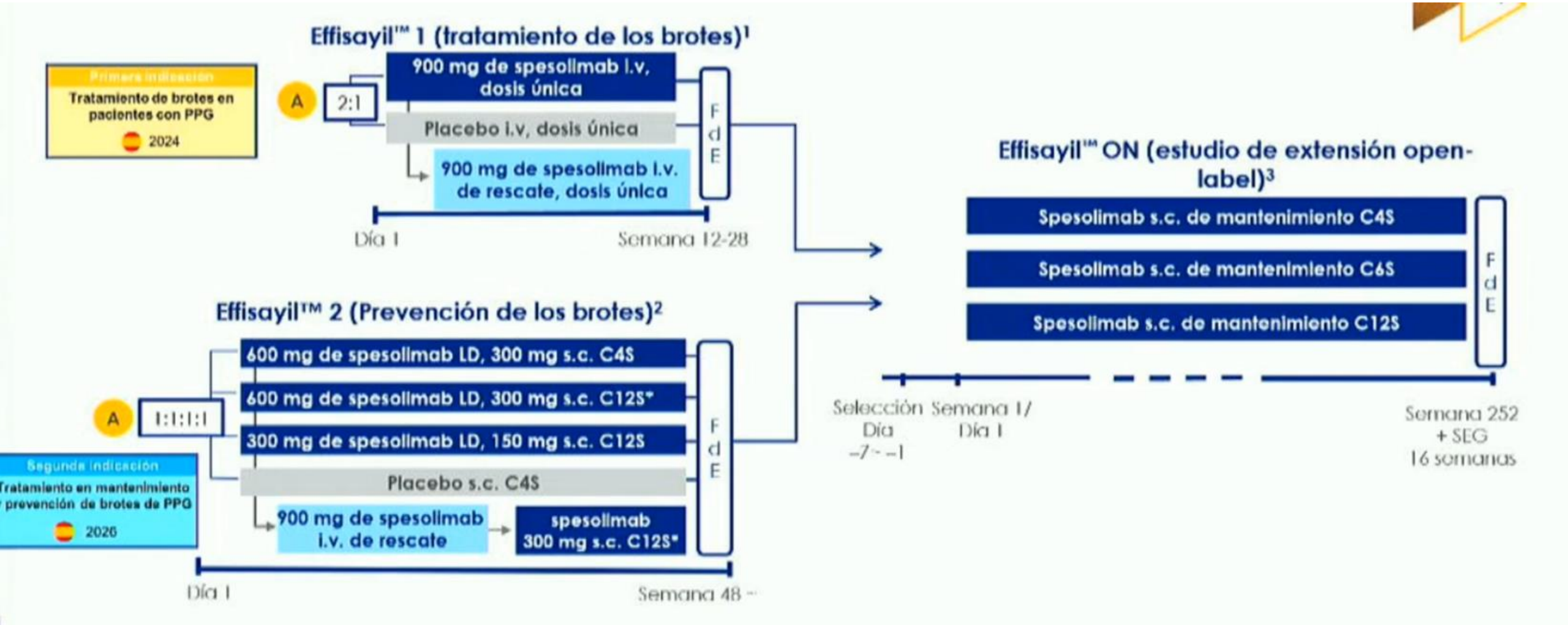
Drug Reaction with Eosinophilia and Systemic Symptoms (DRESS) at 12 Weeks (open-label)
Spesolimab (N=51): 4%
Rate per 100 patient-years, 15.9

CONCLUSIONS

A single infusion of spesolimab was associated with a higher incidence of lesion clearance at 1 week than placebo among patients with GPP but was also linked to systemic drug reactions and infections.



DESARROLLO ADICIONAL



DC-806: blocking the *same step* as the antibodies via allosteric binding event

AAD 2023 New Orleans

IL-17AA + ANTIBODY

IL-17 AA + RECEPTOR

IL-17 AA + DC-806

PRO-INFLAMMATORY SIGNAL

AAD 2023 New Orleans

Phase 1 SAD/MAD in Healthy Participants and P1c in Psoriasis Patients

Safe and well tolerated in Healthy Participants

Healthy Participants

SAD

Healthy Participants: 6:2 (Active:Pbo)

25 mg

75 mg

200 mg → Food Effect

450 mg

800 mg

MAD

175 mg QD x 7d

200 mg BID x 7d

400 mg BID x 7d

800 mg BID x 7d

Psoriasis Patients (4 weeks)

Phase 1c

- PGA score of 2 or 3
- BSA involvement ≥ 3%

200 mg BID x 28d
(2:1 Active:Pbo)

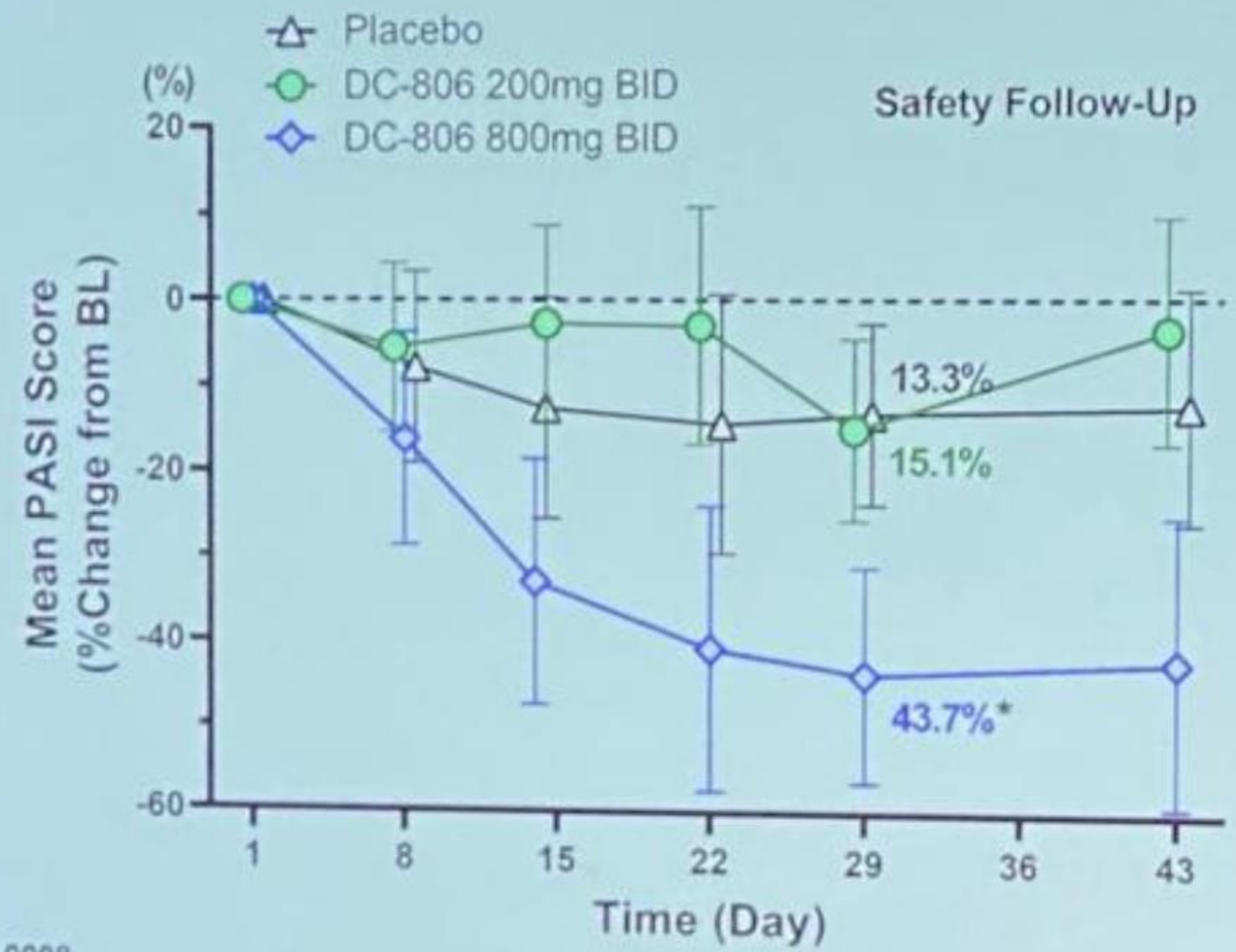
800 mg BID x 28d
(2:1 Active:Pbo)

Key Objective of P1c

- Evaluate the safety, tolerability, and PK and explore preliminary clinical activity and pharmacodynamics of DC-806 in patients with psoriasis

AAD 2023 New Orleans

DC-806 demonstrated clear benefit with reductions in PASI score



*Exploratory p = 0.0008

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Disposition of Psoriasis Patients in P1c

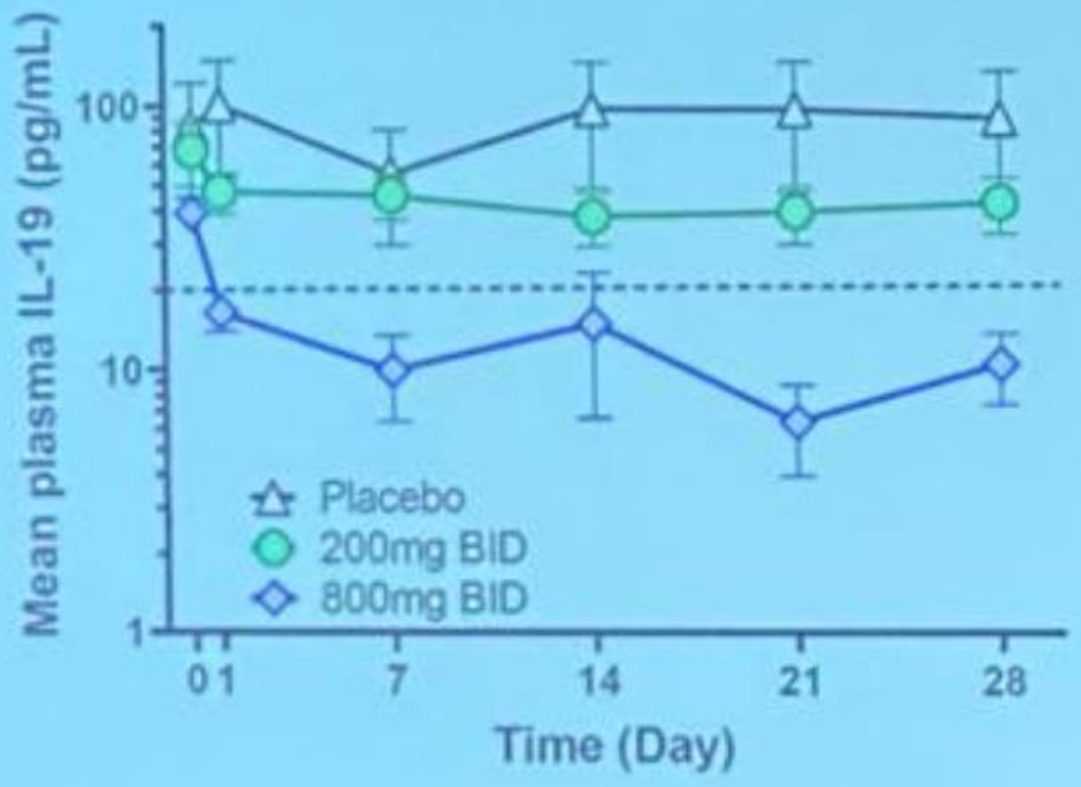
No discontinuations due to treatment-related AEs or lack of efficacy/worsening of psoriasis in DC-806 treatment arms

	DC-806 200mg BID N=13	DC-806 800mg BID N=8	Placebo N=11
Subjects who completed the study, n (%)	10 (76.9)	7 (87.5)	10 (90.9)
Subjects who prematurely discontinued study, n (%)	3 (23.1)	1 (12.5)	1 (9.1)
Reason, n (%)			
Adverse Event/Other Medical Condition/COVID	2 (15.4)[a,b]	0	0
Withdrawal of Informed Consent	0	1 (12.5)[c]	1 (9.1)[d]
Investigator Decision	1 (7.7)[e]	0	0

[a] Withdrew due to left leg cellulitis (Day 22, not treatment related)
[b] Withdrew due to COVID19 (Day 21, not treatment related)
[c] Withdrew consent due to COVID19 (Day 29, not treatment related) – unable to continue with study visits
[d] Withdrew consent due to psoriasis exacerbation (Day 7)
[e] Non-compliance with study drug (Day 23)

Reductions in systemic IL-19 by DC-806 suggest potential for significant long term PASI responses

AAD 2023 New Orleans

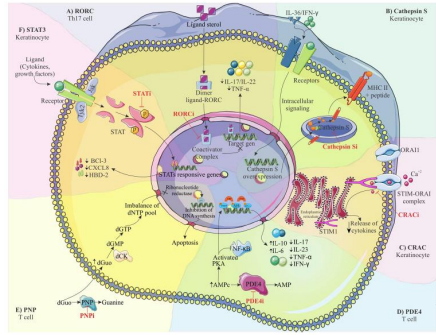


2 weeks of treatment with DC-806		
Cohort	[IL-19] < 21 pg/mL[1]	[IL-19] pg/mL
Placebo	0/9 pts (0%)	93.1
200 mg BID	3/8 pts (38%)	37.0
800 mg BID	6/7 pts (86%)	14.7

IL-19 reductions below ~20 pg/ml after 2 weeks of treatment are associated with PASI90/100 at week 16[2]

1. In patients with baseline IL-19 > 21 pg/ml *[Lower limit of quantification (LLOQ): 7.5 pg/mL]*
2. Konrad, et. al. *Scientific Reports* (2019) 9:521

Moléculas pequeñas



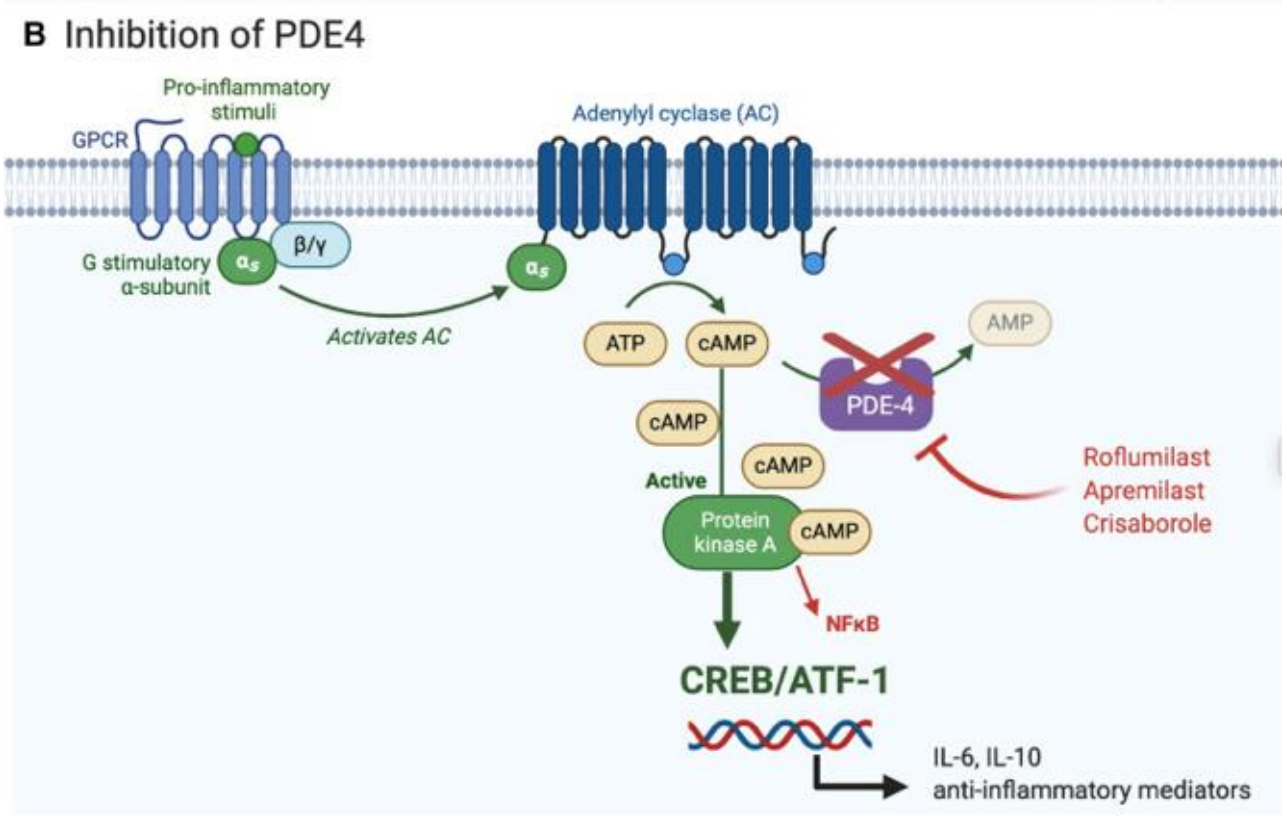
- Peso molecular de < 1 kilodalton.
- Modulan el sistema inmunitario de manera inespecífica a nivel de la señalización intracelular→
  → en el bloqueo de varias citoquinas.

- Más simples y se sintetizan químicamente.
- Pueden atravesar la membrana celular.
- Ausencia de inmunogenicidad.
- Pueden administrarse por vía oral o tópica.
  - Pacientes con psoriasis leve-moderada.
  - Preferencias personales de los pacientes.
- Opción más rentable.

Shobeiri S, et al. *Int Immunopharmacol*. 2021
Gómez-García F, et al. *Front Med (Lausanne)*. 2022
Balogh E, et al. *Expert Opin Emerg Drugs*. 2020

Inhibidores de las fosfodiesterasa-4 (PDE)

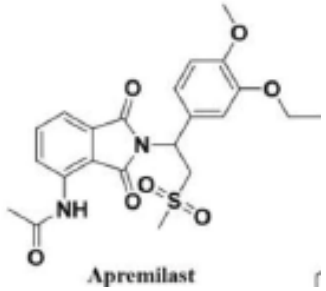
- Apremilast
- Hemay005
- Roflumilast
- Crisaborol



Milakovic M, et al. *Psoriasis (Auckl)*. 2021

Apremilast, Otezla®

Amgen Europe B.V.



Apremilast

- RWE España. APPRECIATE. PASI75: 36.7%
- LIBERATE frente a placebo y ETN. Sin diferencias significativas APR/ETN.
- Fase III. Tasas de respuesta a semana 16, apremilast (30 mg dos veces al día) frente a placebo:
  - PASI75: 33,1 % (placebo 5,3 %). ESTEEM-1.
  - PASI75: 28,8% (placebo 5,8%) y 8,8% (1,5%) ESTEEM-2.
  - PASI90: 9,8 % (placebo 0,4 %). ESTEEM-1.
  - PASI 90: 8,8% (placebo 1,5%) ESTEEM-2.

Aljefri Y, et al *Dermatol Ther.* 2022 ; Reich K, et al*, J Eur Acad Dermatol* . 2017; Papp K, et al. *J Am Acad Dermatol.* 2015; Paul C, et al. *Br J Dermatol*. 2015; Herranz P, et al. *Actas Dermosifiliogr*. 2021

Apremilast: áreas especiales y comorbilidades

- Permite un rápido control del prurito.
- Adecuado si infecciones recurrentes, neoplasias recientes o activas, inmunosupresión.
- Aprobado en PsA. PALACE-2 y PALACE-3.
  - ACR20,50,70 a semana 16 frente a placebo 32,1%; 10,5%; 1,2%.
- Localizaciones especiales (**uñas, cuero cabelludo y palmoplantar**).
  - Estudio **LAPIS-PSO,** RWE, 62% NAPSI-50 a 4 m.
  - Estudio **STYLE**, psoriasis en placa de cuero cabelludo moderada-grave, el 43,4% de los pacientes tratados con apremilast vs. PBO (13,8%) alcanzó el objetivo primario a las 16 semanas.
- Potencial mejora metabólica al inhibir PDE4. **Estudio IMAPA**
- **EMBRACE; DISCREET. Genital; SPROUT (pediátrico 6-17 a); fase II en PPP con 78.3% y un 37.4% más de respuesta que placebo PPPASI50 w16**

Cervantes-Durán C. et al. *Arch Dermatol Res.* 2020; Kavanaugh A, et al. *Arthritis Res Ther*. 2019; Carrascosa J, et al *Actas Dermosifiliogr (Engl Ed).* 2020

Apremilast y perfil de seguridad

- Las reacciones adversas notificadas para apremilast son de leves a moderadas en gravedad.
  - Las más comunes: diarrea, náuseas, cefalea, nasofaringitis, infecciones del tracto respiratorio superior, vómitos y anorexia.
- Efectos adversos más frecuentes:
  - La cefalea y la diarrea secretora→ conducen a la interrupción (20%).

✓No es necesario screening rutinario de tuberculosis y ni del virus de la hepatitis B.

❖Embarazo:

Cervantes-Durán C. et al. *Arch Dermatol Res.* 2020
Kavanaugh A, et al. *Arthritis Res Ther*. 2019
Carrascosa J, et al *Actas Dermosifiliogr (Engl Ed)*. 2020

Apremilast y perfil de seguridad

- Las reacciones adversas notificadas para apremilast son de <u>leves a moderadas</u> en gravedad.
  - Las más comunes: diarrea, náuseas, cefalea, nasofaringitis, infecciones del tracto respiratorio superior, vómitos y anorexia.

- Monitorizar el peso en pacientes con peso inferior al normal.
- Monitorizar periódicamente posibles alteraciones del estado de ánimo.

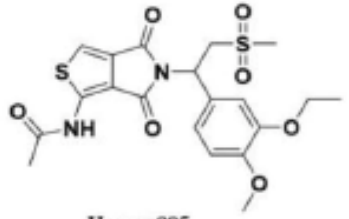
✓No es necesario screening rutinario de tuberculosis y ni del virus de la hepatitis B.

❖Embarazo:

Cervantes-Durán C. et al. *Arch Dermatol Res.* 2020
Kavanaugh A, et al. *Arthritis Res Ther*. 2019
Carrascosa J, et al *Actas Dermosifiliogr (Engl Ed)*. 2020

Hemay005

(S)-N-[5-[1-(3- etoxi-4-metoxifenil)-2-(metilsulfonil)etil]-4,6-dioxo-5,6-dihidro-4Htiofeno [3,4-c] pirrol-1-il] acetamida



Hemay005

- Nuevo inhibidor de la PDE4.
- Estudios preclínicos:
  - Actividades inhibidoras PDE4 similares a las de apremilast.
  - Ha demostrado una mayor eficacia en la psoriasis en un **modelo de ratón** en comparación con apremilast a dosis de20 mg/kg/día.
  - Datos de seguridad satisfactorios.

- Ensayo clínico de fase II (NCT04102241) patrocinado por Tianjin Hemay Bio-Tech Co., Ltd.

Liu X, et al. *Bioanalysis*. 2018.; Cervantes-Durán C. et al. *Arch Dermatol Res.* 2020.

Roflumilast oral, Daxas®

- Inhibidor de la PDE4, enfermedad pulmonar obstructiva crónica (EPOC).
- Ensayo clínico de fase II (NCT04549870), reclutamiento.

Egeberg A. et al. *Br J Dermatol.* 2021.; Lebwohl M, et al. . *N Engl J Med.* 2020; Late breaking Research AAD2023 New Orleans

ROFLUMILAST ORAL

FUERA DE FICHA

- 26 pacientes, 9.02 PASI medio inicial 10.68% BSA
- Pretratados en un 65.38% (17 de ellos con TS) y un 38.42% con más de 2 Y un 15.38 % habían recibido TB
- Dosis de EPOC, 250 microgramos/24 horas con aumento a 500 mcg/24 horas en 1-4 semanas. Y en 9 casos con IBP para minimizar molestias GI
- Efectivo en un 72%, 32% PASI 0 en 30-45 días y 36% mejoría parcial, reduciendo a PASI medio de 2.79 y BSA 4.6 % (no se especifica tiempo)

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Efficacy and safety of oral roflumilast in the treatment of moderate-to-severe psoriasis: a randomized, double-blinded, placebo-controlled trial (PSORRO)

Mette Gyldenløve, MD PhD[1]; Jennifer Astrup Sørensen, MD[2]; Simon Fage, MD PhD[3]; Yiqiu Yao, MD[2]; Lars Iversen, MD DMSc[3]; Howraman Meteran, MD PhD[4]; Mia-Louise Nielsen, MSc[2], **Alexander Egeberg, MD PhD DMSc[2,5]**

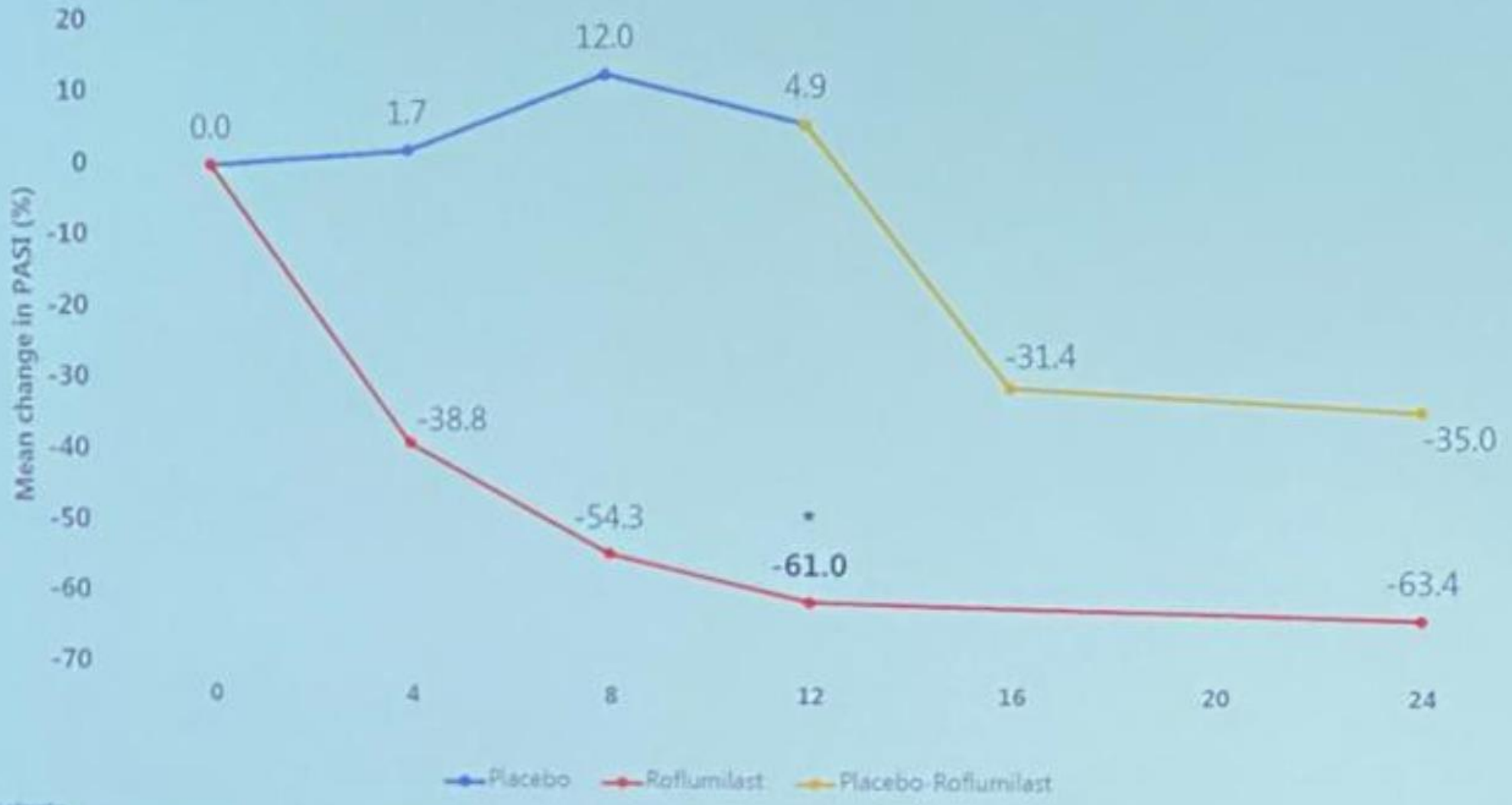
[1]Department of Dermatology and Allergy, Herlev and Gentofte Hospital, University of Copenhagen, Denmark
[2]Department of Dermatology, Bispebjerg and Frederiksberg Hospital, University of Copenhagen, Denmark
[3]Department of Dermatology, Aarhus University Hospital, Denmark
[4]Department of Internal Medicine, Respiratory Medicine Section, Herlev and Gentofte Hospital, University of Copenhagen, Denmark
[5]Department of Clinical Medicine, University of Copenhagen, Denmark

Presented at: The 2023 Annual Meeting of the American Academy of Dermatology (AAD); March 17-21 in New Orleans, Louisiana

UNIVERSITY OF COPENHAGEN

AAD 2023 New Orleans

Mean Change From Baseline in PASI



* p<0.01 versus placebo
Data are reported as intention-to-treat with last observation carried forward
PASI = psoriasis area and severity index

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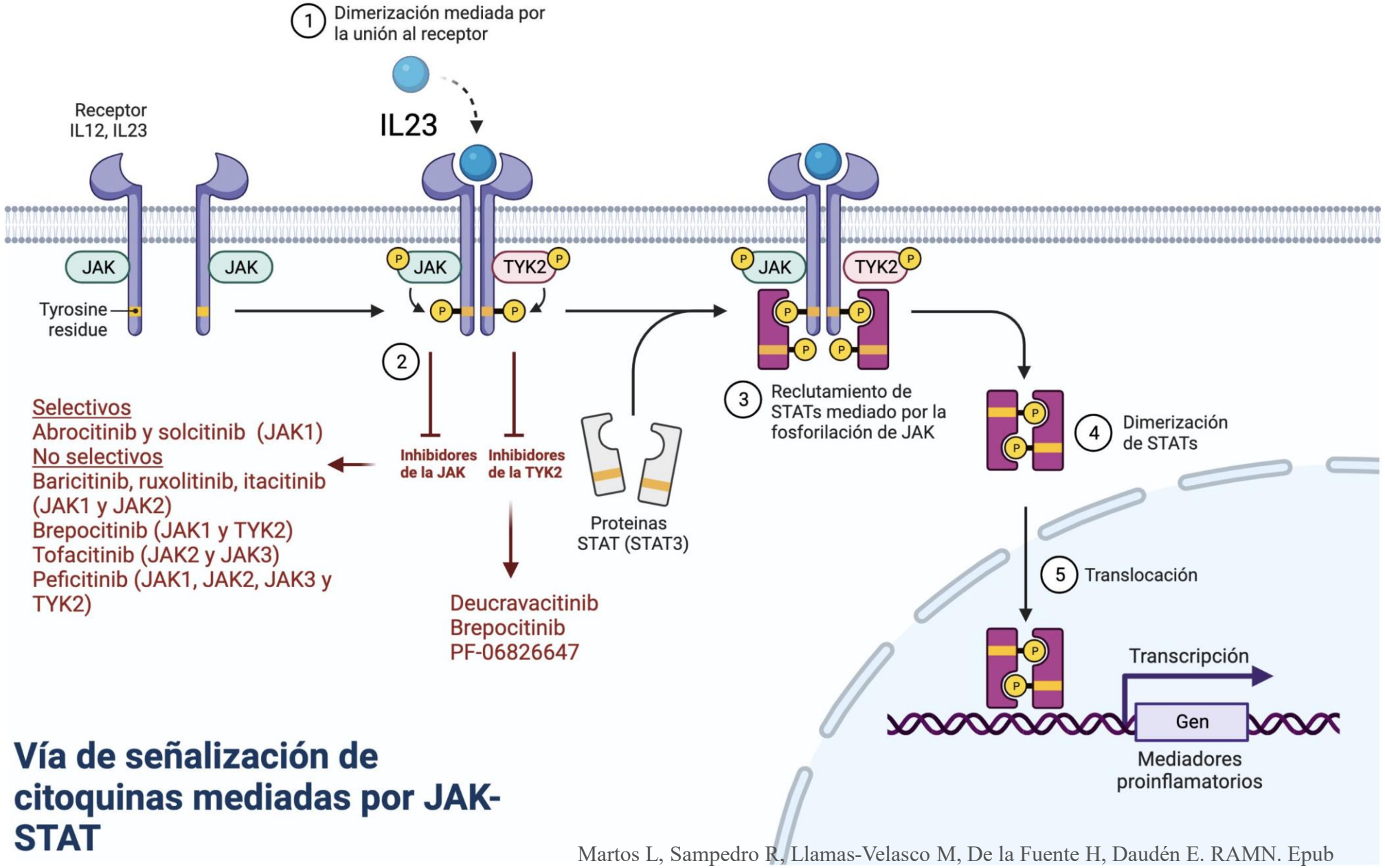
Summary

- Baseline characteristics were generally well balanced
- **Efficacy** – Week 12
  - PASI75: Placebo: **0.0%** Roflumilast: **34.8%**
  - PASI90: Placebo: **0.0%** Roflumilast: **13.0%**
- **Efficacy** – Week 24 (continuous roflumilast since baseline)
  - PASI75: Roflumilast: **43.5%**
  - PASI90: Roflumilast: **21.7%**
  - PASI100: Roflumilast: **8.7%**
- **Safety** – Week 24: No new safety signals were identified
  - Oral roflumilast was generally well-tolerated with AEs being mild and transient

Conclusion

- **The primary endpoint was met for oral roflumilast vs. placebo (PASI75 response at week 12)**
- **With generic versions available, oral roflumilast may represent an inexpensive treatment option for patients with psoriasis that are candidates for systemic therapy**

AE = adverse event; PASI = psoriasis area and severity index



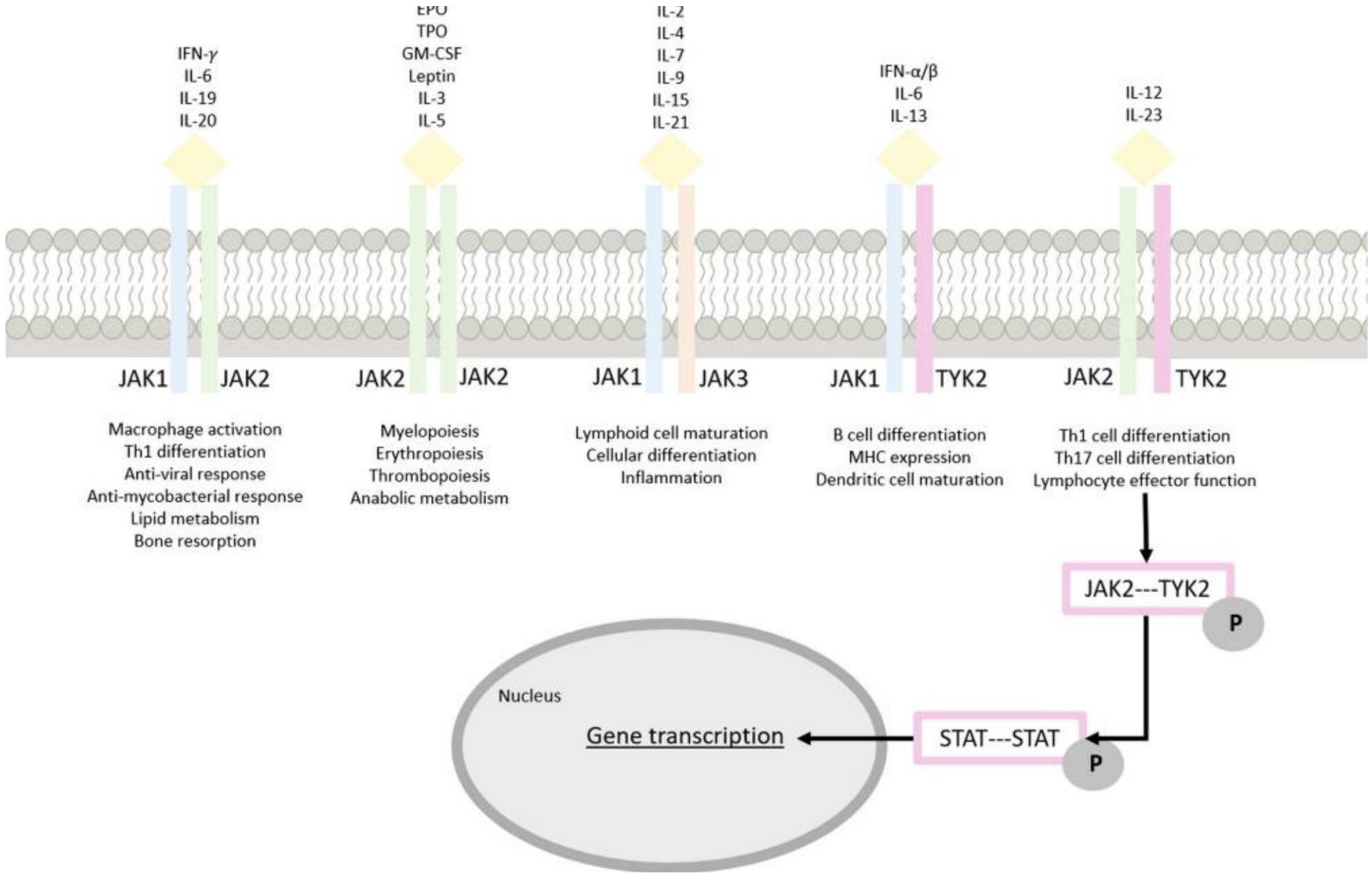
Vía de señalización de citoquinas mediadas por JAK-STAT

Martos L, Sampedro R, Llamas-Velasco M, De la Fuente H, Daudén E. RAMN. Epub

Deucravacitinib for the Treatment of Psoriatic Disease

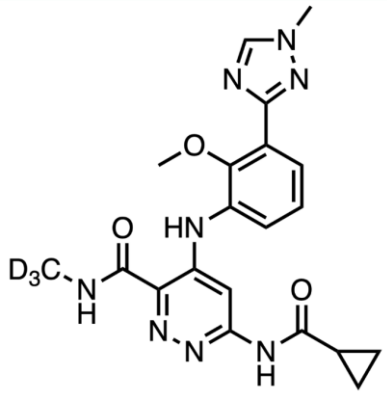
Ana Maria Lé[1] · Luis Puig[2] · Tiago Torres[1,3]

Accepted: 25 July 2022 / Published online: 12 August 2022



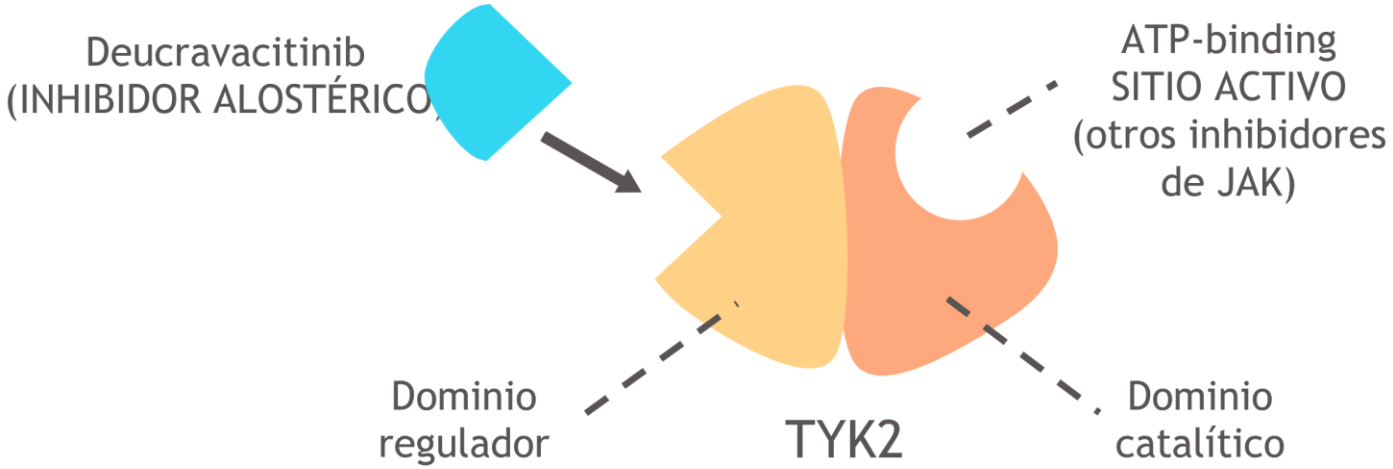
deucravacitinib (Sotyktu)

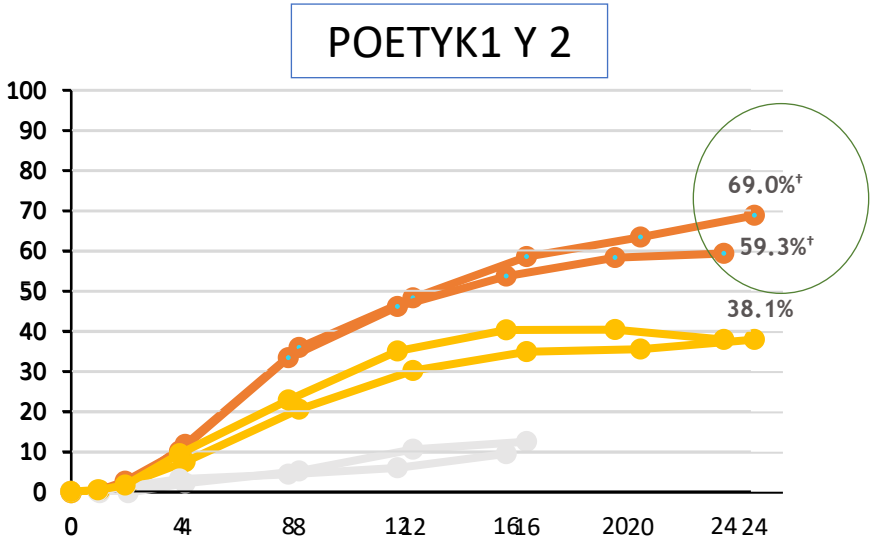
deuterated TYK2 inhibitor



DEUCRACITINIB: SOTYKTU®

- Deucracitinib: 100 more specific for TYK2 than for JAK1/3



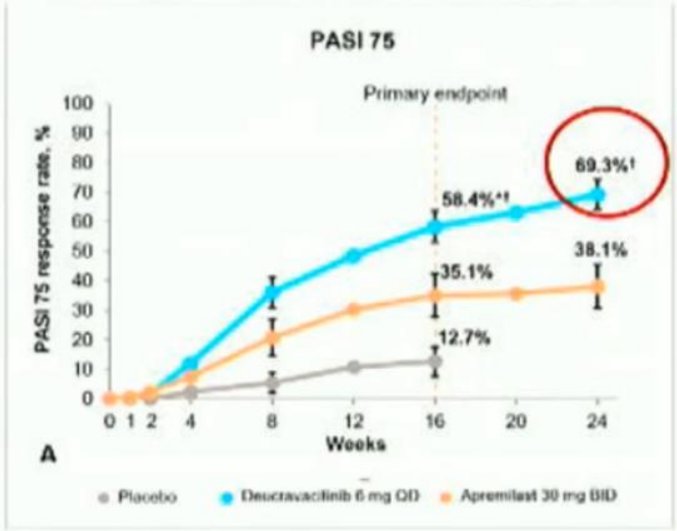


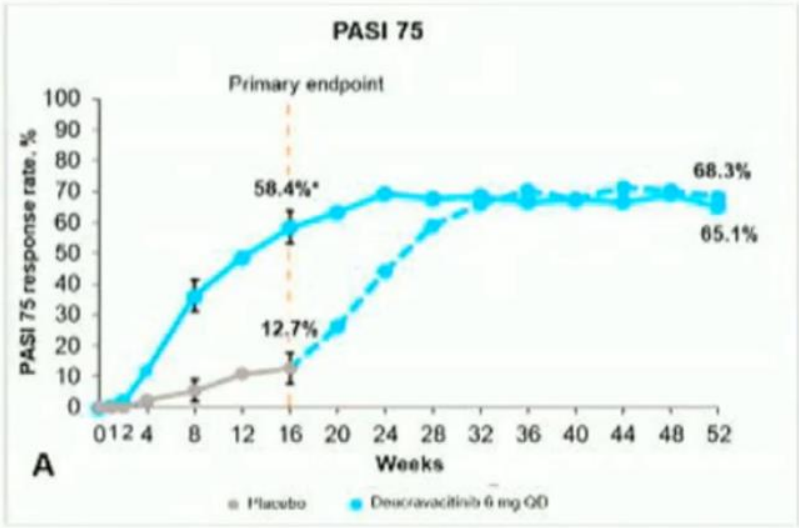
DEUCRACITINIB CE: POETYK

POETYK-PSO1

ORIGINAL ARTICLES

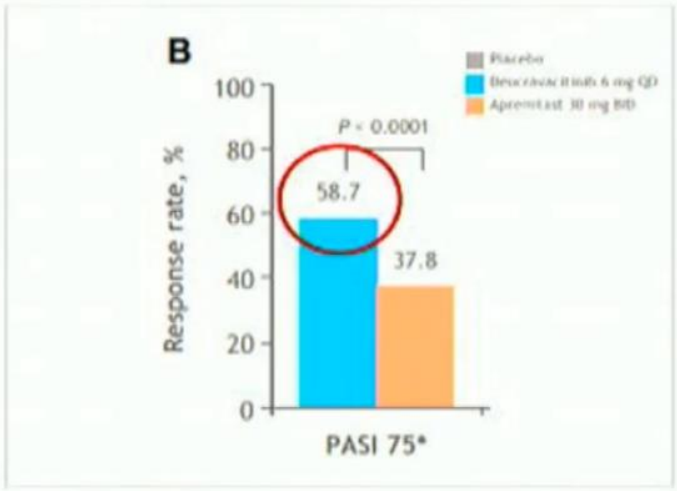
Deucravacitinib versus placebo and apremilast in moderate to severe plaque psoriasis: Efficacy and safety results from the 52-week, randomized, double-blinded, placebo-controlled phase 3 POETYK PSO-1 trial

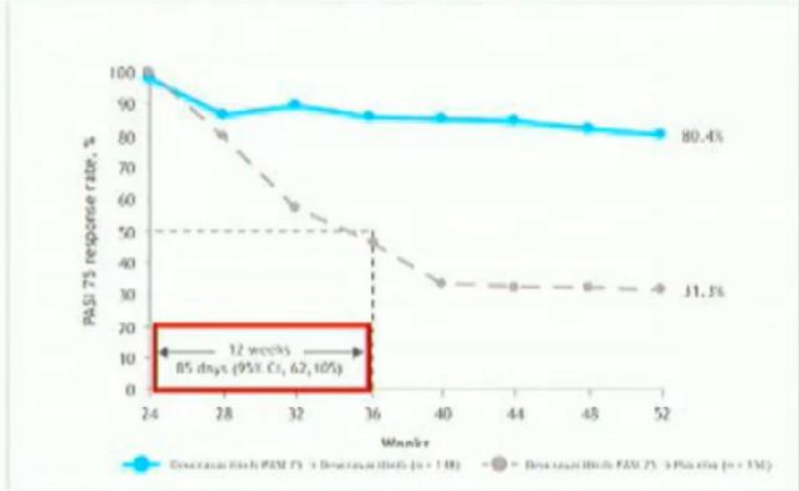




POETYK-PSO2

Deucravacitinib versus placebo and apremilast in moderate to severe plaque psoriasis: Efficacy and safety results from the 52-week, randomized, double-blinded, phase 3 Program fOr Evaluation of TYK2 inhibitor psoriasis second trial





Armstrong AW et al. J Am Acad Dermatol. 2023 Jan;88(1):29-39. 2. Strober B et al. J Am Acad Dermatol. 2023 Jan;88(1):40-51.

DEUCRAVACITINIB: OTROS USOS

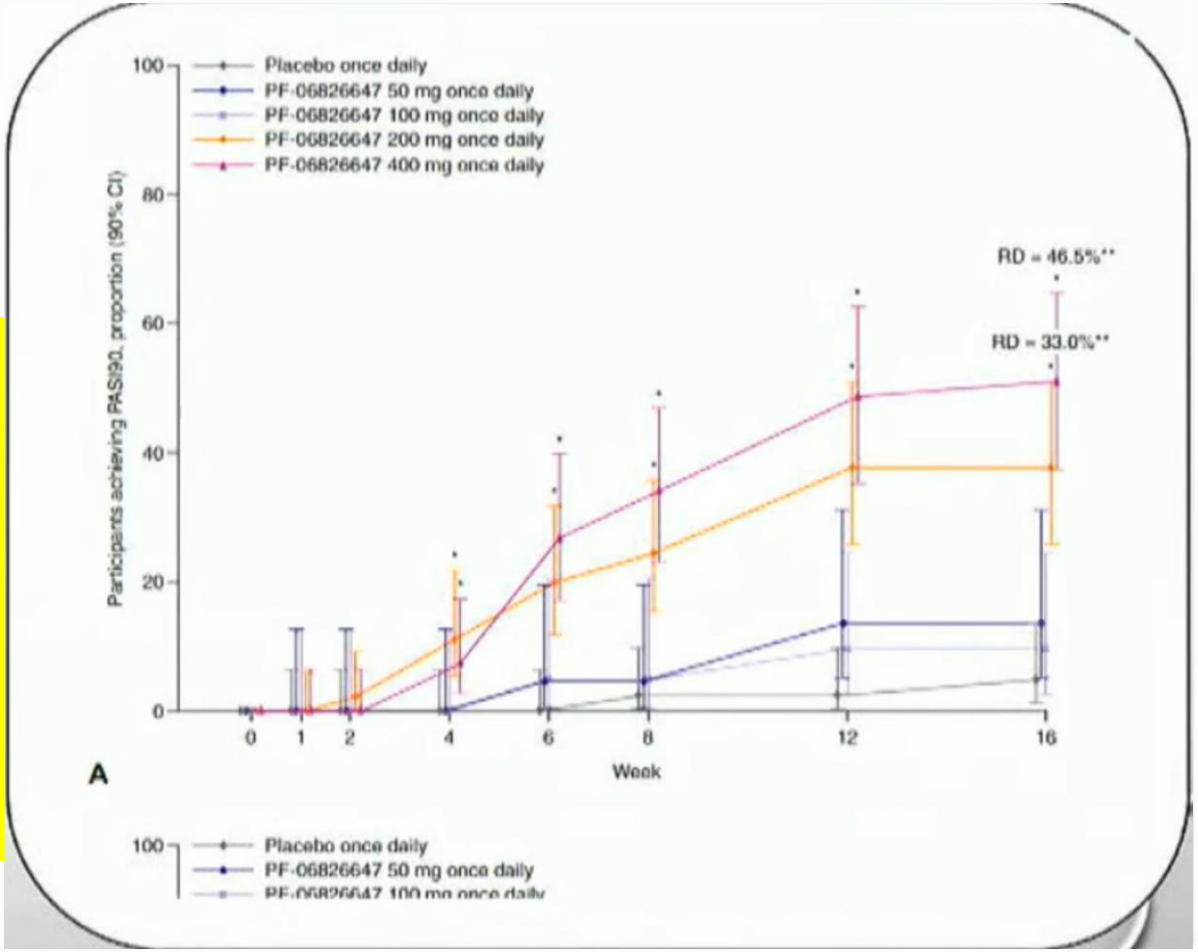
Asset / target pathway[a]	Approved indications[b]	Investigational indications	Phase 1	Phase 2	Phase 3[d]
Deucravacitinib (TYK2)	PsO[c]	Psoriatic arthritis[5]			
		Lupus: SLE[5,7]			
		Lupus: DLE,[5,8] SCLE[9]			
		Ulcerative colitis[5]			
		Crohn's disease[5]			
		Alopecia areata[9]			
		Scalp psoriasis[10]			

ROPSACITINIB/PF-06826647

Oral tyrosine kinase 2 inhibitor PF-06826647 demonstrates efficacy and an acceptable safety profile in participants with moderate-to-severe plaque psoriasis in a phase 2b, randomized, double-blind, placebo-controlled study

SELECTIVE TYK2, JAK1-3 inhibitor

Phase IIb
N=178 patients
Titration 1:1:2:2:2 50:100:200:400: placebo (16 weeks) and them 200 or 400 mg 24 weeks
Well tolerate. Low rates of AE
18 patients stopped due to EA (14 blood test anomalies)



Tehlirian C et al. J Am Acad Dermatol 2022;87:333-42

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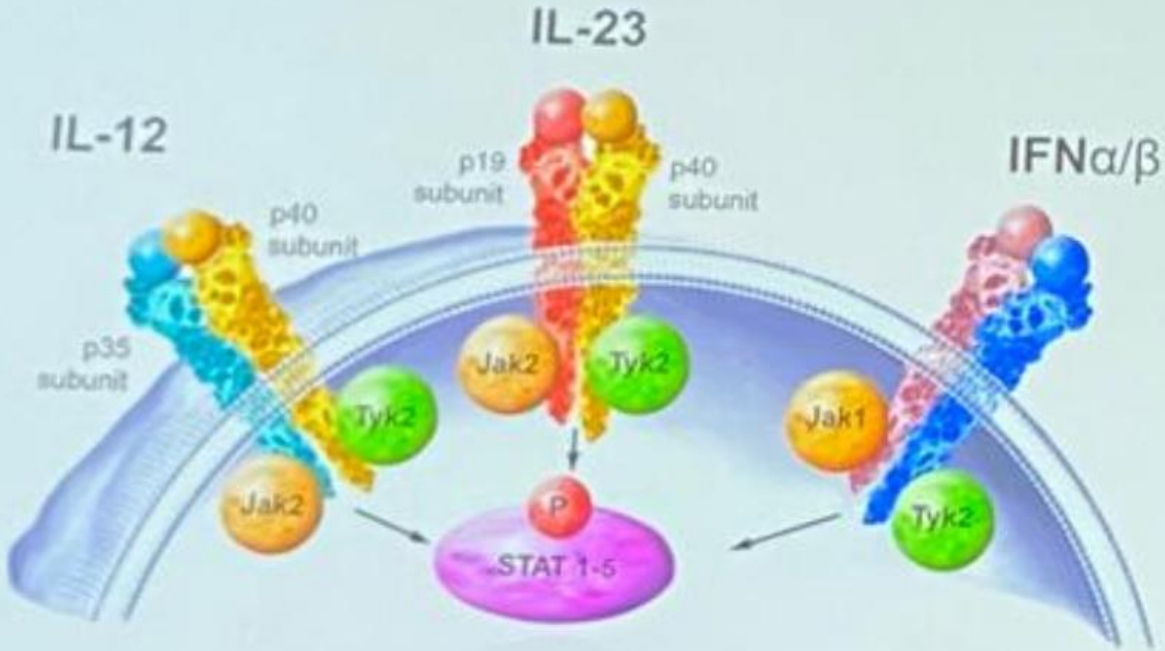
Mechanism of action of NDI-034858 (TAK-279)

TYK2 is a key component of the JAK–STAT signaling pathway. Increased activation of proinflammatory enzymes in this pathway is associated with several autoimmune diseases, including psoriasis



TAK-279 is a highly selective oral allosteric TYK2 inhibitor

TAK-279 is excluded from the allosteric binding pocket of JAK1 owing to a single amino acid difference from TYK2

TYK2–JH2 binding K_d	0.034 nM
JAK1–JH2 binding K_d	5000 nM
Biochemical selectivity (fold)	1 470 588

imbus proprietary structure based computational modeling
AK, Janus kinase; K_d, dissociation constant; IFN, interferon; IL, interleukin; STAT, signal transducer and activator of transcription; TYK, tyrosine kinase

Study design: NCT04999839 (US, Canada)

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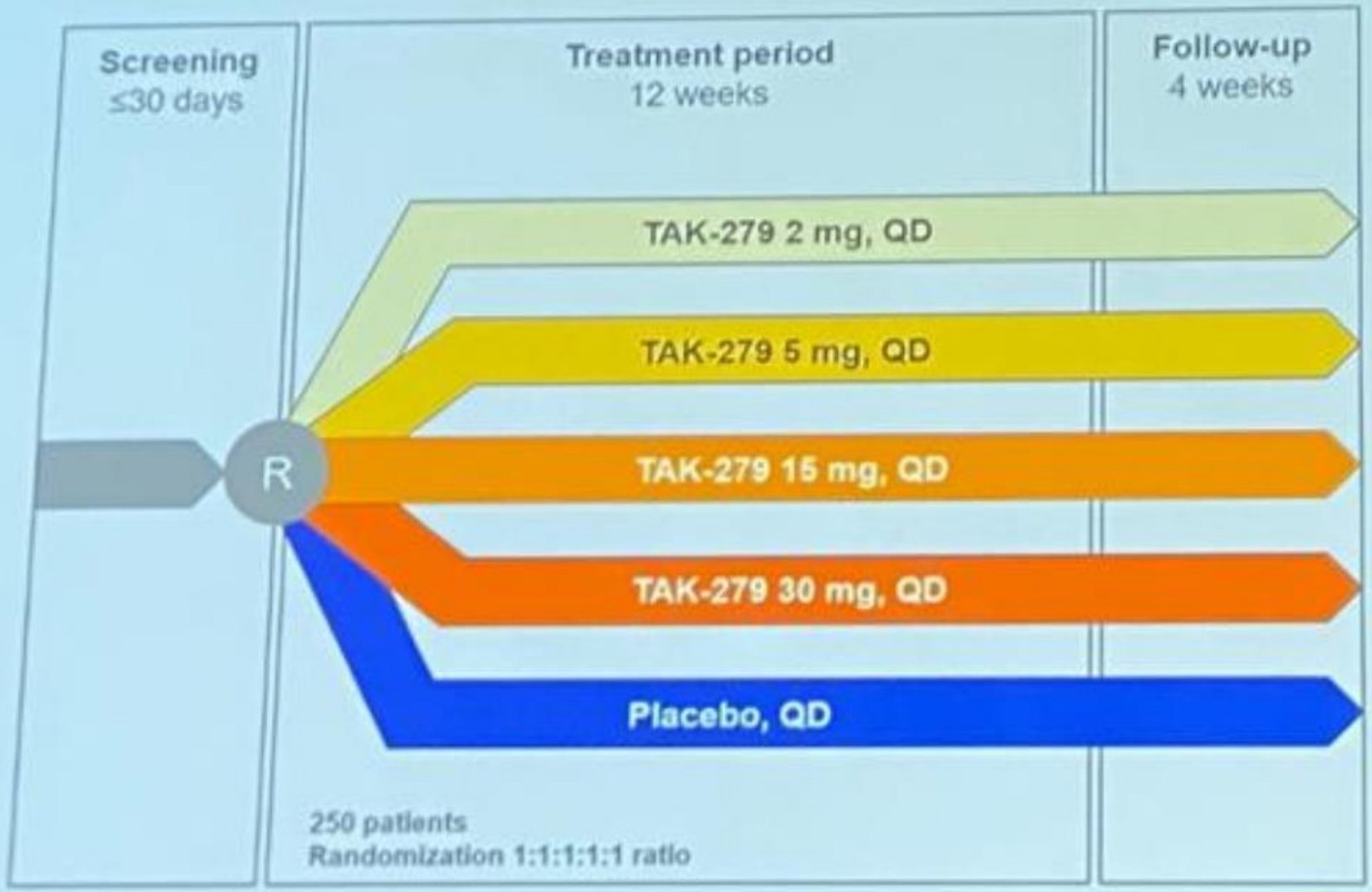

Key eligibility criteria

- Age 18–70 years
- Plaque psoriasis for ≥6 months
  - PASI ≥12
  - PGA ≥3
  - BSA ≥10%
- Candidate for phototherapy or systemic therapy

Primary endpoint:

- PASI 75 at Week 12

Secondary endpoints:

- PGA 0/1 at Week 12
- PASI 90 at Week 12
- PASI 100 at Week 12
- Change from baseline in DLQI at Week 12

BSA, body surface area; DLQI, Dermatology Life Quality Index; PASI, Psoriasis Area and Severity Index; PGA, Physician's Global Assessment; QD, once daily; R, randomization

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Patients achieving PASI 75, 90 or 100 at Week 12

NRI analysis

p values from a Cochran-Mantel-Haenszel 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

Resumen

NIH U.S. National Library of Medicine
ClinicalTrials.gov

Clinical trial	Phase	N	Drugs/dose	Primary enpoint	PASI 75	PGA01	AE
NCT00678210	2	49	Tofacitinib 5 mg BID	12 weeks	40,82%	NDA	Upper respiratoy tract infection
NCT01186744	3	331	Tofacitini 5 mg BID				
		335	Tofacitini 10 mg BI				
NCT01241591	3	329	Tofacitini 5mg BID				
		330	Tofacitinib 10 mg BID	12 weeks	63,64%	68,18%	
NCT01276639	3	363	Tofacitinib 5mg BID	16 weeks	39,94%	41,87%	Nasopha-ryngitis
		360	Tofacitinib 10 mg BID	16 weeks	59,17%	59,17%	Nasopha-ryngitis
NCT01309737	3	376	Tofacitinib 5mg BID	16 weeks	46,01%	46,10%	Nasopha-ryngitis
		374	Tofacitinib 5mg BID	16 weeks	59,63%	59,90%	Nasopha-ryngitis
NCT01710046	2a	8	Tofacitinib	12	62,5%	50%	Nasopha-ryngitis
							ha-ryngitis
							ha-ryngitis
							ha-ryngitis
						3%	Upper respiratoy tract infection
			5mg BID				
		90	Tofacitinib 10 mg BID	16 weeks	81,10%	75,6%	Upper respiratoy tract infection
NCT01736696	1		Tofacitinib 5mg BID	14 days	NDA	NDA	NA
			Tofacitinib 10 mg BID	14 days	NDA	NDA	Headache

En estudios de fase III, aleatorizados, doble ciego y controlados con placebo.

Las tasas de respuesta de respuesta a semana 16-24:

- PASI75: 39,5–54,3 % (5 mg dos veces al día), placebo 5,3 %.
- PASI75: 59,2–81,1 % (10 mg dos veces al día),placebo 5,6–12,5 %.

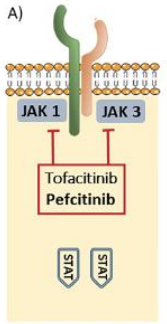
No aprobado en psoriasis, sin ensayos clínicos en curso

Abbreviations: PASI 75:75% reduction Psoriasis Area Severity Index, PGA01: Physician global assessment 01,PGAs change* NDA: No data available. QD: once daily, BID: twice daily

Gómez-García F, et al. *Front Med (Lausanne)*. 2022.

Tofacitinib, Xeljanz® Pfizer

Inhibidor no selectivo de JAK1,3 y 2



- Tofacitinib es el mejor estudiado para el tratamiento de la psoriasis en placas.
- Es un potente inhibidor de JAK1 y JAK3.
  - << JAK2 y Tyk2.
  - Aprobado por la FDA para el tratamiento de:
    - Artritis psoriásica.
    - Artritis reumatoide.
    - Colitis ulcerosa.
    - Espondilitis anquilosante.
    - Artritis idiopática juvenil poliarticular.

Artritis reumatoide

Tofacitinib 10 mg/12h tuvieron una mayor incidencia de oportunistas infecciones (incluida tuberculosis) en comparación con 5 mg /12h

❖ FDA solo aprobó con la dosis de **5 mg/12h.**

Calautti E, et al. *Int J Mol Sci.* 2018.
Gómez-García F, et al. *Front Med (Lausanne)*. 2022.

Otros inhibidores JAK testados

- Peficitinib (ASP015K) Astellas. Datos de Fase II 2020. No EC abiertos
- Barocinib (Olumiant) Eli Lilly. Datos Fase IIb 2017. No EC abiertos
- Abrocitinib (Cibinqo) Pfizer. Fase II a 4 semanas 2014. No EC abiertos
- Solcitinib GlaxoSmithKline. Fase 2 b a 12 semanas. Trombocitopenia grave 3/15 pacientes.
- Itacintinib Corporación Incyte. No selectivo JAK2. 2010. Interrumpido.

DOI: 10.1111/jdv.18263 JEADV

SYSTEMATIC REVIEW

The efficacy and safety of tofacitinib, peficitinib, solcitinib, baricitinib, abrocitinib and deucravacitinib in plaque psoriasis – A network meta-analysis

L. Zhang,[1,2] L. Guo,[1,2] L. Wang,[1,2] X. Jiang[1,2,*]

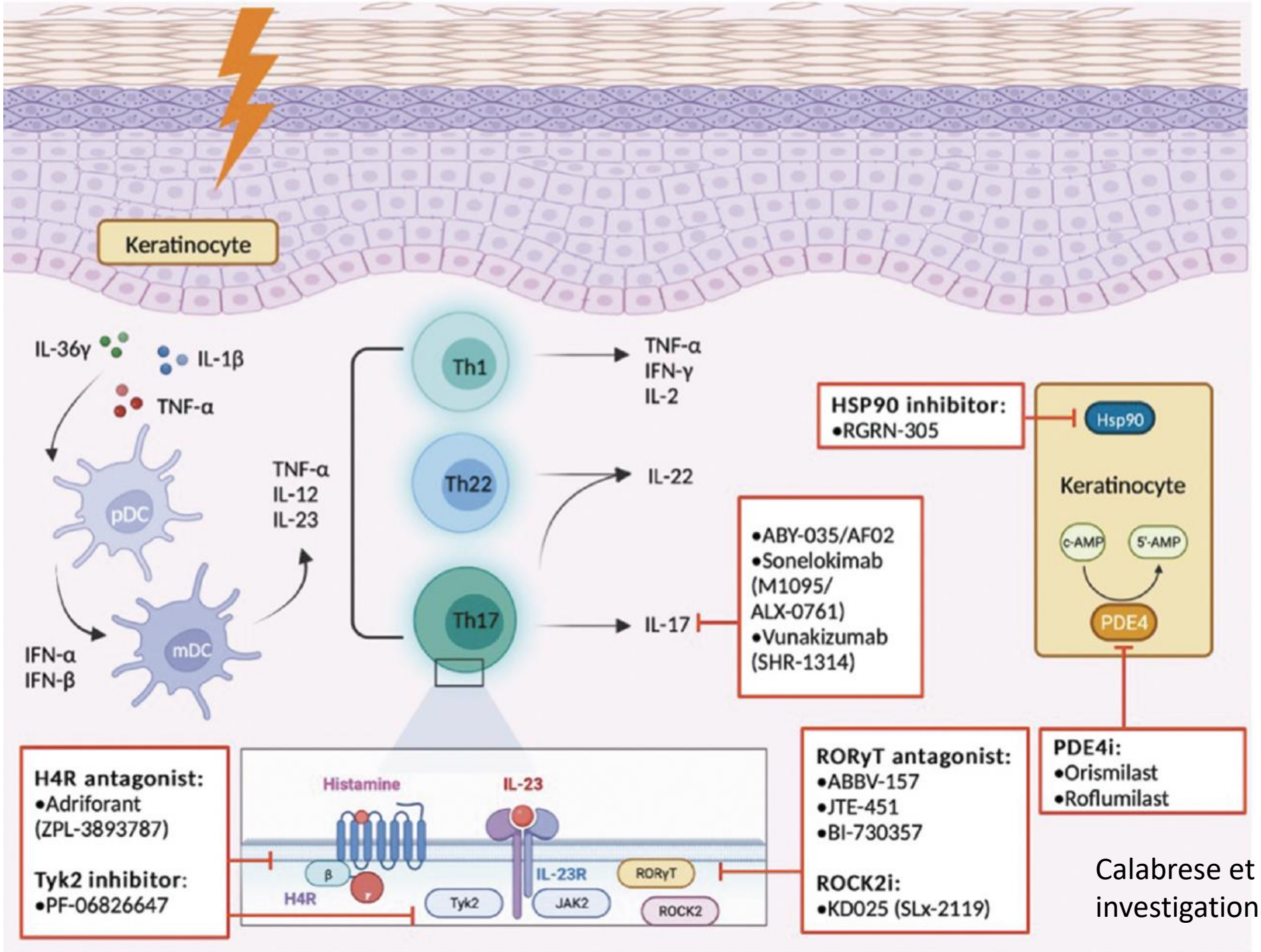
Eficacia: tofacitinib 15 mg/12h → tofacitinib 10 mg/12h→ deucravacitinib 12 mg/6h.

Perfil de seguridad: tofacitinib 2 mg/12h →deucravacitinib 3 mg/6h →tofacitinib 5 mg/12.

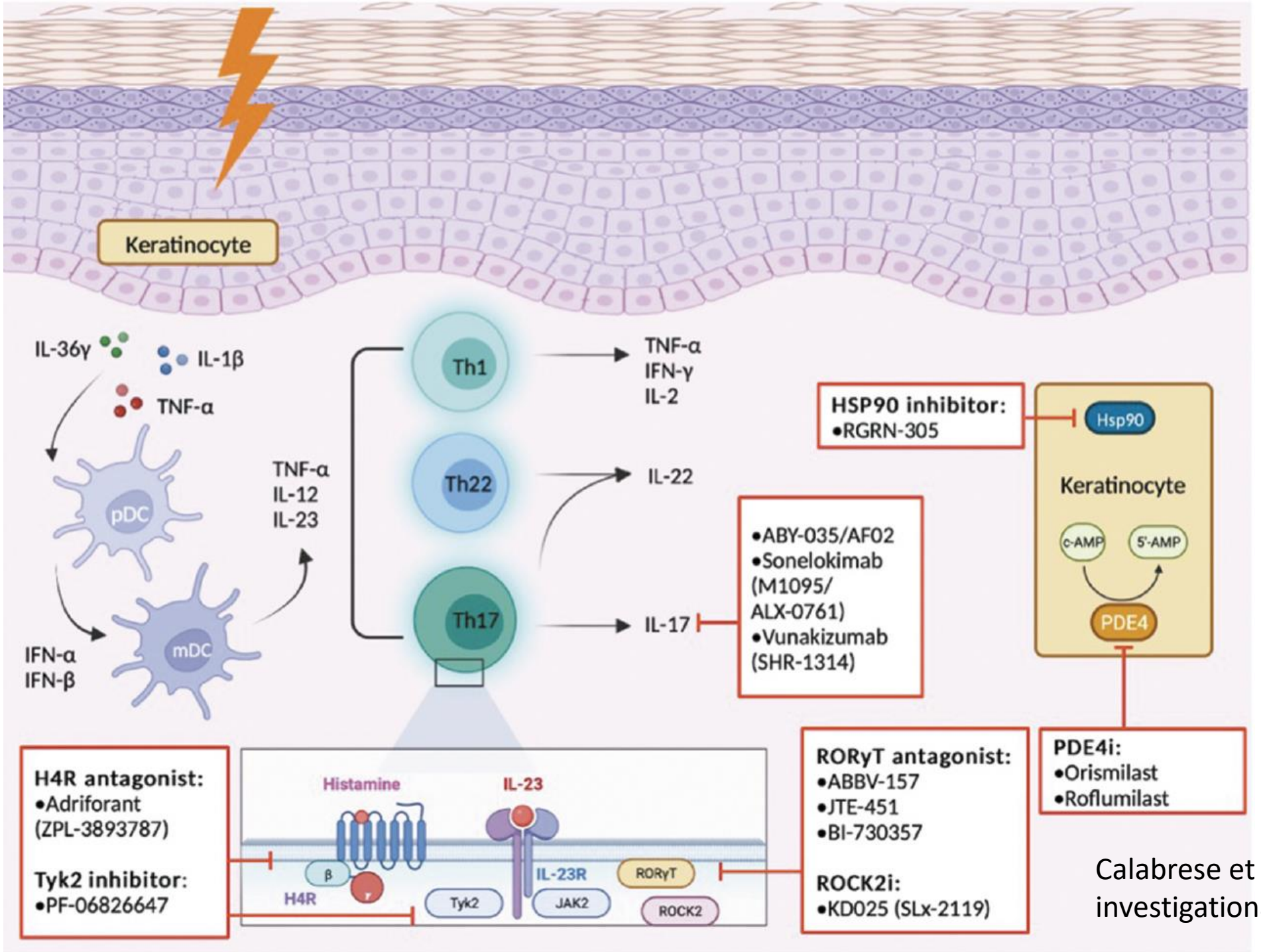
❖La FDA se negó a aprobar tofacitinib con 10 mg/12h para el tratamiento de la psoriasis en placas debido a cierta preocupación de seguridad.

Deucravacitinib con 12 mg/6h se convirtió en el PRIMER clasificado para respuesta PASI-75 y PGA.

Zhang L, et al. J *Eur Acad Dermatol Venereol.* 2022.

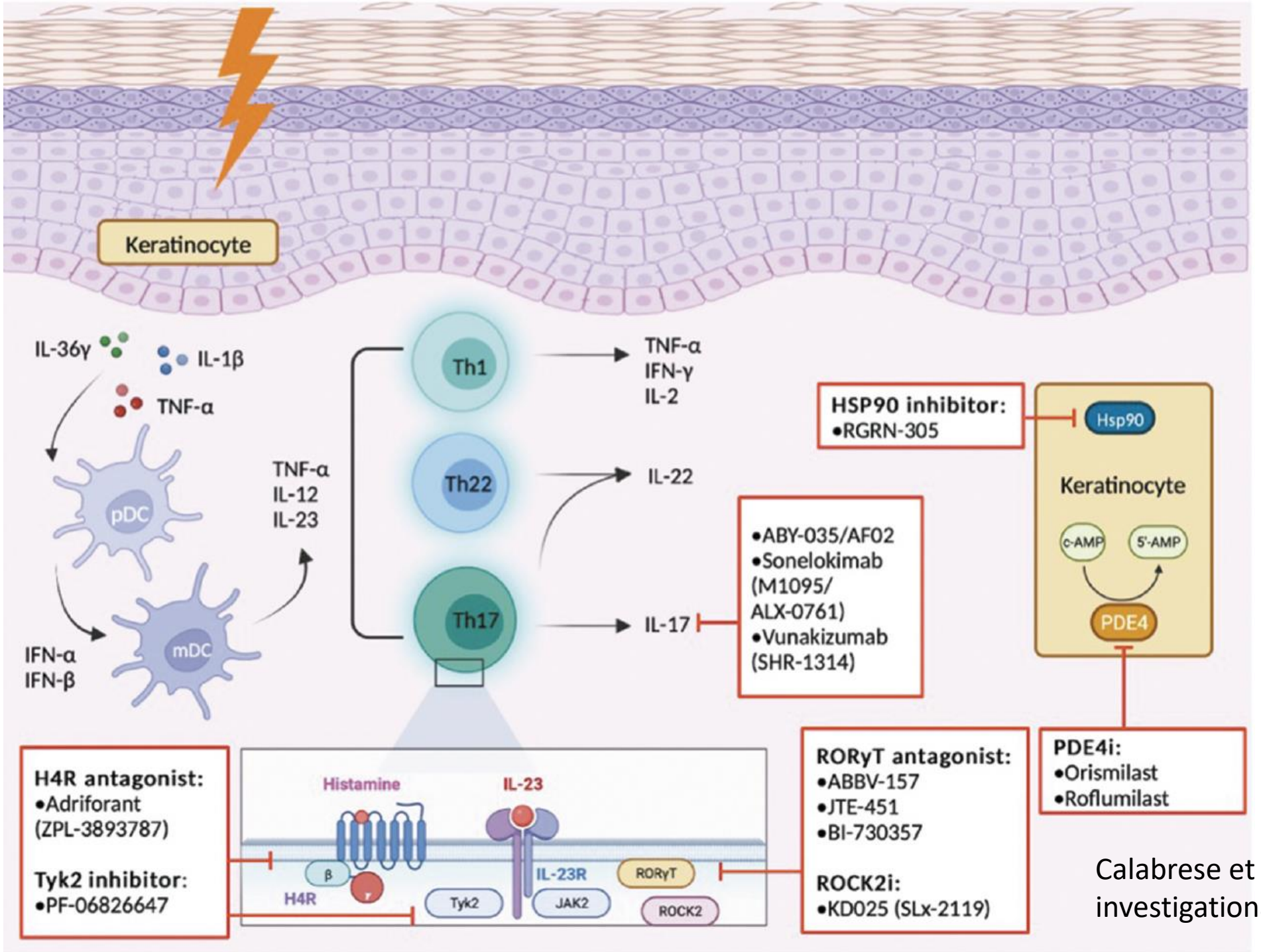


Calabrese et al. Expert opinión on investigational drugs. E pub 22/Feb/2023



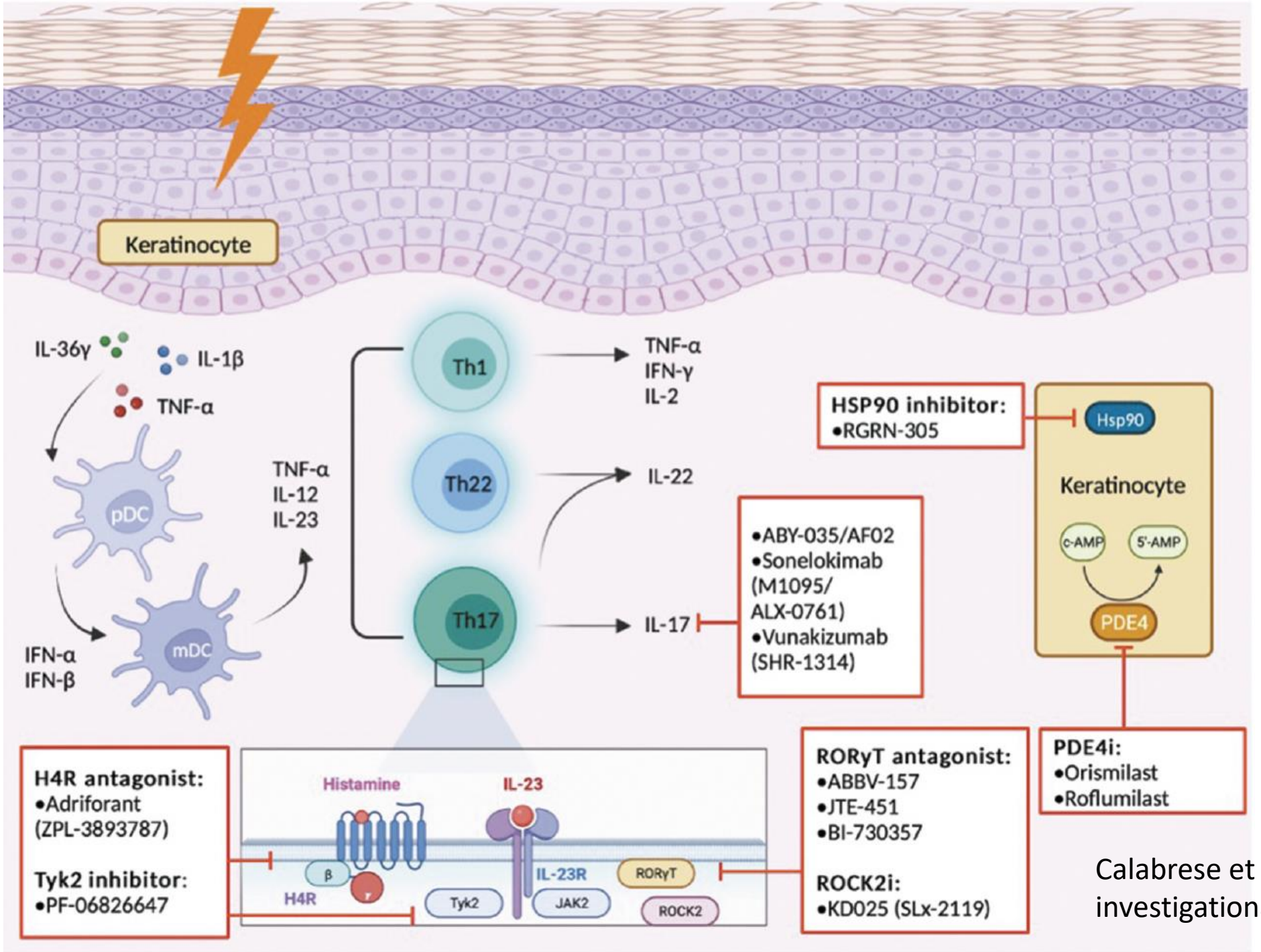
Anti RORyt
Problemas de seguridad, elevación de transaminasas, linfomas tímicos. En busca de alternativas

Calabrese et al. Expert opinión on investigational drugs. E pub 22/Feb/2023



Anti H4H
En superficie Th17
No diferencias con placebo, no parece diana igual que el bloqueo de GM-CSF

Calabrese et al. Expert opinión on investigational drugs. E pub 22/Feb/2023

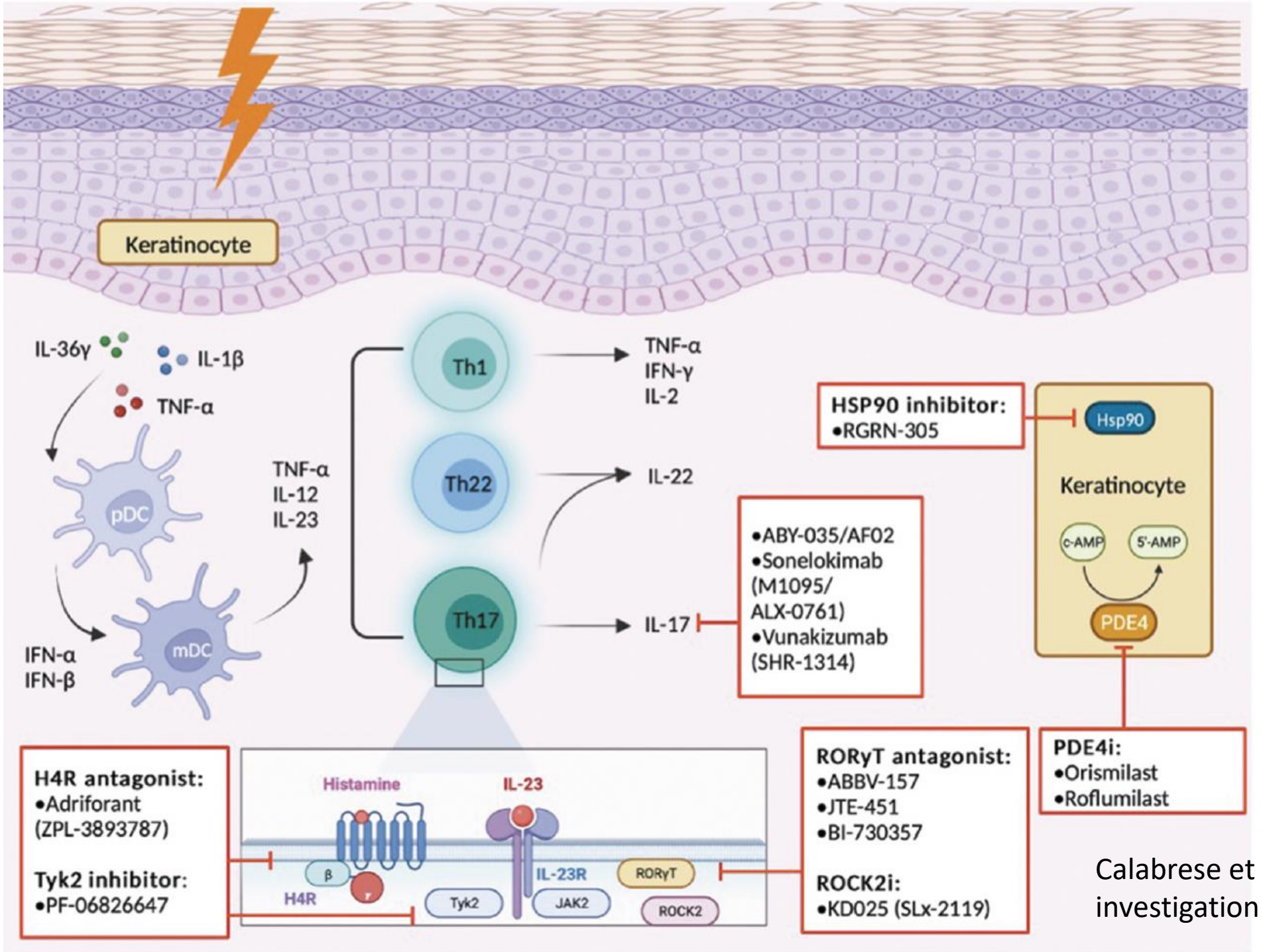


ROCK2 regula secreción de IL17 via STAT3/IRF4/RORγT

Belumosudil, KD025, a 200 o 400 mg/12 h 12 w mejoraba PASI en el 85% y un 45% PASI50.

Hay que validarlo

Calabrese et al. Expert opinión on investigational drugs. E pub 22/Feb/2023



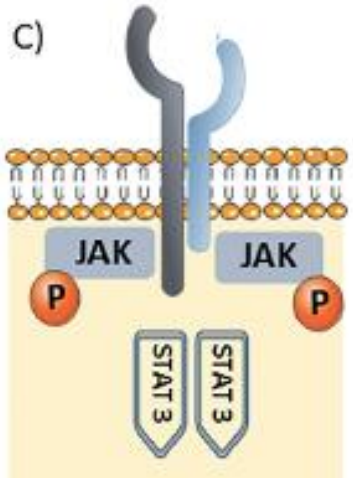
HSP90 chaperona molecular dependiente de ATP y regulador de señalización IL17A

Datos Fase I proof of concept, parece reducir TNF, IL17, IL36 e IL8

Hay que validarlo

Calabrese et al. Expert opinión on investigational drugs. E pub 22/Feb/2023

Inhibidores de la fosforilación de STAT3



- BTH (benzo[b]tiofen-2-il-3-bromo-5-hidroxi-5- furan-2-ona).
  - Se ha sugerido como un nuevo inhibidor de JAK/STAT.
  - Es un análogo sintético de un compuesto natural derivado de una esponja marina.
  - BTH inhibe la fosforilación de STAT3, evitando su translocación en el núcleo y reduciendo la proliferación de queratinocitos.
- STA-21 (Ocromicinona).
  - Se ha sugerido como un nuevo inhibidor de JAK/STAT.
  - Ensayo de fase I/II (NCT01047943).

NIH U.S. National Library of Medicine
ClinicalTrials.gov

Andrés R, et al. *Exp Dermatol. 2013*
Miyoshi K, et al. *J Investig Dermatol Nat Publ. 2011*
Shobeiri S, et al. *Int Immunopharmacol*. 2021

Piclidenoson

Can-Fite BioPharma.

Agonista oral del receptor de adenosina A3 asociado a la proteína Gi (A3AR)

NIH U.S. National Library of Medicine
ClinicalTrials.gov

- Resultados de un **EC fase II**, controlado con placebo, multicéntrico, doble ciego, dosis 1, 2 o 4 mg de piclidenoson/12h, n 75.
  - **2 mg** logró una mejoría frente al placebo en el cambio de PASI en las semanas 8 y 12.
  - PASI50 35,3% de los 17 pacientes tratados con dosis de 2 mg.
  - La incidencia de EVENTOS ADVERSOS en el brazo de 4, 2 y 1 mg fue del 58,3 %, 17,6 % y 13,3 %.

- El fármaco se encuentra en fase III controlado con placebo y comparador activo (apremilast).

Cohen S, et al. *J Immunol Res*. 2018.
Cohen S, et al. *Drug Des Devel Ther*. 2019

Sobre las moléculas pequeñas…

¿Eficacia clínica?

- Las moléculas pequeñas en ensayos Objetivo principal: eficacia medida sobre PASI 75.

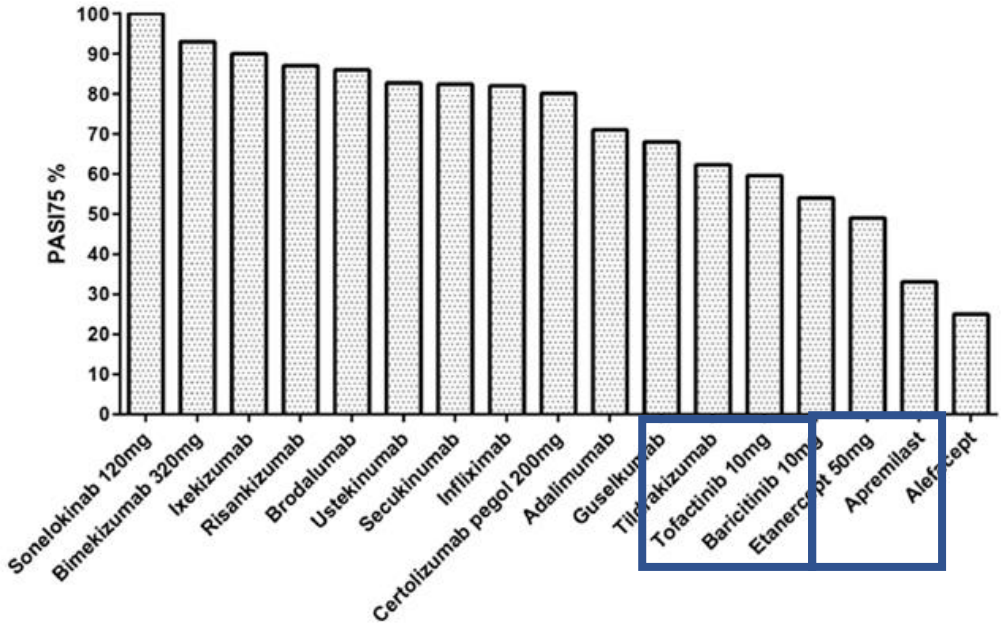


Fig. 6. Comparison of Psoriasis Treatments Based on Primary Endpoint Effectiveness (PASI 75 percentage).

La eficacia a corto plazo de varios medicamentos utilizados en la psoriasis

Shobeiri S, et al. *Int Immunopharmacol*. 2021

¿Qué lugar ocuparán dentro de los esquemas terapéuticos?

Resto de moléculas pequeñas

- Estructura simple, costo-efectividad

- Alternativa terapéutica
  - Pacientes sin respuesta completa a los tratamientos biológicos
  - **¿Tratamientos combinados?**
  - Preferencias de los pacientes (vía oral)


ZORYVE™
(roflumilast) cream 0.3%
For Topical Use Only
Rx Only
Net Wt. 60 g
ZORYVE™
(roflumilast) cream 0.3%
NDC 80610-130-60
Net Wt. 60 g
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For Topical Use Only
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Wynzora®
50 micrograms/g + 0.5 mg/g cream
calcipotriol/betamethasone
60 g cream
Cutaneous use
almirall
Declobán 500 microgramos/g
Propionato de clobetasol
USO CUTÁNEO
Pomada 30 g
Enstilar®
50 microgramos/g
+ 0,5 mg/g
espuma cutánea
Uso cutáneo
Adventan® 1 mg/g
emulsión cutánea
Metilprednisolona aceponato
Emulsión cutánea
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Uso cutáneo
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(ruxolitinib) cream 1.5%
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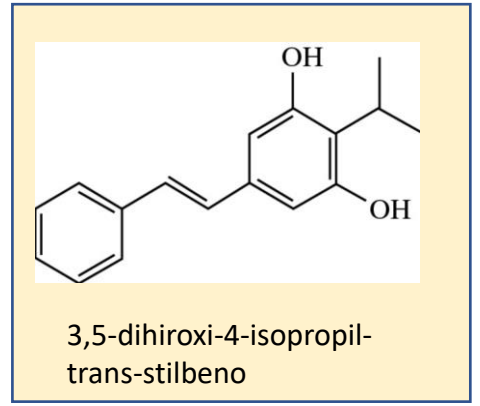
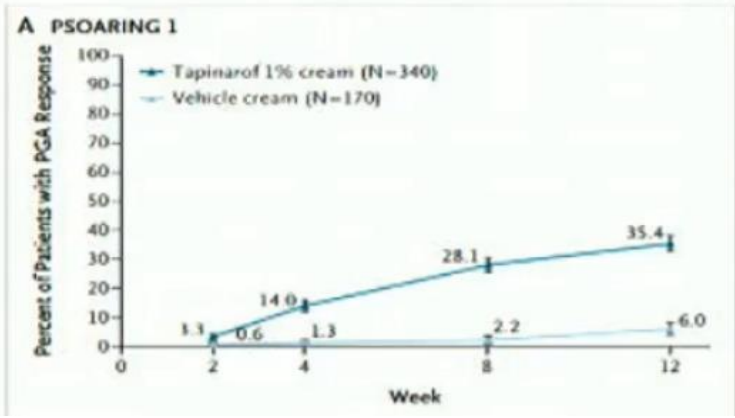
(ruxolitinib) cream 1.5%
For Topical Use Only.
60 g

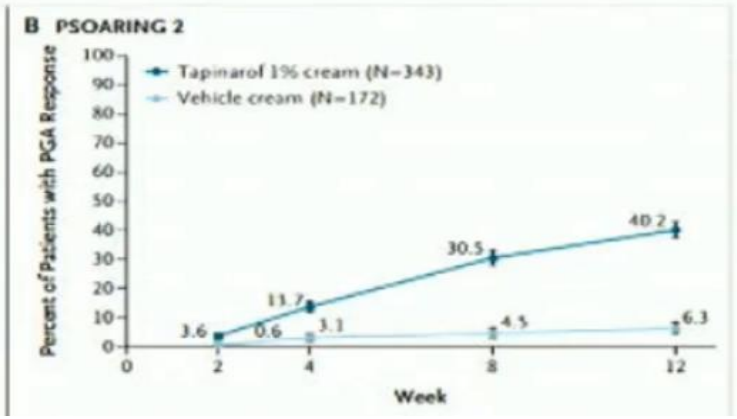
TAPINAROF : FDA MAYO 2022 VTAMA®

- Fase III PSOARING 1 con 692 pacientes y 2 con 674 pacientes
- ENDPOINT PGA 0/1 o mejora de 2 puntos en IGA.
- Tapiranof crema 1% una vez al día 12 semanas
- Mismo principio activo que Benvitimod crema 1% aprobada en china en 2019

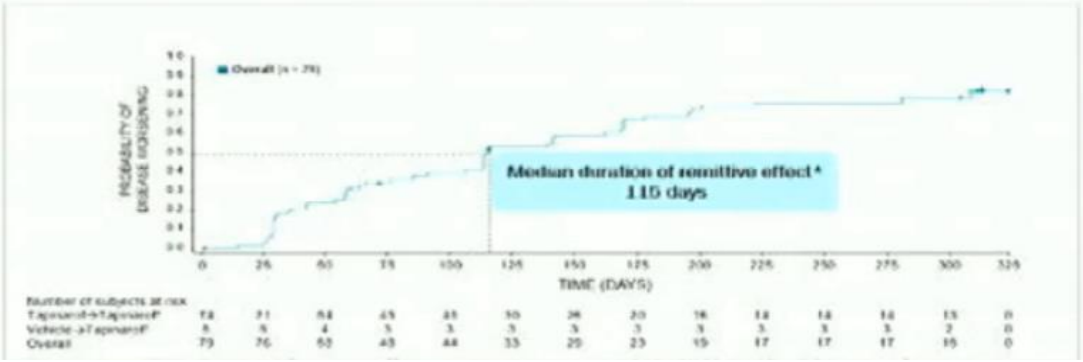


3,5-dihiroxi-4-isopropil-trans-stilbeno





Agente modulador del receptor de aril hidrocarburo



Lebwhol MG et al. N Engl J Med 2021; 385:2219-29; Strober B. J Am Acad Dermatol 2022; 87:800-6.

ROFLUMILAST. FDA JULIO 2022 ZORYVE®

JAMA. 2022 Sep 20; 328(11): 1073–1084.
Published online 2022 Sep 20. doi: 10.1001/jama.2022.15632: 10.1001/jama.2022.15632

PMCID: PMC9490499
PMID: 36125472

Effect of Roflumilast Cream vs Vehicle Cream on Chronic Plaque Psoriasis

The DERMIS-1 and DERMIS-2 Randomized Clinical Trials

Mark G. Lebwohl, MD,[1] Leon H. Kircik, MD, [1,2,3,4] Angela Y. Moore, MD, [5,6] Linda Stein Gold, MD, [7] Zoe D. Draelos, MD, [8] Melinda J. Gooderham, MD, [9,10,11] Kim A. Papp, MD, PhD, [12,13] Jerry Bagel, MD, [14] Neal Bhatia, MD, [15] James Q. Del Rosso, DO, [16,17] Laura K. Ferris, MD, [18] Lawrence J. Green, MD, [19] Adelaide A. Hebert, MD, [20] Terry Jones, MD, [21] Steven E. Kempers, MD, [22] David M. Pariser, MD, [23,24] Paul S. Yamauchi, MD, PhD, [25,26] Matthew Zirwas, MD, [27,28,29] Lorne Albrecht, MD, [30,31] Alim R. Devani, MD, [32,33] Mark Lomaga, MD, PhD, [34,35] Amy Feng, PhD, [36] Scott Snyder, PharmD, [36] Patrick Burnett, MD, PhD, [36] Robert C. Higham, MPAS, [36] and David R. Berk, MD [36]

- Fase III DERMIS 1 con 439 y DERMIS 2 cor 443 pacientes
- Roflumilast 0,3% diario 8 semanas.
- Mejora IGA >2 puntos.

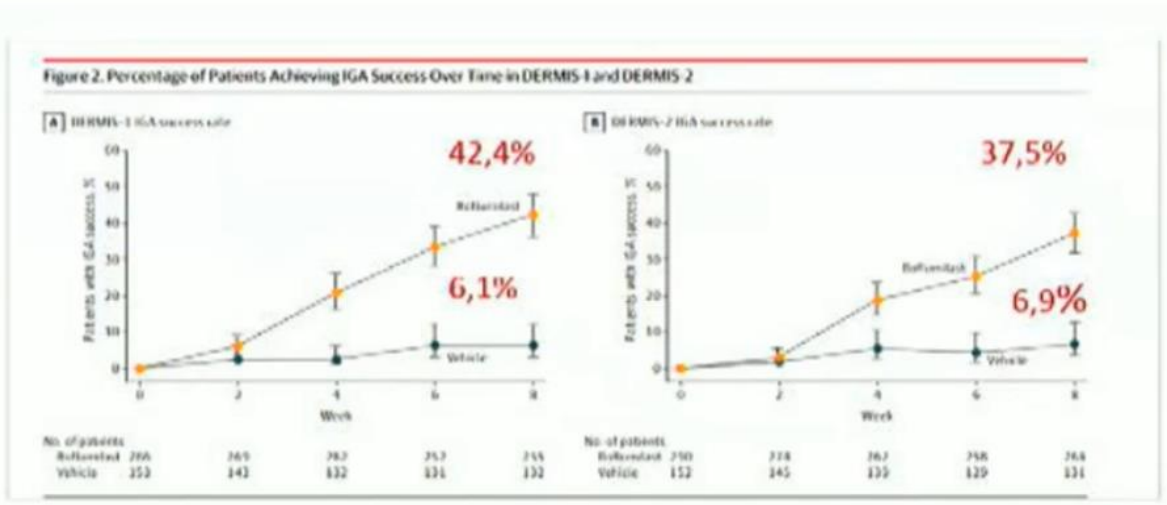


Table 3. Adverse Events

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