SCUOLA DERMATOLOGICA
SERGIO CHIMENTI

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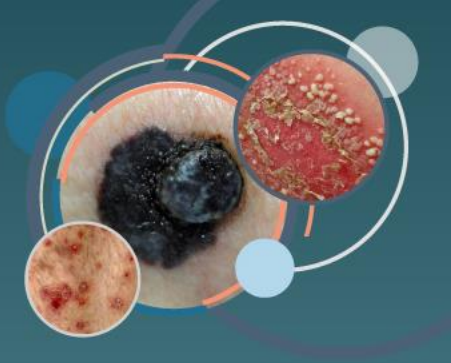
1° INCONTRO 2024
YES or NO CONTEST
Dermatology Update



YES OR NOT sul ruolo delle *Small Molecules* nella terapia della psoriasi

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SYSTEMATIC REVIEW

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

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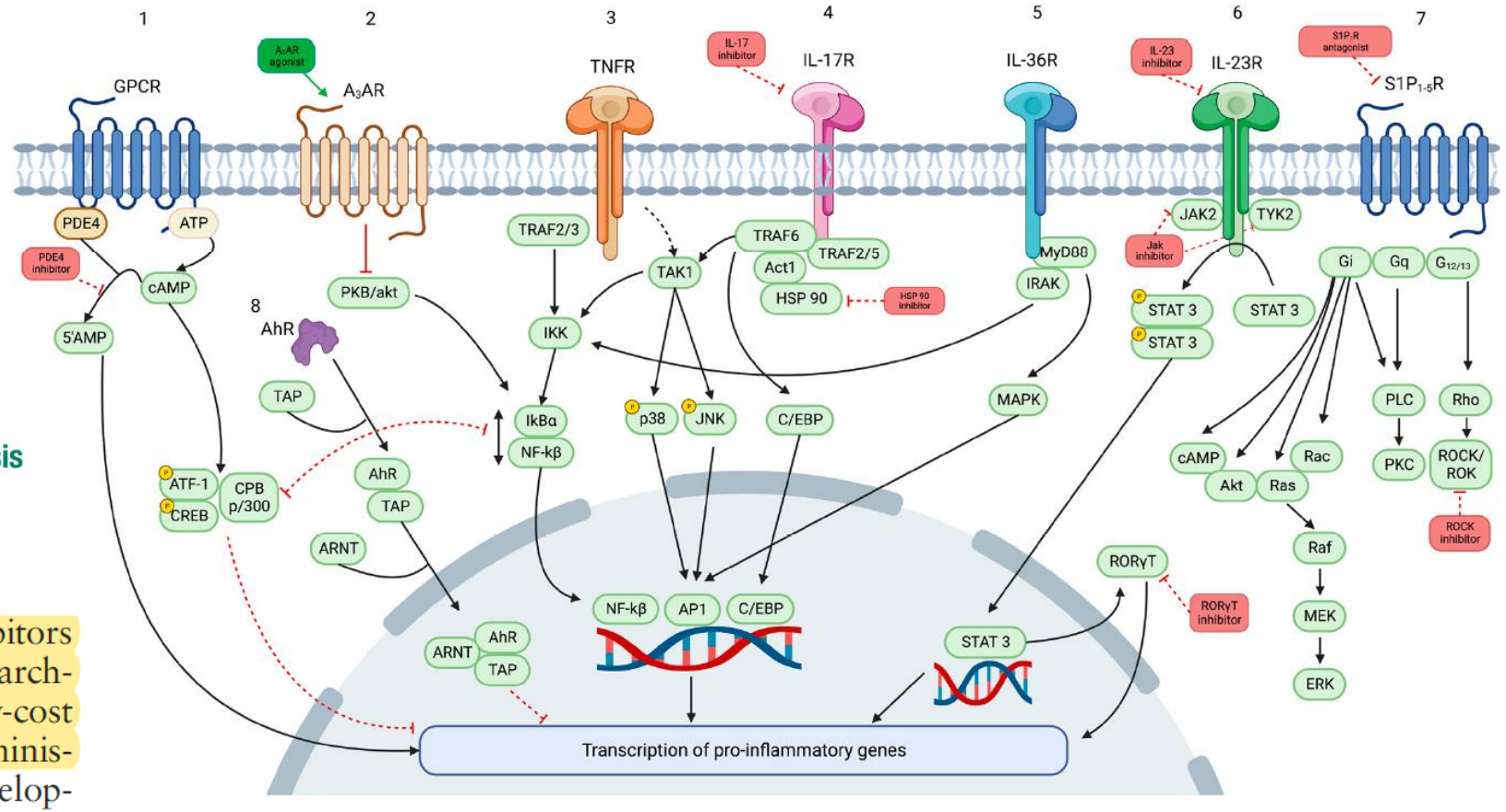
Nella terapia della psoriasi cronica a placche di grado moderato si aggingono nuove molecole con meccanismi d'azione pleiotropici: **le small molecules**

Le small molecules sono farmaci di peso molecolare **inferiore a 1 KDa** ed in grado, pertanto, di essere assorbite per via enterale



Advances in small molecule inhibitors for treatment of psoriasis

Wen-Juan Chen[1,2], Chen Peng[1,2], Jia-Jing Lu[1,2], Yang-Feng Ding[1,2], Xing-Zi Li[1,2]

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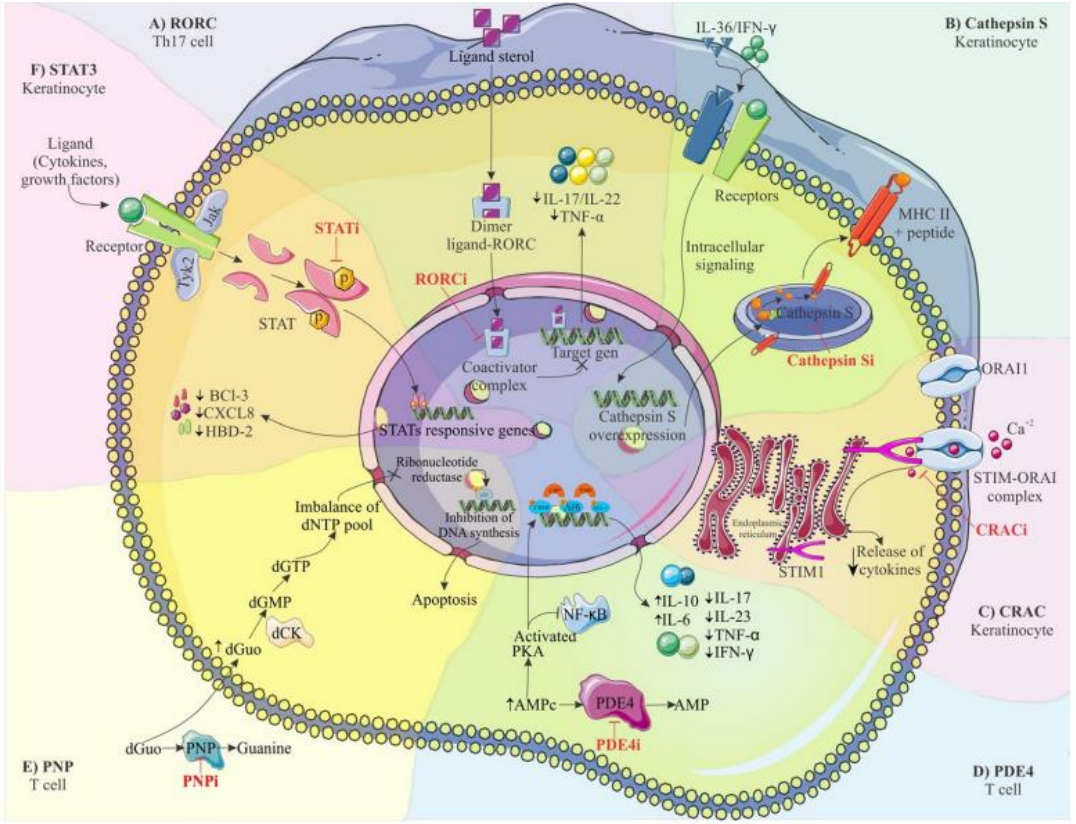
applications are still limited. Thus, small molecule inhibitors (SMIs) have gained considerable attention among researchers, owing to the simplified synthesis processes, low-cost production, and the possibility of oral or topical administration. This article summarizes SMIs in clinical development and those approved for the treatment of psoriasis.

Novel targets for psoriasis treatment

Novel targets for psoriasis treatment

- Retinoic acid receptor-related orphan receptor C (RORC)
- Cathepsin S
- Calcium-release activated calcium channel (CRAC)
- Purine nucleoside phosphorylase (PNP)
- **Phosphodiesterase-4**
- **Signal transducer and activator of transcription (TyK/JAK)**



Oral bioavailable small molecule drugs (SMDs)

- Oral bioavailable small molecule drugs (SMDs) have advantages respect to biologically active large molecules (LMs) that can specifically modulate key nodes of extracellular targets, such as cytokines and their receptors :
- **Intracellular targeting, easy of use in combination therapies**
- Simultaneously **block multiple cytokines** downstream of their receptors,
- The cost of production and easy of delivery but also regarding the potential of reduced infection-related side effects
- **The lack of anti-drug antibodies formation against these new drugs**, as eventually occurs in some cases against anti-TNF drugs
- Unlike biologics, which chronically block IL-17 production, **SMDs are more likely to transiently blunt IL-17 production, which may break the cycle of inflammation** without suppressing the protective effects of IL-17 against infection.
- However, off-target toxicity can be an issue with some SMDs.

Jak inhibitors	Tofacitinib	Jak1/Jak3 inhibitor	Week 12: 66.7% Week 52: 79.4%	Mild cytopenia, headache, upper respiratory tract infections, urinary tract infections, and diarrhea	FDA refused its approval for psoriasis treatment in October 2015
	Peficitinib	Jak3 > Jak1 > Jak2 inhibitor	Week 6: 58.8%	Nasopharyngitis, diarrhea, acne, back pain, and contact dermatitis	No ongoing clinical trial
	Solcitinib	Jak1 > Jak2 inhibitor	Week 12: 57%	Headache, nasopharyngitis, nausea, diarrhea, fatigue, and upper abdominal pain	No ongoing clinical trial
	Abrocitinib	Jak1 inhibitor	Week 4: 60%	Nausea, headache, neutropenia, and thrombocytopenia	No ongoing clinical trial
	Baricitinib	Jak1/Jak2 inhibitor	Week 12: 54.1%	Nasopharyngitis	No ongoing clinical trial
	Itacitinib adipate	Jak1 inhibitor	Week 4: 27.7%	Nasopharyngitis, increased AST, headache, and hypertriglyceridemia	No ongoing clinical trial
	Brepocitinib	Tyk2/Jak1 inhibitor	Week 12: 86.2%	Nasopharyngitis, upper respiratory tract infection, and headache	Discontinued
	Ropsacitinib	Tyk2/Jak2 inhibitor	Week 16: 73.2%	Nasopharyngitis, upper respiratory tract infections, and increased blood pressure	No ongoing clinical trial
	Deucravacitinib	Tyk2 inhibitor	Week 12: 75% Week 52: 53%	Nasopharyngitis	Approved
	BMS-986202	Tyk2 inhibitor			Results from phase I trial have not been posted yet
	SAR-20347	Tyk2/Jak1 inhibitor			No trials yet
	TAK-279 (zasocitinib)	Tyk2 inhibitor	Week 12: 68%	Mild or moderate: cytopenias, diarrhea, respiratory tract infections, increased alanine transaminase or creatine kinase serum levels, acne	Two phase III trials are ongoing
	VTX958	Tyk2 inhibitor	No results yet	No serious adverse events	Discontinued
PDE4 inhibitors	Orismilast	PDE4B/PDE4D inhibitor	Week 16: 44.4%	Nausea and diarrhea	Results from phase IIb show inconsistencies, as reported by the FDA
	Mufemilast	PDE4 inhibitor	No results yet		Phase II and phase III trials ongoing
	ME3183	PDE4 inhibitor	Week 16: 61.5%	Nausea, diarrhea, and headache	Phase IIa ongoing
TNF inhibitors	SAR441566	TNF inhibitor	No results yet	No results yet	Results from phase I trial have not been posted yet
IL-17 inhibitors	LY3509754	IL-17 inhibitor	Not reported	Liver toxicity	Trial terminated due to safety concerns related to hepatic function
	DC-806	IL-17 inhibitor	Week 4: 43.7%	Mild or moderate (not specified)	Phase II ongoing
	LEO 153339	IL-17 inhibitor	No results yet	No results yet	Results from phase I trial have not been posted yet
Oral IL-23 inhibitors	JNJ-77242113	Receptor antagonist	Week 16: significant higher PASI75 response compared with placebo	Not reported	Phase I and phase II trials are currently ongoing
RORγT inhibitors	VTP-43472	Inhibition of RORγT	Week 4: 30%	Hepatic toxicity	Discontinued; replaced by VTP-43742
	JTE-451	Inhibition of RORγT	Week 16: 22%	Not reported	No ongoing clinical trial
	AUR1γ01	Inhibition of RORγT	Week 12: 63.3% (phase II); no differences compared with placebo (phase IIb)	Not reported	Development interrupted
	BI 730357	Inhibition of RORγT	Week 12: 30%	Upper respiratory tract infections	No ongoing clinical trial
S1P$_1$R antagonist	Ponesimod	Modulator of S1P1R	Week 16: 48.1% Week 28: 77.4%	Dyspnea, liver enzyme abnormalities, and dizziness	No ongoing clinical trial

Non approvato per PSO
Approvato in PsA

Approvato per PSO

Apremilast è stata la prima small molecule ad essere approvata per il trattamento della psoriasi

Oral small-molecule tyrosine kinase 2 and phosphodiesterase 4 inhibitors in plaque psoriasis: a network meta-analysis

Yuanyuan Xu[1,2], Zhixuan Li[1,2], Shuwei Wu[1,2], Linghong Guo[1,2]* and Xian Jiang[1,2]*

[1]Department of Dermatology, West China Hospital, Sichuan University, Chengdu, China, [2]Laboratory of Dermatology, Clinical Institute of Inflammation and Immunology, Frontiers Science Center for Disease-related Molecular Network, West China Hospital, Sichuan University, Chengdu, China

TYPE Systematic Review
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DOI 10.3389/fimmu.2023.1180170

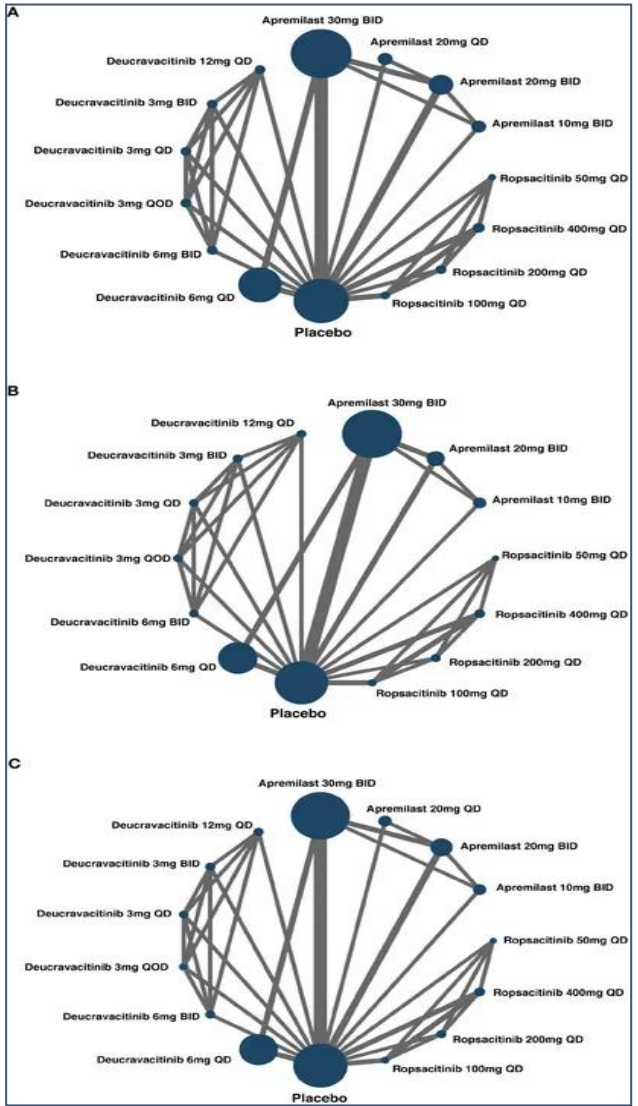
NETWORK OF INCLUDED STUDIES WITH THE AVAILABLE DIRECT COMPARISONS. The size of the nodes is proportional to the number of patients to receive the treatment.

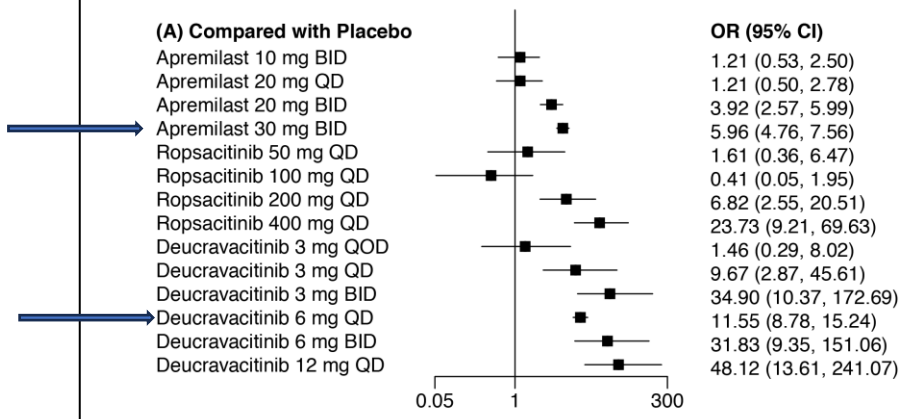
The width of the lines is proportional to the number of trials comparing the connected treatments.

(A) For PASI-75 response direct comparisons;

(B) (B) for PGA 0/1 response direct comparisons;

(C) (C) for AEs direct comparisons.





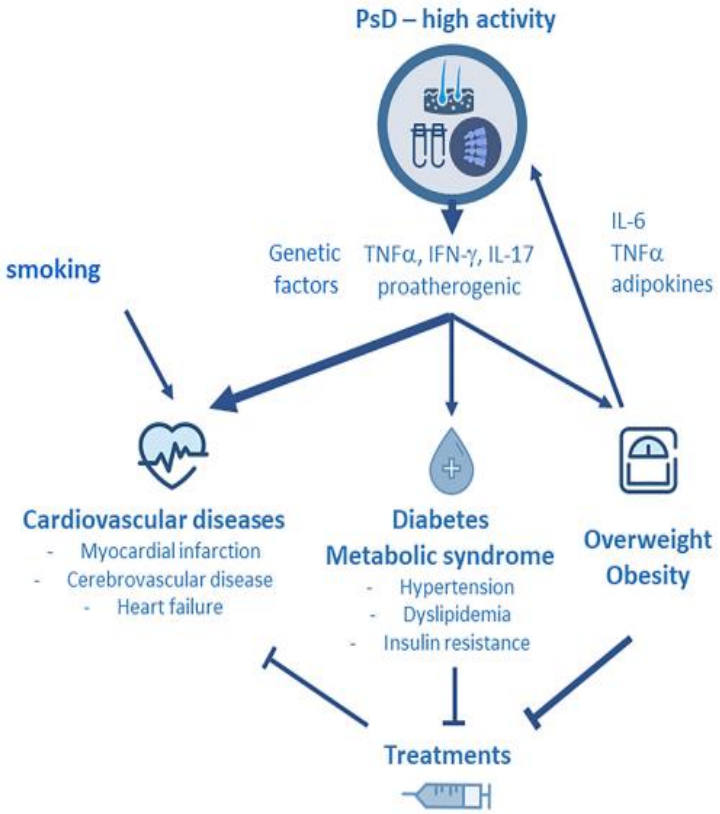
The result of the NMA revealed that, in comparison to placebo, the low-dose groups of oral TYK2 and PDE4 inhibitors did not exhibit superior efficacy. However, when administered at sufficient dosages, the oral TYK2 and PDE4 inhibitors displayed significantly greater PASI-75 response rates than placebo. Notably, apremilast 20 or 30 mg BID, ropsacitinib 200 or 400 mg QD, and deucravacitinib at all dosages except for 3 mg QOD exhibited significantly greater efficacy than placebo. Moreover, **when compared to apremilast 30 mg BID, the NMA demonstrated that oral TYK2 inhibitors**, specifically deucravacitinib 3 mg BID, deucravacitinib 6 mg QD, deucravacitinib 6 mg BID, deucravacitinib 12 mg QD, and ropsacitinib 400 mg QD, **displayed significantly higher efficacy, as shown in the forest plot** (Figure S2).

1. Le Small Molecules agiscono legandosi alle interleuchine neutralizzandone l’effetto?

1. **Sì**
2. **No**

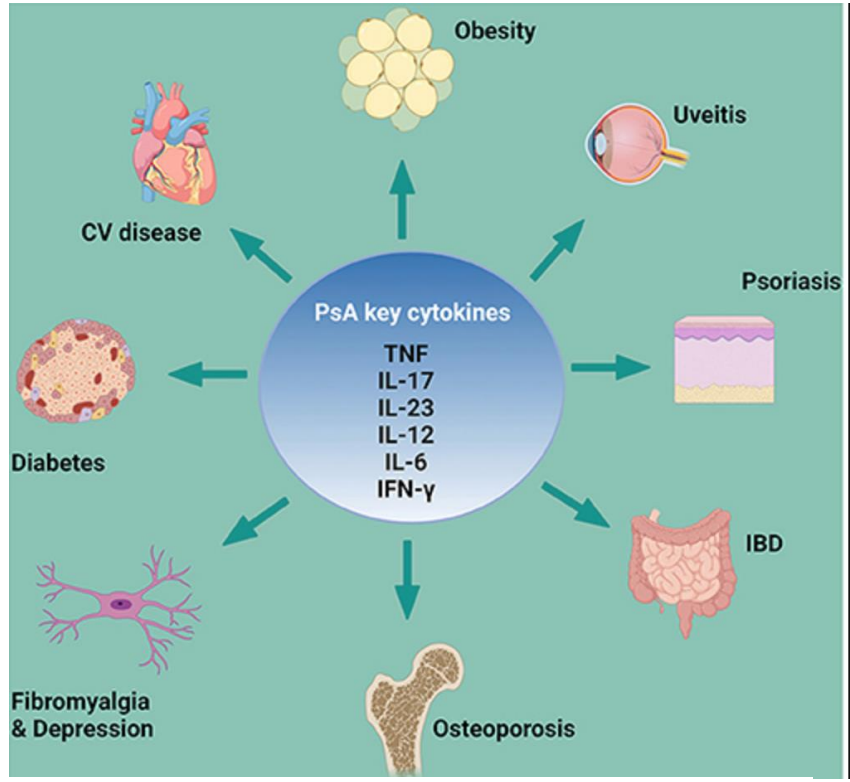
«Psoriatic disease»

Psoriasis is an **extremely multifaced** disease, with a systemic, articular and cutaneus involvement



Deep sharing of a panel of cytokines between metabolic diseases and psoriasis

Effetto su angiogenesi, via insulinica, adipogenesi,metabolismo li pidico, «trafficking» immunologico.



Extra-Articular Manifestations and Comorbidities in Psoriatic Disease: A Journey Into the Immunologic Crosstalk

Lucia Novelli[1†], Ennio Lubrano[2†], Vincenzo Venerito[3], Fabio Massimo Perrotta[2], Francesca Marando[1], Giacomo Curradi[1] and Florenzo Iannone[3*]

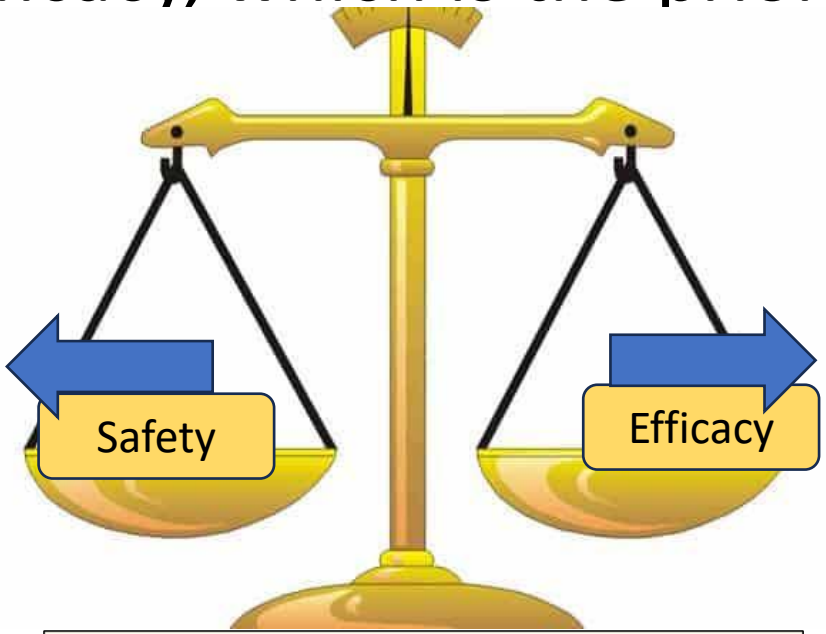
Safety e/o Efficacy, which is the priority and in which patient

Patient's age (elderly)

Burden of Pso

PsA

Comorbidities (drugs for other diseases)



Patient's age
Burden of PsO (Difficult to treat areas)
PsA
Comorbidities

Life style
(Worsening is been associated to smoking, alcool, sedentary status,obesity)

Patient need
QoL

Frequencies of patient needs in psoriasis treatment

Treatment needs	Responses number	Percent of cases
Rapid skin clearance	1,793	90.2%
Reducing treatment expenses	853	42.9%
Less hospital visits or treatment time	766	38.5%
Reducing itching	762	38.3%
Improving mental state	732	36.8%
Reducing side effects	655	32.9%
Reducing social discrimination	573	28.8%
Engaging in social activities and work normally	570	28.7%
Relieving pain and burning	485	24.4%
Sum	7,189	361.6%

International Journal of
Molecular Sciences

MDPI

Review

PDE4 Phosphodiesterases in Cardiovascular Diseases: Key Pathophysiological Players and Potential Therapeutic Targets

Lídia Puertas-Umbert [1,2], Judith Alonso [1,2,3], Leif Hove-Madsen [1,2,3], José Martínez-González [1,2,3,*,†] and Cristina Rodríguez [1,2,3,*,‡]

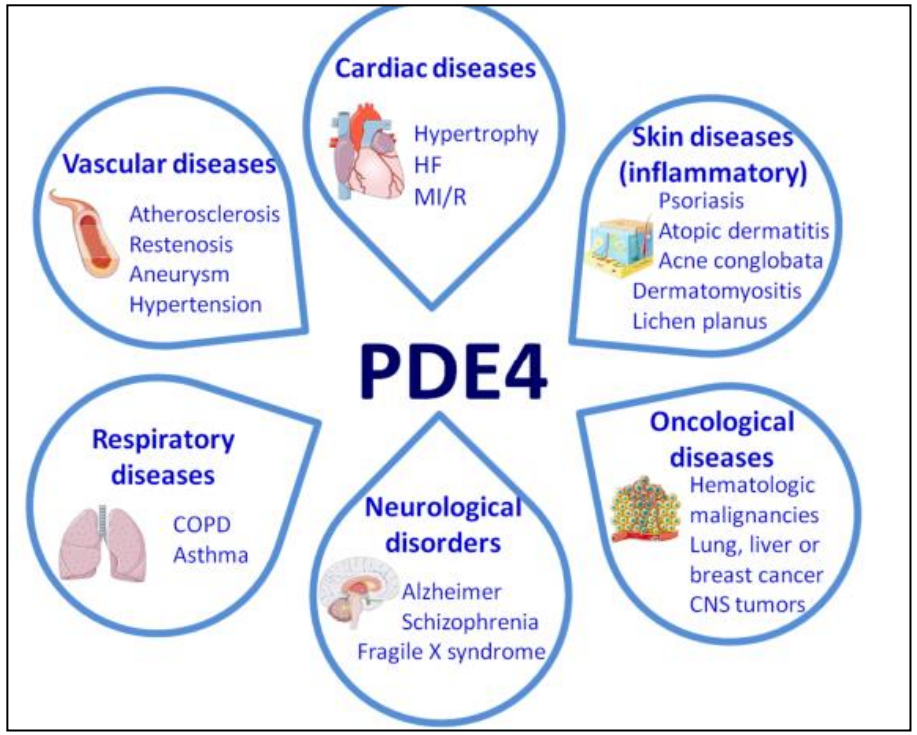


Figure 1. PDE4 in disease. This scheme depicts the diseases that have been associated with disturbances in PDE4 expression/activity. HF: Heart failure; MI/R myocardial ischemia/reperfusion; COPD: chronic obstructive pulmonary disease; CNS: central nervous system. This figure was partly

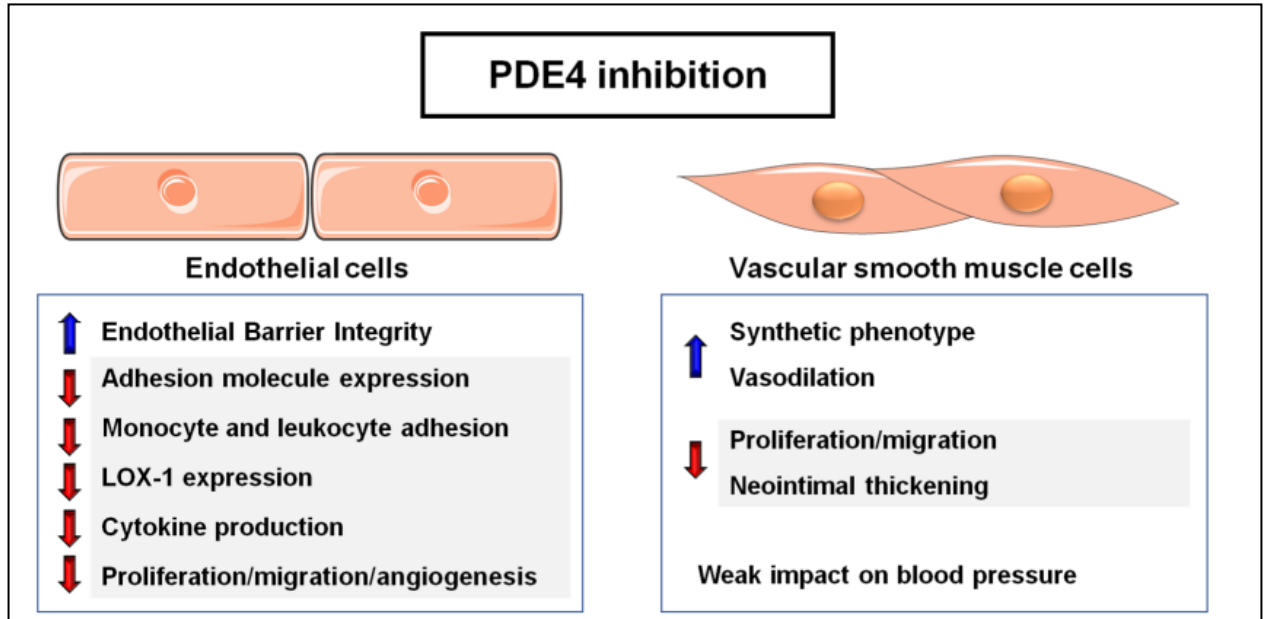


Figure 3. Potential effects of PDE4 inhibition on endothelial cells and vascular smooth muscle cells. LOX-1: Lectin-like oxidized low-density lipoprotein receptor-1.

Figure 1. PDE4 in disease. This scheme depicts the diseases that have been associated with disturbances in PDE4 expression/activity. HF: Heart failure; MI/R myocardial ischemia/reperfusion; COPD: chronic obstructive pulmonary disease; CNS: central nervous system. This figure was partly

Several studies have evidenced that systemic inflammation is accompanied **by a decrease in endothelial cAMP levels and that cAMP signaling iscompromised in this pathological scenario**

Apremilast : MoA

- Apremilast **is a selective inhibitor of PDE4 inhibits all PDE4 subtypes (A, B, C and D)**
- **Elevates intracellular cAMP**
- Activates protein kinase A, resulting in phosphorylation and activation of CREB/ATF-1 transcription factors **Inhibits NF-κB-driven transcription**
- Regulates cytokine expression, **inhibiting TNF, IL-23 and IL-17 and increasing the expression of anti-inflammatory mediators such as IL-10**
- It has greater effects on innate immunity than adaptive immunity
- **It inhibits toll-like receptor activation in monocytes, dendritic cells and neutrophils**

1. Schafer PH, et al. *Cell Signal*. 2014;26:2016-2029. 2. Schafer P. *Biochem Pharmacol*. 2012;83:1583-1590. 3. Schafer P et al. *Br J Pharmacol*. 2010;159:842-855.

Key Points: A Unique Opportunity To Improve Disease Management and Impact the Course of the Disease

- **Apremilast may offer unique opportunity to control the systemic inflammation, while improving the metabolic profile**

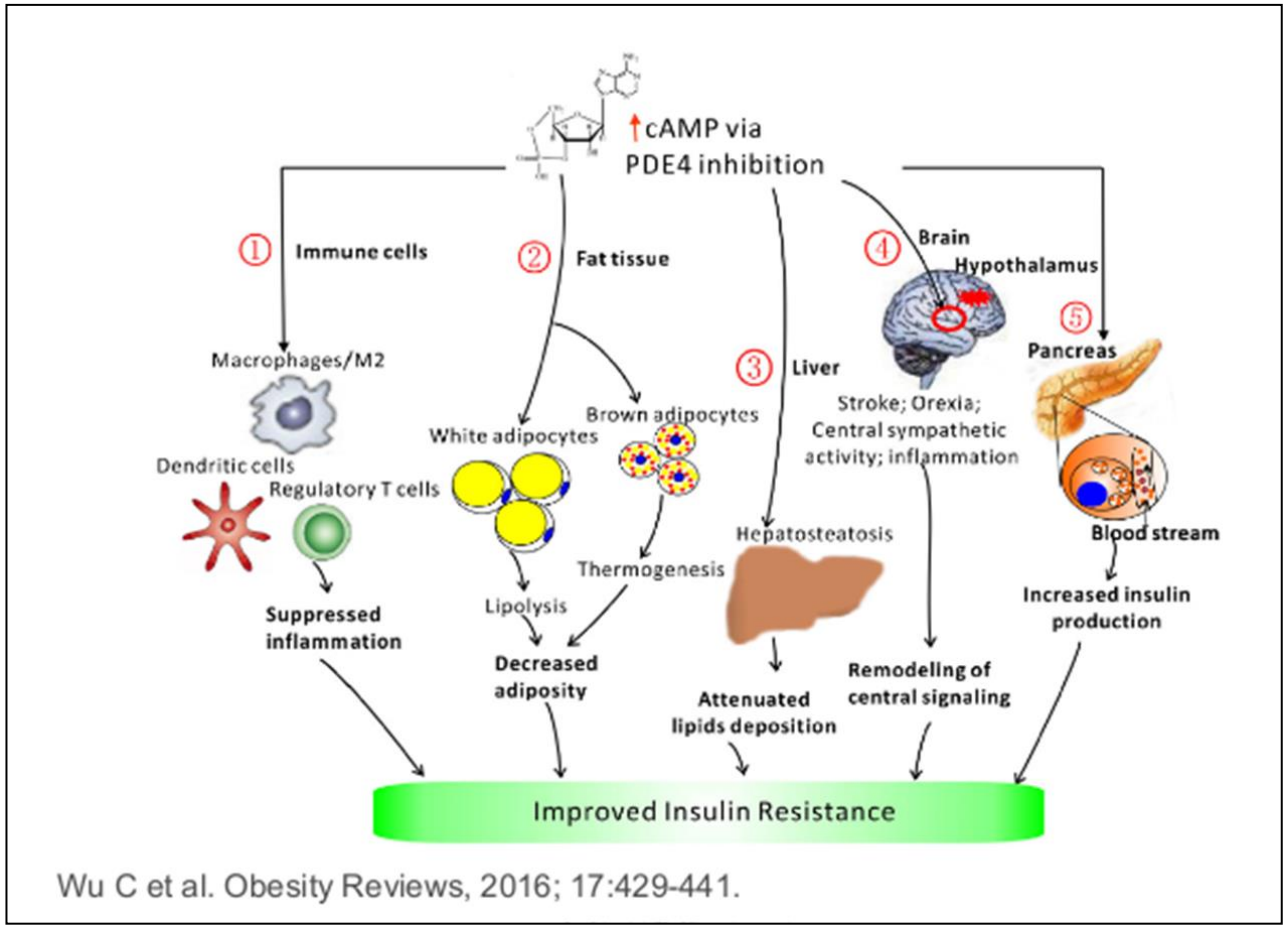
- Apremilast is associated with **reduction in weight and improvement of visceral adiposity**.

- **Increases in HDL** observed in Apremilast studies support an impact of PDE4 inhibition on lipid metabolism.

- **Improve glucose control** and complications from high blood glucose levels, as **reductions in HbA1c have been observed in some studies.**

.

- Low long-term risk of CV events have been reported in multiple studies. These findings are meaningful and fulfill a clear, unmet need for psoriatic patients.



Wu C et al. Obesity Reviews, 2016; 17:429-441.

2. La disregolazione delle fosfodiesterasi può condurre ad un quadro di disfunzione endoteliale?

1. **Sì**
2. **No**

Open Access Full Text Article

CASE REPORT

Small Molecules, Big Promises: Improvement of Psoriasis Severity and Glucidic Markers with Apremilast: A Case Report

This article was published in the following Dove Press journal:
Diabetes, Metabolic Syndrome and Obesity: Targets and Therapy

Caterina Lanna*
Gaia Maria Cesaroni*
Sara Mazzilli
Luca Bianchi
Elena Campione

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*These authors contributed equally to this work

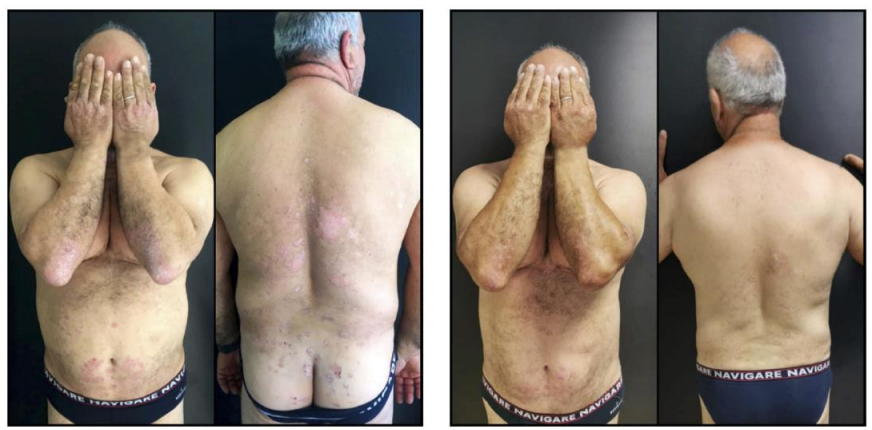
Abstract: Psoriasis is a common inflammatory skin condition frequently associated with cardiometabolic diseases such as diabetes. Indeed, the state of systemic inflammation typical of psoriasis leads to an increase in the level of IL-1, IL-6 and TNF-alpha which may cause a reduced sensitivity to insulin and, ultimately, can lead to type 2 diabetes mellitus. Particularly, the derangement of PDE4-cAMP signaling has a critical role in disordered glucose and lipid metabolism. Apremilast, as a selective inhibitor of PDE4-cAMP signalling, represents an innovative therapeutic strategy for psoriasis. Here, we report a case of a patient affected by psoriasis and diabetes, who – after using Apremilast – improved his glucose metabolism as well as his need of anti-diabetic drugs and his psoriasis. This suggests that, in addition to its role against psoriasis, Apremilast may even act as a metabolic modulator.

Keywords: psoriasis, diabetes, PDE4-inhibitor

Results after 6 months of treatment with apremilast

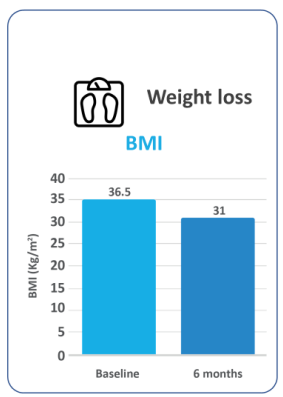
- After 6 months of treatment the patient reached an almost complete resolution of his plaque Pso (PASI 1), with an improvement of the quality of life (DLQI 0) and no evidence of side effects.

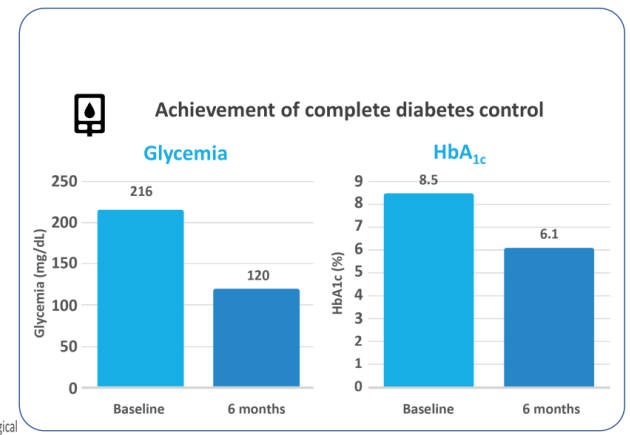
Baseline | **After 6 months of apremilast treatment**



Reproduced from Figure 1 and 2.

Results after 6 months of treatment with apremilast



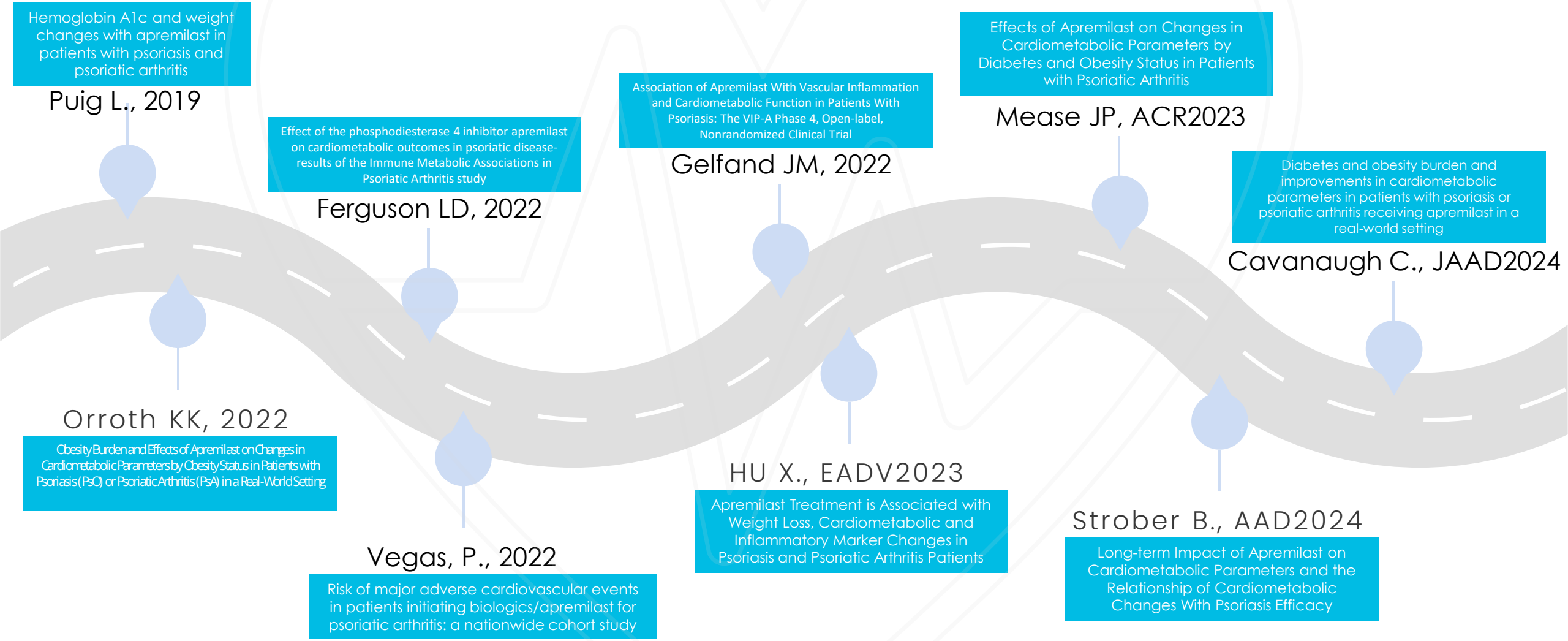


- Beside its proven efficacy on Pso symptoms, Apremilast can provide additional pharmacological benefits to patients, due to the improvement of metabolic parameters.
- This could be of great importance for that cohort of patients suffering from Pso and diabetes, as it would allow improvements in both diseases using just one drug, due to its partially common pathogenetic basis.

The patient was able to eliminated insulin from the daily drug routine

Graphic elaboratin of textual data.

Evidence about Apremilast Cardiometabolic Outcomes

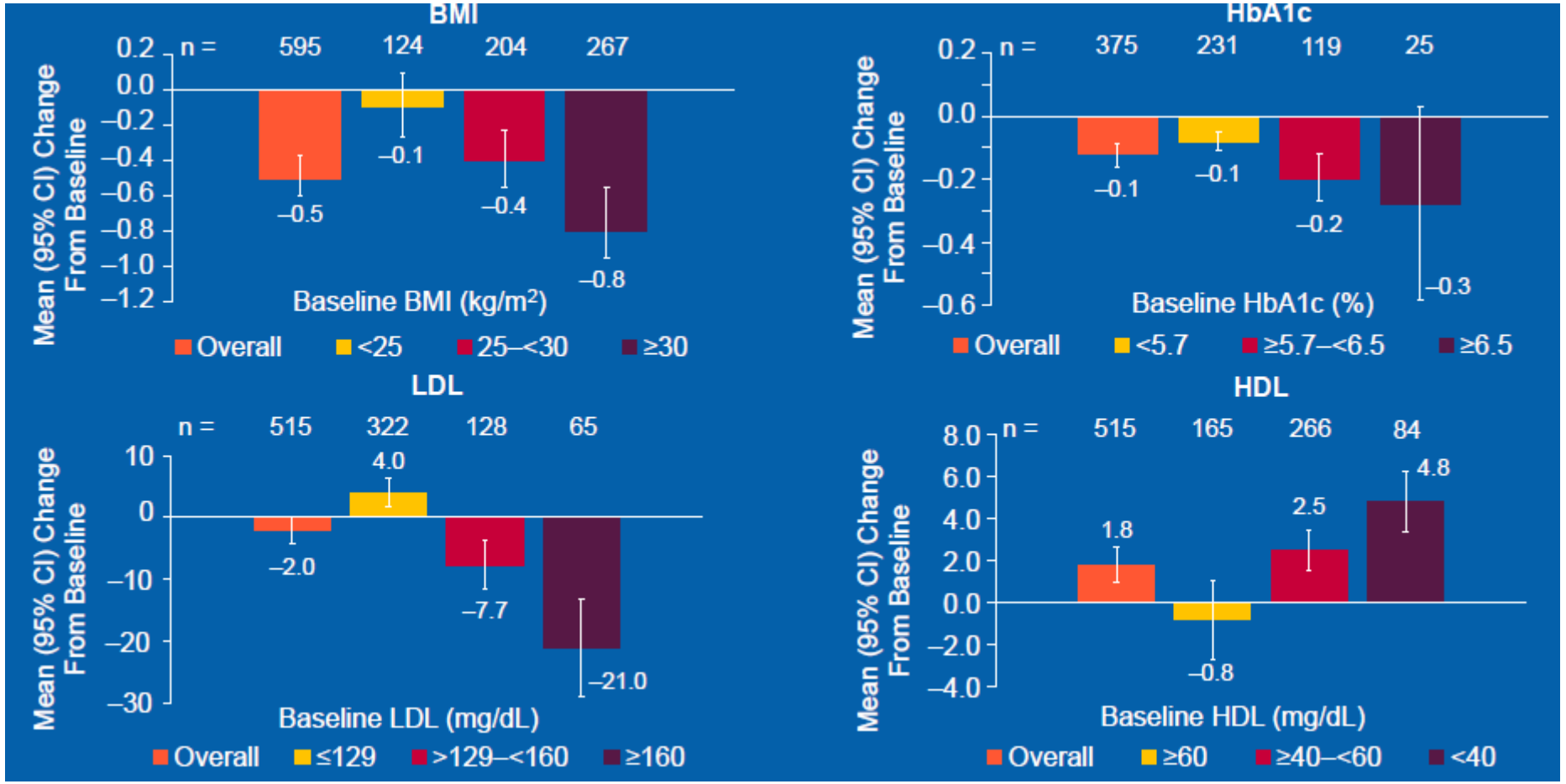


Effects of Apremilast on Changes in Cardiometabolic Parameters by Diabetes and Obesity Status in Patients with Psoriatic Arthritis

Phillip J. Mease[1], Dafna D. Gladman[2], Iain B. McInnes[3], Sue Cheng[4], Stephen Colgan[4], Yuri Klyachkin[4], Lichen Teng[4], Nehal N. Mehta[5]

[1]Swedish Medical Center/Providence St. Joseph Health and University of Washington School of Medicine, Seattle, WA, USA; [2]Schroeder Arthritis Institute, Krembil Research Institute, Toronto Western Hospital, ON, Canada; [3]College of Medical, Veterinary and Life Sciences, University of Glasgow, Glasgow, United Kingdom; [4]Amgen Inc., Thousand Oaks, CA, USA; [5]The George Washington University School of Medicine, Washington, DC, USA

Improvements in BMI, HbA1c, LDL, and HDL after 52 weeks of APR treatment were greater in patients in higher risk categories at baseline



- Riduzione del BMI
- Riduzione dell'emoglobina glicata
- Riduzione LDL
- Aumento HDL

3. L’impatto positivo di apremilast sulle comorbidità metaboliche può ulteriormente contribuire alla riduzione del carico di malattia cutaneo?

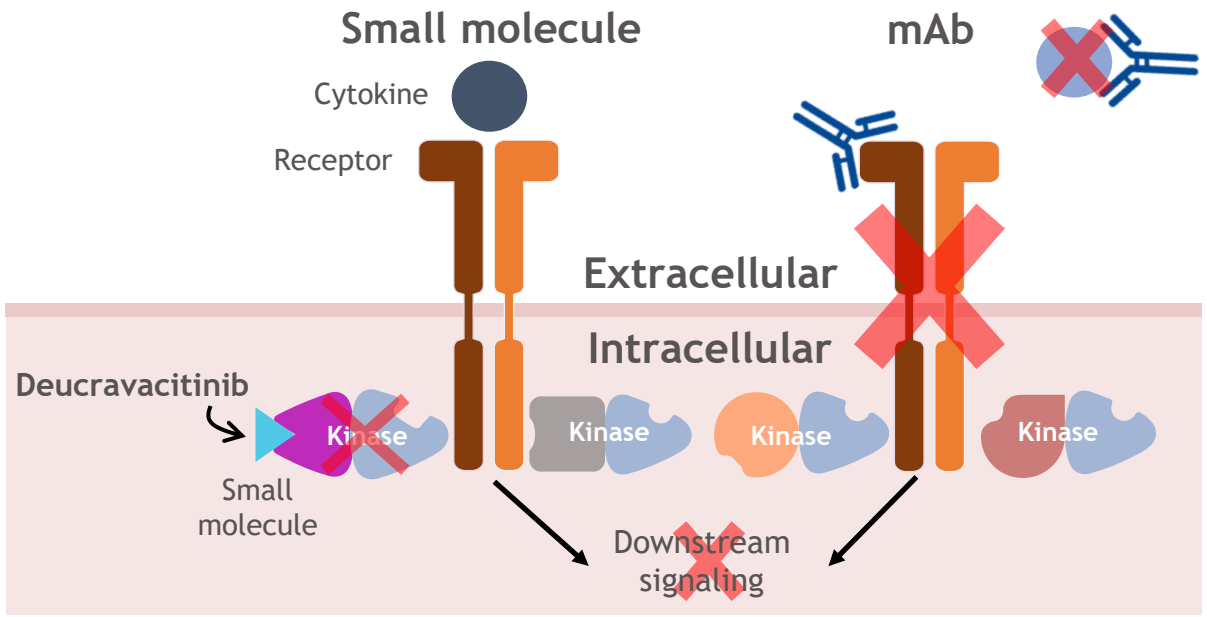
1. **Sì**
2. **No**

4. Apremilast ha mostrato un elevato profilo di sicurezza in relazione ai valori di LDL, HDL ed emoglobina glicata?

1. **Sì**
2. **No**

Small molecules, non solo apremilast: JAK/TYK inhibitors

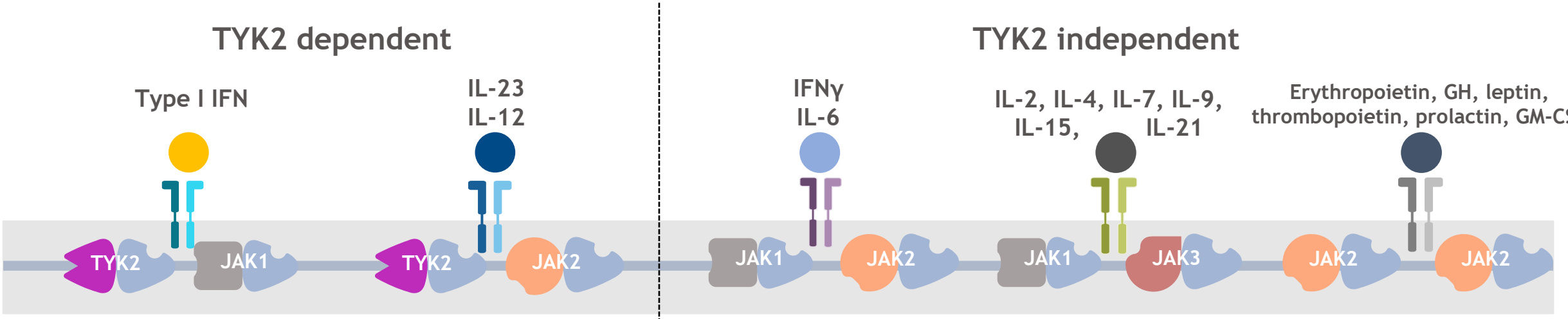
Small-molecule inhibitors vs monoclonal antibodies



Small molecules vs mAbs (biologics): considerations		
	Small molecule	**mAb**
Administration[1-3]	Oral	IV/SC
Half-life[2,3]	Short (e.g. dosed daily or multiple times a day)	Long (e.g. dosed biweekly or monthly)
Target[2,3]	Extra/intracellular	Extracellular
Immunogenicity[1,3]	Non-immunogenic	Neutralizing ADA potential
Toxicity[1,3]	Off-target effects of compound and metabolites	Receptor mediated
Drug interaction[3]	Possible	Rare
Production[1,3]	Chemical synthesis, easy	Biological production, complex

Adapted with permission from *Nat Rev Cancer*,[1] *Mol Cancer*,[2] and *Clin Transl Sci*[3]
ADA, antidrug antibody; IV, intravenous; mAb, monoclonal antibody; SC, subcutaneous.
1. Imai K, Takaoka A. *Nat Rev Cancer*. 2006;6:714-727. 2. Sierra JR et al. *Mol Cancer*. 2010;9:75-88. 3. Ovacik M. *Clin Transl Sci*. 2018;11:540-552.

The TYK2/JAK family
TYK2-dependent and TYK2–independent pathways



- **Dendritic cell maturation**
- **B-cell differentiation**
- **Antibody production**
- **T-cell survival**
- **MHC expression**

- **Th1 differentiation**
- **Th17 differentiation**
- **ILC activation**
- **Dendritic cell activation**
- **IL-17, TNFα and IFNγ secretion**

- Th1 differentiation
- Osteoclast formation
- Neuronal survival
- Lipid metabolism
- Granulopoiesis

- Lymphoid cell maturation and function
- T-cell survival
- Th2 differentiation
- Treg maintenance

- Hematopoiesis
- Growth factor response
- Metabolic activity regulation
- Myelopoiesis

Immune responses
Non-immune homeostatic functions

Adapted with permission from *Immunotherapy*[4]

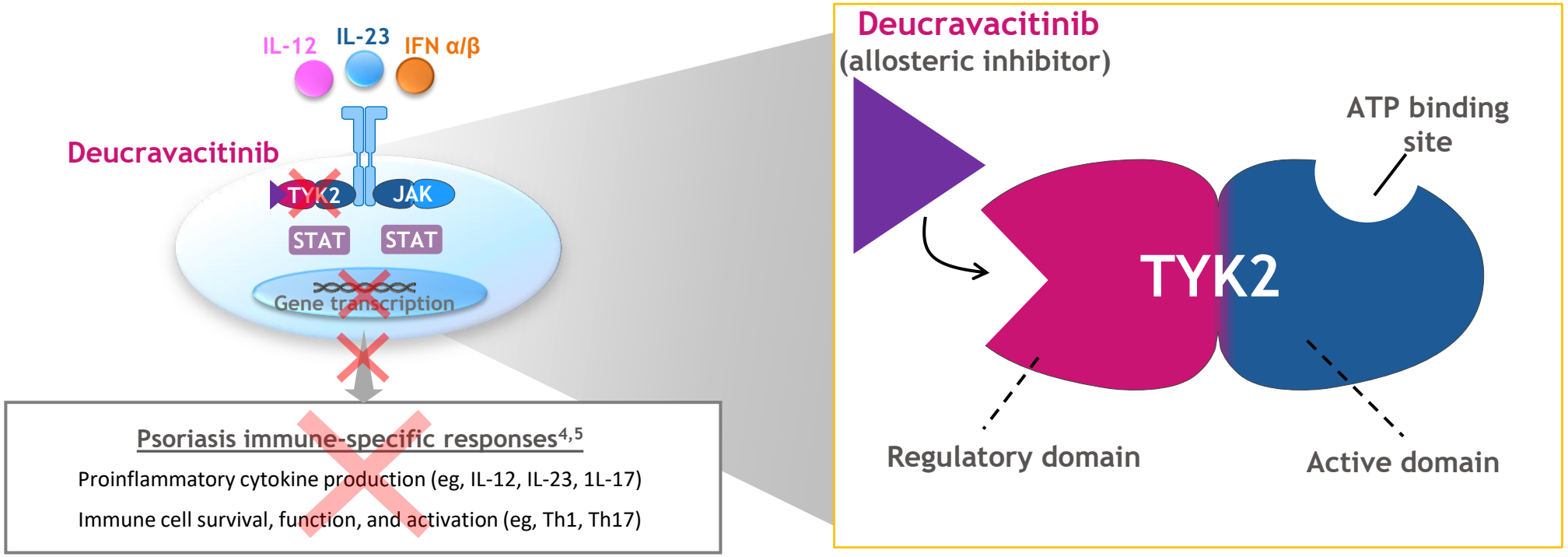
GH, growth hormone; GM-CSF, granulocyte-macrophage colony-stimulating factor; IFN, interferon; IL, interleukin; ILC, innate lymphoid cell; JAK, Janus kinase; MHC, major histocompatibility complex; Th, helper T cell; TNFα, tumor necrosis factor alpha; Treg, regulatory T cell; TYK2, tyrosine kinase 2.

1. Wrobleski ST et al. *J Med Chem.* 2019;62:8973–8995. 2. Burke JR et al. *Sci Transl Med.* 2019;11:502. 3. Baker KF, Isaacs JD. *Ann Rheum Dis*. 2018;77:175–187. 4. Gonciarz M et al. *Immunotherapy*. 2021;13:1135-1150. 5. Morris R et al. *Protein Sci*. 2018;27:1984-2009. 6. Marroqui L et al. *Diabetes*. 2015;64:3808-3817. Goldstein JD et al. *PLoS ONE.* 2016;11:e0153682.

Deucravacitinib mechanism of action

Deucravacitinib is an oral, selective, small molecule TYK2 inhibitor with a unique mechanism of action that is distinct from other kinase inhibitors, such as JAK 1–3 inhibitors[1-3]

Deucravacitinib uniquely binds to the regulatory domain of TYK2 with high selectivity and only blocks specific cytokine-driven responses that contribute to pathogenesis of psoriasis[1,2,4]



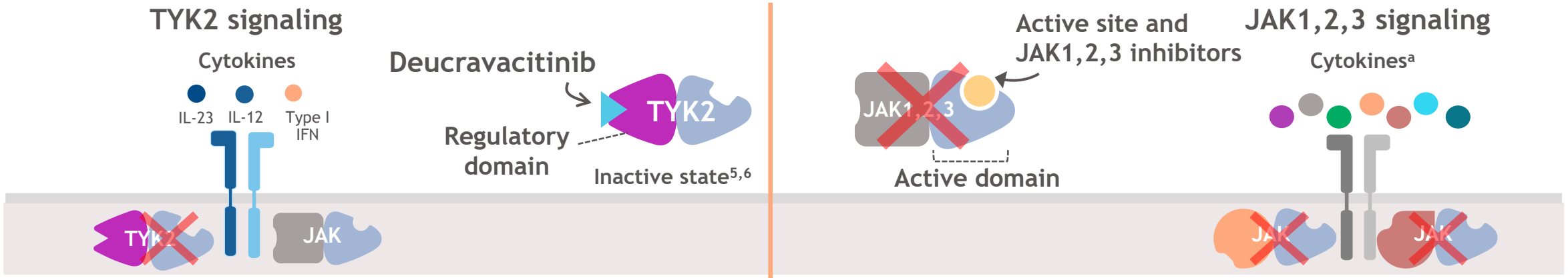
Inhibition of TYK2 occurs via an allosteric mechanism[2]

ATP, adenosine triphosphate; IFN, interferon; IL, interleukin; JAK, Janus kinase; PsO, psoriasis; STAT, signal transducer and activator of transcription; Th, helper T; TYK, tyrosine kinase.

Adapted from 1. Wrobleski ST et al. *J Med Chem.* 2019;62:8973-8995. 2. Burke JR et al. *Sci Transl Med.* 2019;11:eaaw1736. 3. Papp K et al. *N Engl J Med.* 2018;379:1313-1321. 4. Baker KF, Isaacs JD. *Ann Rheum Dis.* 2018;77:175-187. 5. Mahil SK et al. *Semin Immunopathol.* 2016;38:11–27.

Selective TYK2 inhibition by deucravacitinib

Deucravacitinib uniquely binds to the regulatory domain of TYK2 and only blocks IL-23, IL-12, and Type I IFN-driven responses, but not those driven by JAK1,2,3 kinases[1-7]



Immune-specific responses

- Th1, Th17 differentiation
- Cytokine secretion (IL-17, TNFα, IFNγ)
- T-cell survival
- Dendritic cell maturation and activation
- ILC activation
- B-cell differentiation and antibody production
- MHC expression

Deucravacitinib uniquely binds to the regulatory domain of TYK2, which leads to a broad therapeutic range while reducing off-target effects[1-3]

JAK1,2,3 inhibitors competitively bind to the highly conserved active site, which leads to a narrow therapeutic range, resulting in potential off-target effects[7]

Immune-specific/broad systemic responses

- **Myelopoiesis**
- **Metabolic activity regulation**
- **Granulopoiesis**
- **Lymphoid cell maturation and function**
- **Hematopoiesis**
- **Lipid metabolism**
- Th2 differentiation
- Treg maintenance
- Growth factor response
- Osteoclast formation
- Neuronal survival

Adapted with permission from *Ann Rheum Dis*[3]

[a]A number of different cytokines and signaling factors bind to and activate the JAK-JAK dimer receptors.

IFN, interferon; IL, interleukin; ILC, innate lymphoid cell; JAK, Janus kinase; MHC, major histocompatibility complex; Th, helper T; TNFα, tumor necrosis factor alpha; Treg, regulatory T cell; TYK2, tyrosine kinase 2.

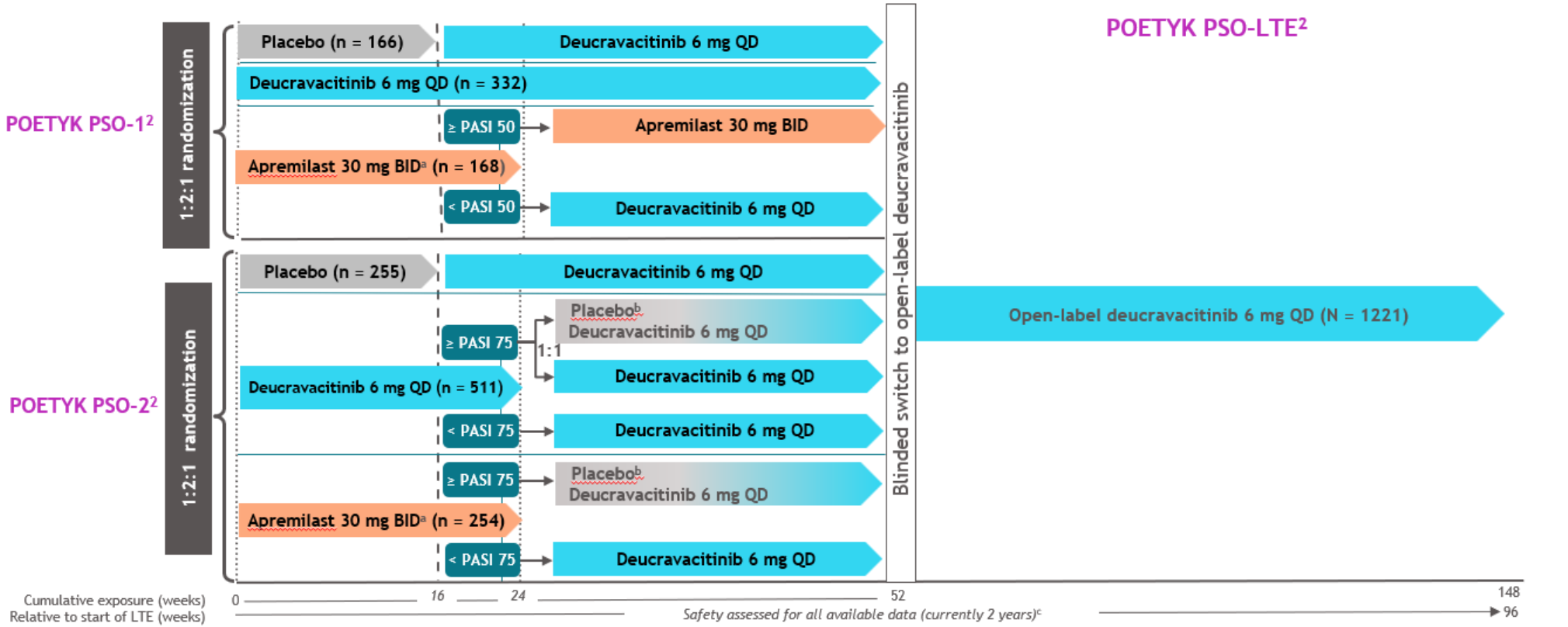
1. Wrobleski ST et al. *J Med Chem*. 2019;62:8973–8995. 2. Burke JR et al. *Sci Transl Med*. 2019;11:502. 3. Baker KF, Isaacs JD. *Ann Rheum Dis*. 2018;77:175–187. 4. Gonciarz M et al. *Immunotherapy*. 2021;13:1135-1150. 5. Borzilleri RM et al. *Burger's Medicinal Chemistry, Drug Discovery and Development*. 8th ed. John Wiley & Sons; 2021. 6. Tokarski JS et al. *J Biol Chem*. 2015;290:11061–11074. 7. Virtanen AT et al. *BioDrugs*. 2019;33:15–32.

5. L’inibizione del TYK2 da parte del deucravacitinib agisce sul metabolismo dei lipidi, sull’attivita’ degli osteoclasti**?**

1. **Sì**
2. **No**

Trial di fase 3

POETYK PSO-LTE (IM011-075): study design[1,2]



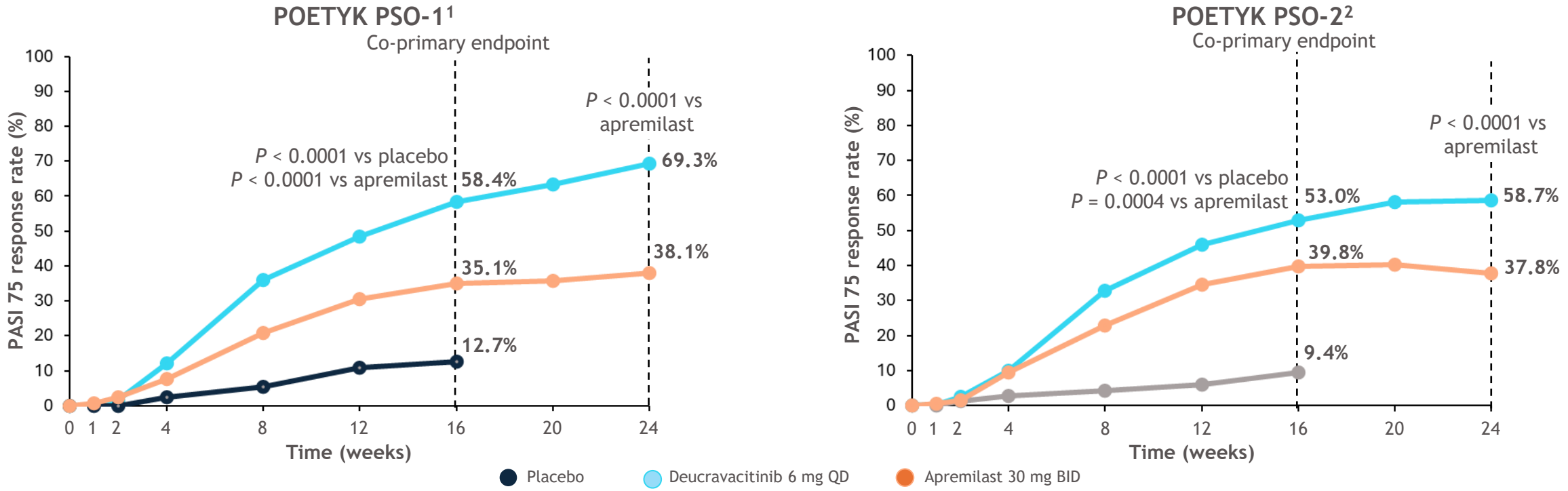
Adapted from with permission from Warren RB.[2]

[a]Apremilast was titrated from 10 mg QD to 30 mg BID over the first 5 days of dosing.[2] [b]Upon relapse (≥ 50% loss of Week 24 PASI percent improvement from baseline), patients were switched to deucravacitinib 6 mg QD.[2] [c]Safety assessed through the cutoff date of October 1, 2021.[2]

BID, twice daily; LTE, long-term extension; PASI, Psoriasis Area and Severity Index; PASI 50, ≥50% reduction from baseline in PASI; PASI 75, ≥75% reduction from baseline in PASI; QD, once daily.

1. ClinicalTrials.gov. Accessed March 2021. https://clinicaltrials.gov/ct2/show/NCT04036435. 2. Warren RB et al. Poster presentation at San Diego Dermatology Symposium; March 11-13, 2022; San Diego CA.

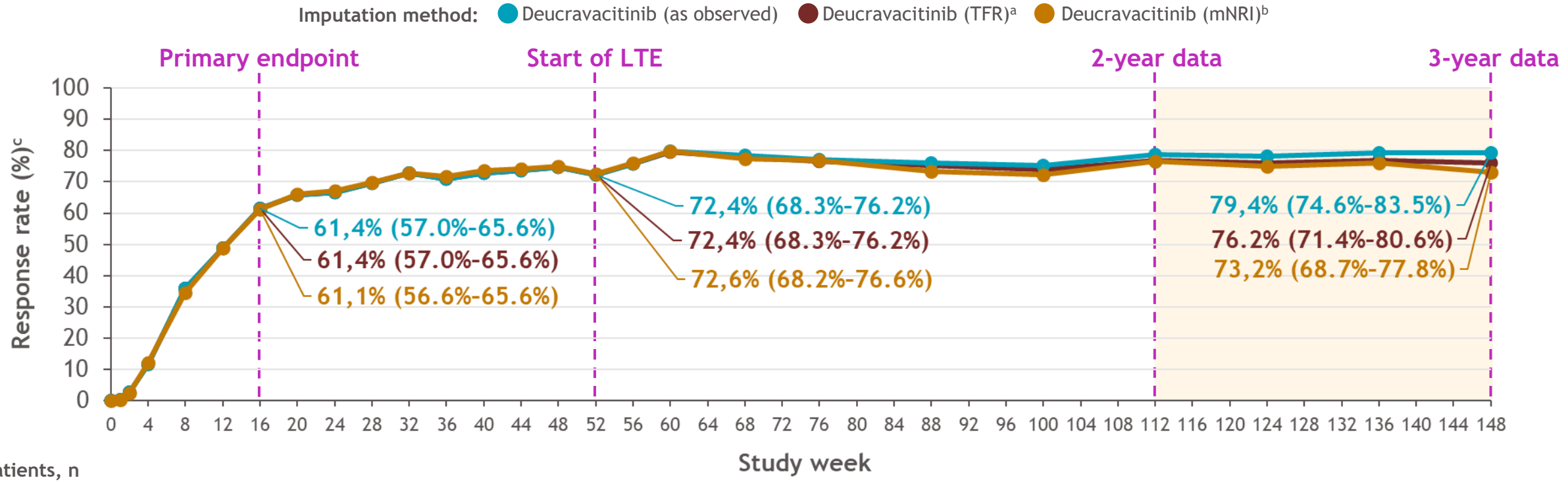
Co-primary endpoint: PASI 75 response at Week 16, and through Week 24 (NRI)



- A **significantly greater proportion of patients receiving deucravacitinib achieved PASI 75 responses compared** with patients receiving placebo ($P < 0.0001$) and apremilast ($P < 0.0001$ in POETYK PSO-1; $P = 0.0004$ in POETYK PSO-2) at Week 16[1,2]
- This statistically significant difference between the deucravacitinib and apremilast arms was also observed at Week 24 ($P < 0.0001$)[1,2]

Reproduced with permission from *J Am Acad Dermatol*[1] and Warren RB[2]
BID, twice daily; NRI, nonresponder imputation; PASI 75, 75% improvement in Psoriasis Area and Severity Index score; QD, once daily.
1. Armstrong AW et al. *J Am Acad Dermatol*. 2022. doi:10.1016/j.jaad.2022.07.002. 2. Warren RB et al. Oral presentation at EADV Annual Meeting; September 29–October 2, 2021; Virtual. Abstract FC03.06.

PASI 75 response rates with continuous deucravacitinib treatment from Day 1 to 3 years



Patients, n																									
As observed	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

PASI 75 response was sustained well from Week 52 (beginning of the POETYK LTE trial) through Week 148

Reproduced with permission from Armstrong AW.
[a]TFR analysis captures discontinuations coded as "lack of efficacy." [b]For mNRI analyses, if there are no missing data (ie, no imputed values in the dataset), 95% CI was obtained using the Clopper-Pearson method based on the observed data. [c]Data callouts represent the response rate (95% CI).
CI, confidence interval; LTE, long-term extension; mNRI, modified nonresponder imputation; PASI 75, ≥ 75% improvement in Psoriasis Area and Severity Index score; TFR, treatment failure rules.
Armstrong AW et al. Presentation at EADV; October 11–14, 2023; Berlin, DE.

Safety summary (integrated): Weeks 0–52

AE category, n,[a] EAIR events per 100 PY	Placebo (n = 666) (total PY, 240.9)		Deucravacitinib (n = 1364) (total PY, 969.0)		Apremilast (n = 422) (total PY, 221.1)	
	n (%)	EAIR/ 100 PY	n (%)	EAIR/ 100 PY	n (%)	EAIR/ 100 PY
Any AEs[1]	347 (52.1)	217.4	995 (72.9)	229.2	299 (70.9)	281.1
Serious AEs[1]	14 (2.1)	5.7	55 (4.0)	5.7	9 (2.1)	4.0
AEs leading to discontinuation[1]	23 (3.5)	9.3	43 (3.2)	4.4	26 (6.2)	11.6
Deaths[1b]	1 (0.2)	0.4	2 (0.1)[b]	0.2	1 (0.2)	0.4
Most common AEs (≥ 5%) in any active treatment group[1]						
Nasopharyngitis[1]	54 (8.1)	22.7	229 (16.8)	26.1	54 (12.8)	25.9
Upper respiratory tract infection[1]	33 (5.0)	13.5	124 (9.1)	13.4	27 (6.4)	12.4
Headache[1]	21 (3.2)	8.6	80 (5.9)	8.5	53 (12.6)	26.0
Diarrhea[1]	28 (4.2)	11.5	69 (5.1)	7.3	54 (12.8)	26.5
Nausea[2]	10 (1.5)	4.1	20 (1.5)	2.1	47 (11.1)	22.9

- Per each study design, patients receiving placebo switched to deucravacitinib at Week 16 and patients receiving apremilast who failed to meet study-specific efficacy thresholds (PASI 50 in POETYK PSO-1, PASI 75 in POETYK PSO-2) switched to deucravacitinib at Week 24[2]
- Skin events of interest: folliculitis and acne[2]
  - Folliculitis, 2.0% (EAIR, 2.8) and acne, 2.1% (EAIR, 2.9) with deucravacitinib
  - All cases were mild to moderate; 1 patient with folliculitis discontinued deucravacitinib treatment
- No new safety signals observed during Weeks 16–52[2]

Adapted with permission from Alexis A[1] and Armstrong AW.[2]

[a]Includes AEs between first dose and 30 days following last dose or rollover to long-term extension.[2] [b]There was 1 additional death between Weeks 16 and 52 due to hepatocellular carcinoma in a patient with a history of HCV infection and liver cirrhosis.[2]

AE, adverse event; EAIR, exposure-adjusted incidence rate; HCV, hepatitis C virus; PASI 50/75, 50%/75% improvement in Psoriasis Area and Severity Index score; PY, patient-years.

1. Alexis A et al. Poster presented at Winter Clinical Dermatology Conference; January 14–19, 2022; Kauai, HI, and Virtual. 2. Armstrong AW et al. Oral presentation at AAD VMX; April 23-25, 2021; Virtual.

Cumulative safety summary through 2 years and 3 years (as-treated population)

AE category	Cumulative through 2 years[a] (POETYK PSO-1 + PSO-2 + LTE) Deucravacitinib (n = 1519) Total PY = 2482.0		Cumulative through 3 years[b] (POETYK PSO-1 + PSO-2 + LTE) Deucravacitinib (n = 1519) Total PY = 3294.3	
	n (%)	EAIR/100 PY (95% CI)	n (%)	EAIR/100 PY (95% CI)
AEs	1214 (79.9)	**154.4 (146.0-163.4)**	1269 (83.5)	**144.8 (137.1-153.0)**
SAEs	145 (9.5)	**6.1 (5.2-7.2)**	167 (11.0)	**5.5 (4.7-6.4)**
Discontinued treatment due to AEs	69 (4.5)	**2.8 (2.2-3.5)**	78 (5.1)	**2.4 (2.0-3.0)**
Deaths	10 (0.7)[c]	**0.4 (0.2-0.7)**	10 (0.7)[d]	**0.3 (0.2-0.6)**
Most common AEs (EAIR/100 PY ≥5)				
Nasopharyngitis	271 (17.8)	**12.9 (11.5-14.5)**	302 (19.9)	**11.4 (10.2-12.7)**
COVID-19[e]	124 (8.2)	**5.1 (4.3-6.1)**	242 (15.9)	**8.0 (7.1-9.1)**
Upper respiratory tract infection	150 (9.9)	**6.5 (5.6-7.7)**	182 (12.0)	**6.2 (5.4-7.2)**

Aside from a slightly higher COVID-19 rate, AE rates through 3 years remained consistent with rates observed through 2 years

Reproduced with permission from Armstrong AW.
Not all patients were receiving deucravacitinib 6 mg QD continuously throughout this period.
[a]This represents the pooled POETYK PSO-1, PSO-2, and LTE population through the cutoff date of October 1, 2021. [b]This represents the pooled POETYK PSO-1, PSO-2, and LTE population through the cutoff date of June 15, 2022. [c]In POETYK PSO-1 and PSO-2 through 1 year, 1 patient discontinued deucravacitinib after 4 days of treatment due to prohibited medication (leflunomide) and died 9 days later due to heart failure and sepsis. Another death occurred between Weeks 16 and 52 and was due to hepatocellular carcinoma in a patient with a history of hepatitis C virus infection and liver cirrhosis. After Week 52, 6 deaths were due to COVID-19 (all in patients with risk factors for severe disease), and 1 was due to a ruptured aortic aneurysm in a patient with cardiovascular risk factors. One patient died due to an unknown cause >30 days after discontinuing treatment but was originally included in the 2-year data; this patient was not included in the 3-year data. [d]One additional death was due to COVID-19. [e]POETYK PSO-1, PSO-2, and LTE trials were conducted during the COVID-19 pandemic.
AE, adverse event; CI, confidence interval; EAIR, exposure-adjusted incidence rate; LTE, long-term extension; PY, patient-years; QD, once daily; SAE, serious adverse event.
Armstrong AW et al. Presentation at EADV; October 11–14, 2023; Berlin, DE.

Conclusioni

Le **small molecules consolidano il loro posizionamento nel trattamento della psoriasi, con un effetto positivo nel caso di apremilast sulle comorbidità**

Grazie alla loro peculiare **farmacocinetica** possono essere assunte per via orale con schemi posologici sempre più tollerabili

Il loro **meccanismo d'azione** permette una modulazione ottimale e mai eccessiva delle citochine proinfiammatorie (no rischio di candidosi)

La loro azione su enzimi espressi in molteplici sottotipi cellulari può sortire benefici **extracutanei** ed un'efficacia anche in pazienti «**difficili**»

6. Il dosaggio del deucravacitinib per la PsO è di 6 mg una v al giorno senza titolazione iniziale?

1. **Sì**
2. **No**

7. Deucravacitinib rappresenta una nuova opzione terapeutica efficace grazie al suo meccanismo d'azione di tipo inibitorio allosterico?

1. **Sì**
2. **No**

Grazie per l’attenzione!

- Dr Fabio Artosi Dr.ssa Ruslana Gaeta Shumack
- Dr.ssa Cristiana Borselli Dr.ssa Antonia Rivieccio
- Dr. Francesco Bonacci Dr.ssa Caterina Lanna
- Dr.ssa Tania Costanza