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RESEARCH HOSPITAL

UNIVERSITÀ
DEGLI STUDI
DI MILANO

# PDE4 inhibition: a new therapeutic approach in psoriatic arthritis

OSTEO RHEUMATOLOGY 2016

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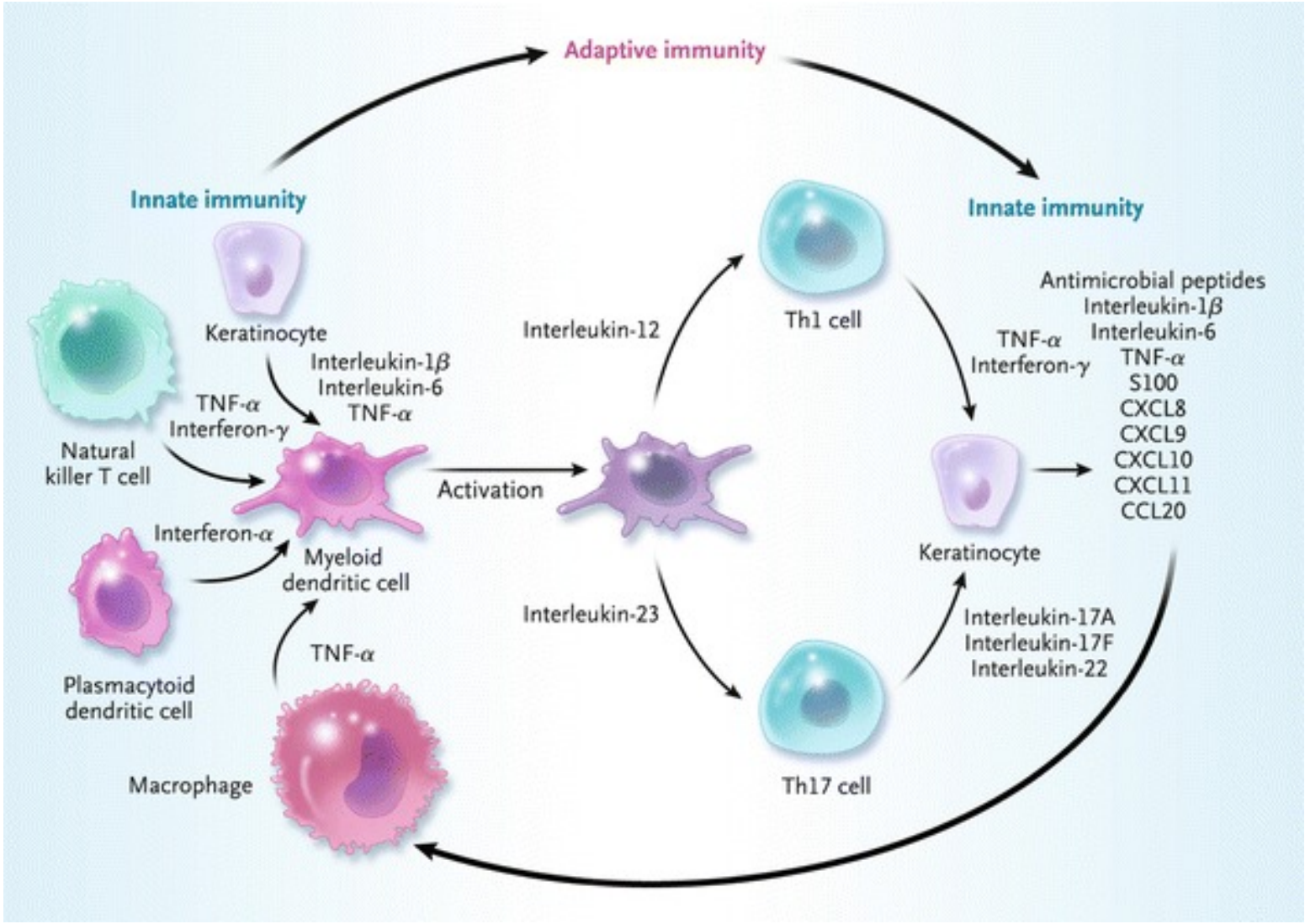
*Università degli Studi di Milano*

Genova, October 21, 2016

# The immunological crossroads of psoriatic disease

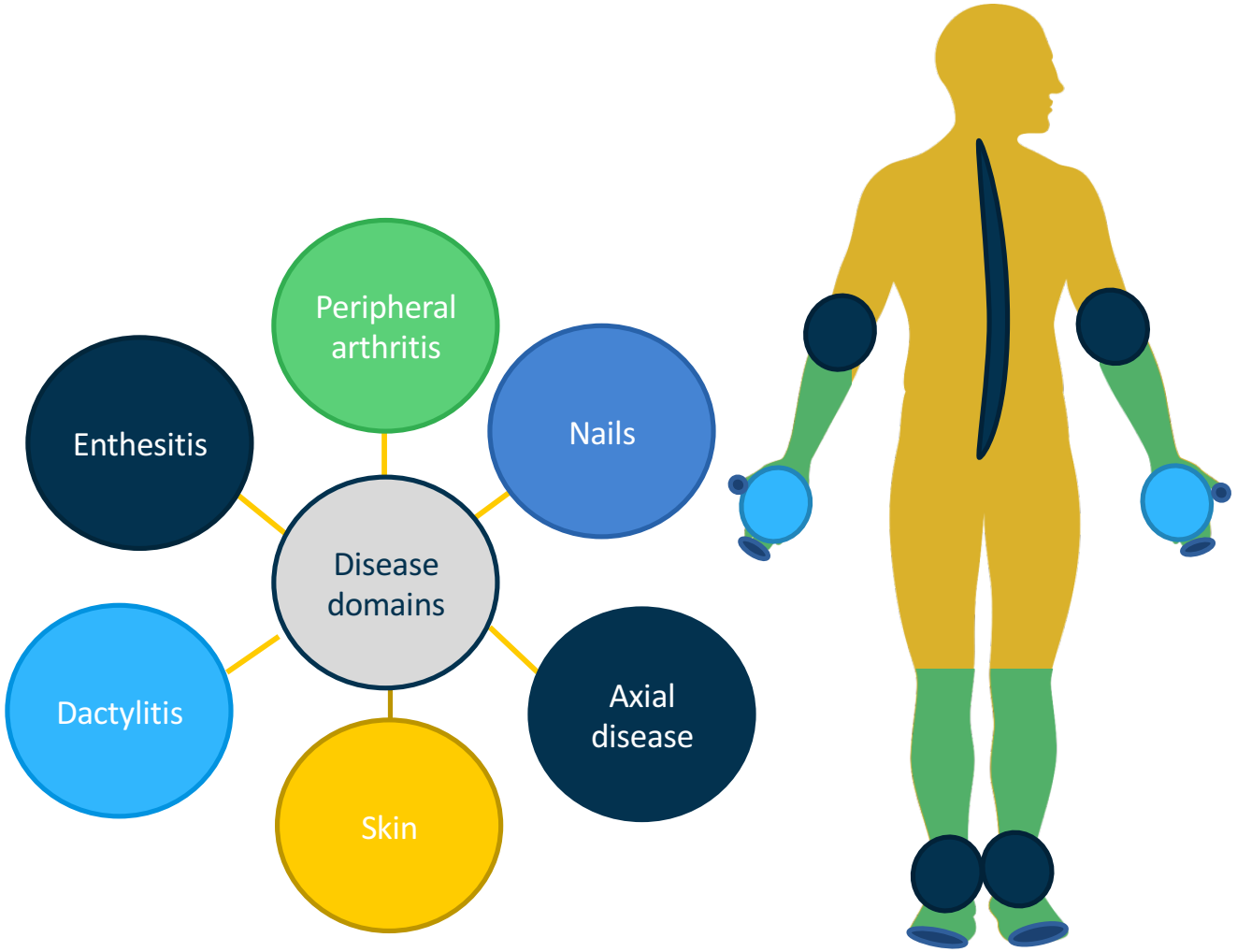



Mease PJ, et al, Drugs 2014

# Outline

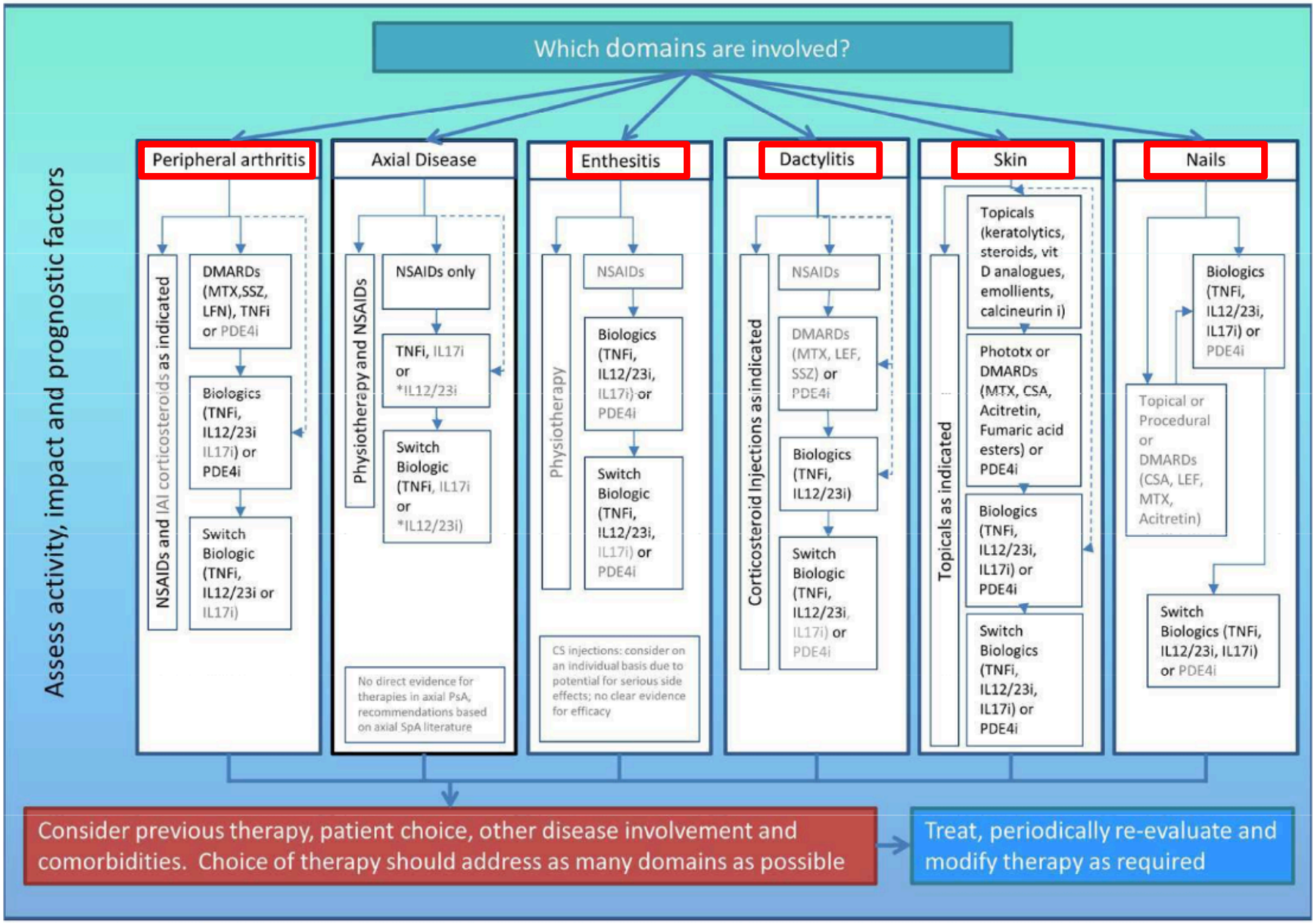
1. GRAPPA recommendations
2. PDE4 inhibition
3. The evidence from clinical trials
4. New perspectives

# GRAPPA divides patients according to the predominant domains



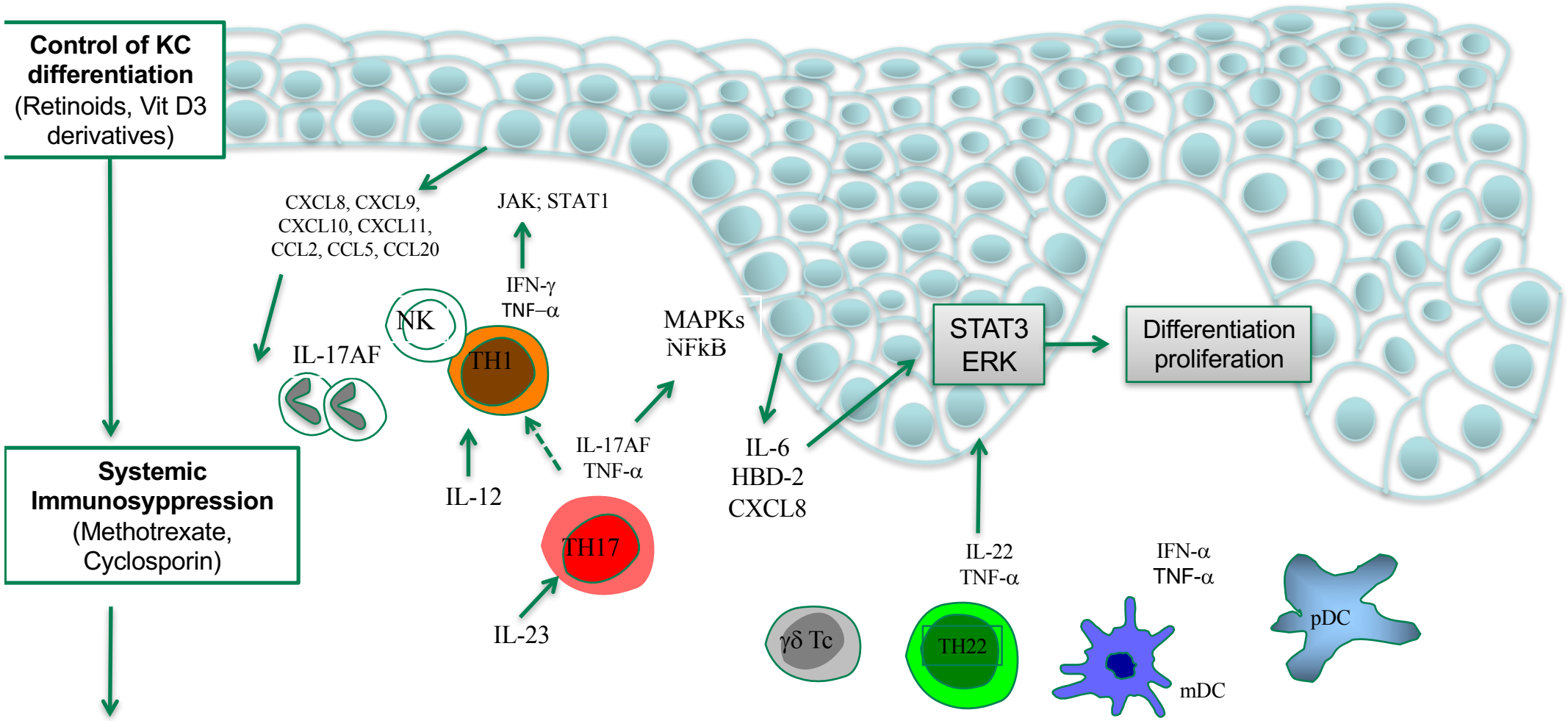

Coates LC, *et al*. *Arthritis Rheum.* 2016 [Epub].

# 2016 GRAPPA Treatment scheme for active PsA




Coates LC et al, Arthritis Rheum 2016

# Psoriatic disease: cytokine network and potential targets




**Inhibition of T cell functions**
(alefacept, anti-CD2)
Efalizumab
(anti-CD11a)

**Anti-TNF**
Infliximab
Etanercept
Adalimumab

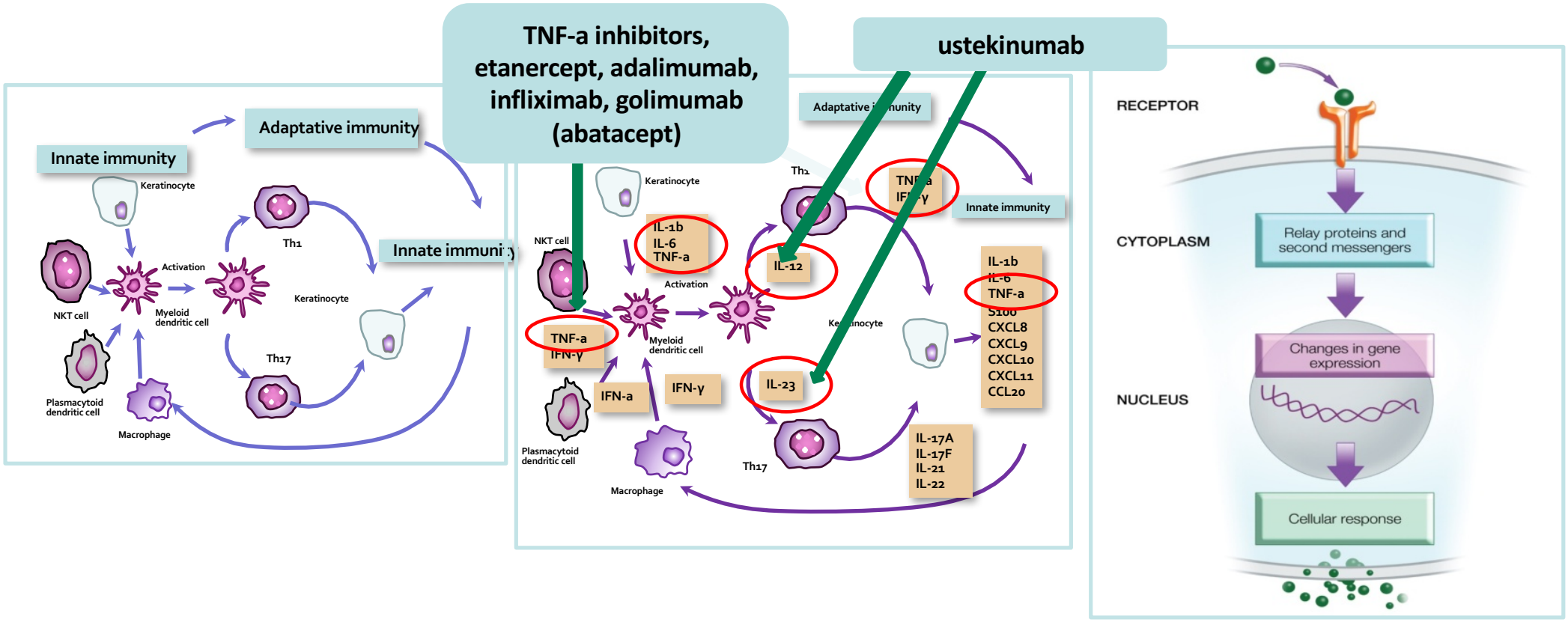
**Inhibition of Th1/17 development/expansion**
Ustekinumab, Briakinumab
(Anti-p40)
MK-3222, CNTO 1959 (anti-p19)

**Anti-IL-17 and IL-17R**
Secukinumab
Ixekizumab,
Brodalumab
**Anti-IL-22**
Fezakinumab

JAK kinase inhibitors
protein kinase C blocker
p38 MAP kinase blocker
**phosphodiesterase-4 inhibitor**
sirtuin agonist
S1P1 agonist
Adenosine A3 receptor inhibitor

# Targeted therapies are being developed to address all parts of the inflammatory pathway

Targeting **cells** → Biologics targeting **cytokines** and **extracellular** signalling → Small molecules targeting **intracellular** signalling pathways




Nestle FO et al. N Engl J Med 2009

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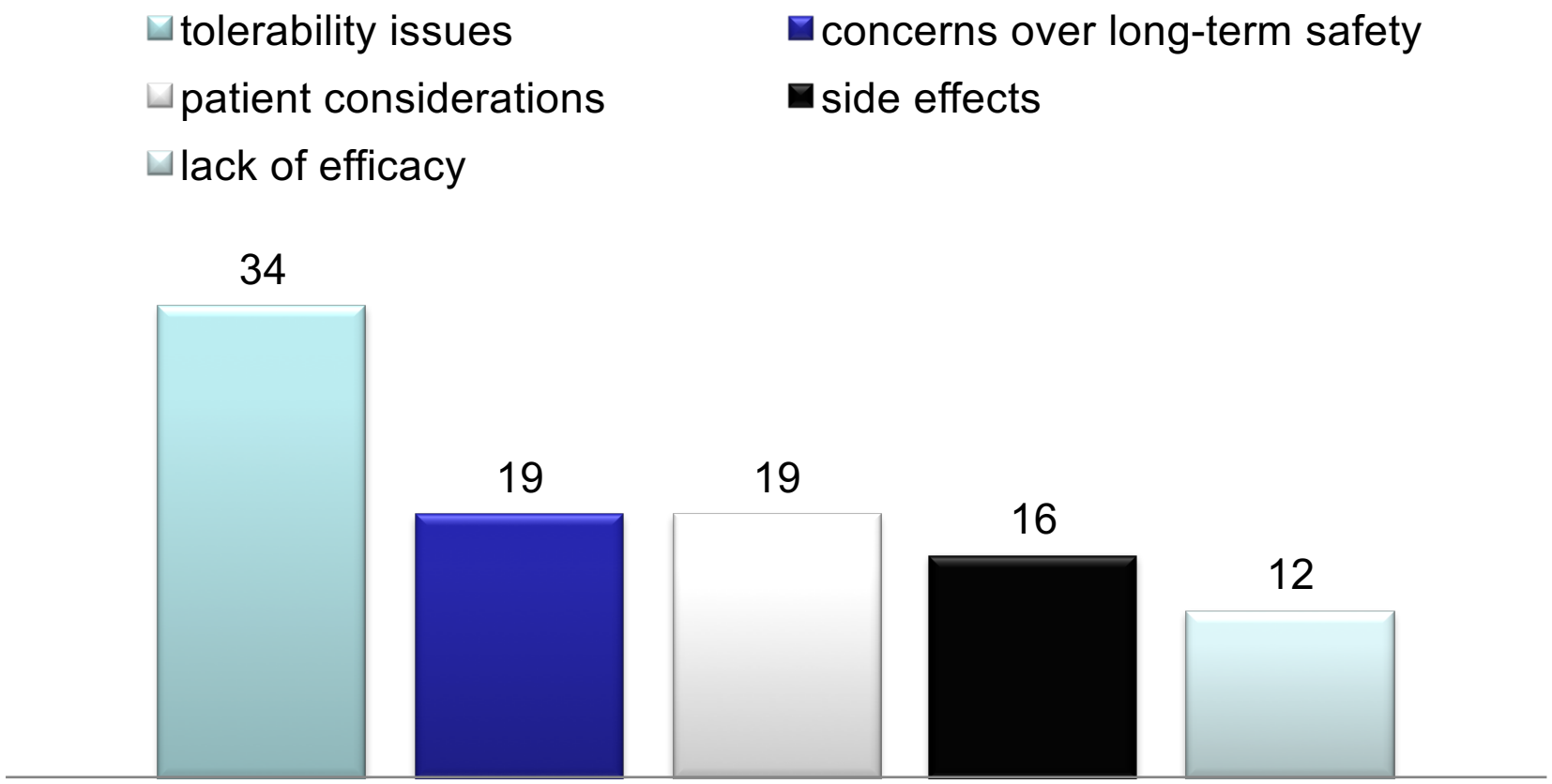
# Management of PsA with current DMARDs

## Reasons for not initiating DMARDs

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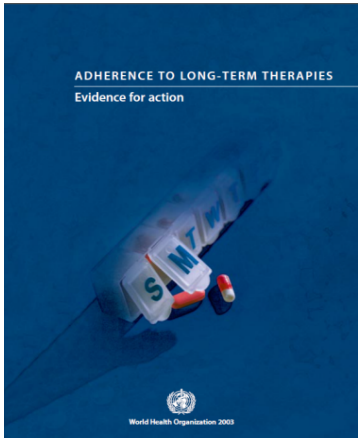
van de Kerkhof et al JEADV 2015 April 16 E-pub

# Oral-Subcutaneous-Intramuscular-Intravenous drug administration. Which Do Patients Prefer?

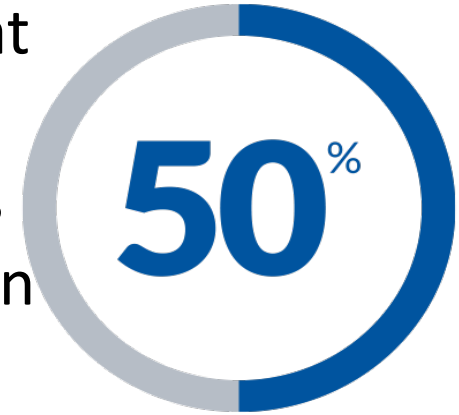
| | <40 | 41-50 | 51-60 | 61-70 | >70 |
|---|---|---|---|---|---|
| Oral | 63% | 46% | 41% | 27% | 28% |
| Subcutaneous | 14% | 38% | 38% | 50% | 55% |
| Intramuscular | 9% | 7% | 4% | 9% | 5% |
| Intravenous | 14% | 9% | 17% | 14% | 13% |

E. Bruschi. ABSTRACT SIR 2015

# Non-adherence is a significant issue in chronic diseases




World Health Organisation estimates that adherence to long-term therapy for chronic illnesses in developed countries averages 50%. The rates are even lower in developing countries.




WHO 2003
www.who.int/chp/knowledge/publications/adherence_full_report.pdf

# Outline

1. GRAPPA recommendations
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# Small Molecules

- Inhibitors of the JAK-STAT signaling pathway
- Syk kinase inhibitors
- MAPK p38 inhibitors
- Phosphodiesterase-4 inhibitors

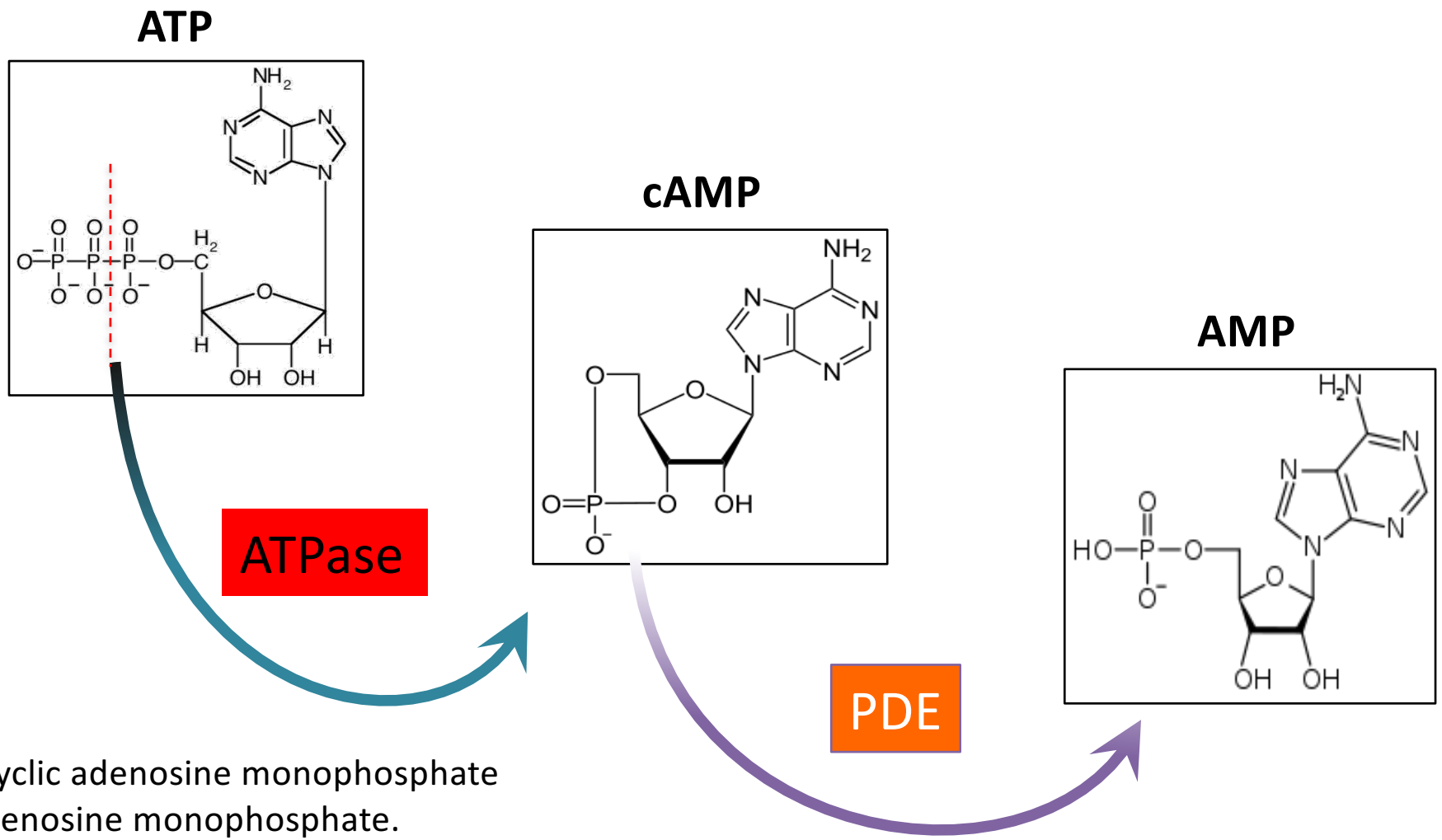
Jacques P, Van den Bosch F. Expert Opin Emerging Drugs 2013

# Small Molecules

- Inhibitors of the JAK-STAT signaling pathway
- Syk kinase inhibitors
- MAPK p38 inhibitors
- **Phosphodiesterase-4 inhibitors**

Jacques P, Van den Bosch F. Expert Opin Emerging Drugs 2013

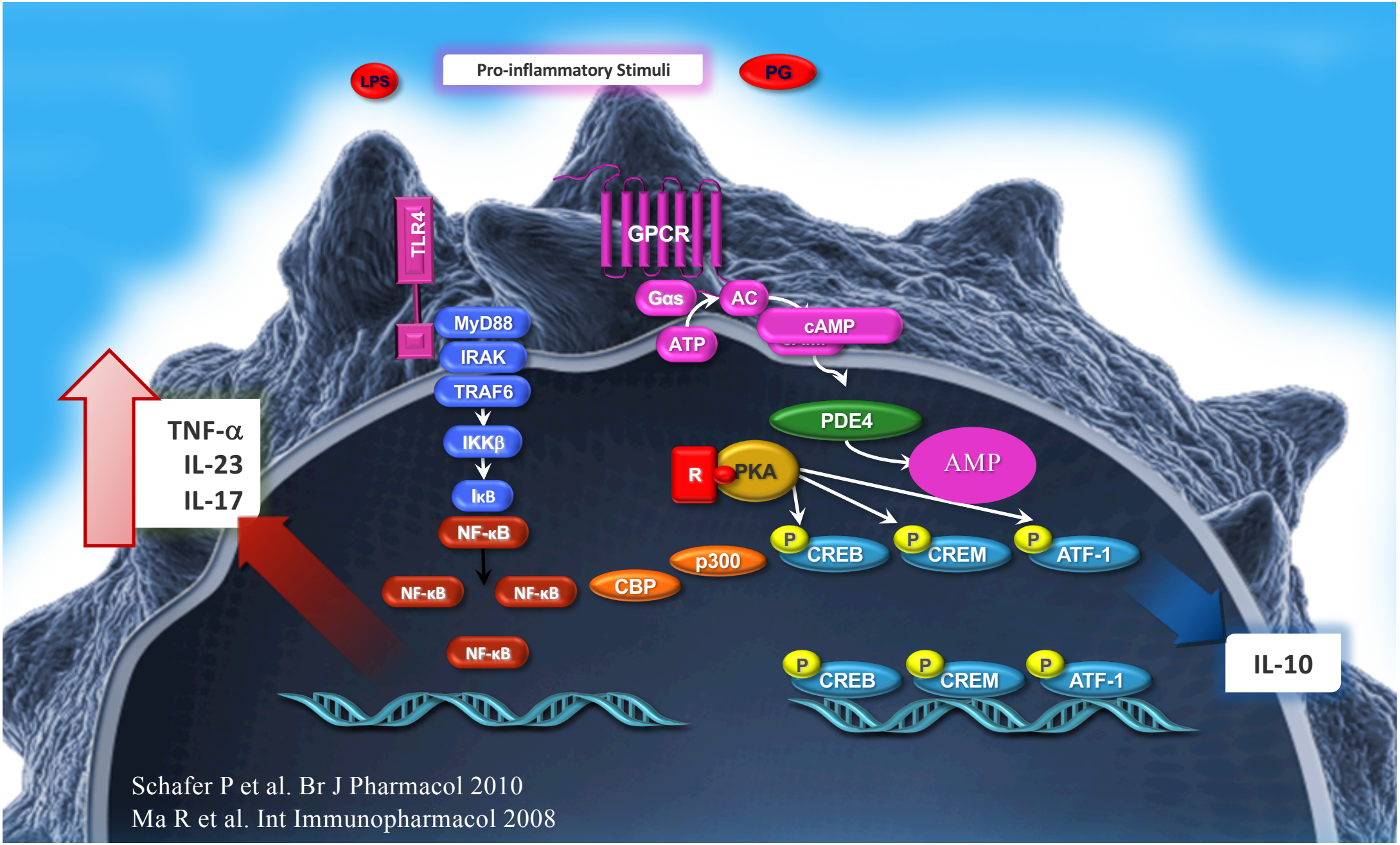
# Phosphodiesterase (PDE) Metabolizes cAMP Into AMP




cAMP = cyclic adenosine monophosphate
AMP = adenosine monophosphate.

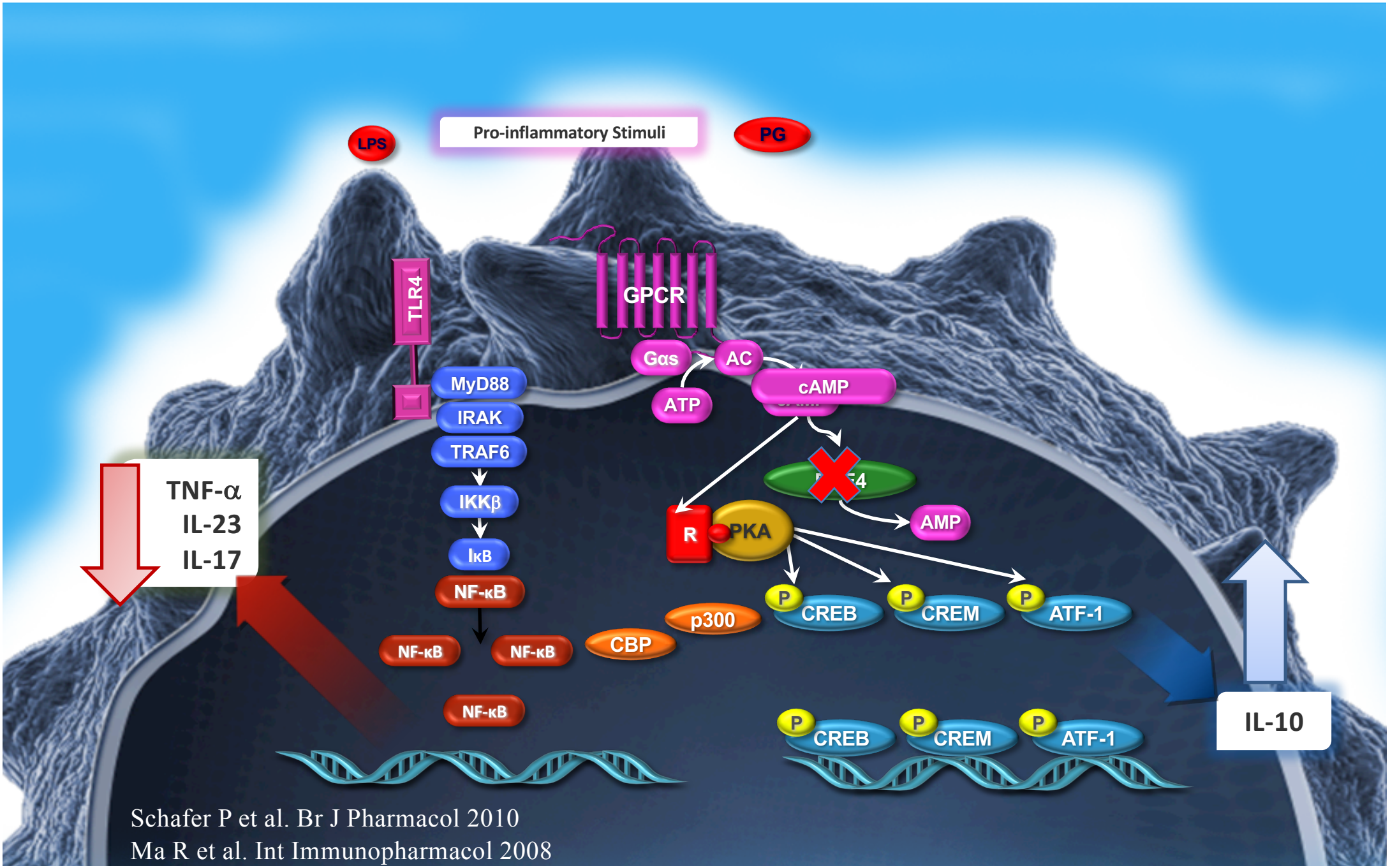
McDonough KA and Rodriguez A. Nat Rev Microbiol 2012

# Apremilast Mechanism of Action




Schafer P et al. Br J Pharmacol 2010
Ma R et al. Int Immunopharmacol 2008

# Apremilast Mechanism of Action




Schafer P et al. Br J Pharmacol 2010
Ma R et al. Int Immunopharmacol 2008

# PDE subtypes

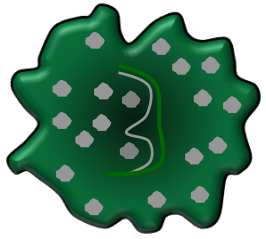
| Type | Metabolite | Tissue Expression | Drugs |
|---|---|---|---|
| 1 | calcium | heart, brain, liver, smooth muscle | |
| 2 | cGMP | adrenal glands, thrombocytes, heart | |
| 3 | cGMP | heart, smooth muscle | Milrinone |
| 4 | cAMP | leukocytes, testis, liver | Apremilast |
| 5 | cGMP | smooth muscle, thrombocyte | Sildenafil |
| 6 | cGMP | thrombocytes, eye (photo receptor) | Dipyridamole |
| 7 | cAMP | skeletal muscle, heart, brain | |
| 8 | cAMP | testis, eye, liver | |
| 9 | cGMP | kidney, liver, lung | |
| 10 | cGMP | testis, brain | |
| 11 | cGMP | skeletal muscle, prostate, kidney | |

Noel S, et al. Front Pharmacol 2012
Kulkarni Sk and Patil CS. Exp Clin Pharmacol 2004

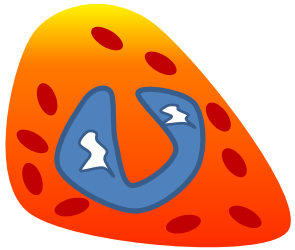
# PDE4 Is the Predominant PDE in Inflammatory Cells

Dendritic cells

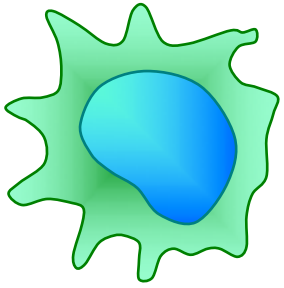
Neutrophils



Eosinophils

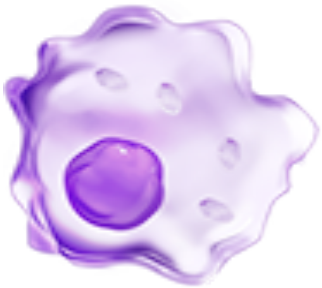


Monocytes



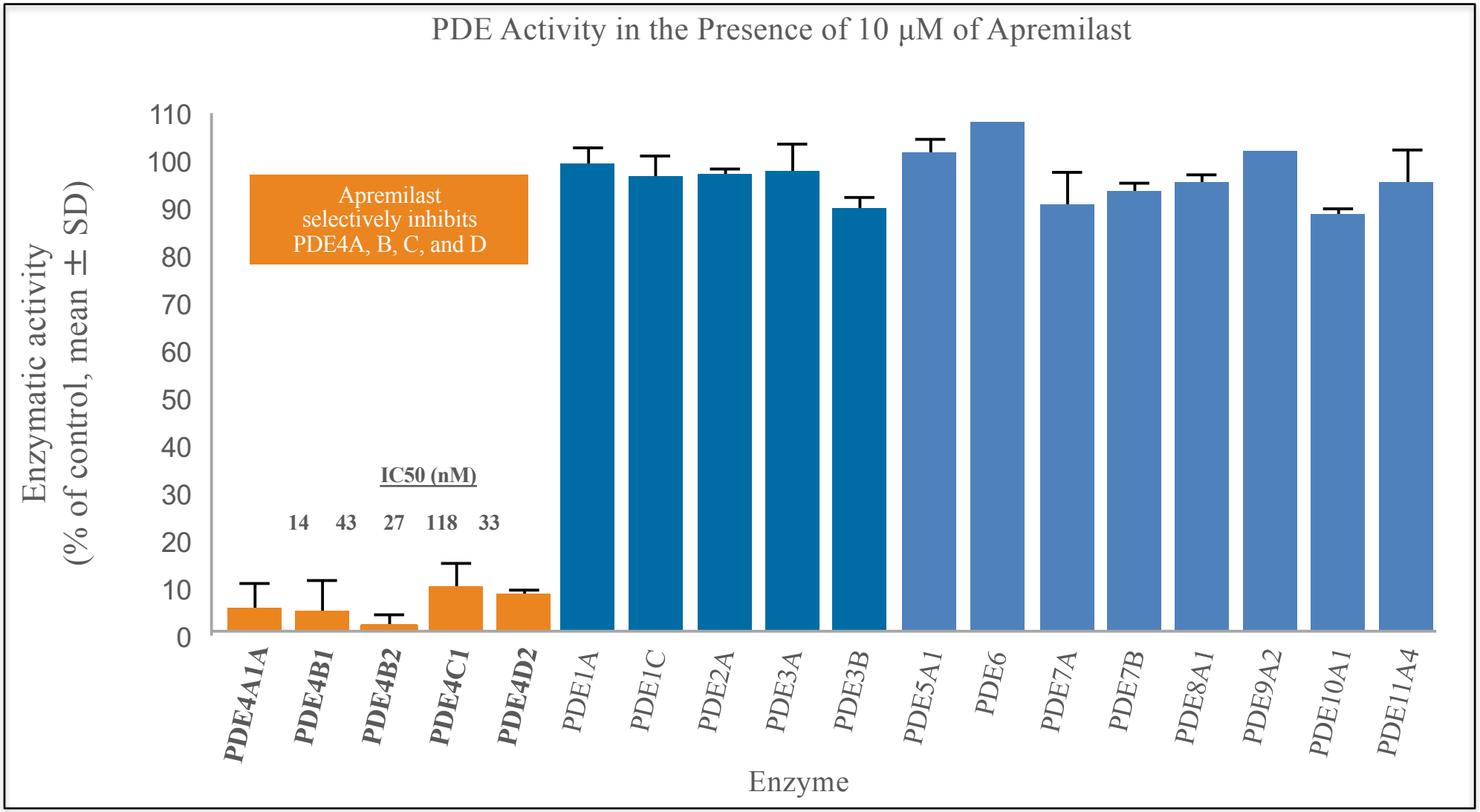
T cells

Macrophages



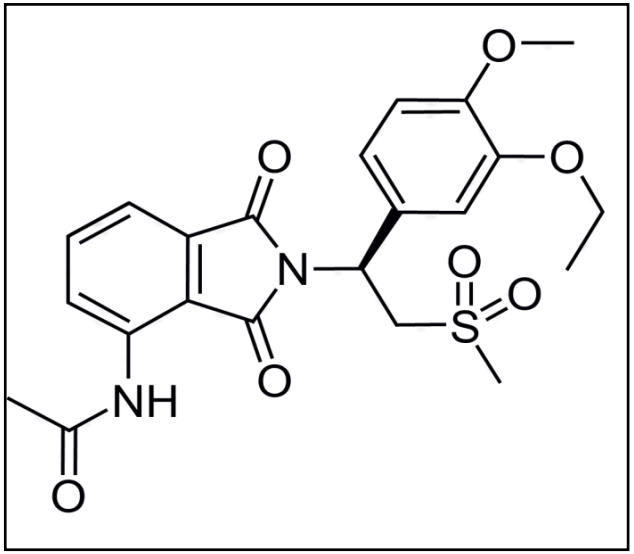
Heystek H et al. Int Immunol 2003
Baumer W et al. Inflam Allergy Drug Targets 2006

# Apremilast effects on PDEs




Schafer P et al. Cell Signal 2014

# Apremilast: Oral pharmacokinetic profile



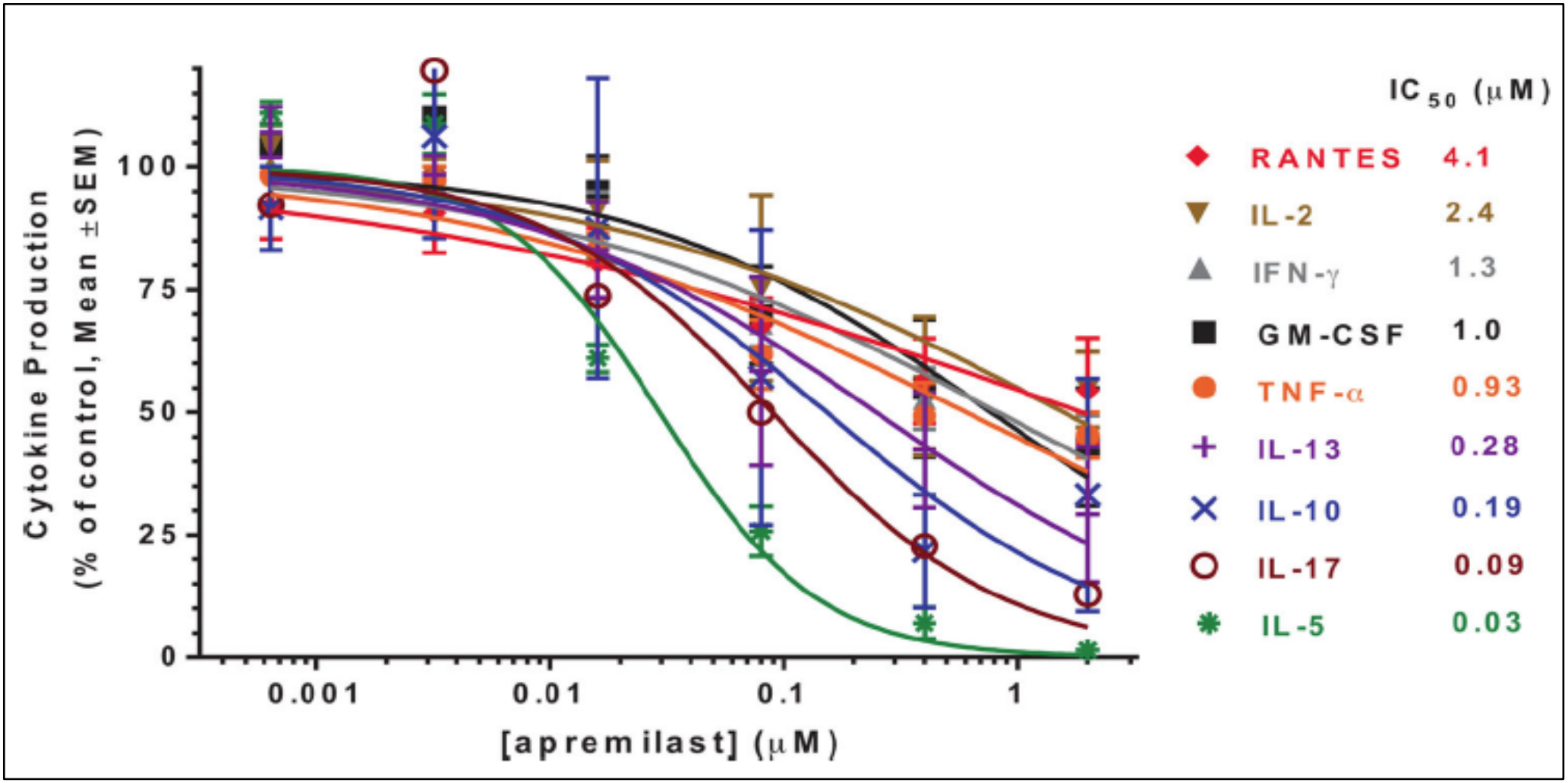
*The dose of apremilast should be reduced to 30 mg once daily in patients with severe renal impairment (CrCL <30 mL/min estimated by the Cockroft-Gault equation)

- †Use with strong cytochrome P450 enzyme inducers (eg rifampicin, phenobarbital, carbemazepine, phenytoin) is not receommended because loss of efficacy may occur

| Attribute | Outcome |
|---|---|
| Absolute bioavailability[1] | ~73% |
| Time to peak plasma concentration[1,2] | $T_{max}$ = ~2.5 hours |
| Food effect [3] | Not clinically significant (AUC ↑24%; $T_{max}$ delayed by 3 hours) |
| Plasma protein binding[2] | 68% |
| Dose proportionality[4] | AUC dose proportional over 10 to 100 mg/day |
| Metabolism[3,5] | CYP oxidative metabolism (primarily CYP3A4), glucoronidation<br>Non-CYP hydrolysis |
| Plasma clearance [3] | 10 L/hour |
| Elimination [2] | $t_{1/2}$ = 6–9 hours |
| Special populations[2]<br>Hepatic impairment<br>Renal impairment*<br>Age >65 years | <br>No effect<br>AUC ↑88%, $C_{max}$ ↑42%<br>AUC ↑13%, $C_{max}$ ↑6% |
| Drug-drug interactions[2,6,7]<br>Methotrexate<br>Ketoconazole<br>Rifampin† | <br>AUC, $C_{max}$ unchanged<br>AUC ↑36% (not significant)<br>AUC ↓72%; $C_{max}$ ↓43% |

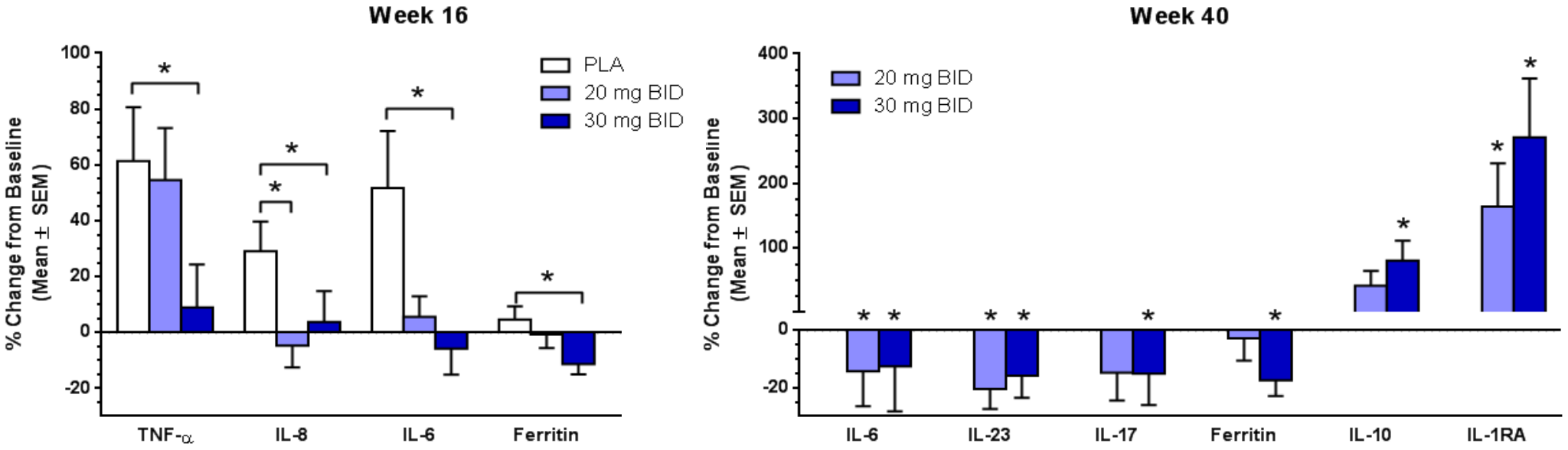
1. Wu A et al. AAPS 2011; 2. OTEZLA [package insert] Celgene Corporation 2014; 3. Wan Y et al. AAPS 2011;
4. Wu A et al. SID 2011; 5. Hoffman M et al. SID 2011; 6. Nissel J et al. EULAR 2011; 7. Wu A et al. AACP 2006

# Apremilast inhibition of Th1, Th2, and Th17 cytokines from primary human T cells stimulated via CD3




Schafer P et al. Cell Signal. 2014

# Inflammatory serum biomarkers during apremilast treatment




*p<0.05 Apremilast vs. Placebo (rank ANCOVA 2 –sided p value);

*p<0.05 Wilcoxon signed rank test (2-sided p value for testing median of zero)

- Significant reduction of circulating **inflammatory cytokines**1
- Significant increases of circulating **anti-inflammatory cytokines IL-10 and IL-1RA**1

IL = interleukin; IL-1RA = interleukin 1 receptor antagonist.

1. Schafer PH, et al. EULAR 2014 [poster SAT0402)

# Outline

1. GRAPPA recommendations
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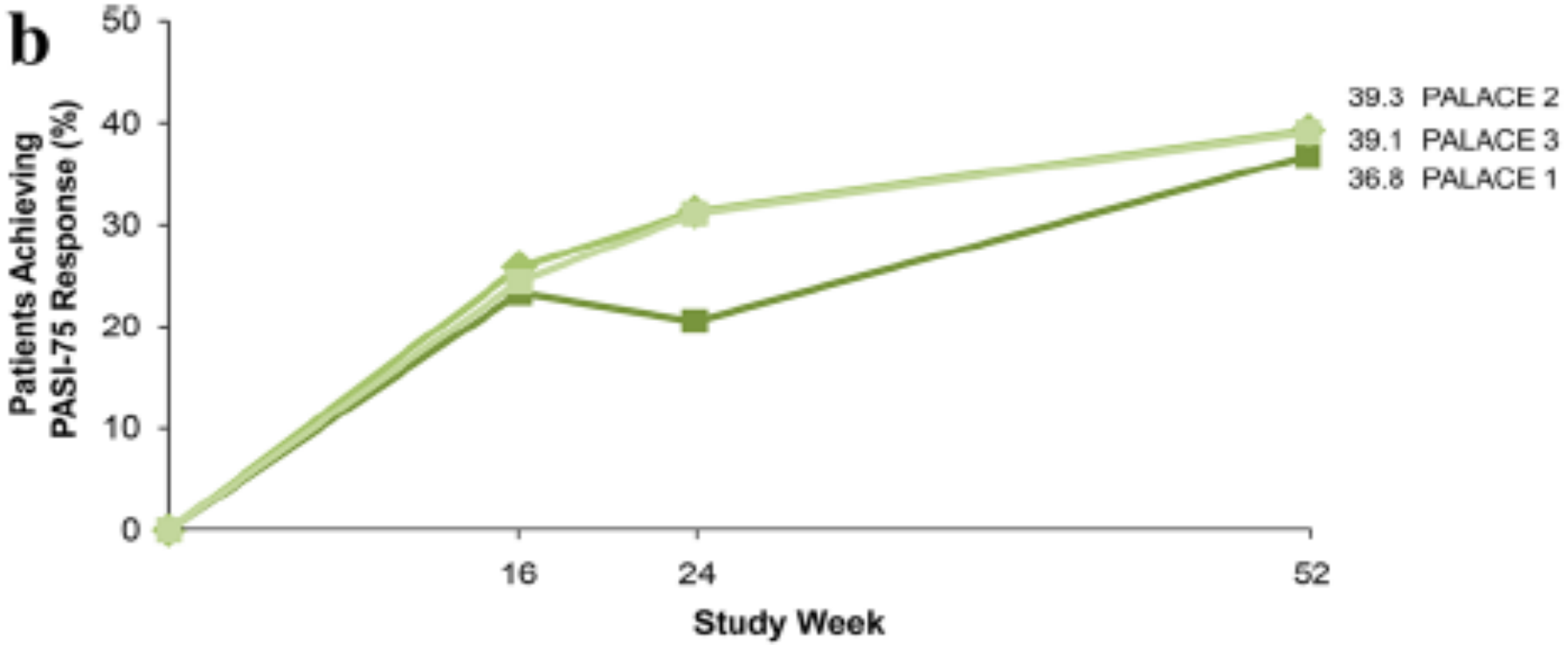
# Summary of Apremilast Trials

| Study | Phase | Indication | Study Design | Status | Patients |
|---|---|---|---|---|---|
| **PSOR-001** | II | Severe psoriasis | Open-label, single-arm | Completed | 19 |
| **PSOR-003** | II | Moderate to severe psoriasis | Double-blind, placebo-controlled, dose-finding | Completed | 259 |
| **PSOR-004** | II | Psoriasis – recalcitrant | Open-label, single-arm, dose-escalation | Completed | 30 |
| **PSOR-005** | IIb | Moderate to severe psoriasis | Double-blind, placebo-controlled, dose-finding | Completed | 352 |
| **PSA-001** | II | Active psoriatic arthritis | Double-blind, placebo-controlled | Completed | 204 |
| **BCT-001** | II | Behçet's disease | Double-blind, placebo-controlled | Completed | 111 |
| **BCT-002** | III | Behçet's disease | Double-blind, placebo-controlled | Recruiting | 204 |
| **AD-001** | II | Moderate to severe atopic dermatitis | Double-blind, placebo-controlled, parallel-group | Recruiting | 189 |
| **RA-002** | II | Rheumatoid arthritis | Double-blind, placebo-controlled | Completed | 237 |
| **POSTURE I** | III | Ankylosing spondylitis | Double-blind, placebo-controlled | Ongoing | 491 |
| **PALACE 1 – 4** | III | Active psoriatic arthritis | Double-blind, placebo-controlled | Completed/ongoing | 2,025 |
| **ESTEEM 1 – 2** | III | Moderate to severe psoriasis | Double-blind, placebo-controlled | Completed/ongoing | 1,257 |

# PASI-75 response over 52 weeks in patients with > 3% body surface area at baseline initially randomized to apremilast 30 mg BID




| | Week 16 | Week 24 | Week 52 |
|---|---|---|---|
| PALACE 1, n/m | 17/74 | 15/73 | 25/68 |
| PALACE 2, n/m | 17/66 | 21/67 | 22/56 |
| PALACE 3, n/m | 19/78 | 23/74 | 25/64 |

Kavanaugh A et al. EULAR Paris 2014

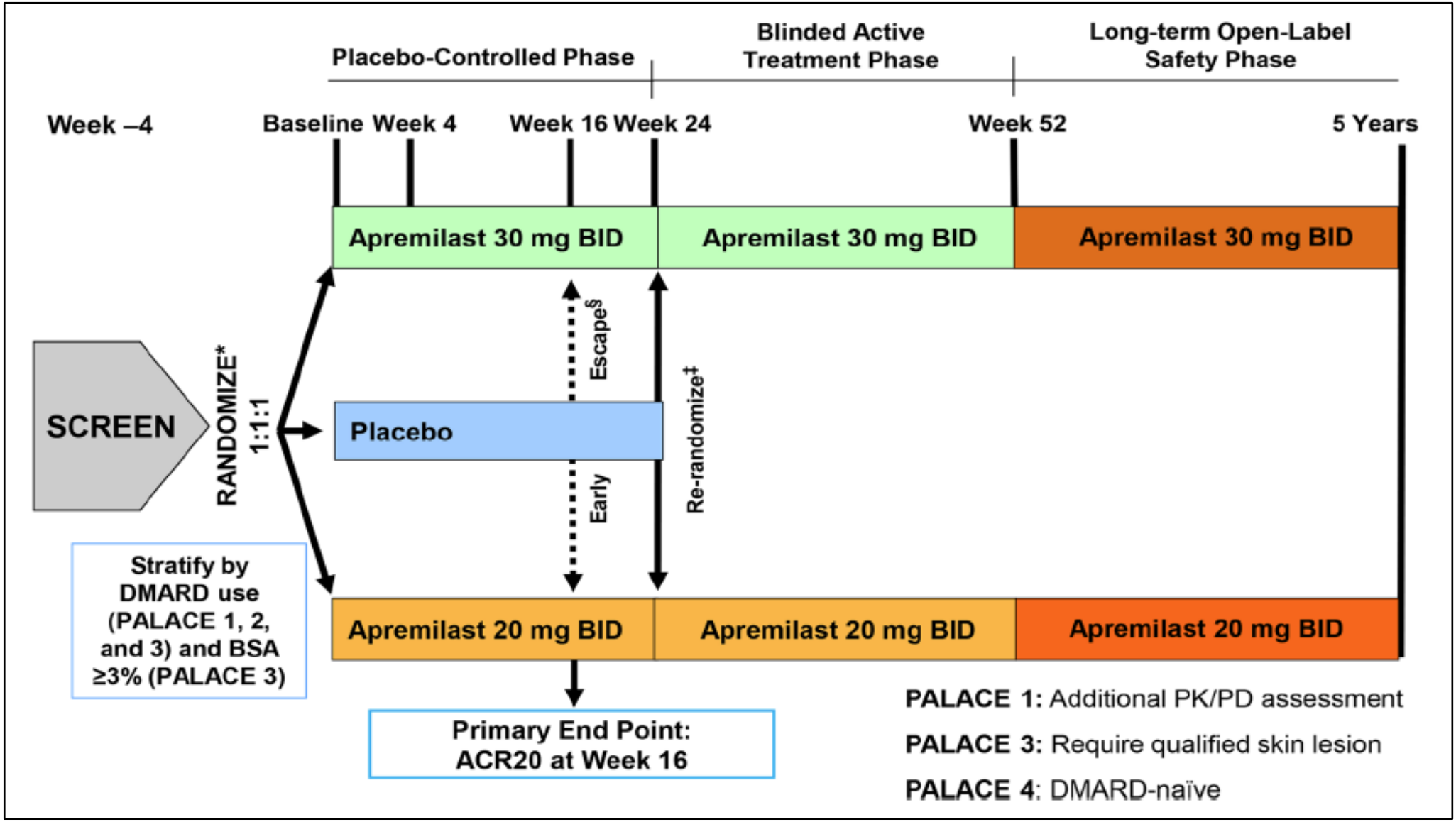
Mease P. Rheumatol Ther 2014

# PALACE Phase III Program Overview

4 large multi-centre studies
200+ sites in 25 countries
2,026 patients recruited globally

| Study | Patient population | Endpoints |
|---|---|---|
| PALACE 1 (n=504) | Active PsA; DMARD-experienced | **Primary**<br>ACR20 at Week 16 |
| PALACE 2 (n=488) | | **Key secondary**<br>Mean change in HAQ-DI at Week 16 |
| PALACE 3* (n=505) | (*also with psoriatic skin lesion ≥ 2 cm) | **Other secondary**<br>ACR50, ACR70, TJC, SJC, SF-36, pain VAS score, dactylitis severity score, MASES (enthesitis) score, PASI-75 |
| PALACE 4 (n=529) | Active PsA: DMARD naive | |

# PALACE: Study Design




Gladman D et al. ACR 2013
Edwards C et al. EULAR 2014

Mease P. Rheumatol Ther 2014

# PALACE: Study Population

- Documented diagnosis of PsA for ≥ 6 months (CASPAR criteria)
- A minimum of both three swollen and three tender joints
- Prior or current treatment with traditional DMARDs and/or biologic treatment
- Concurrent treatment with stable dose of Methotrexate, sulfasalazine and/or leflunomide was allowed
- Stable doses of oral corticosteroids
- Key exclusion criteria were failure of more than three agents for PsA (DMARDs or biologics) or more than one tumour necrosis factor blocker.
- PALACE 3: at least one ≥2 cm plaque psoriasis lesion

# PALACE Program: Baseline Demographics and Disease Characteristics

**Pooled PALACE 1, 2, and 3**

| | Placebo (n=496) | Apremilast 30 mg BID (n=497) |
|---|---|---|
| Age, mean, years[1] | 50.6 | 50.6 |
| Female, n (%)[1] | 256 (51.6) | 275 (55.3) |
| White, n (%)[1] | 463 (93.3) | 472 (95.0) |
| Weight, mean, kg[1] | 86.41 | 85.27 |
| BMI, mean, kg/m$^2$ [(1)] | 30.0 | 29.7 |
| Duration of PsA, mean, years[1] | 7.3 | 7.5 |
| PsA subtype[2] | | |
| Asymmetrical oligoarthritis | 138 (27.8) | 136 (27.4) |
| Symmetric polyarthritis | 298 (60.1) | 309 (62.2) |
| Predominant distal interphalangeal | 34 (6.9) | 28 (5.6) |
| Predominant spondylitis | 7 (1.4) | 12 (2.4) |
| Arthritis mutilans | 18 (3.6) | 12 (2.4) |

Otezla SmPC January 2015

Mease PJ et al. ACR 2013

# PALACE Program:
# Prior and Concomitant Treatments

Pooled PALACE 1, 2, and 3

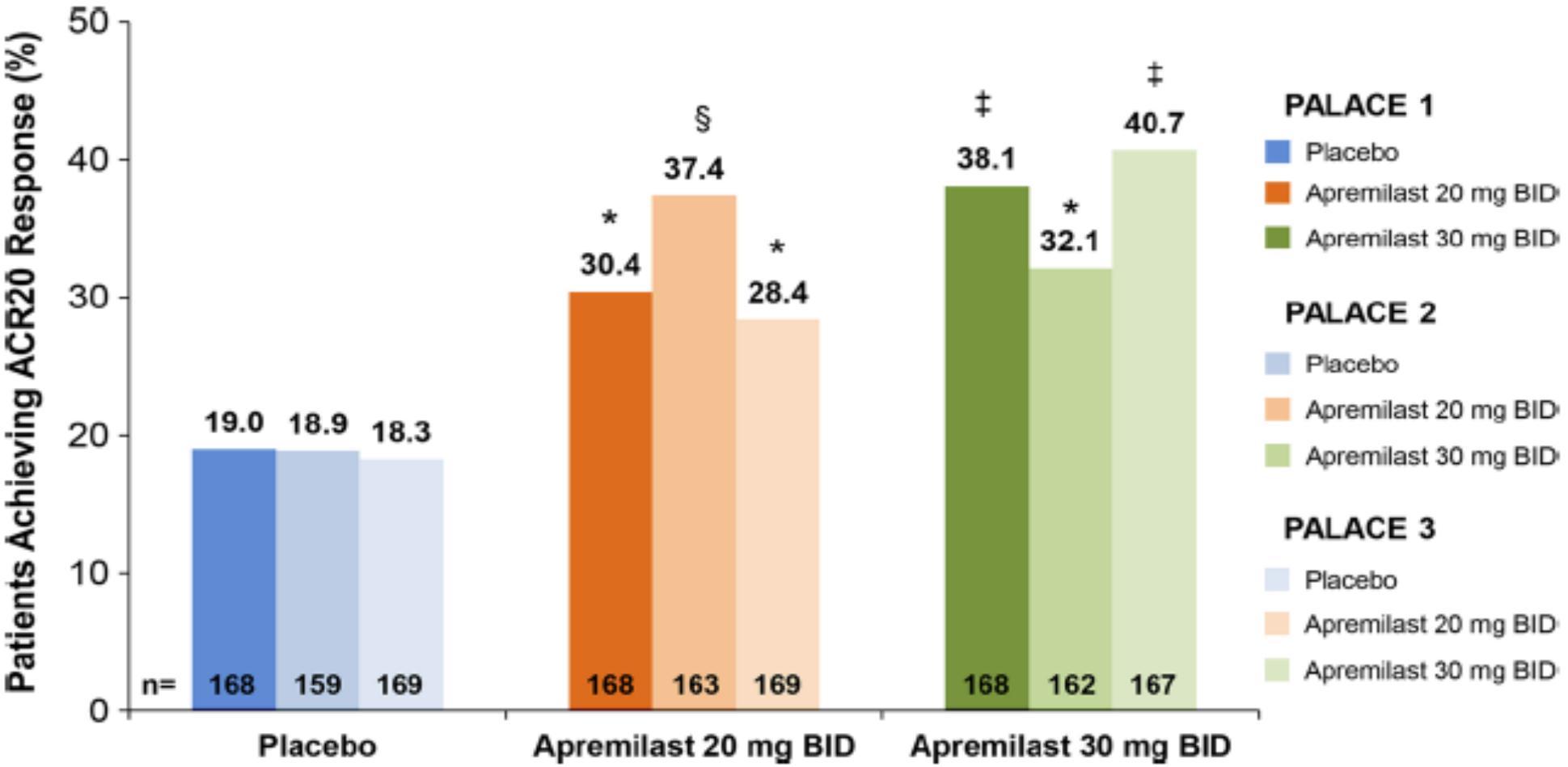
| Treatments, n (%) | Study Population (N=1493) |
|---|---|
| **Prior therapy[1]** | |
| Small-molecule DMARD only | 1140 (76.4) |
| Biologic | 334 (22.4) |
| **Concomitant therapy[2]** | |
| 0 small-molecule DMARDs | 520 (34.8) |
| ≥1 small-molecule DMARDs | 973 (65.2) |
| Low-dose corticosteroids | 207 (13.9) |
| NSAIDs | 1055 (70.7) |

Concomitant therapy with biologics was not permitted in the PALACE studies

Otezla SmPC January 2015

Mease PJ et al. ACR 2013

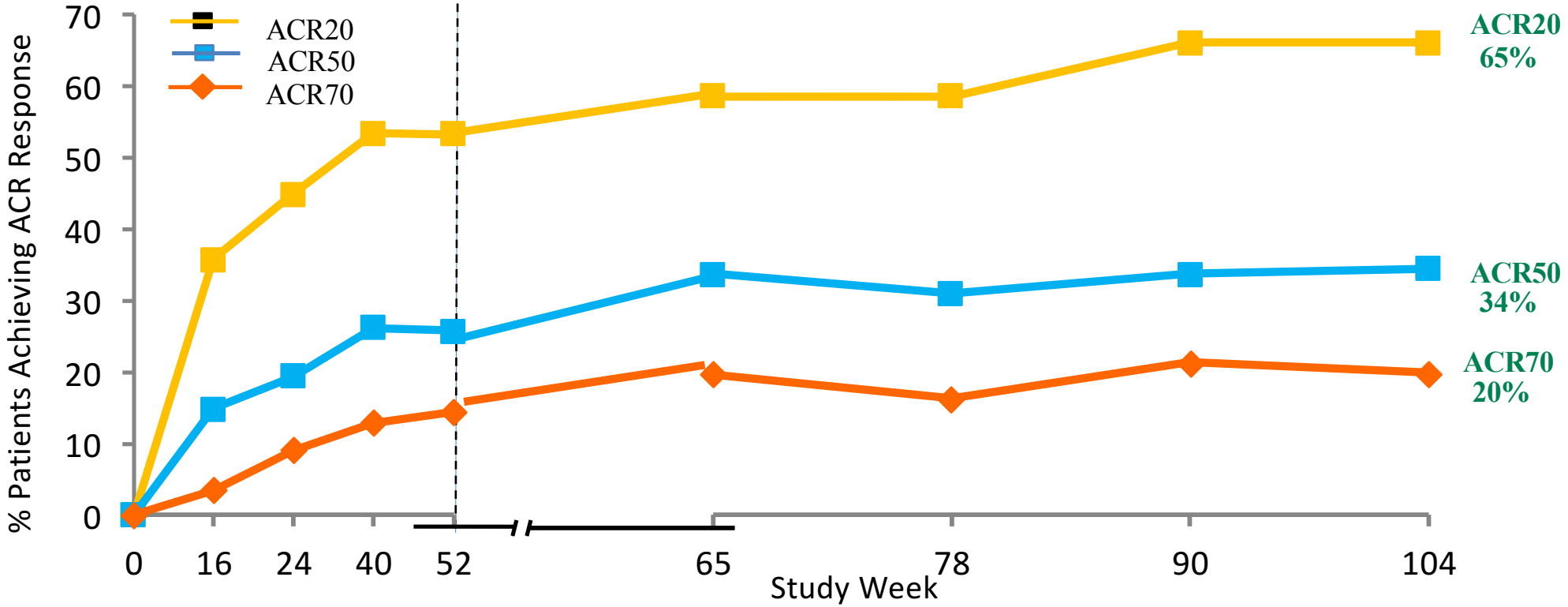
# ACR20 response at week 16 in PALACE 1, 2, and 3 trials




Blanco F et al. PANLAR 2014

Mease P. Rheumatol Ther 2014

# Patients achieving modified ACR20/50/70 over a 2-year apremilast (30 mg BID) treatment period

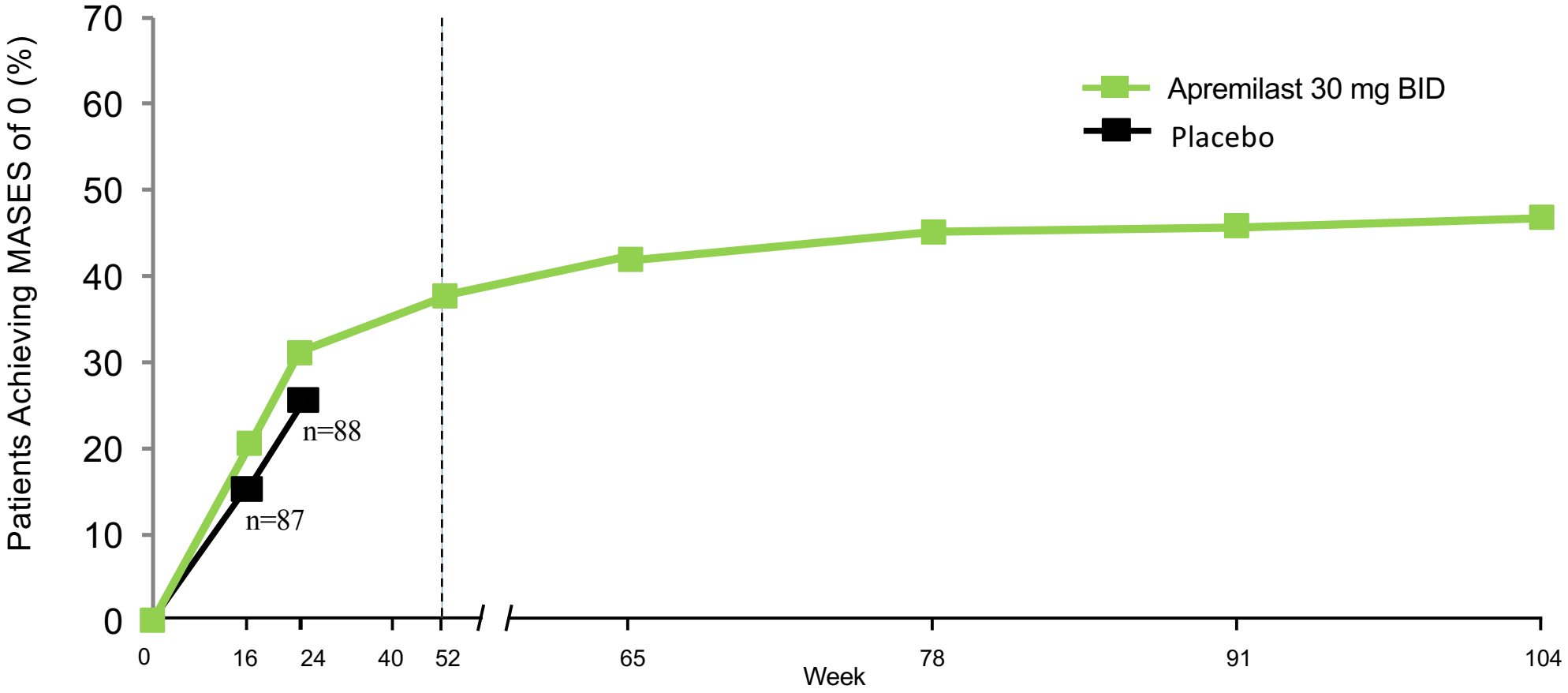



| | | | | | |
|---|---|---|---|---|---|
| ACR20: Apremilast 30 mg BID, n/m | 101/190 | 96/166 | 92/159 | 98/150 | 94/144 |
| ACR50: Apremilast 30 mg BID, n/m | 49/191 | 56/168 | 49/160 | 50/150 | 49/144 |
| ACR70: Apremilast 30 mg BID, n/m | 27/191 | 33/169 | 26/161 | 32/152 | 28/143 |

Analyses includes all patient data, including the placebo-controlled period, regardless of when patients started taking apremilast (baseline, Week 16 or Week 24). n/m=number of responders/patients with sufficient data for evaluation.

Kavanaugh A et al. ACR 2014

# Patients with complete resolution of enthesitis symptoms over a 2-year apremilast treatment period

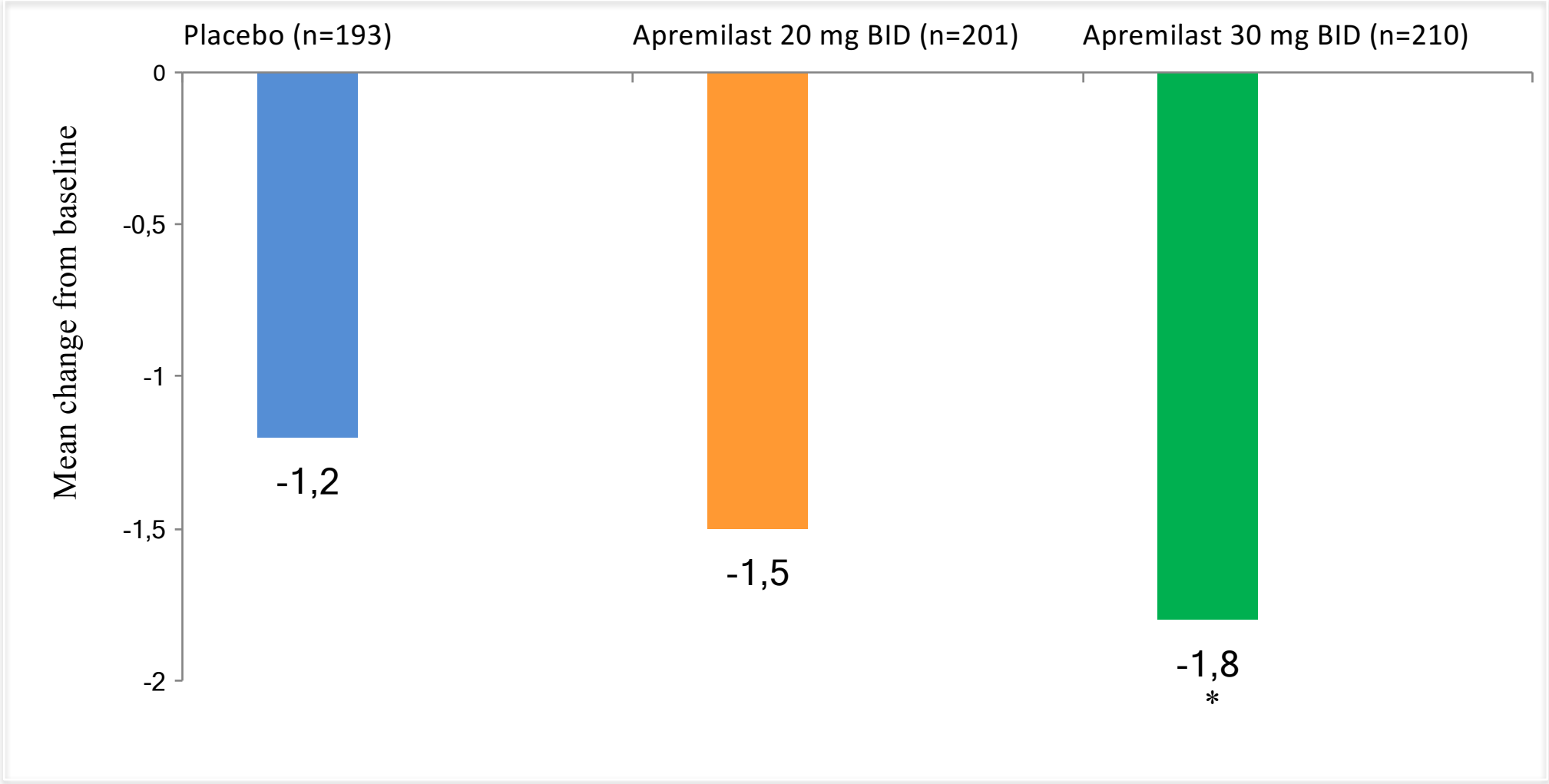



| | | | | | |
|---|---|---|---|---|---|
| Apremilast 30 mg BID, n/m | 142/377 | 147/341 | 154/329 | 149/314 | 147/302 |

PALACE 1-3 Pooled

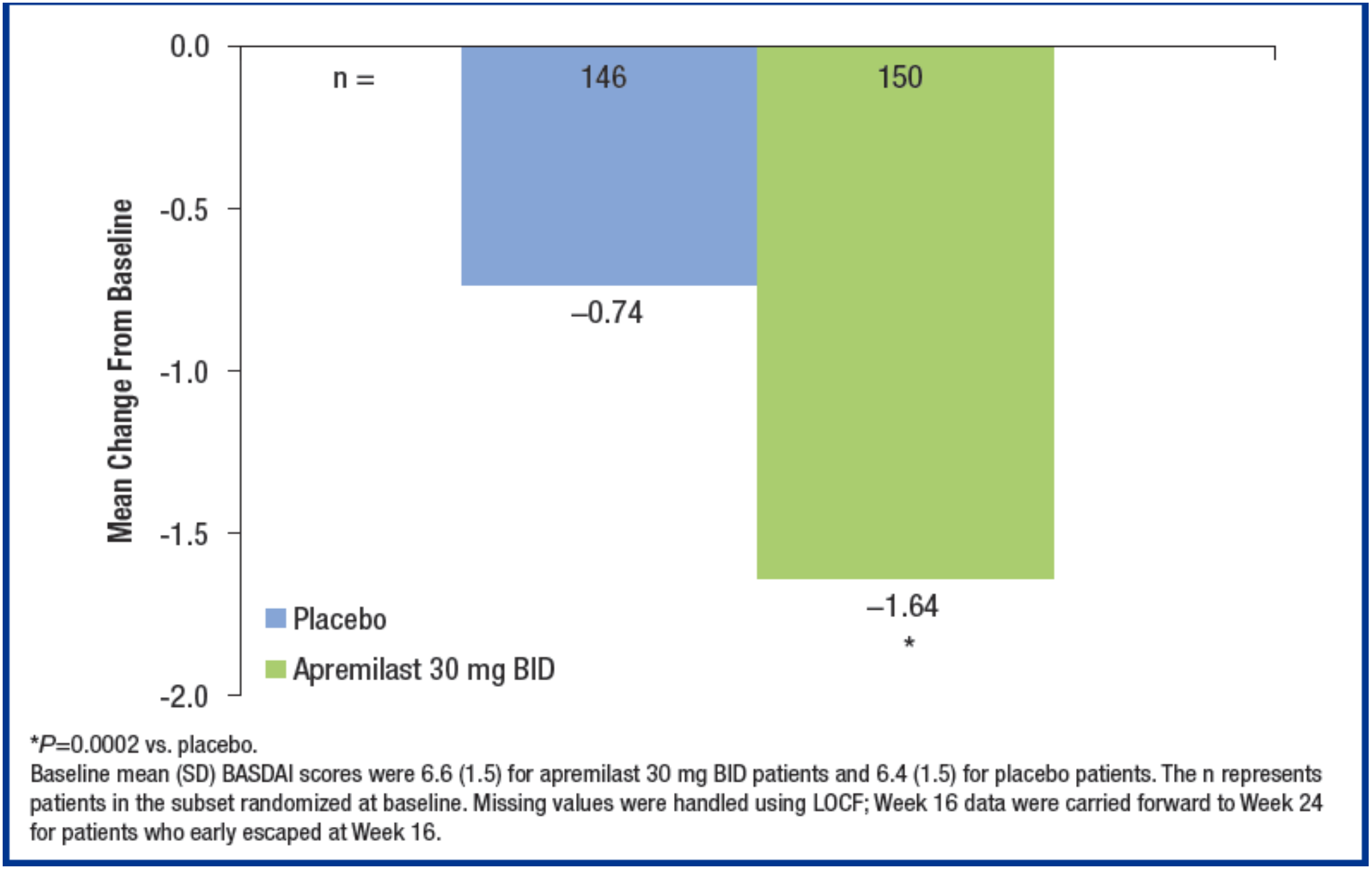
Gladman D et al. EULAR 2015

# Apremilast significantly improved dactylitis count at Week 24




Gladman D et al. ACR 2013

# Mean BASDAI Change From Baseline at Wk 24 in the BADSAI > 4 Subset



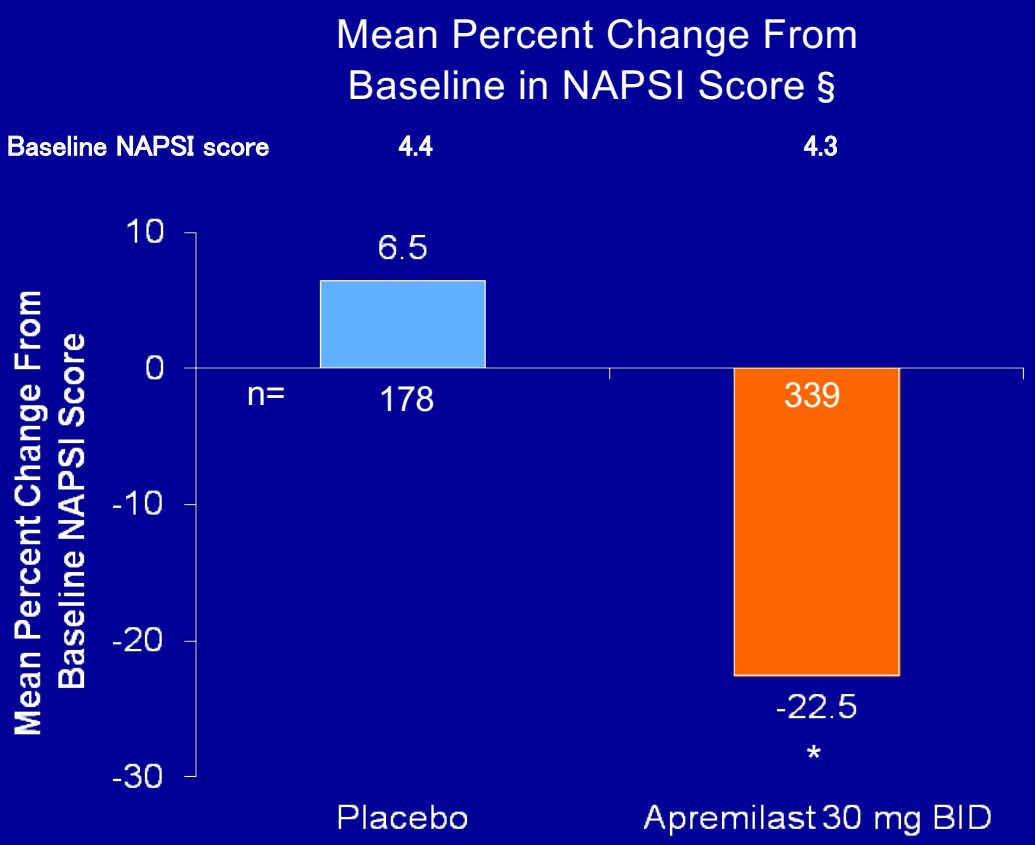

*$P$=0.0002 vs. placebo.

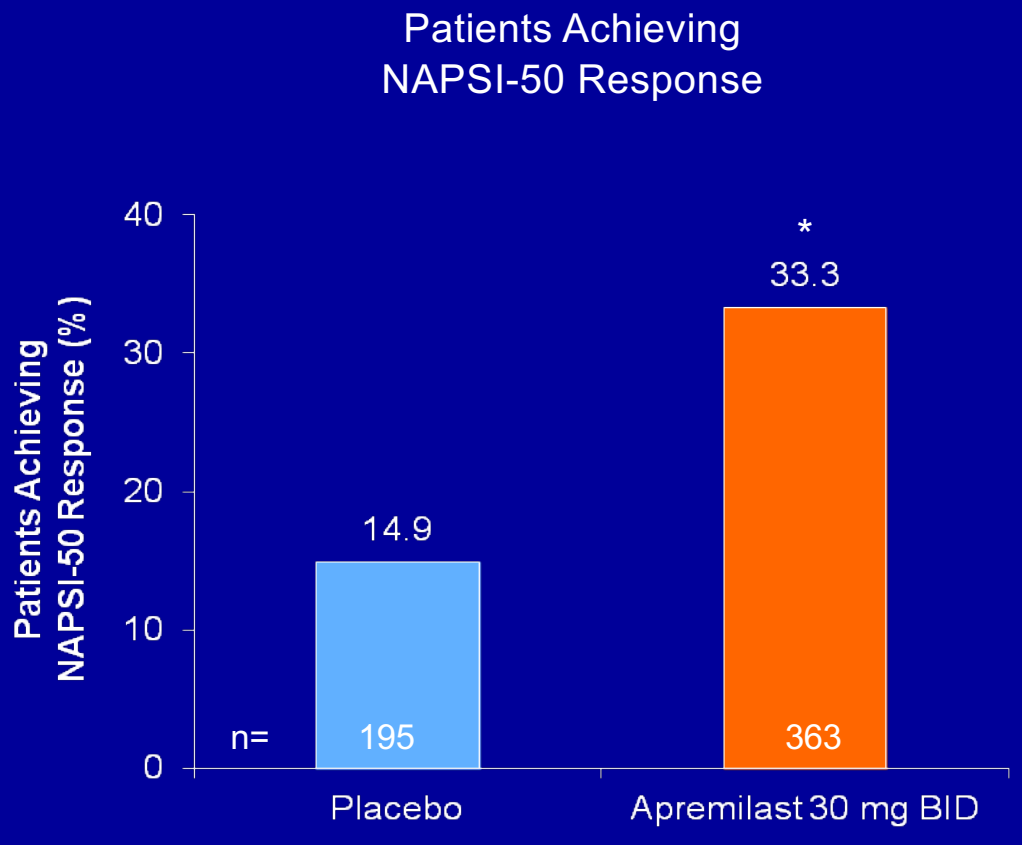
Baseline mean (SD) BASDAI scores were 6.6 (1.5) for apremilast 30 mg BID patients and 6.4 (1.5) for placebo patients. The n represents patients in the subset randomized at baseline. Missing values were handled using LOCF; Week 16 data were carried forward to Week 24 for patients who early escaped at Week 16.

Mease PJ et al, EULAR 2016, Poster THU0420

# ESTEEM: Mean Percent Change in NAPSI and NAPSI-50 Response at Week 16

**Period A**
**Full Analysis Set, LOCF**




*$P$<0.0001 vs. placebo.

§ Patients with a non-zero baseline value and at least one post-baseline value are included.

Papp K, et al. *J Am Acad Dermatol.* Published online: doi: 10.1016/j.jaad.2015.03.049. Reich K, et al. AAD 2013 [LB oral presentation]. Data on file, Celgene.

# Overview of AEs (Wk ≤156)

| | Apremilast-Exposure Period* Weeks 0 to ≤52 Apremilast | | Apremilast-Exposure Period* Weeks >52 to ≤104 Apremilast | | Apremilast-Exposure Period* Weeks >104 to ≤156 Apremilast | |
|---|---|---|---|---|---|---|
| | 30 mg BID n=721 | 20 mg BID n=720 | 30 mg BID n=520 | 20 mg BID n=508 | 30 mg BID n=443 | 20 mg BID n=422 |
| **Patients, n (%)** | | | | | | |
| ≥1 AE | 524 (72.7) | 507 (70.4) | 315 (60.6) | 324 (63.8) | 276 (62.3) | 267 (63.3) |
| ≥1 SAE | 47 (6.5) | 40 (5.6) | 35 (6.7) | 40 (7.9) | 37 (8.4) | 33 (7.8) |
| AE leading to drug withdrawal | 56 (7.8) | 52 (7.2) | 13 (2.5) | 12 (2.4) | 6 (1.4) | 8 (1.9) |
| Death | 0 (0.0) | 1§ (0.1) | 1‡ (0.2) | 0 (0.0) | 0 (0.0) | 0 (0.0) |
| **AEs in ≥5% of patients, any treatment group, n (%)** | | | | | | |
| Diarrhea | 112 (15.5) | 88 (12.2) | 20 (3.8) | 10 (2.0) | 11 (2.5) | 13 (3.1) |
| Nausea | 108 (15.0) | 69 (9.6) | 11 (2.1) | 8 (1.6) | 10 (2.3) | 4 (0.9) |
| Upper respiratory tract infection | 60 (8.3) | 71 (9.9) | 27 (5.2) | 40 (7.9) | 23 (5.2) | 29 (6.9) |
| Headache | 75 (10.4) | 61 (8.5) | 17 (3.3) | 14 (2.8) | 12 (2.7) | 11 (2.6) |
| Nasopharyngitis | 41 (5.7) | 48 (6.7) | 31 (6.0) | 29 (5.7) | 19 (4.3) | 30 (7.1) |

*Includes all patients who received apremilast during the time interval relative to the start of apremilast administration.

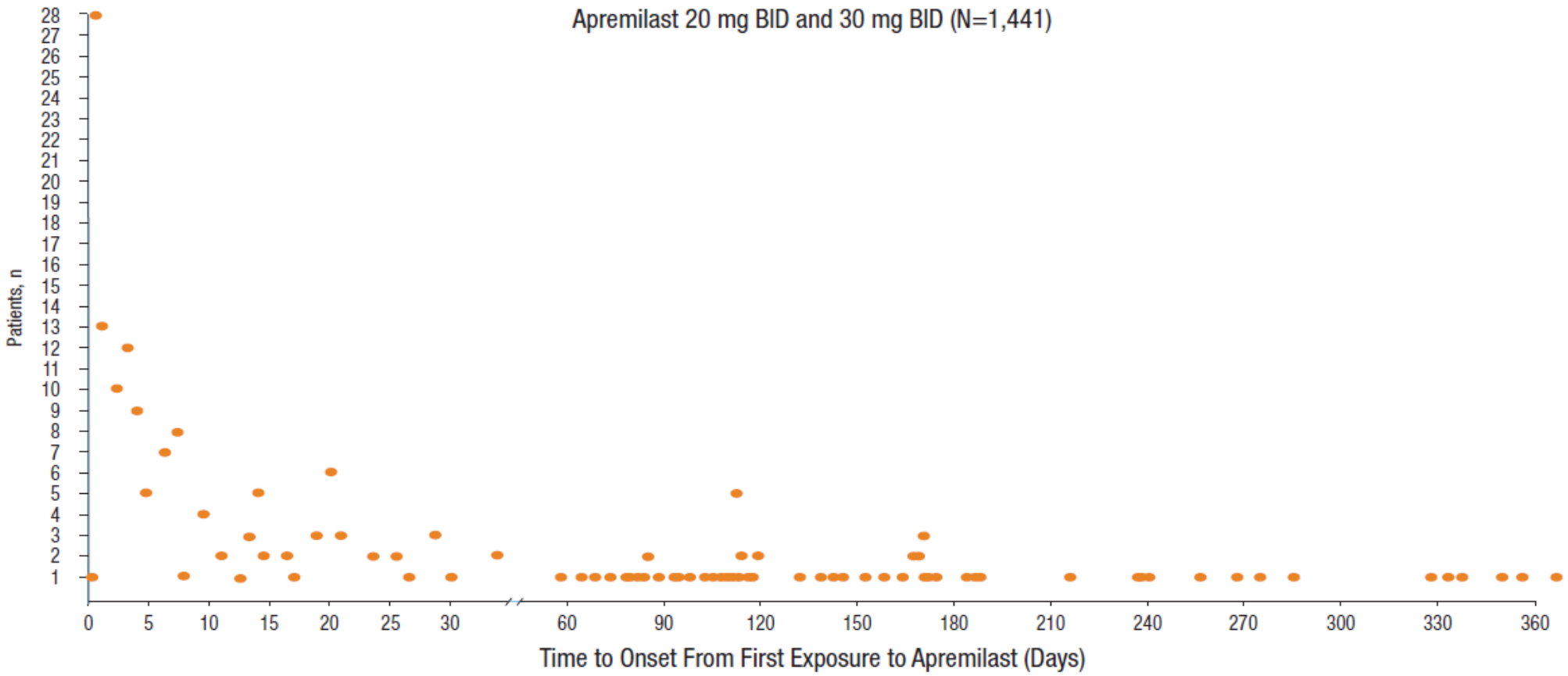
§Multiorgan failure not suspected to be treatment related.

‡Motor vehicle accident on Study Day 489.

Mease PJ, et al. EULAR 2016

*PAL1-3, 3 Yr Pooled Safety*

# Time to Onset of Nausea




- Nausea occurred most often in the first 2 weeks of exposure to apremilast; a reduced incidence of these AEs was seen after the first month of dosing

AEs=adverse events.

Mease P, et al. Presented at: EULAR 2014 (SAT0408)

# Most Common GI AEs leading to discontinuation (Wk ≤104)

| | Apremilast-Exposure Period* Weeks 0 to ≤52 Apremilast | | Apremilast-Exposure Period* Weeks >52 to ≤104§ Apremilast | |
|---|---|---|---|---|
| Patients, n (%) | 20 mg BID n=245 | 30 mg BID n=245 | 20 mg BID n=173 | 30 mg BID n=171 |
| GI AE leading to drug withdrawal | 4 (1.6) | 12 (4.9) | 0 (0.0) | 1 (0.6) |
| Diarrhea | 0 (0.0) | 6 (2.4) | 0 (0.0) | 1 (0.6) |
| Nausea | 3 (1.2) | 4 (1.6) | 0 (0.0) | 0 (0.0) |
| Upper abdominal pain | 0 (0.0) | 2 (0.8) | 0 (0.0) | 0 (0.0) |
| Gastroesophageal reflux disease | 0 (0.0) | 2 (0.8) | 0 (0.0) | 0 (0.0) |
| Vomiting | 1 (0.4) | 1 (0.4) | 0 (0.0) | 0 (0.0) |
| Dyspepsia | 1 (0.4) | 0 (0.0) | 0 (0.0) | 0 (0.0) |
| Abdominal discomfort | 1 (0.4) | 0 (0.0) | 0 (0.0) | 0 (0.0) |

*Includes all patients who received apremilast during the time interval relative to the start of apremilast administration.

GI=gastrointestinal; AEs=adverse events.

Mease PJ, et al. ACR 2014 [poster 1564].

# Pooled PALACE 1, 2, and 3: Adverse Events of Special Interest

| | Exposure-adjusted incidence rate/100 patient-years[a] | | |
|---|---|---|---|
| | **Placebo (168.2 patient-years)** | **Apremilast 20 mg (766.4 patient-years)** | **Apremilast 30 mg (769.0 patient-years)** |
| **Major adverse cardiac events** | 0.0 | 0.3 | 0.1 |
| **Malignancies** | | | |
| Hematologic | 0.0 | 0.1 | 0.0 |
| Skin (excluding melanoma) | 1.2 | 0.4 | 0.5 |
| Solid tumors | 0.6 | 0.3 | 0.1 |
| **Infections** | | | |
| Non-opportunistic serious | 0.6 | 0.4 | 0.5 |
| Opportunistic (systemic) | 0.6 | 0.0 | 0.0 |
| New cases of tuberculosis (TB)[b] | 0.0 | 0.0 | 0.0 |
| Reactivation of TB | 0.0 | 0.0 | 0.0 |

aExposure-adjusted incidence rate/100 patient-years is 100 times the number (n) of patients reporting the event divided by patient-years (up to the first event start date for patients reporting the event).
bPatients with a history of active or incompletely treated TB were excluded from the trials. The trials included 32 patients with a history of fully treated TB, a positive PPD or QuantiFERON, or a history of receiving preventive medication for TB.

Mease PJ et al. ACR 2013

# Pooled PALACE 1, 2, and 3: marked lab abnormalities

| Patients, n/m (%)[b] | Apremilast-Exposure Period[a] Up to 52 Weeks of Exposure | | Apremilast-Exposure Period[a] 52 to 104 Weeks of Exposure | |
|---|---|---|---|---|
| | Apremilast 20 mg BID (n=245) | Apremilast 30 mg BID (n=245) | Apremilast 20 mg BID (n=173) | Apremilast 30 mg BID (n=171) |
| Alanine aminotransferase >3 × ULN | 4/243 (1.6) | 3/245 (1.2) | 1/170 (0.6) | 1/171 (0.6) |
| Creatinine >1.7 × ULN | 0/243 (0.0) | 0/245 (0.0) | 0/170 (0.0) | 0/171 (0.0) |
| Leukocytes <1.5, $10^9$/L | 0/243 (0.0) | 0/245 (0.0) | 0/170 (0.0) | 0/171 (0.0) |
| Neutrophils <1, $10^9$/L | 0/243 (0.0) | 0/245 (0.0) | 1/170 (0.6) | 3/171 (1.8) |
| Platelets <75, $10^9$/L | 0/243 (0.0) | 0/245 (0.0) | 0/170 (0.0) | 0/171 (0.0) |
| Hemoglobin, males <10.5 g/dL, females <8.5 g/dL | 1/243 (0.4) | 1/245 (0.4) | 0/170 (0.0) | 0/171 (0.0) |

- The Prescribing Information for apremilast has no requirement for routine laboratory monitoring[2]

ULN = upper limit of normal.
aIncludes all patients who received apremilast during the time interval relative to the start of apremilast administration.
bRepresents the number of patients with ≥1 occurrence of the abnormality at any time point/number of patients with ≥1 post-baseline value.

Otezla SmPC January 2015

Mease PJ et al. ACR 2013

# Apremilast: oral therapy administered as one 30 mg tablet twice daily

**Initial 5-day titration period:**

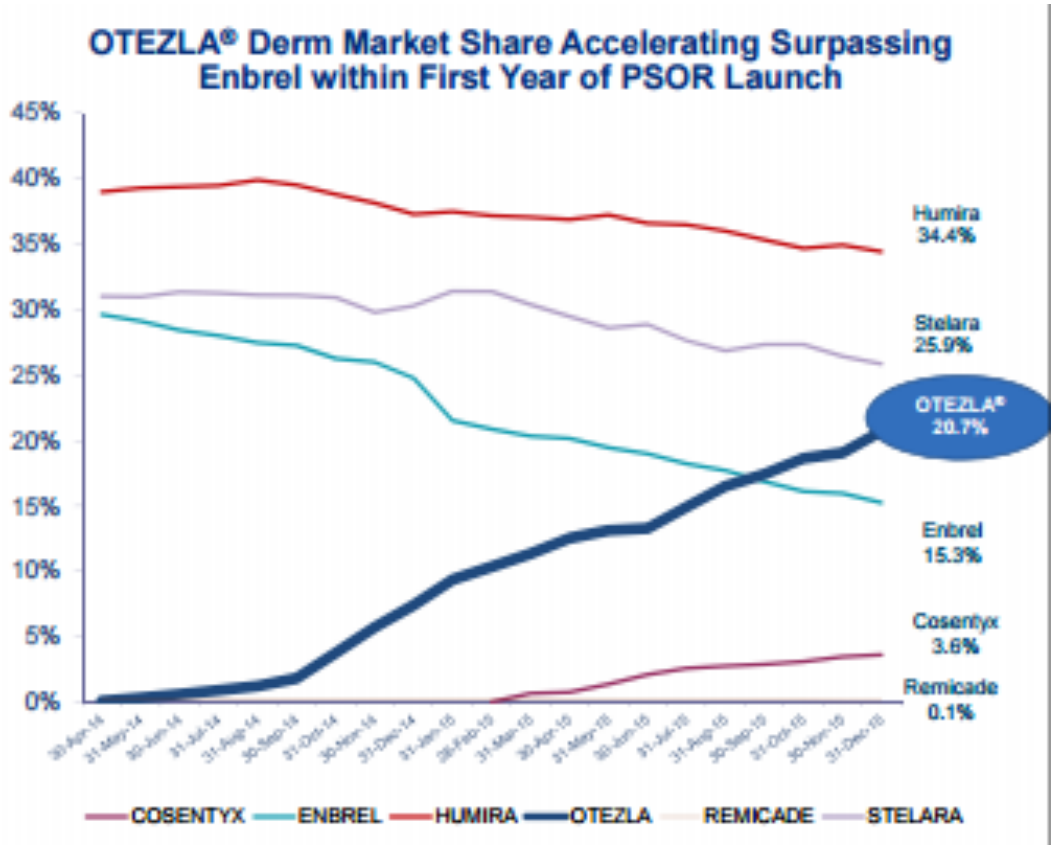
| Day 1 | Day 2 | | Day 3 | | Day 4 | | Day 5 | | Day 6 and Thereafter | |
|---|---|---|---|---|---|---|---|---|---|---|
| AM | AM | PM | AM | PM | AM | PM | AM | PM | AM | PM |
| 10 mg | 10 mg | 10 mg | 10 mg | 20 mg | 20 mg | 20 mg | 20 mg | 30 mg | 30 mg | 30 mg |

- Recommended dose of Apremilast is 30 mg twice daily taken orally, morning and evening, without regard to meals
- No dosage adjustments are required based on body weight, age, hepatic impairment
- No tuberculosis screening requirement; no ongoing laboratory monitoring requirements
- Dosage adjustments in patients with severe renal impairment (less than 30 mL per minute)
- Apremilast dosage should be reduced to 30 mg once daily in patients with severe renal impairment
- No clinically meaningful drug-drug interaction with methotrexate, oral contraceptives and potent CYP3A4 inhibitor such as ketoconazole
- Underweight patients at start of treatment should have their body weight monitored regularly
- Controindicated during pregnancy
- The use of strong CYP3A4 enzyme inducers (e.g. rifampicin, phenobarbital, carbamazepine, phenytoin and St. John's Wort) with apremilast is not recommended

a No retitration is required after initial titration.

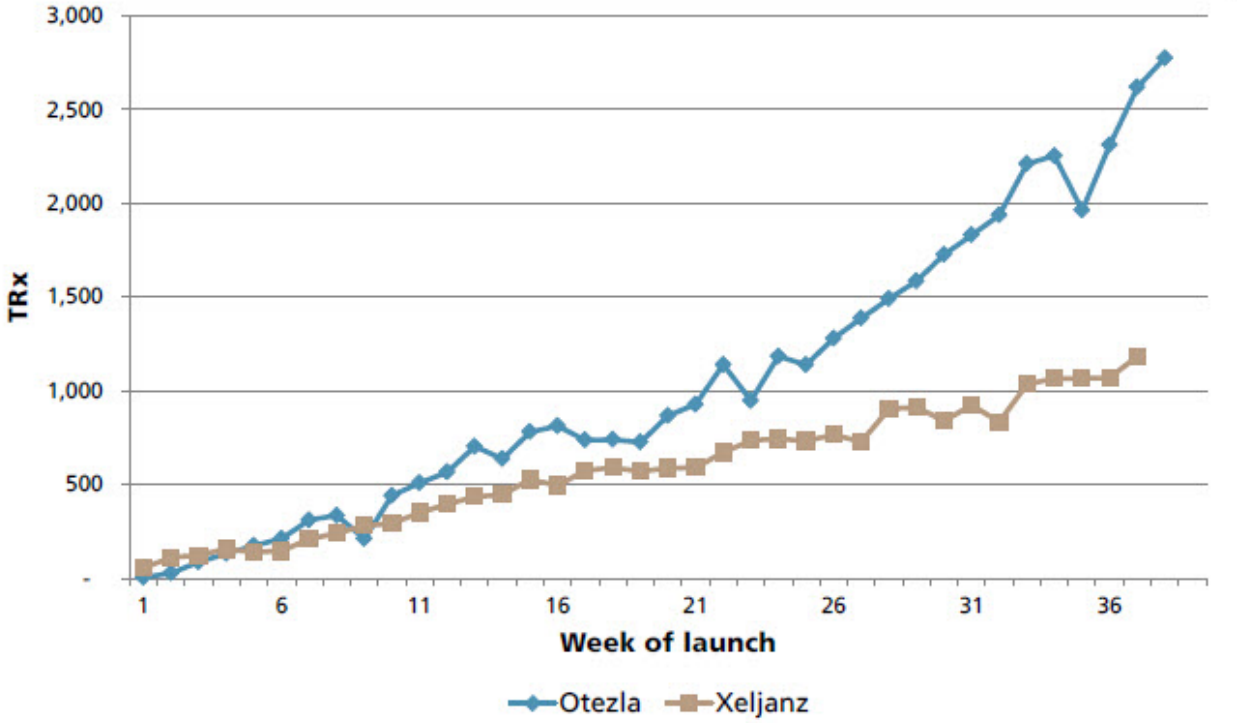
Apremilast SmPC. January 2015

# Real-life use



# Real-life use

**Figure 2: Otezla launch compared to Xeljanz**




Source: IMS, UBS research

# Outline

1. GRAPPA recommedations
2. PDE4 inhibition
3. The evidence from clinical trials
4. New perspectives

## A role for B cells in psoriatic disease?

- B cells may play a role in the pathogenesis, as they act also as **antigen presenting cells**, regulate **CD4+ T cell responses to foreign and self-antigens**, produce **cytokines**, provide **costimulatory signals**, and promote naïve CD4+ T cell differentiation into Th1 or Th2 subsets
- A new B cells subset has been recently identified in several autoimmune conditions as **regulatory B cells**, which are characterized by IL-10 production
- Bregs may counteract chronic inflammation suppressing Th1 response, Th17 differentiation, and supporting Treg differentiation
- PDE4 activity is the main source of AMP in B cells
- PDE4 inhibition lead to increased B cells proliferation → **Bregs?**
- Activated B cells show low levels of PDE4 → **Regulatory mechanism?**

Yanaba K. J Leukoc Biol. 2013
C. Mauri Int Immunol 2015
Gantner F, Brit Journal Pharcol 1998

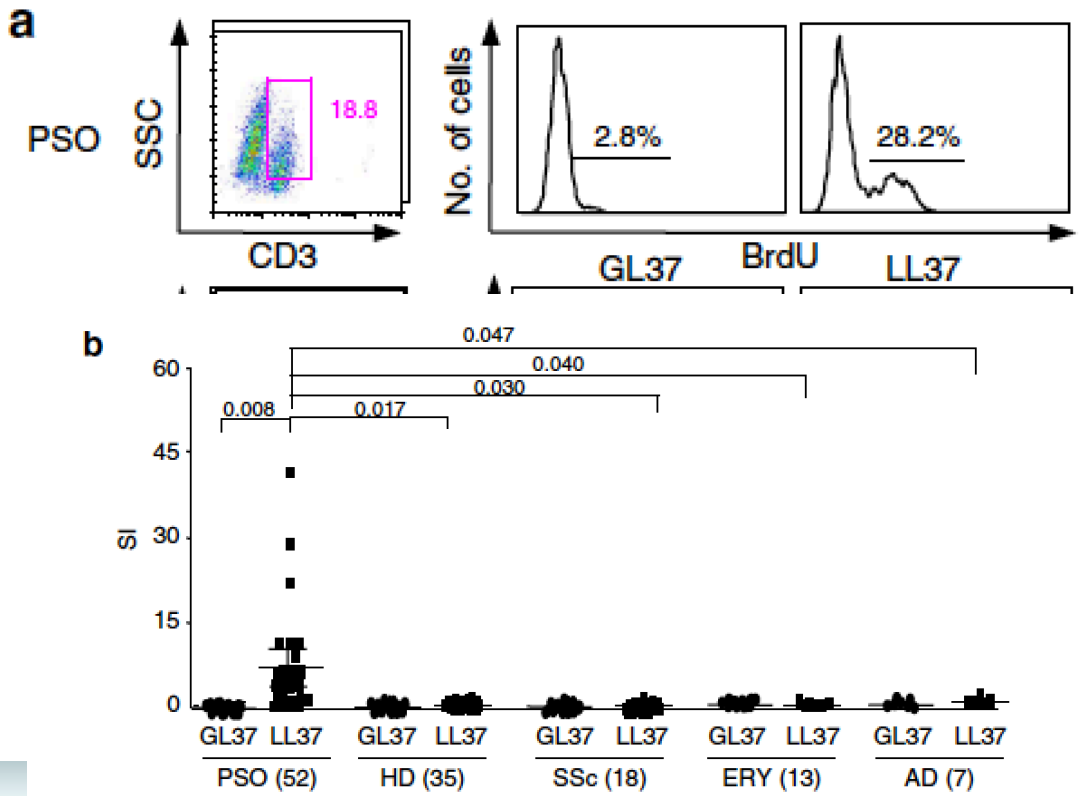
ARTICLE

Received 19 May 2014 | Accepted 20 Oct 2014 | Published 3 Dec 2014

DOI: 10.1038/ncomms6621

# The antimicrobial peptide LL37 is a T-cell autoantigen in psoriasis

**LL37 frequently induces proliferation of psoriatic T cells**




Lande R et al Nat Comm 2014

## A role for B cells in psoriatic disease?

- LL37 is induced after cAMP level increase
- CREB, AP-1 and ICER are the effectors inducing LL37 increase

- Could be a role of B cells in LL37 induced response?
- Do anti-LL37 antibodies exists?

Chasckraborty K, J Biol Chemistry 2009

# Conclusions

- PDE4 is a new target for psoriasis and PsA;
- Apremilast is a PDE4 inhibitor for the treatment of active PsA in adults;
- In the phase III PALACE trials, apremilast demonstrated sustained efficacy;
- Ongoing PALACE and ESTEEM open-label extension trials of up to 4 years will provide information regarding the long-term clinical effects and safety of apremilast therapy;
- The safety and tolerability profile of apremilast indicates no need for laboratory monitoring nor dose reduction in liver impairment;
- International guidelines suggest that apremilast may be used at early stages of the treatment ladder

# The current status

**FDA (**aprile 2015)

**Psoriasis**. Otezla is indicated for the treatment of moderate to severe chronic plaque psoriasis in adult patients who failed to respond to or who have a contraindication to, or are intolerant to other systemic therapy including cyclosporine, methotrexate or psoralen and ultraviolet-A light (PUVA)

**Psoriatic arthritis**. Otezla, alone or in combination with Disease Modifying Antirheumatic Drugs (DMARDs), is indicated for the treatment of active psoriatic arthritis (PsA) in adult patients who have had an inadequate response or who have been intolerant to a prior DMARD therapy

**AIFA** Posizione del 20 aprile 2015

Gazzetta Ufficiale del 6 maggio 2015

**Artrite psoriasica**: «Otezla», da solo o in associazione a farmaci antireumatici modificanti la malattia (Disease Modifying Antirheumatic Drugs, DMARD), è indicato per il trattamento dell'artrite psoriasica (PsA) attiva in pazienti adulti che hanno avuto una risposta inadeguata o sono risultati intolleranti a una precedente terapia con DMARD (vedere paragrafo 5.1).

**Psoriasi**: «Otezla» è indicato per il trattamento della psoriasi cronica a placche da moderata a grave in pazienti adulti che non hanno risposto, che hanno una controindicazione o che sono intolleranti ad altra terapia sistemica comprendente ciclosporina, metotrexato o psoralene e raggi ultravioletti di tipo A (PUVA).

# Thanks for your attention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