South Beach Symposium
clinical + aesthetic dermatology

SBS PART I

THE MEDICAL DERMATOLOGY Summit

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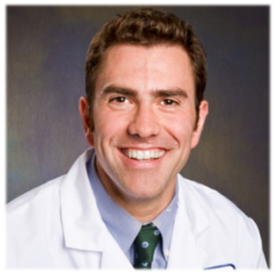

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2

Disclosures

Joseph Merola

- J.F. Merola is a consultant and/or investigator for: Merck, Abbvie, Dermavant, Eli Lilly, Novartis, Janssen, UCB, Celgene, Sanofi, Regeneron, Arena, Sun Pharma, Biogen, Pfizer, EMD Sorono, Avotres Therapeutics and LEO Pharma.

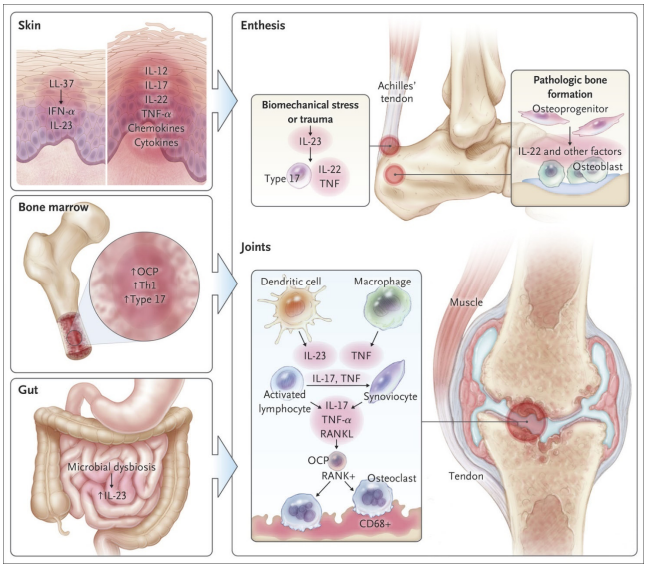
3

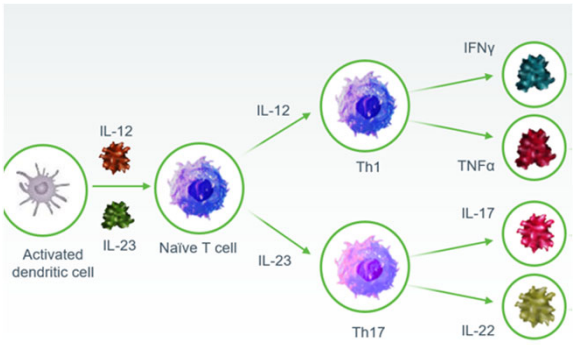
Diagnosing and Managing PsA

Psoriatic Disease Treatment by Domain of Disease

4

A Shared Pathogenesis



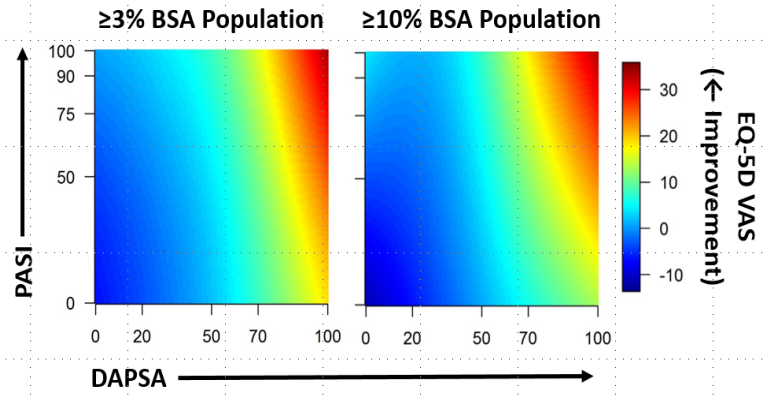


IFN = Interferons
Ritchlin CT, et al. *N Engl J Med.* 2017;376:957-970.

5

For PsA patients with psoriasis, optimal improvements in patients' HRQoL, as measured by select domains of patient reported outcomes, were dependent on successful treatment of both joint and skin symptoms

Kavanaugh A, Gottlieb A, Morita A, **Merola JF,** Birt J, Lin CY, Shuler CL, Thaçi D. Presented at: 2017 American College of Rheumatology Annual Meeting (ACR/ARHP); November 3-8, 2017; San Diego, CA. Poster presentation (abstract 2539).



6

PsA Treatment Options: 2021

Traditional DMARDs
- Methotrexate
- Leflunomide
- Sulfasalazine
- Cyclosporine

Anti-TNFa
- Adalimumab
- Etanercept
- Infliximab
- Golimumab
- Certolizumab

Other targeted therapies
- Secukinumab (IL17A)
- Ixekizumab (IL17)
- Ustekinumab (IL12/23)
- Tofacitinib (JAK)
- Abatacept (CTLA4-Ig)
- Apremilast (PDE4)
- Guselkumab (IL23)

In development
- Bimekizumb (IL17A/F)
- Risankizumab (IL23)
- Brodalumab (IL17R)
- Tildrakizumab (IL23)
- Upadacitinib (JAK)

Other
- NSAIDs
- Corticosteroid injections
- Corticosteroids (oral)

7

Treatment by Domains of Disease

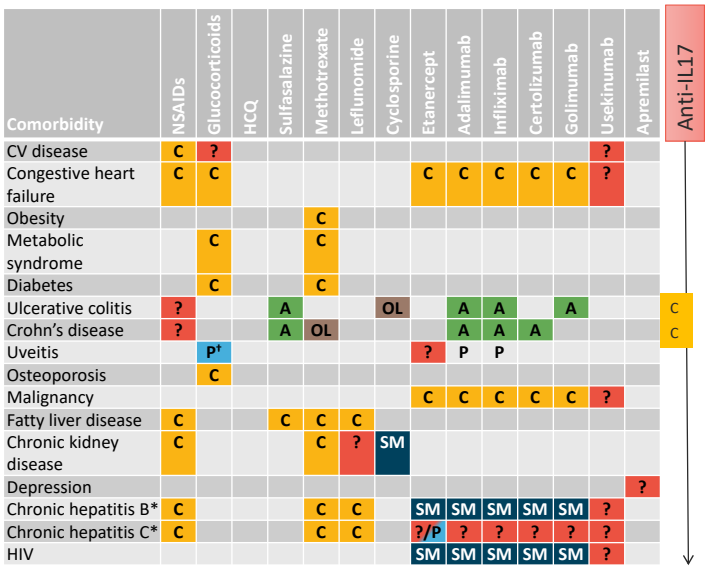
Mechanism	Peripheral Arthritis	Skin and Nail Disease	Axial Disease*	Dactylitis	Enthesitis	GI / IBD
NSAIDs	✓		✓			
Intra-articular steroids	✓					
Topicals		✓				
Psoralen UVA/UVB		✓				
DMARDS (MTX, CsA, SSZ, Lef)	✓	✓				
Apremilast	✓	✓		✓	✓	
Anti-TNF	+++	++	✓	✓	✓	✓
Anti-IL12/23	+	++	X	✓	✓	✓
Anti-IL23 (p19)	++	+++	?	✓	✓	?
Anti-IL17	+++	+++	✓ 3	✓	✓	X
JAK inhibitors	++	?	✓ 1	✓	✓	✓ 2

Merola JF, adapted from:
J Rheumatol. 2006;33:1417-1456.

Notes:
* Based on data from ankylosing spondylitis trials (used as surrogate for Axial PsA)
1 Based on tofacitinib ankylosing spondylitis data; selectivity may impact other JAKs
2 Ulcerative colitis only, not crohn's
3 Dedicated Axial PsA study (MAXIMISE)

8

Considerations for Treatment of Patients With PsA and Concomitant Comorbidities



Comorbidity	NSAIDs	Glucocorticoids	HCQ	Sulfasalazine	Methotrexate	Leflunomide	Cyclosporine	Etanercept	Adalimumab	Infliximab	Certolizumab	Golimumab	Usekinumab	Apremilast	Anti-IL17
CV disease	C	?											?		
Congestive heart failure	C	C						C	C	C	C	C	?		
Obesity					C										
Metabolic syndrome		C			C										
Diabetes		C			C										
Ulcerative colitis	?			A			OL		A	A		A			C
Crohn's disease	?			A	OL				A	A	A				C
Uveitis		P†						?	P	P					
Osteoporosis		C													
Malignancy								C	C	C	C	C	?		
Fatty liver disease	C			C	C	C									
Chronic kidney disease	C				C	?	SM								
Depression														?	
Chronic hepatitis B*	C				C	C		SM	SM	SM	SM	SM	?		
Chronic hepatitis C*	C				C	C		?/P	?	?	?	?	?		
HIV								SM	SM	SM	SM	SM	?		

A Approved for primary therapy
C Reason for caution
OL Off-label use
P Preferred therapy
SM Requires special monitoring
? Data insufficient, concerns raised

Coates LC, et al. *Arthritis Rheumatol.* 2016;68(5):1060-71.

*When treating patients with chronic infections that can affect the liver, consider consultation with providers having expertise in the area. †Corticosteroids used as preferred therapy for uveitis are most commonly given as topical and/or intraocular injections (IAIs) in preference to oral steroids.
NSAIDs = nonsteroidal anti-inflammatory drugs; HCQ = hydroxychloroquine; CV = cardiovascular disease; HIV = human immunodeficiency virus.

9

MIPA Trial: MTX Is Not a DMARD in Psoriatic Arthritis (???)

- Double-blind, parallel-group randomized controlled trial (N=221)
- Patients randomized to receive MTX **(target dose 15 mg/week)** or placebo (PBO)

Global Index	OR (95% CI)	*P* Value
PsARC (primary endpoint)	1.77 (0.97, 3.23)	.06
ACR20 responders	2.00 (0.65, 6.22)	.23
DAS28 responders	1.70 (0.90, 3.17)	.10

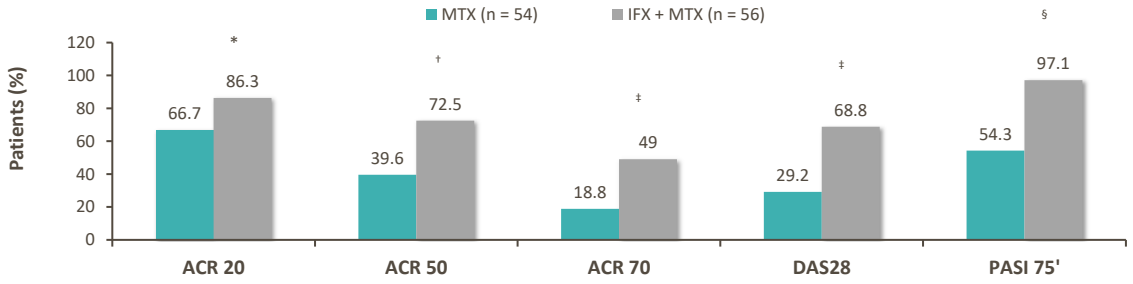
- There was **no difference between groups in CRP/ESR, SJC, or TJC at 3 months or 6 months**
- There were significant improvements in patient and physician global assessment & PASI scores (*P*=.02, .01, and .02, respectively)
- **"There was no evidence MTX improves inflammatory synovitis in active PsA and thus that it has true DMARD activity"**

CRP = C-reactive protein; ESR = erythrocyte sedimentation rate; PsARC = PsA response criteria.
Kingsley GH, et al. *Rheumatology (Oxford)*. 2012;51(8):1368-1377.

10

RESPOND: MTX vs MTX + IFX in PsA

- Randomized, prospective, open-label, controlled trial
  - **MTX 15 mg/wk** vs MTX + **IFX <u>5 mg/kg</u>** for 16 weeks
  - All patients MTX-naïve (N=115)
  - Primary endpoint: ACR20 response at week 16



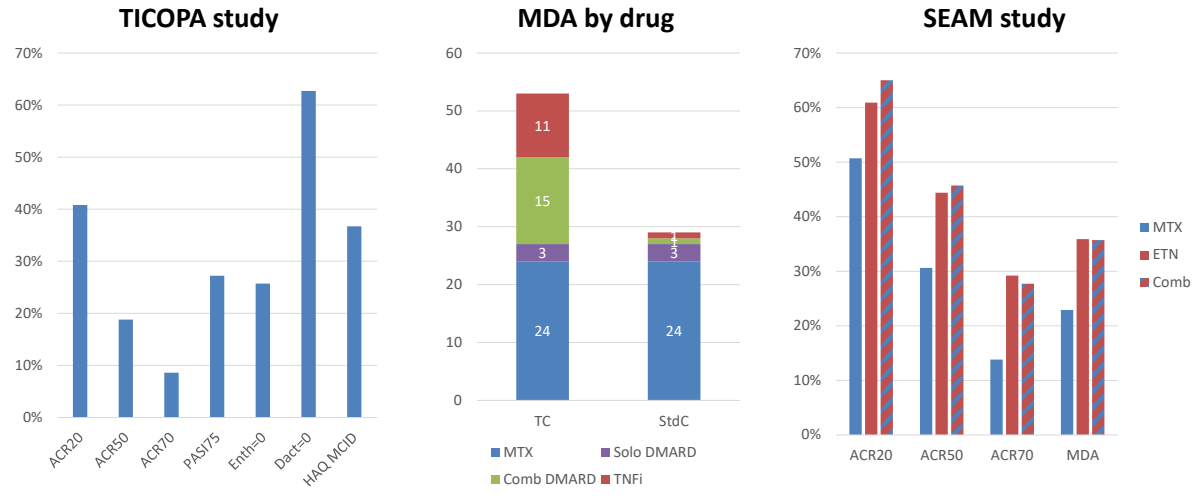
➤ IFX + MTX are superior to MTX, but MTX alone appears efficacious

*P<.05 vs MTX; †P<.001; ‡P<.01; §P<.0001; ‖among patients with a PASI score ≥ 2.5 at baseline (n=34 in IFX + MTX group, n=35 in the MTX group).

Baranauskaite A, et al. *Ann Rheum Dis*. 2012;71:541-548.

11

MTX outcomes in PsA: A suggestion of efficacy



Coates et al, J Rheum 2016 Feb;43(2):356-61, Coates et al, Lancet. 2015 Dec 19;386(10012):2489-98, Mease et al Arthritis Rheumatol. 2019 Jul;71(7):1112-1124.

12

Anti-TNF Therapies in PsA: ACR and PASI Responses

Trial	n	ACR20 % Rx	ACR20 % P	ACR50 % Rx	ACR50 % P	ACR70 % Rx	ACR70 % P	PASI75 %[X] Rx	PASI75 %[X] P
Adalimumab 2/3[x]	315	58	14	36	4	20	1	59	1
Certolizumab 3[+]	409	58	24	36	11	25	3	62	15
Etanercept 2*	60	74	14	48	5	13	0	26*	0*
Etanercept 3*	205	59	15	38	4	11	0	23	3
Golimumab[X]	405	52	8	32	3.5	18	0.9	61	1
Infliximab 2[+]	100	69	8	49	9	29	0	68	0
Infliximab 3**	200	58	11	36	3	15	1	60	1

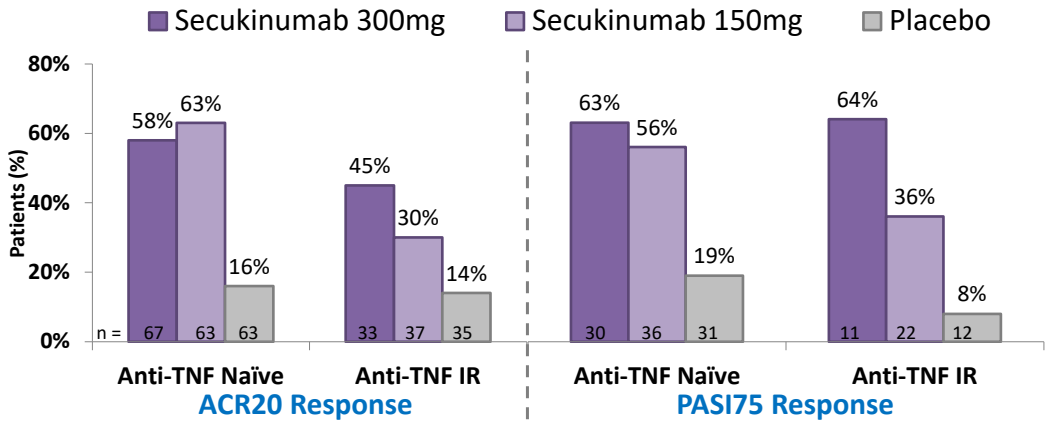
60 40 20

*12 weeks; **14 weeks; [+]16 weeks; [X]24 weeks
PASI = Psoriasis Area and Severity Index
Mease PJ, et al. *Lancet*. 2000;356(9227):385-390. Antoni CE, et al. *Arthritis Rheum*. 2005;52(4):1227. Mease PJ, et al. *Arthritis Rheum*. 2004;50(7):2264-2272. Antoni CE, et al. *Ann Rheum Dis*. 2005;64(8):1150-1157. Mease PJ, et al. *Ann Rheum Dis*. 2005;52(10):3279-3289. Kavanaugh A, et al. *Arthritis Rheum*. 2007. Mease PJ, et al. *Ann Rheum Dis*. 2014;73(1):48-55.

13

Efficacy of Secukinumab (Anti-IL17A) in PsA Patients

FUTURE 2: Phase 3 Trial

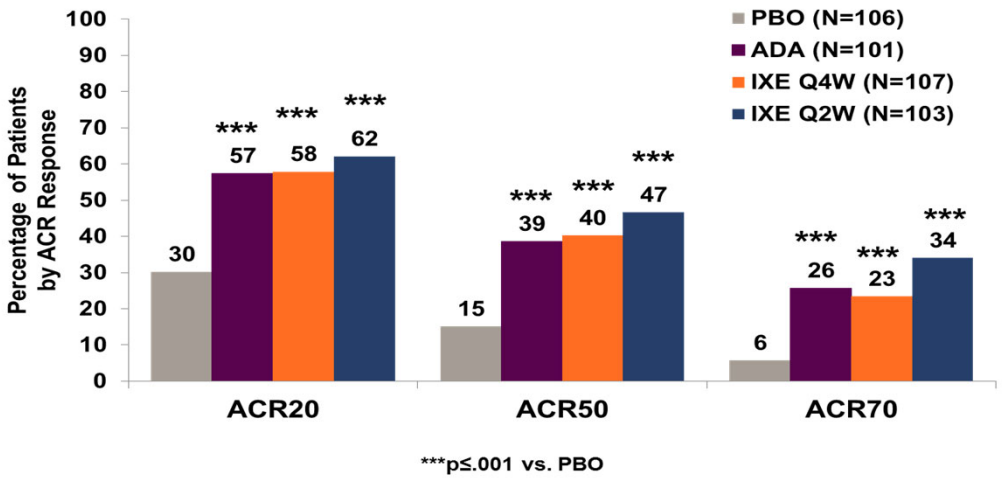


*Secukinumab was given QW from week 0–4, then Q4W thereafter
IR = Inadequate Response
McInes IB, et al. *Lancet*. 2015;386(9999):1137–1146.

14

14

Ixekizumab: ACR Responses at Week 24



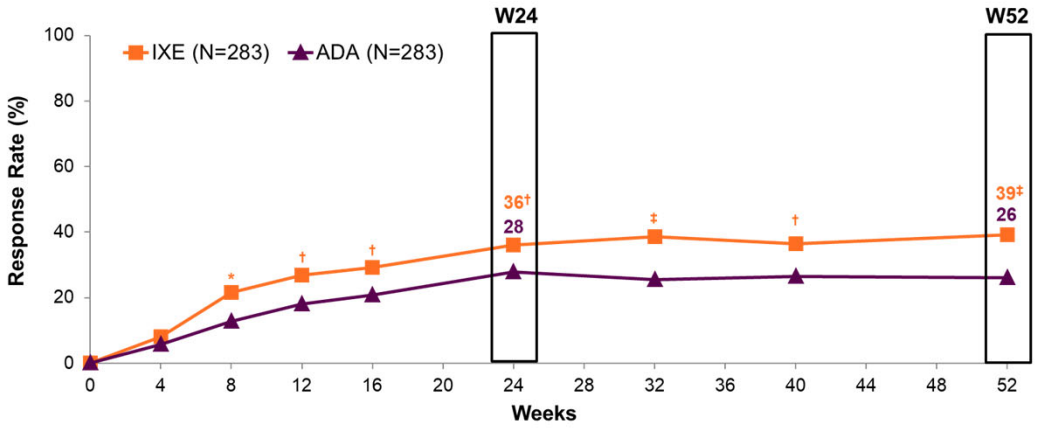
ACR20/50/70 = American College of Rheumatology 20%/50%/70% response rate; ADA = 40 mg adalimumab every 2 weeks; IXE Q2W = 80 mg ixekizumab every 2 weeks; IXE Q4W = 80 mg ixekizumab every 4 weeks; PBO = placebo every 2 weeks

Mease PJ, et al. *Ann Rheum Dis.* 2017;76(1):79-87.

15

SPIRIT H2H: Ixekizumab vs. Adalimumab

Percentage of Patients Achieving Simultaneous ACR50 and PASI 100 by Treatment Week, NRI



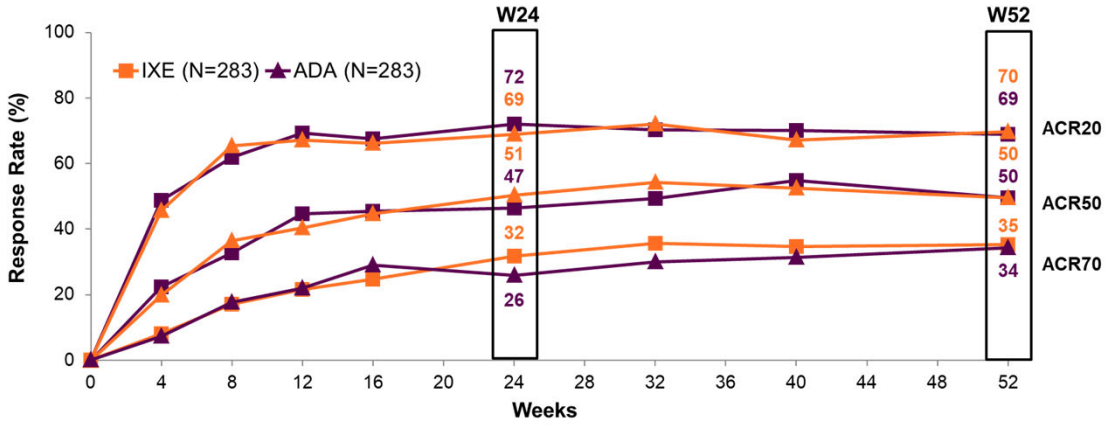
*p<.01 vs. ADA; †p<.05 vs. ADA; ‡p<.001 vs. ADA.

NRI was used for imputation of all missing data, including drop-outs as non-responders.

Mease PJ, et al. *Ann Rheum Dis.* 2020;79(1):123-131

16

ACR20/50/70 Response by Treatment Week, NRI



Note: NRI was used for imputation of all missing data, including drop-outs as non-responders.

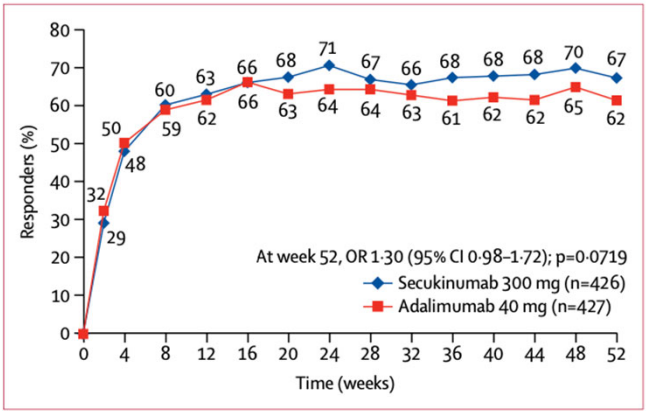
Mease PJ, et al. *Ann Rheum Dis.* 2020;79(1):123-131

17

Secukinumab versus adalimumab for treatment of active psoriatic arthritis (EXCEED):

a double-blind, parallel-group, randomised, active-controlled, phase 3b trial

McInnes et al. Lancet (395) 1496. May 9, 2020



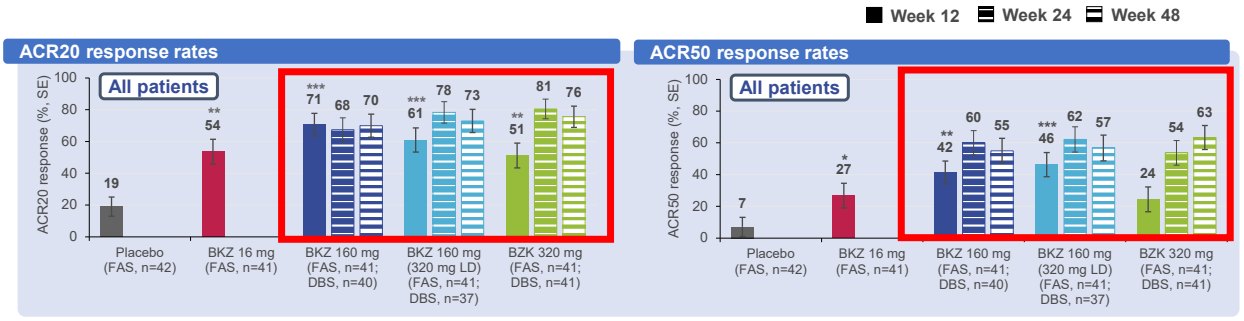
18

	Secukinumab 300 mg	Adalimumab 40 mg	Odds ratio (95% CI)	p value (unadjusted)*
Primary endpoint				
ACR20	67% (426)	62% (427)	1·30 (0·98 to 1·72)	0·0719
Prespecified sensitivity analysis using non-responder imputation				
ACR20	67% (426)	59% (427)	1·38 (1·04 to 1·83)	0·0239
Key secondary endpoints				
PASI 90	65% (215)	43% (202)	2·49 (1·67 to 3·71)	<0·0001
ACR50	49% (426)	45% (427)	1·18 (0·90 to 1·55)	0·2251
HAQ-DI score, change from baseline, mean (SE) [n]	−0·58 (0·03) [363]	−0·56 (0·03) [318]	−0·02† (−0·10 to 0·05)	0·5465
Resolution of enthesitis (based on Leeds Enthesitis Index)	61% (234)	54% (264)	1·30 (0·91 to 1·87)	0·1498
Combined endpoint				
ACR50 plus PASI100‡	31% (215)	19% (202)	1·85 (1·17 to 2·92)	0·0087

McInnes et al. Lancet (395) 1496. May 9, 2020

19

Bimekizumab BE ACTIVE: ACR20 and ACR50 response rates achieved at Week 12 continued to increase to Week 24 and were sustained up to Week 48 (NRI)

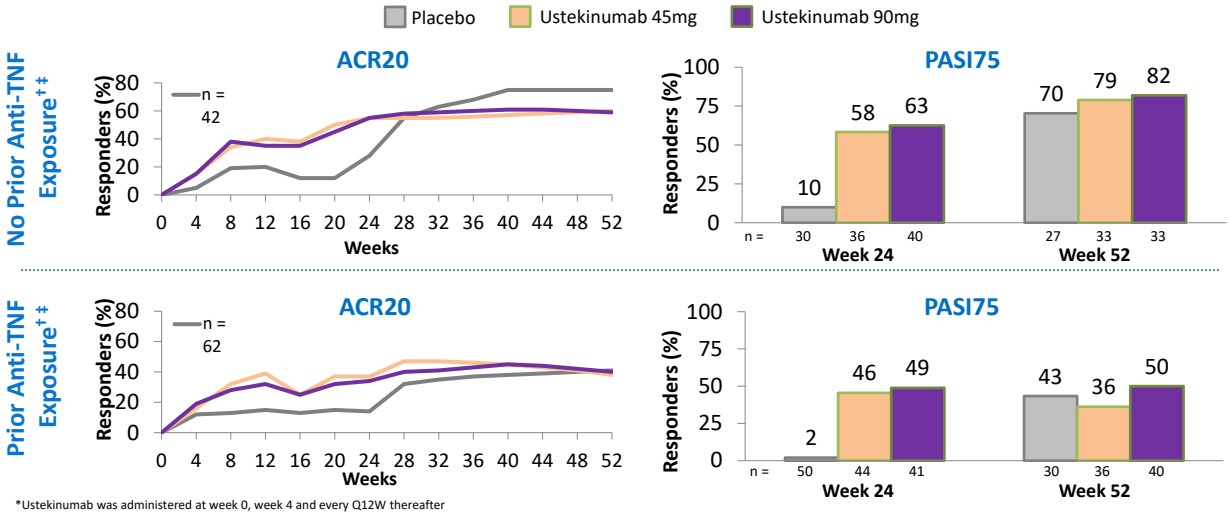


FAS: Week 12; DBS: Week 48 (NRI). *nominal p<0.05 vs placebo; **nominal p<0.01 vs placebo; ***nominal p<0.001 vs placebo. The p values were derived at Week 12 from a logistic regression model including fixed effects for treatment, geographic region and prior TNF inhibitor exposure. Per protocol, p values were not calculated for subgroup analyses (ACR20/50 response rates in the TNFi naïve population). The following data are not presented: placebo →
BKZ 160 mg, placebo → BKZ 320 mg, BKZ 16 mg → BKZ 160 mg, BKZ 16 mg → BKZ 320 mg (Weeks 24 and 48)
ACRXX, XX% improvement from baseline in the American College of Rheumatology criteria.
BKZ = bimekizumab; DBS = dose-blind set; FAS = full analysis set; NRI = non-responder imputation; SE = standard error

NOT FDA Approved for PsA

20

Efficacy of Ustekinumab (Anti-IL12/23) in PsA Patients with Prior Anti-TNF Exposure: PSUMMIT 2 Trial



*Ustekinumab was administered at week 0, week 4 and every Q12W thereafter

†Among randomized patients with ≥ 3% body surface area with PsO skin involvement at baseline

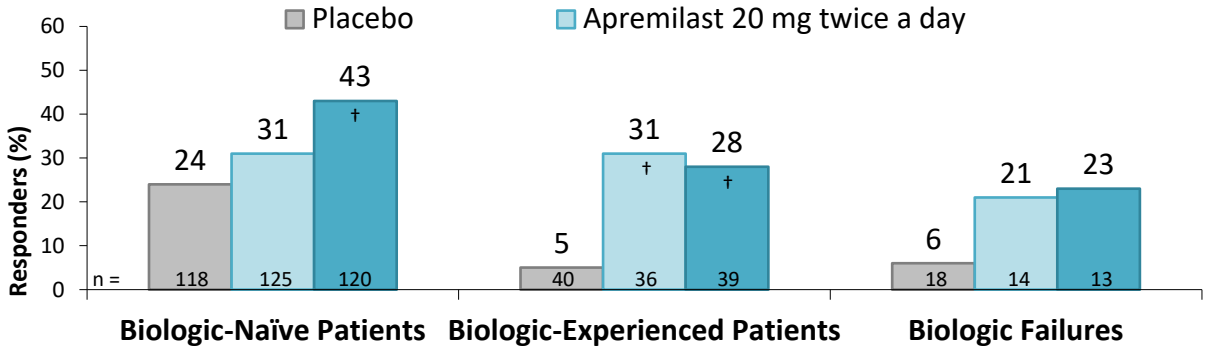
‡For patients who qualified for early escape, data at or prior to Week 16 were carried forward through Week 24. After Week 24, observed data were used

Ritchlin C, et al. *Ann Rheum Dis.* 2014;73(6):990–999.

21

Efficacy of Apremilast (PDE4) in PsA Patients with Prior Biologic-Therapy Exposure or Failure

Results from PALACE-1 Trial
ACR20 Response by Biologic Experience



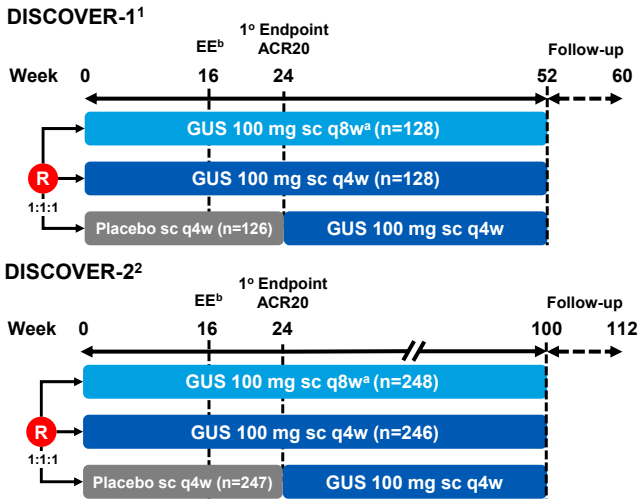
†$P < .007$

Kavanaugh A, et al. *Ann Rheum Dis.* 2014;73(6):1020–1026.

22

22

DISCOVER-1 and -2: Phase 3 trials of guselkumab for patients with active psoriatic arthritis: Week 24 results



Inclusion criteria

- Inadequate response to csDMARDs, apremilast, NSAIDs

DISCOVER-1

- ≥3 swollen joints, ≥3 tender joints, CRP ≥0.3 mg/dL
- Anti-TNF experienced included

DISCOVER-2

- ≥5 swollen joints, ≥5 tender joints, CRP ≥0.6 mg/dL
- Biologic naïve

Baseline characteristics

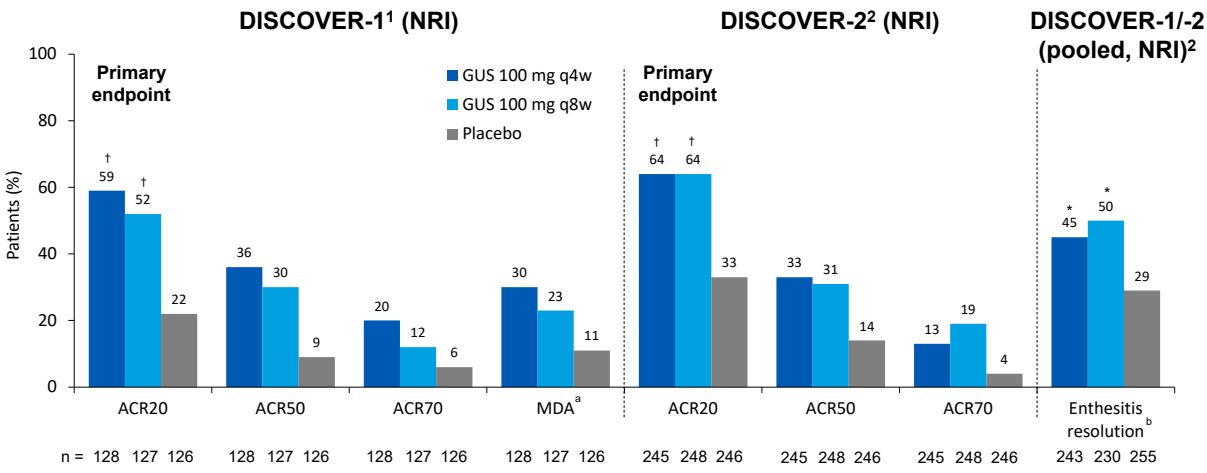
	DISCOVER-1 (N=382)	DISCOVER-2 (N=741)
Mean PASI score	8.5	9.9
Patients with enthesitis, n (%)	222 (58.4)	506 (68.5)

- In DISCOVER-1, 31% of patients had previous TNF inhibitor experience and 55% were receiving MTX at baseline

- [a]GUS 100 mg q8w group received 100 mg loading dose at Weeks 0 and 4; [b]EE, early escape (patients were eligible to initiate/increase doses of background medications if <5% improvement from baseline in both tender/swollen joint counts at Week 16)
- 1. Deodhar A, et al. Lancet 2020;395:1115–25; 2. Mease PJ, et al. Lancet 2020;395:1126–36; Deodhar A, et al. ACR 2019, OP807

23

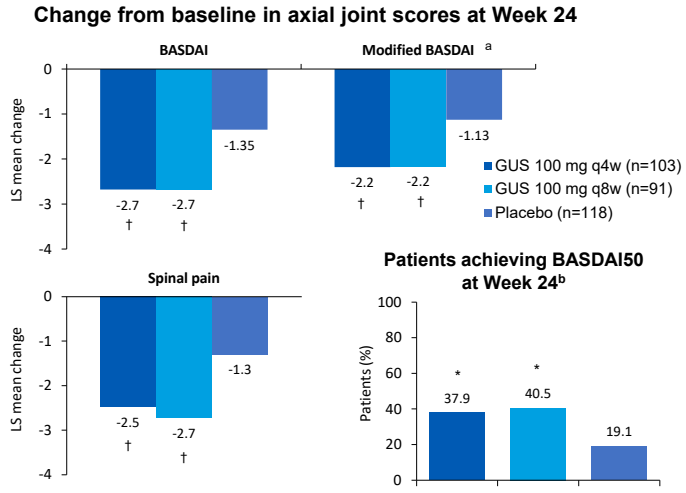
DISCOVER-1 and -2: ACR responses, enthesitis resolution, and MDA after 24 weeks of guselkumab for patients with active psoriatic arthritis



- *P<0.05, †P<0.0001 vs placebo (controlled for multiplicity)
  [a]MDA (minimal disease activity) considered fulfilment of 5 of the following 7 criteria: tender joint count ≤1, swollen joint count ≤1, PASI ≤1, patient pain VAS ≤15, patient global disease activity VAS ≤20, HAQ-DI ≤0.5, tender entheseal points ≤1
  [b]Enthesitis measured by Leeds Enthesitis Index
- 1. Deodhar A, et al. Lancet 2020;395:1115–25; 2. Mease PJ, et al. Lancet 2020;395:1126–36

24

DISCOVER-1 and -2: Effect of guselkumab on **axial outcome measures** after 24 weeks among patients with active PsA with axial involvement

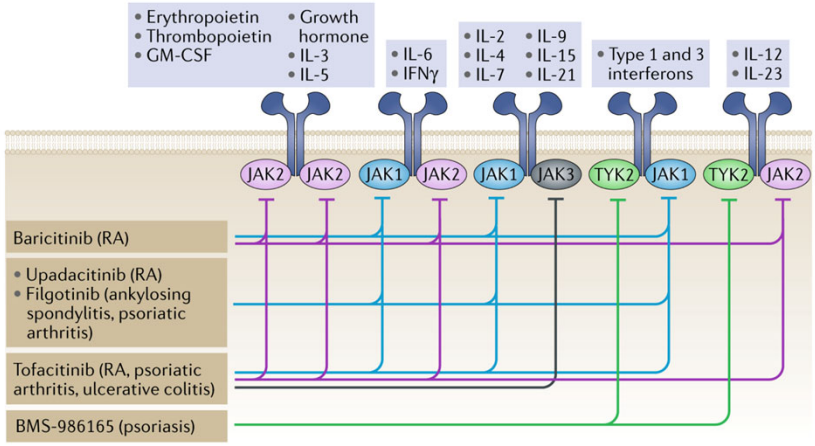


- Investigators confirmed sacroiliitis either by documented prior imaging or pelvic radiograph at screening
- Axial-specific studies are needed to definitively answer this question

- *P<0.01 (unadjusted), †P<0.001 (unadjusted) vs placebo
- BASDAI, Bath Ankylosing Spondylitis Disease Activity Index. aExcludes question 3 of the BASDAI (How would you describe the overall level of pain/swelling in joints other than neck, back, hips you have had?); bAmong patients with BASDAI >0 at baseline, n=95, 84, 110 for GUS q4w, q8w, and placebo, respectively
- Helliwell P, et al. EULAR 2020, OP0054

25

From: Selective Janus kinase inhibitors come of age



Different cytokine receptors signal via different Janus kinases (JAKs). First-generation JAK inhibitors affect a broad spectrum of cytokines, whereas selective JAK inhibitors have the potential to limit the activity of a much smaller subset of cytokines and thereby enable signalling via other JAK-dependent pathways to be maintained and, potentially, reduce the incidence of adverse effects. GM-CSF, granulocyte–macrophage colony stimulating factor; RA, rheumatoid arthritis.

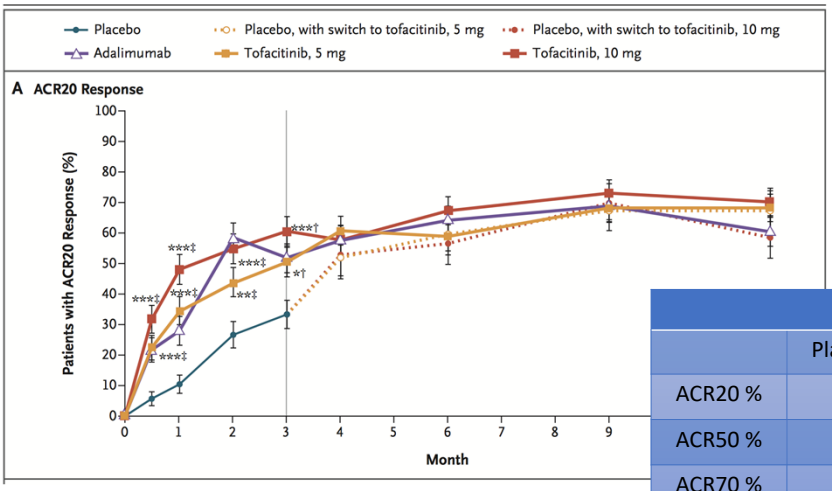
RA = Rheumatoid arthritis; GM-CSF = Granulocyte-macrophage colony-stimulating factor; JAK = Janus kinase
O'Shea JJ, et al. *Nat Rev Rheumatol.* 2019;15:74–75.

26

The NEW ENGLAND JOURNAL of MEDICINE

Tofacitinib or Adalimumab versus Placebo for Psoriatic Arthritis

P. Mease, S. Hall, O. FitzGerald, D. van der Heijde, J.F. Merola, F. Avila-Zapata, D. Cieślak, D. Graham, C. Wang, S. Menon, T. Hendrikx, and K.S. Kanik

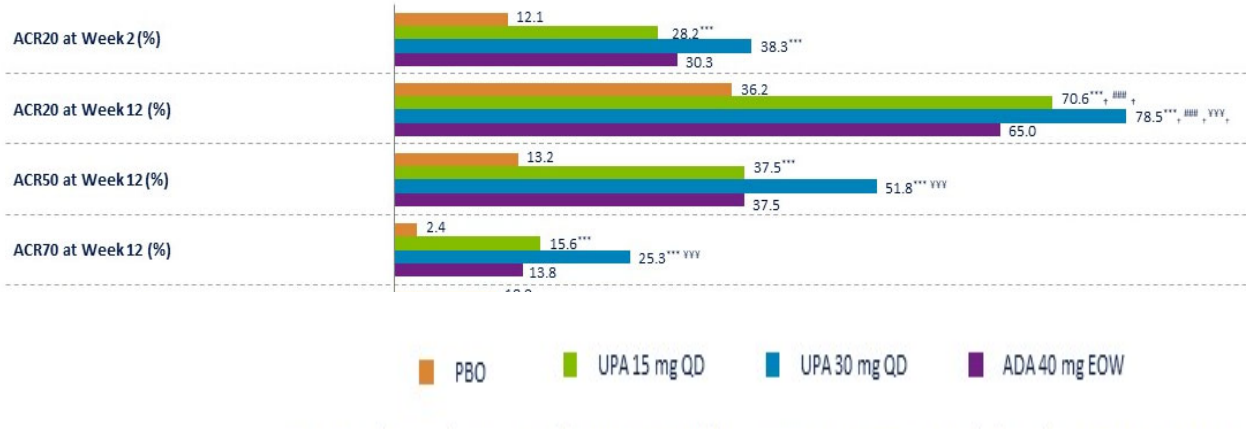


	At 3 Months		
	Placebo	Tofa 5 mg	Tofa 10 mg
ACR20 %	35	54	63
ACR50 %	10	30	42
ACR70 %	5	18	15

Mease PJ, et al. *N Engl J Med*. 2017;377:1537-1550.

27

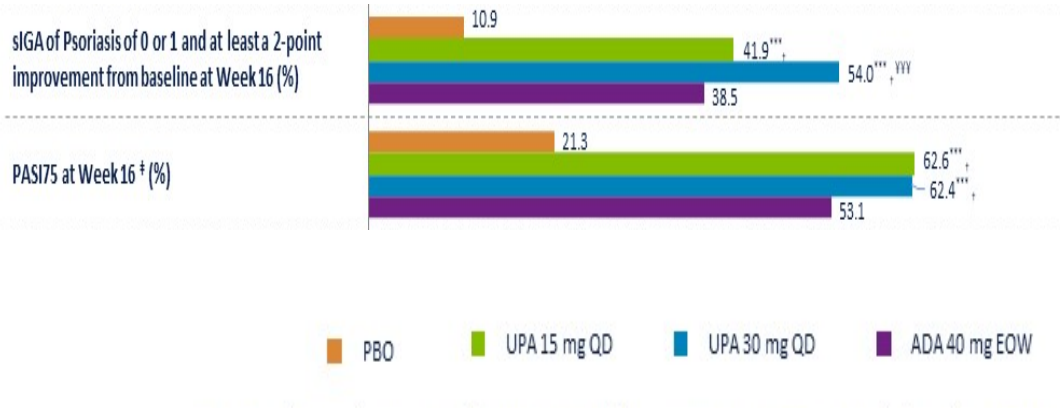
Efficacy and Safety of Upadacitinib Versus Placebo and Adalimumab in Patients with Active Psoriatic Arthritis and Inadequate Response to Non-Biologic DMARD (SELECT-PsA-1): Phase 3



McInnes IB, et al. EULAR E-Congress 2020; Abstract LB00001.

28

Efficacy and Safety of Upadacitinib Versus Placebo and Adalimumab in Patients with Active Psoriatic Arthritis and Inadequate Response to Non-Biologic DMARD (SELECT-PsA-1): Phase 3



McInnes IB, et al. EULAR E-Congress 2020; Abstract LB00001.

29

Radiographic Progression

- Anti-TNF, secukinumab, ixekizumab

30

Treatment by Domains of Disease

Mechanism	Peripheral Arthritis	Skin and Nail Disease	Axial Disease*	Dactylitis	Enthesitis	GI / IBD
NSAIDs	✔		✔			
Intra-articular steroids	✔					
Topicals		✔				
Psoralen UVA/UVB		✔				
DMARDS (MTX, CsA, SSZ, Lef)	✔	✔				
Apremilast	✔	✔		✔	✔	
Anti-TNF	+++	++	✔	✔	✔	✔
Anti-IL12/23	+	++	X	✔	✔	✔
Anti-IL23 (p19)	++	+++	?	✔	✔	?
Anti-IL17	+++	+++	✔ 3	✔	✔	X
JAK inhibitors	++	?	✔ 1	✔	✔	✔ 2

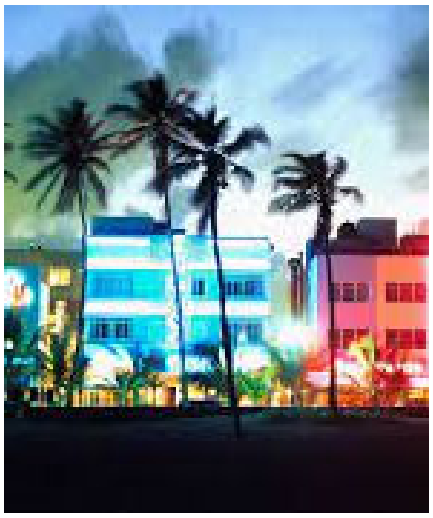
Merola JF, adapted from:
J Rheumatol. 2006;33:1417-1456.

Notes:
* Based on data from ankylosing spondylitis trials (used as surrogate for Axial PsA)
1 Based on tofacitinib ankylosing spondylitis data; selectivity may impact other JAKs
2 Ulcerative colitis only, not crohn's
3 Dedicated Axial PsA study (MAXIMISE)

31

Thank You!

See you in MIAMI 2022 !



32

33

Case 1:

- 58-year-old woman with plaque psoriasis, 5% BSA
- Scalp and nail disease history
- FH of mother with PsO, PsA
- Treated with topicals only to date

- Given a PEST screening through electronic patient portal:
  - **Positive screen**
- PSAID completed in waiting room on tablet; self-scored at **PSAID=8**
  - (PSAID 'PASS'>4 means unacceptable symptom level)

- Upon further questioning:
  - + back pain
  - + plantar fasciitis / achilles insertion pain (enthesitis) noted

34

Case 2:

- 52-year-old woman with plaque psoriasis 15% BSA at baseline; scalp and nail in the past

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- **Diagnosed with PsA** several years ago
- Treated with a biologic approved for PsA
  - currently < 1% BSA, treated; uses topicals as needed

- Rheumatology diagnosis, so NO PEST screen
- Patient given PSAID=3 ('PASS' <=4 means acceptable symptom level)
  - Consider co-management, continue therapy

35