Δεδομένα από το κλινικό πρόγραμμα του Guselkumab στην Ψωριασική Αρθρίτιδα

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Δ ππκ ,ΠΓΝ «Αττικόν»

Σύγκρουση συμφερόντων

Παρούσα παρουσίαση :Τιμητική αμοιβή από JANSSEN

Εκπαιδευτικές-ερευνητικές-συμβουλευτικές επιχορηγήσεις την τελευταία διετία:
Lilly, AEnorasis, Genesis-Pharma, Pfizer, Abbvie,
Mylan, Novartis, Amgen , GSK,

Guselkumab- κλινικό πρόγραμμα (RTCs)

DISCOVER 1

A Phase 3, multi-centre, randomised, double-blind, placebo-controlled study evaluating the efficacy and safety of guselkumab administered subcutaneously in subjects with active psoriatic arthritis including tnf(i)-experenced NCT03162796

DISCOVER 2

A Phase 3, multi-centre, randomised, double-blind, placebo-controlled study evaluating the efficacy and safety of guselkumab administered subcutaneously in subjects with active PsA NCT03158285

Guselkumab- χαρακτηριστικά των συμμετεχόντων

- *DISCOVER 1*

5-7 έτη διάρκεια νόσου

- **Adults** ≥18 years of age with documented diagn
  PsA for ≥6 months and meeting **CASPAR** at screening
- Active arthritis defined as **≥3 swollen joints**,
  ≥3 tender joints,
  CRP ≥0.3 mg/dL
- **At least one PsA subset**: DIP involvement, p
  arthritis with absence of rheumatoid nodules,
  mutilans, asymmetric peripheral arthritis, or spondylitis
  with peripheral arthritis
- Currently active or **s**
- **Inadequate response or intolerance** to **nbDMARD**s,
  apremilast ,**NSAIDs** and/or
  up to 2 anti-TNFα agents (must document rea
  for discontinuation

Ενεργότητα νόσου

- **Mean Tender joints : 21**
- **Mean Swollen joints: 11**
- **Mean HAQ-DI : 1,15**

30%-tnf(i) -experienced

68%- MTX κατά την έναρξη

- *DISCOVER 2*

Adults ≥18 years of age with documented diagnosis of **PsA for ≥6 months** and meeting **CASPAR** at screening

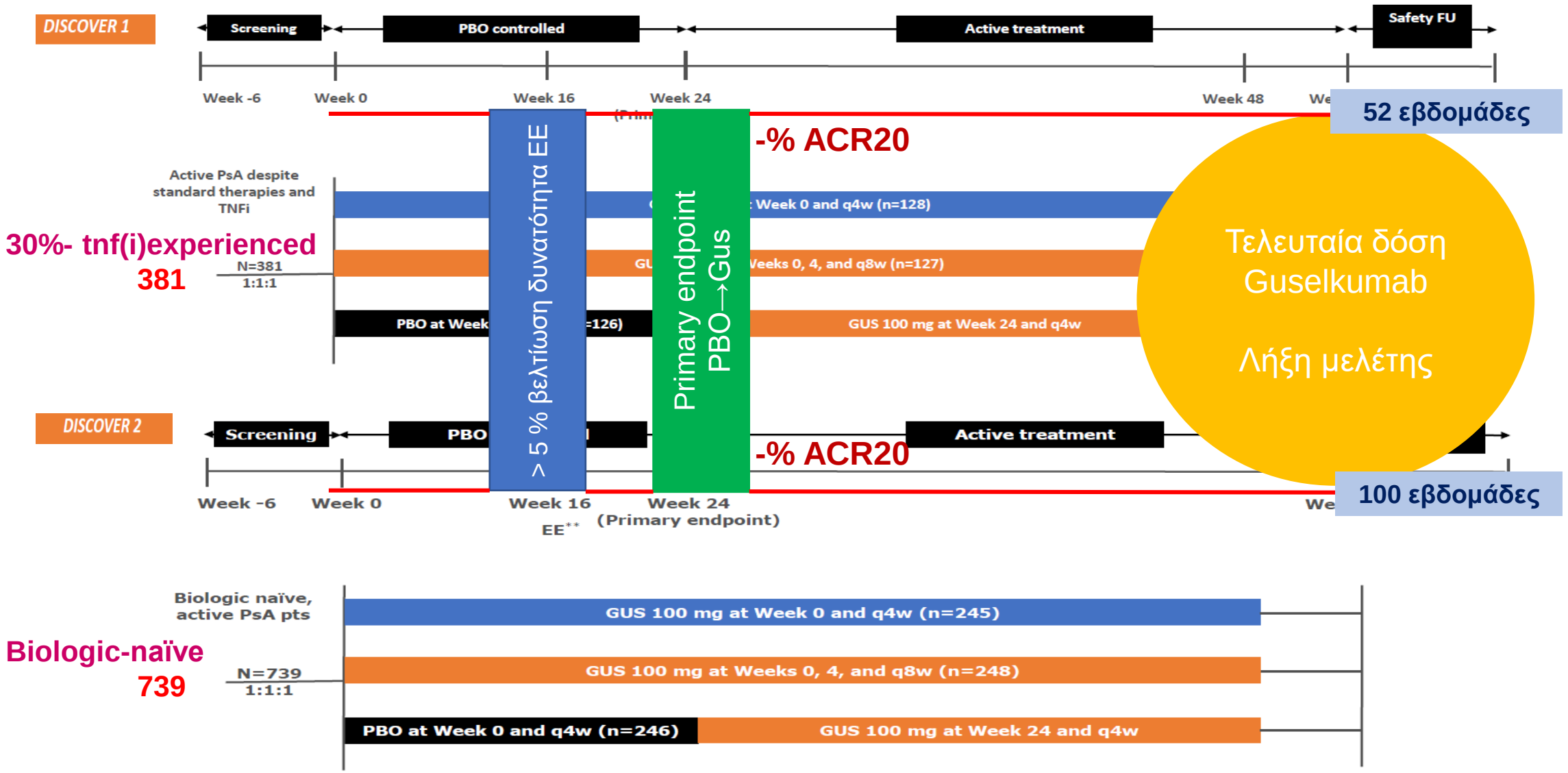
thritis defined as **≥5 swollen joints**,
≥5 tender joints, and
CRP ≥0.6 mg/dL

one PsA subset: DIP involvement, polyarticular
with absence of rheumatoid nodules, arthritis
mutilans, asymmetric peripheral arthritis, or spondylitis
with peripheral arth

Biologic-naïve

- Currently active **asis**
- **Inadequate response or intolerance** to **nbDMARDs, apremilast** and/or **NSAIDs**

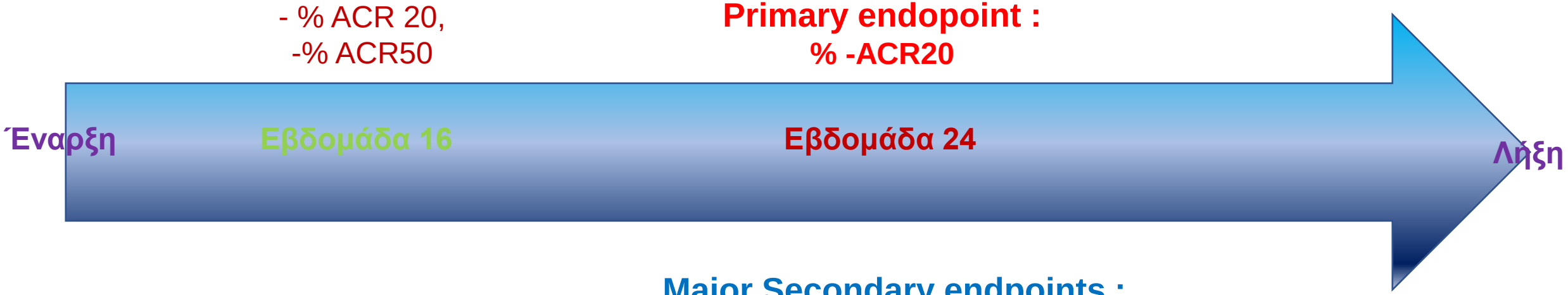
Σχεδιασμός κλινικών μελετών Discover 1 και Discover 2



Καταληκτικά σημεία Discover 1 και Discover 2

Major Secondary endpoints :
- % ACR 20,
-% ACR50

Primary endopoint :
% -ACR20



Major Secondary endpoints :

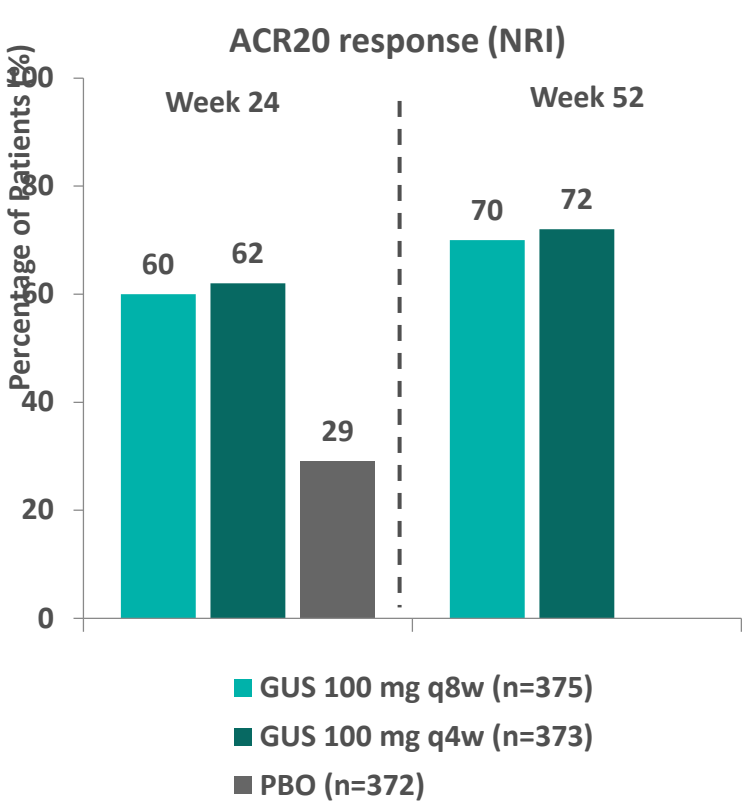
-Ενεργότητα νόσου : % ACR 50,/ACR70 , change from baseline DAS28(crp)
-Λειτουργικό επίπεδο: change from baseline in HAQ-DI and in SF-36 mpc/mcs
-Ψωρίαση : % IGA respone
-Ενθεσίτιδα : % αποδρομής, change from baseline in LEI
-Δακτυλίτιδα : % αποδρομής, change from baseline in Dactylitis score
-Ακτινολογική εξέλιξη : modified vdHs

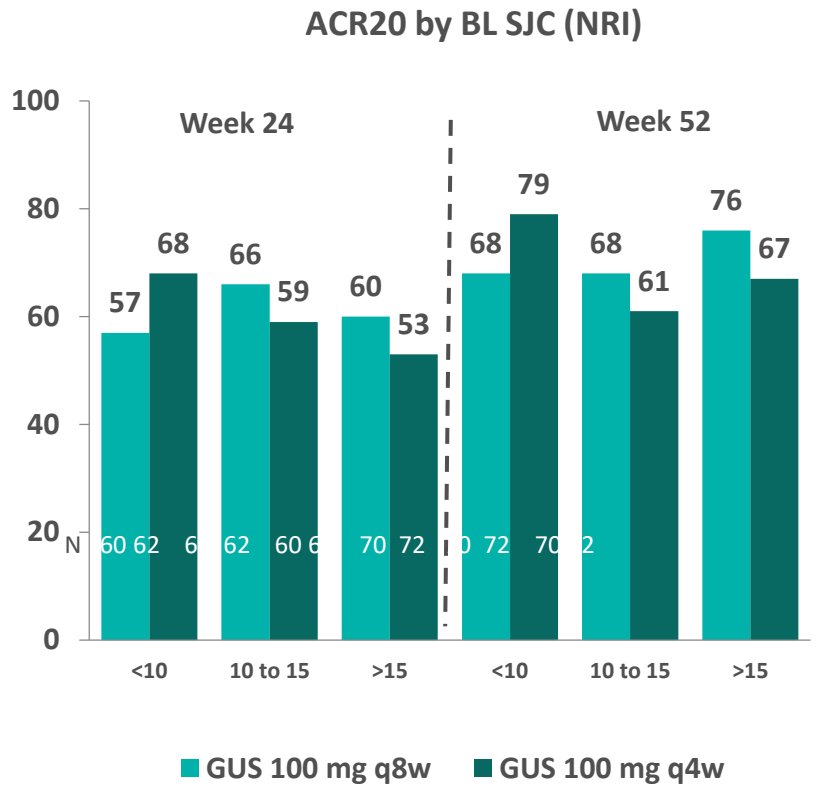
Αποτελέσματα : pooled Discover 1 και Discover 2

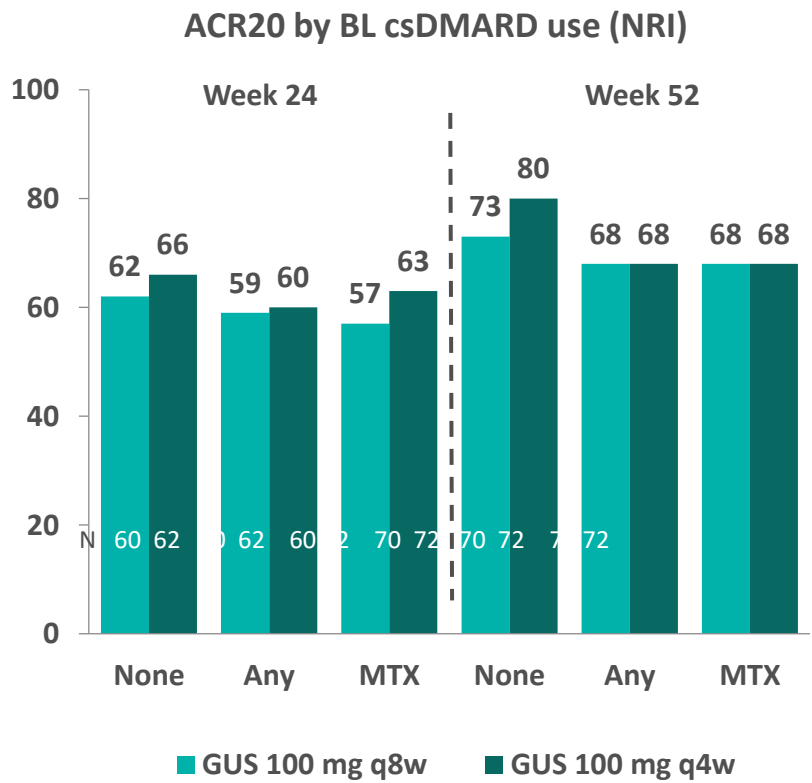
- **ACR20 through Week 52 by baseline characteristics**

- Pooled data from DISCOVER 1 and DISCOVER 2 (**N=1120**)
- Mean SJC=11, mean TJC=21, 68% used csDMARDs

Η συγχορήγηση με csDmards δεν φαίνεται να επηρεάζει την αποτελεσματικότητα







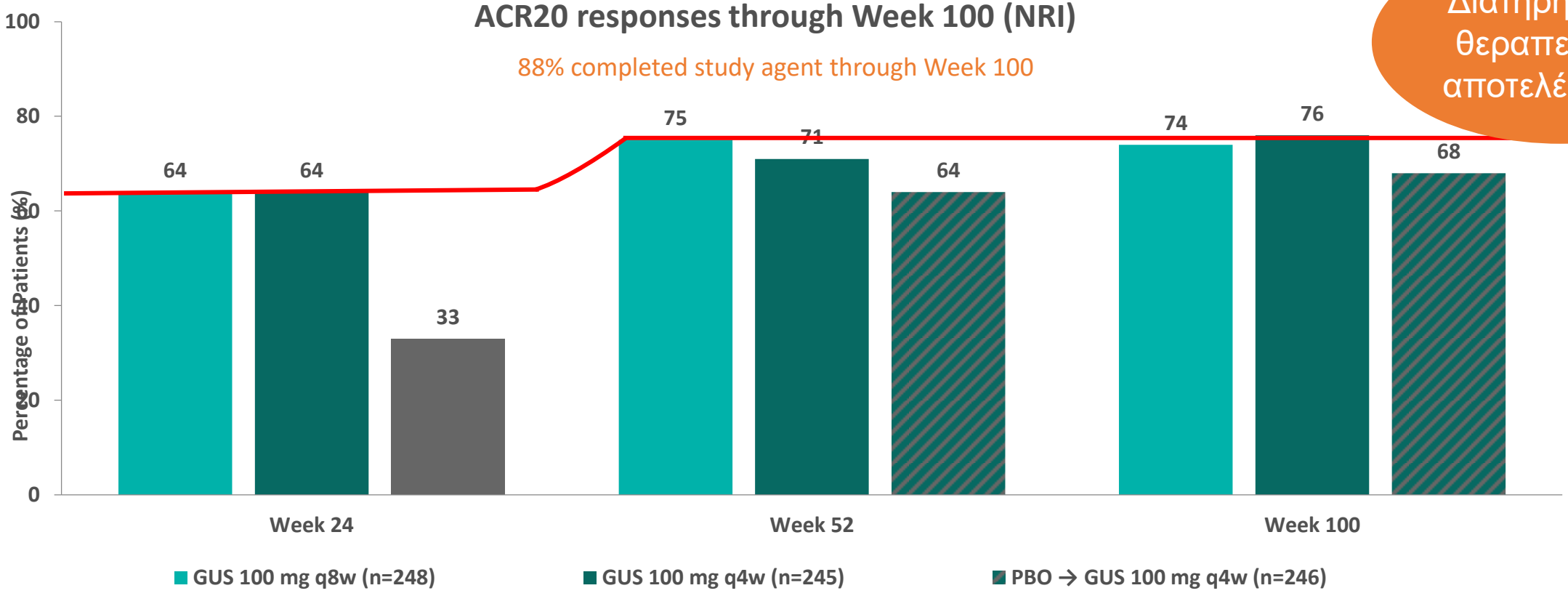
ACR, American College of Rheumatology; BL, baseline; csDMARD, conventional synthetic disease-modifying anti-rheumatic drug; MTX, methotrexate; PBO, placebo; q4w, every 4 weeks; q8w, every 8 weeks; SJC, swollen joint count; TJC, tender joint count.

Ritchlin et al. EULAR 2021 AB0526.

Αποτελέσματα : η διατήρηση της ανταπόκρισης

- **GUS maintained ACR20 responses through Week 100 (NRI)**

DISCOVER 2



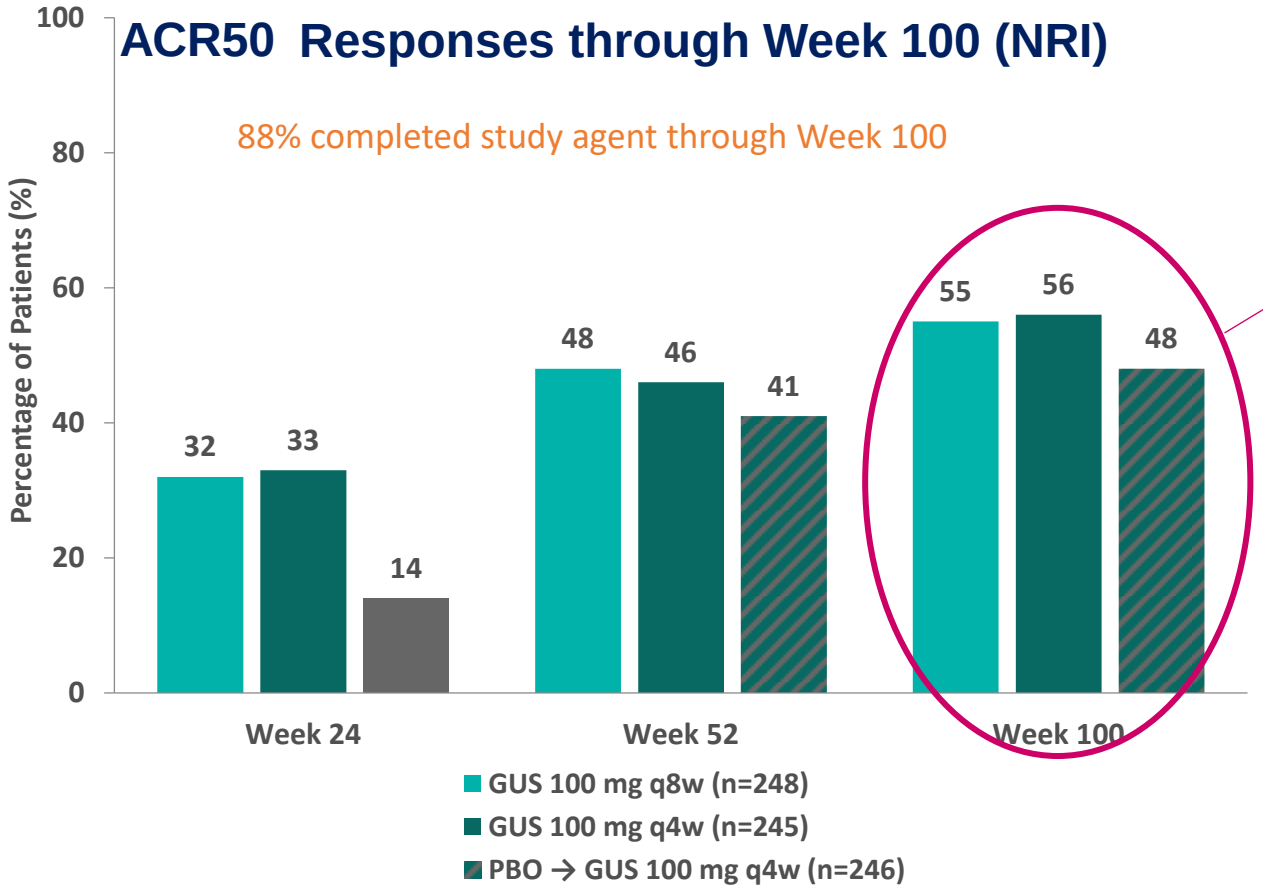
- ACR, American College of Rheumatology; GUS, guselkumab; NRI, non-responder imputation; PBO, placebo; q4w, every 4 weeks; q8w, every 8 weeks.

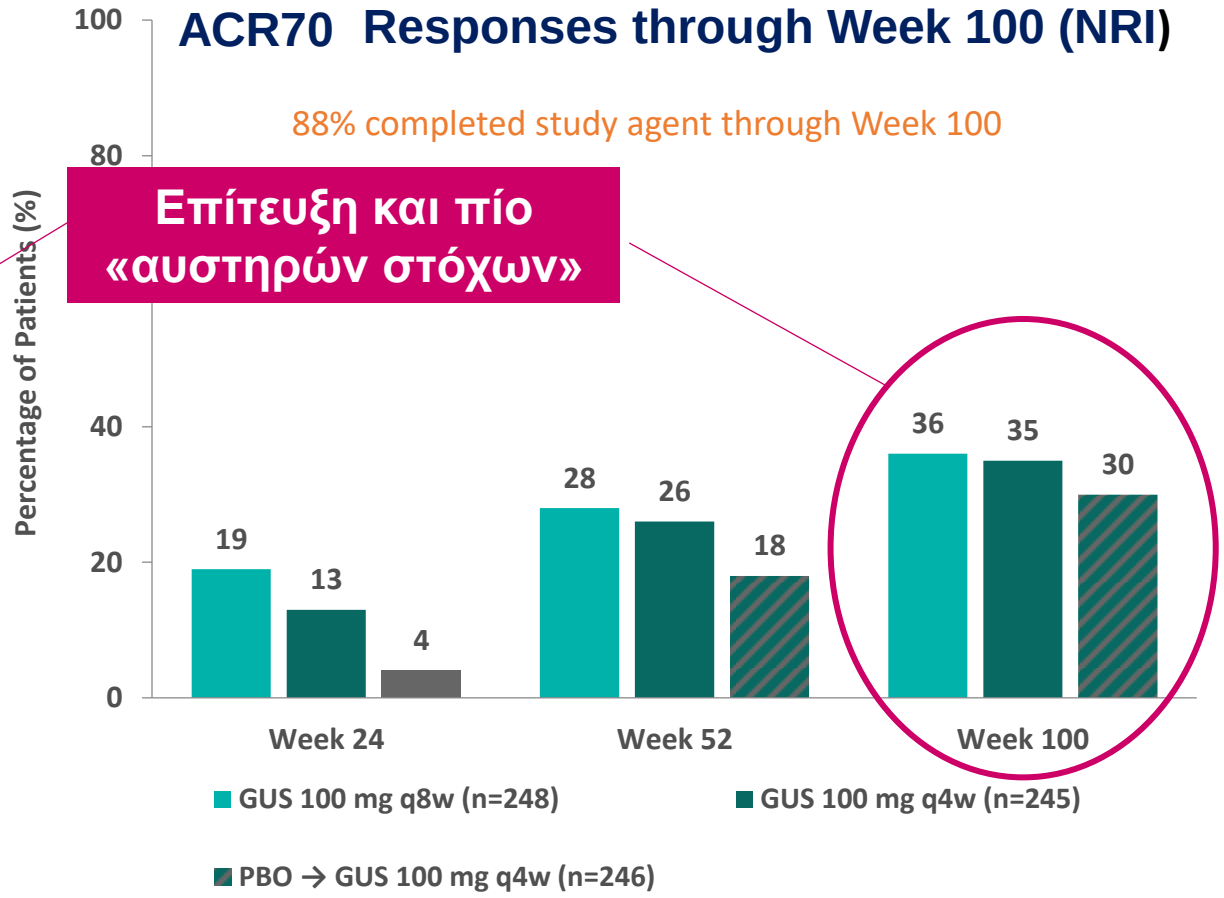
McInnes et al. EULAR 2021 POS1027.

Αποτελέσματα : η ανταπόκριση κατά ACR50 και ACR70

- **GUS maintained ACR responses through Week 100 (NRI)**

DISCOVER 2





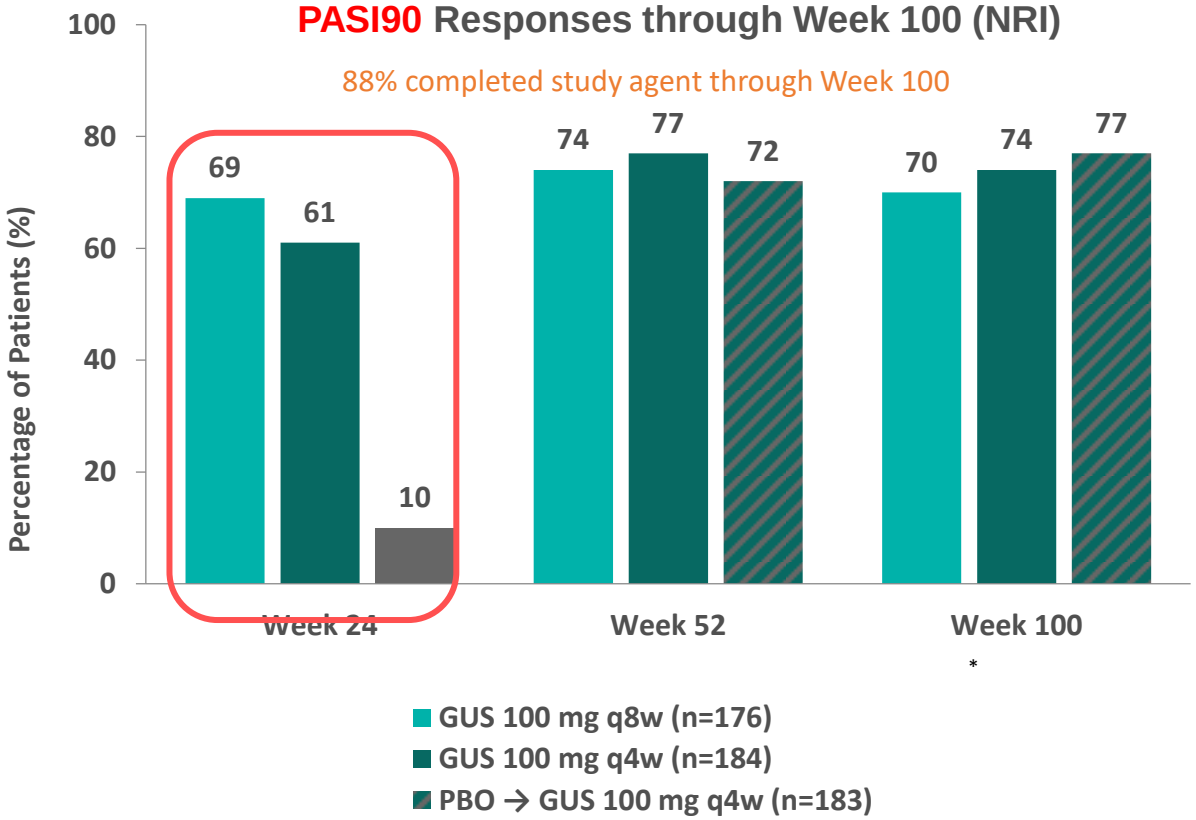
ACR, American College of Rheumatology; GUS, guselkumab; NRI, non-responder imputation; PBO, placebo; q4w, every 4 weeks; q8w, every 8 week.**McInnes et al. EULAR 2021 POS1027**

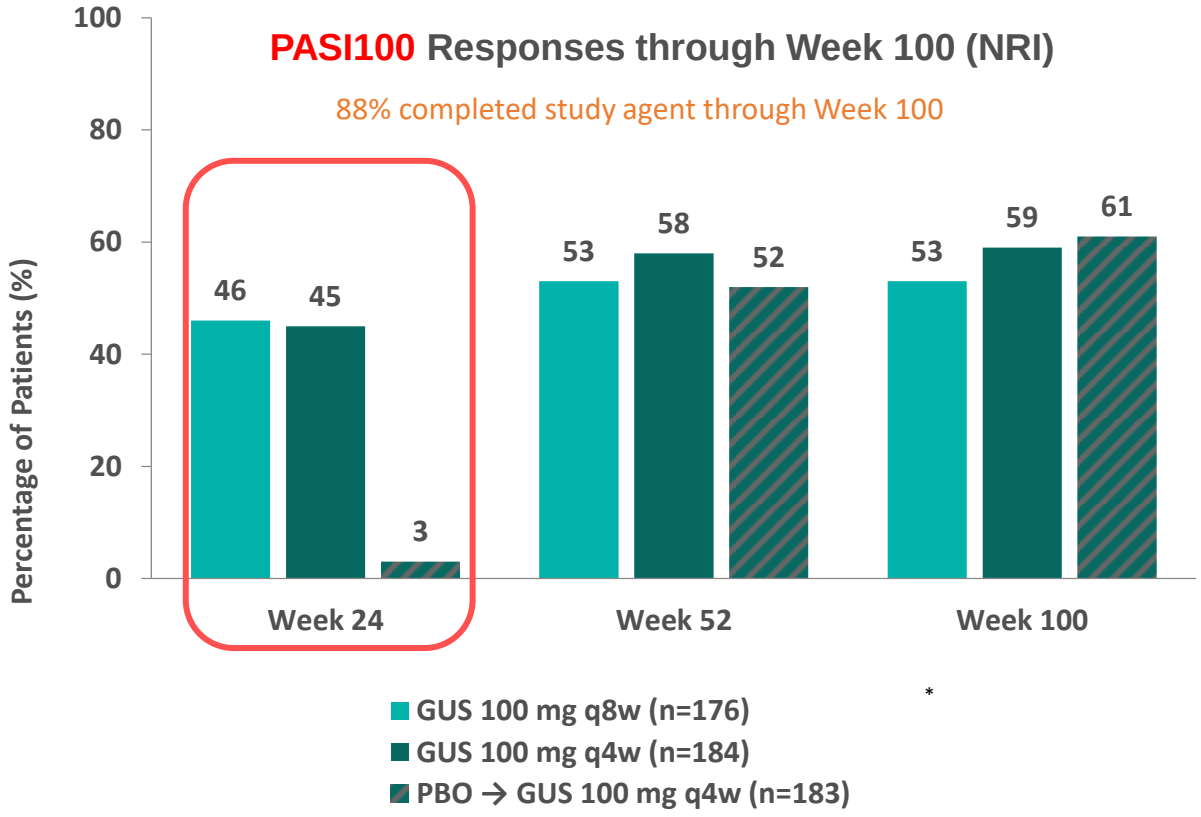
Αποτελέσματα : η ανταπόκριση στην Ψωρίαση

- **GUS maintained PASI responses through Week 100 (NRI)**

mean baseline PASI : 11
mean baseline BSA : 18%

DISCOVER 2





GUS, Guselkumab; NRI, Non-responder imputation**McInnes et al. EULAR 2021 POS1027**.

Δεδομένα για Ενθεσίτιδα και Δακτυλίτιδα

Οι ασθενείς με δακτυλίτιδα και ενθεσίτιδα κατά την έναρξη των κλινικών μελετών Discover 1 και 2

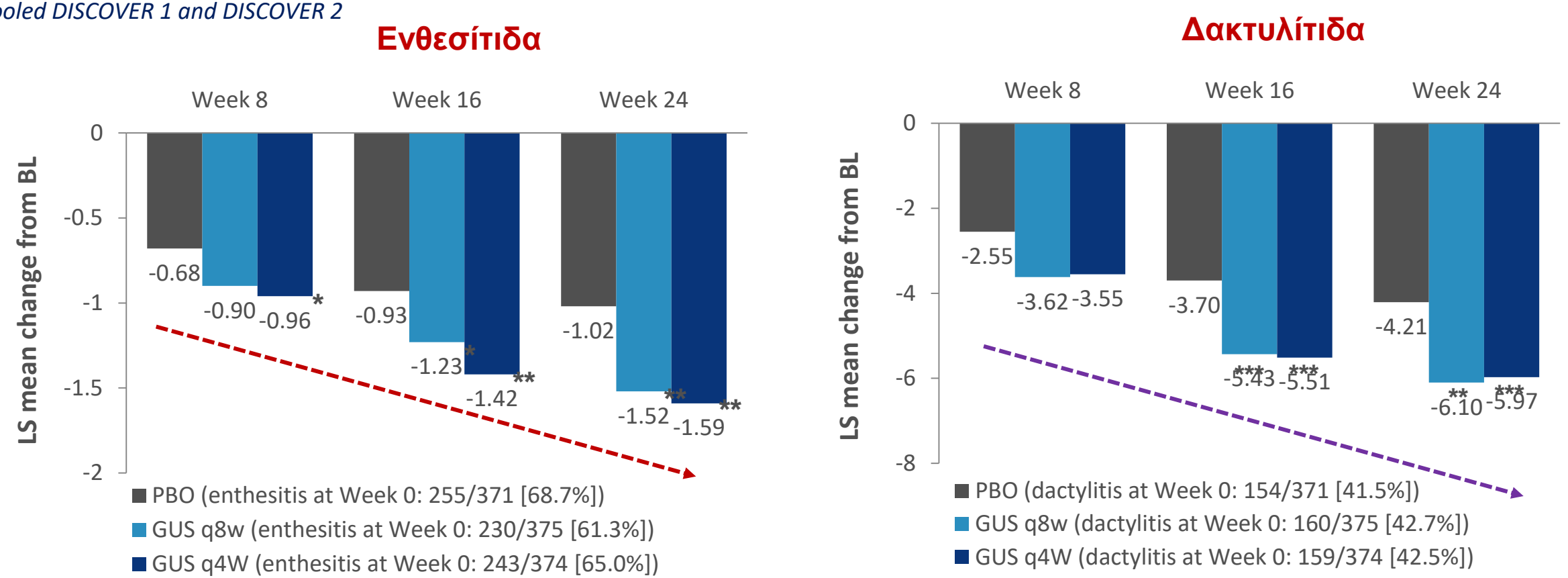
 	Discover-1 (381 pts)	Discover-2 (739 pts)	Pooled patients from Discover 1& 2	Total patients of Discover-1 & Discover-2
Proportion of patients with, dactylitis ， n (%)	142 (37,27%)	331 (44,7%)	473 (42,23%)	1120
Proportion of patients with enthesitis, n (%)	222 (57,74%)	506 (68,47%)	728 (65%)	1120

1. Deodhar A, et al. *Lancet* 2020;395:1115–1125
2. Mease P, et al. *Lancet* 2020;395:1126–1136..

Η αποτελεσματικότητα στην Ενθεσίτιδα και Δακτυλίτιδα

- **Changes in enthesitis and dactylitis through Week 24**

Pooled DISCOVER 1 and DISCOVER 2



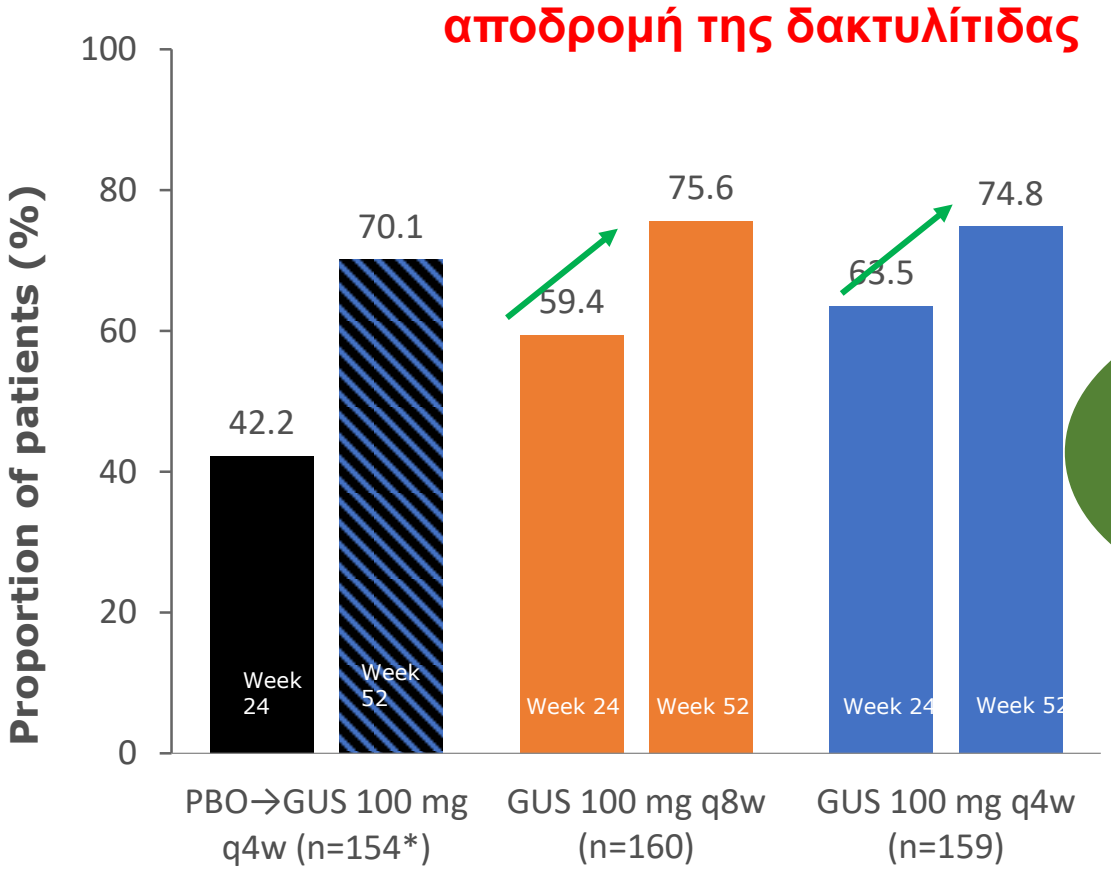
LS mean changes from baseline over time in enthesitis (LEI) and dactylitis scores

*p<0.005 vs PBO, **p<0.001 vs PBO; ***p<0.01 vs PBO. Unadjusted (nominal) p-values, not controlled for multiplicity; interpret only as supportive.
BL, baseline, GUS, guselkumab; LEI, Leeds Enthesitis Index; LS, least square; PBO, placebo; q4w, every 4 weeks; q8w, every 8 weeks.

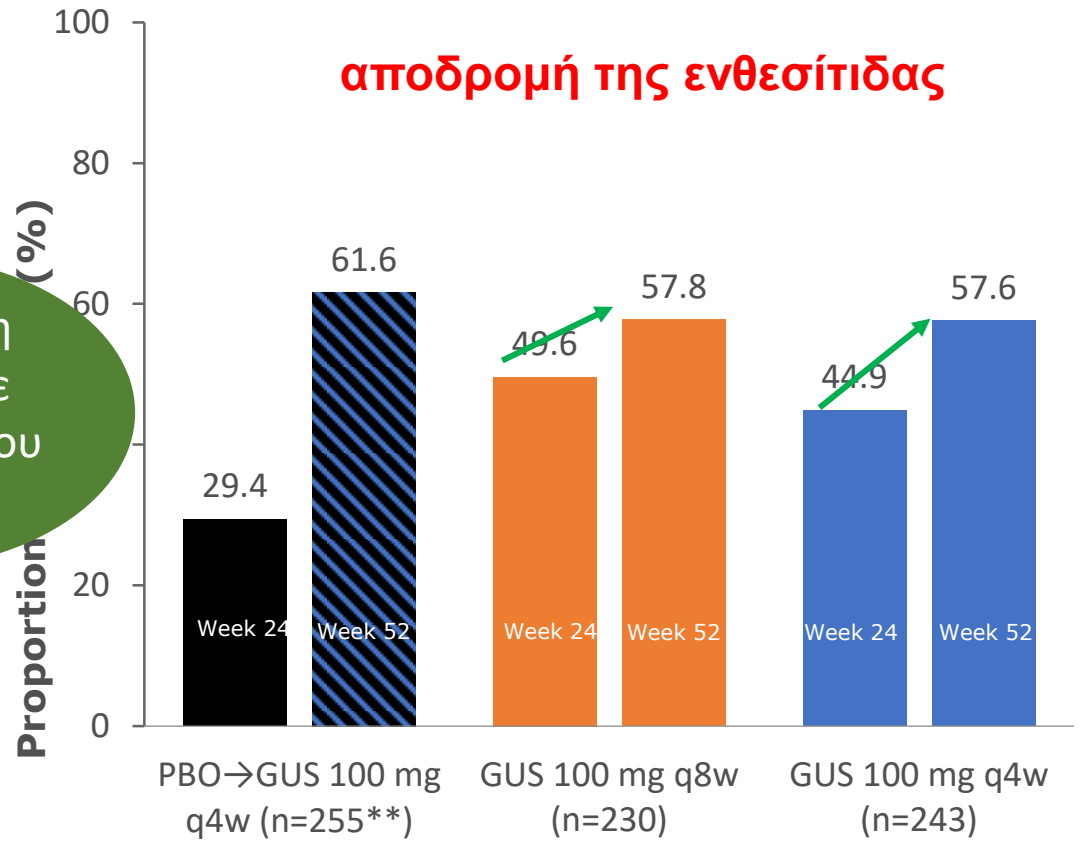
1. McGonagle D, et al. Presented at the EULAR e-Congress, June 2020. Abstract 0801.

Η αποτελεσματικότητα στην Ενθεσίτιδα και Δακτυλίτιδα

- **Resolution of dactylitis and enthesitis at Week 24 and Week 52**



Μεγαλύτερη βελτίωση με την πάροδο του χρόνου



*142 patients crossed over from PBO to GUS q4w at Week 24 and 12 received PBO only before study agent discontinued; **243 patients crossed over to GUS q4w at Week 24 and 12 received PBO only before study agent discontinued.
GUS, guselkumab; PBO, placebo; q4w, every four weeks; q8w, every eight weeks.

1. McInnes IB, et al. Presented at the EULAR e-Congress, June 2020. Poster 0402.

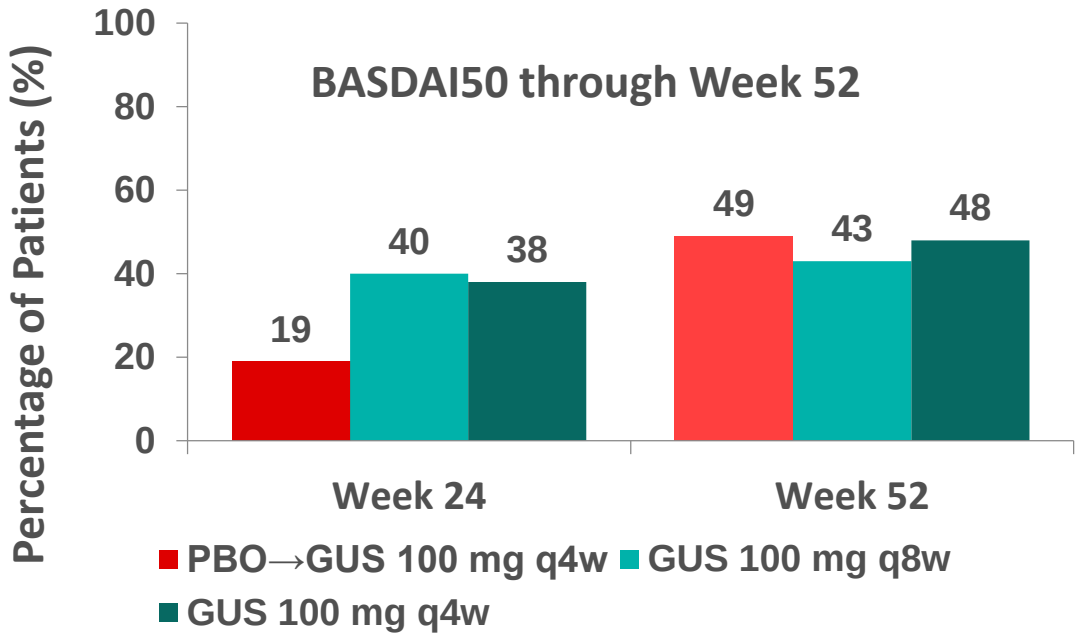
Δεδομένα για την Ψωριασική σπονδυλίτιδα

Efficacy of Guselkumab Across BASDAI Components in Treating Axial-related Symptoms of PsA

Pooled DISCOVER 1 and DISCOVER 2

- Post hoc analyses included pts who were identified by the investigator as having axial symptoms and sacroiliitis (prior X-ray or MRI or screening X-ray)
- BASDAI scores were assessed at Weeks 0, 8, 16, 24, and 52

	PBO	GUS 100 mg q8w	GUS 100 mg q4w
N	118	91	103
Age (years), mean	45.3	45.0	44.9
Male, %	59	59	66
BASDAI mean	6.6 (n=110)	6.5 (n=84)	6.4 (n=95)
BASDAI components, mean			
Fatigue	6.5	6.7	6.4
Spinal pain	6.7	6.5	6.6
Joint pain	6.8	6.5	6.3
Enthesitis	6.3	6.4	6.3
Qualitative morning stiffness	7.0	6.7	6.8
Quantitative morning stiffness	6.1	5.7	6.2

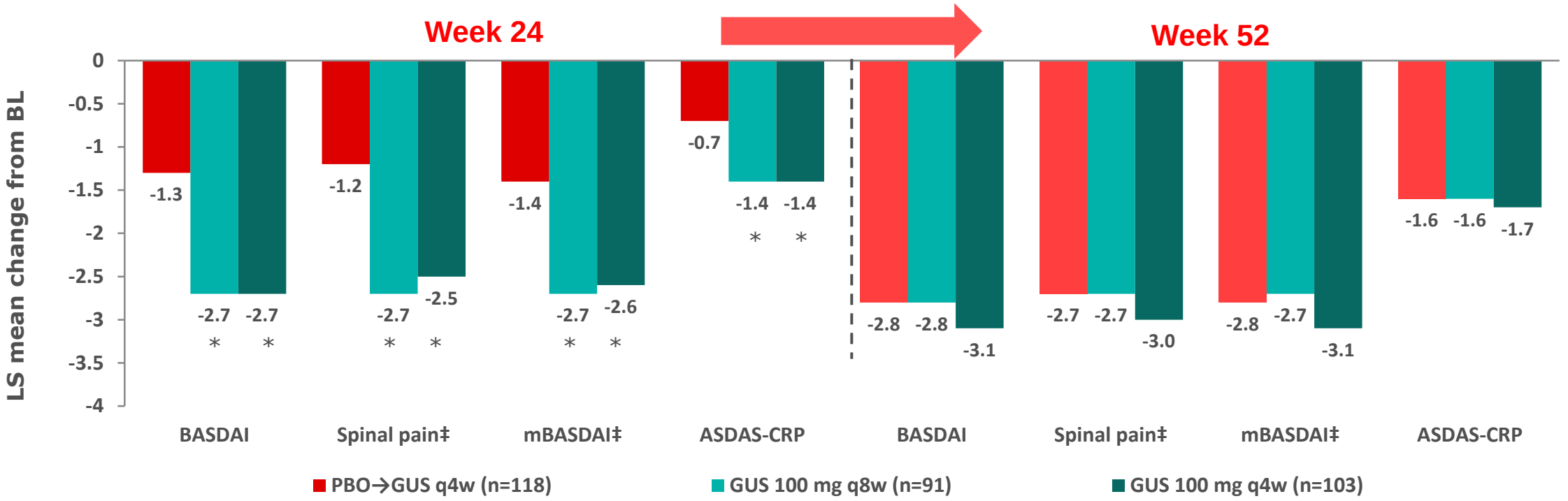


Behrens et al. EULAR 2021 #AB0524.

Δεδομένα για την Ψωριασική σπονδυλίτιδα

Maintenance of axial symptoms improvements through Week 52 in GUS-treated patients with PsA with imaging-confirmed sacroiliitis

Pooled DISCOVER 1 and DISCOVER 2



PBO→GUS group patients received PBO from Week 0 and crossed over to GUS 100 mg q4w at Week 24. Unadjusted p-values: *p<0.001; †Patients with axial involvement consistent with sacroiliitis at baseline and either a history of imaging confirmation or pelvic X-ray at screening (pooled data DISCOVER-1 and -2); ‡Measured by question 2 of the BASDAI (how would you describe the overall level of AS neck, back or hip pain you have had?); ¶Modified BASDAI: excludes 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?).
ASDAS, Ankylosing Spondylitis Disease Activity Score; BASDAI, Bath Ankylosing Spondylitis Disease Activity Index; BASDAI50, 50% improvement in BASDAI; BL, baseline; CRP, C-reactive protein;
GUS, guselkumab; PBO, placebo; PsA, psoriatic arthritis; q4w, every 4 weeks; q8w, every 8 weeks

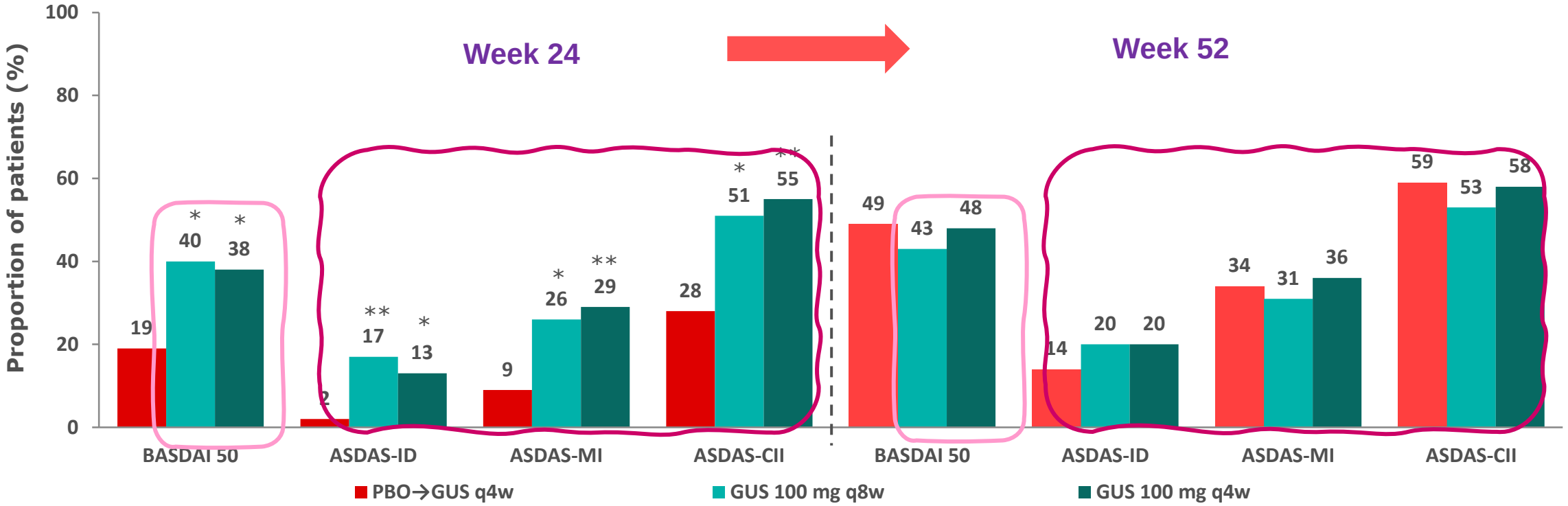
. Mease PJ, et al. ACR Convergence 2020, November 5-9. Abstract 2025.

Δεδομένα για την Ψωριασική σπονδυλίτιδα

Maintenance of axial symptoms improvements through Week 52 in GUS-treated patients with PsA with imaging-confirmed sacroiliitis

Pooled DISCOVER 1 and DISCOVER 2

Efficacy results of GUS in patients with PsA with axial involvement†



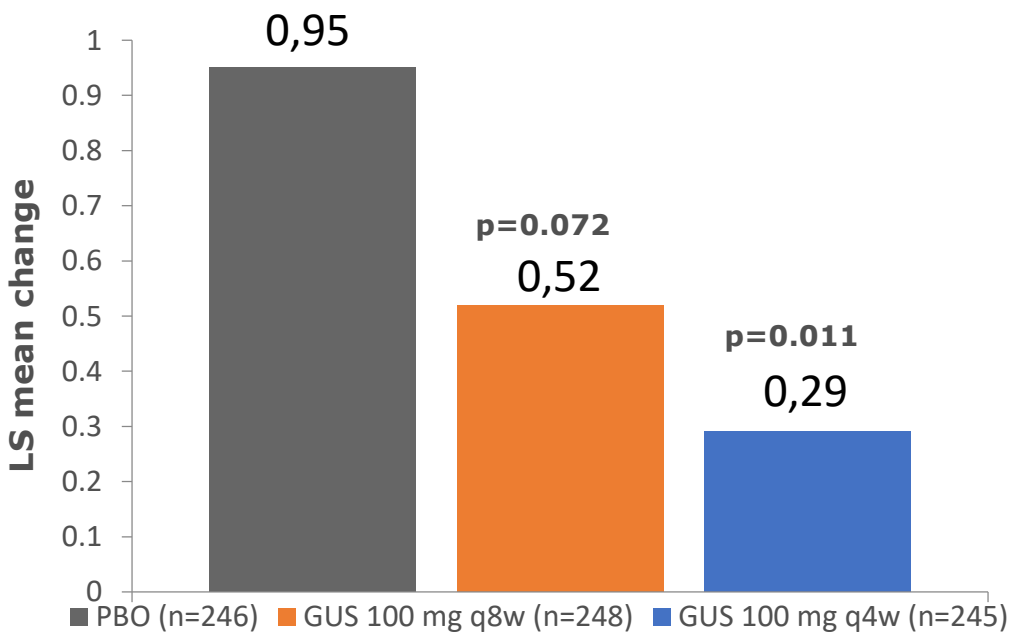
Unadjusted p-values: *p<0.01; **p<0.001 vs. PBO; †Patients with axial involvement consistent with sacroiliitis at baseline and either a history of imaging confirmation or pelvic X-ray at screening (pooled data DISCOVER-1 and -2). ASDAS-ID/MI/CII, Ankylosing Spondylitis Disease Activity Score inactive disease (<1.3)/major improvement (decrease ≥2.0)/clinically Important improvement (decrease ≥1.1); BASDAI, Bath Ankylosing Spondylitis Disease Activity Index; BASDAI50, 50% improvement in BASDAI; CRP, C-reactive protein; GUS, guselkumab; PBO, placebo; PsA, psoriatic arthritis; q4w, every 4 weeks; q8w, every 8 weeks.

Mease PJ, et al. ACR Convergence 2020, November 5-9 Abstract 2025.

Δεδομένα για την ακτινολογική εξέλιξη και τις δομικές αλλοιώσεις

DISCOVER 2

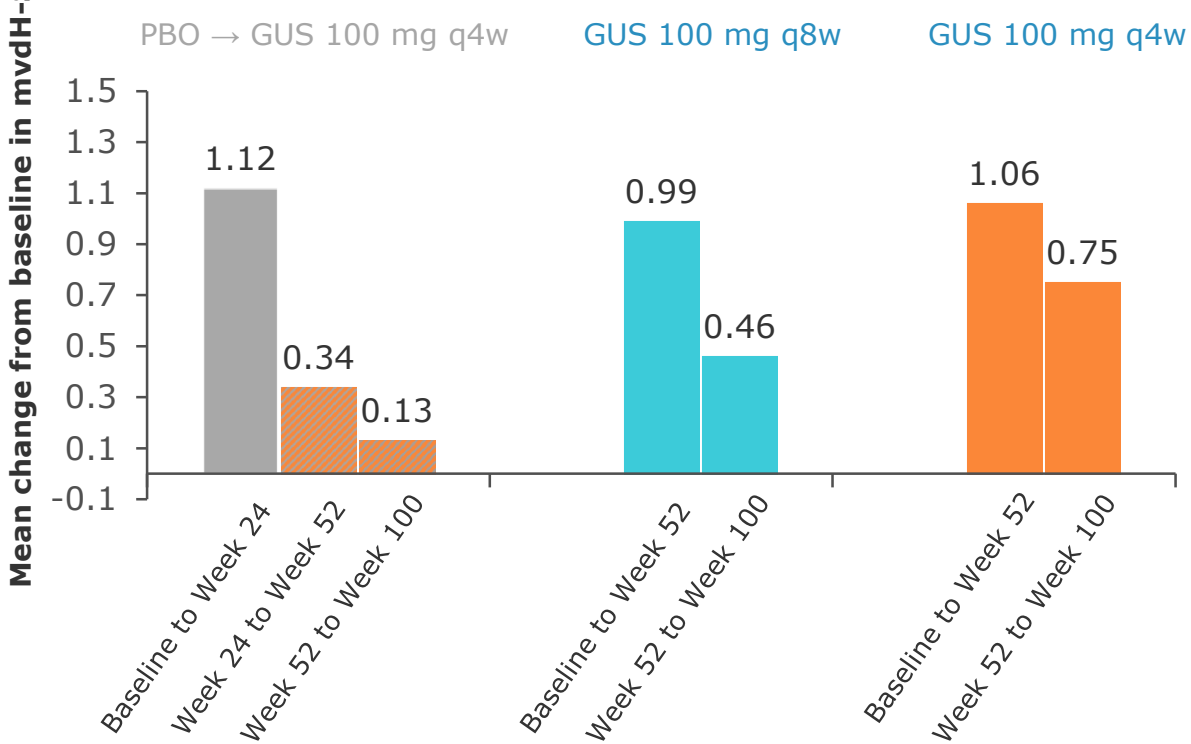
Μικρότερη ακτινολογική «πρόοδος» στους ασθενείς υπο θεραπεία με GUS σε σχέση με το εικονικό φάρμακο την 24 εβδομάδα



LS Mean Change in modified vdHSS from BL to Week 24

BL, baseline; GUS, guselkumab; PBO, placebo; q4w, every four weeks; q8w, every eight weeks; vdHSS, van der Heijde Sharp Score.

Η ακτινολογική πρόοδος των ασθενών στα 2 έτη υπό θεραπεία με GUS



PsA-Modified vdH-S Scores through Week 100 for PBO

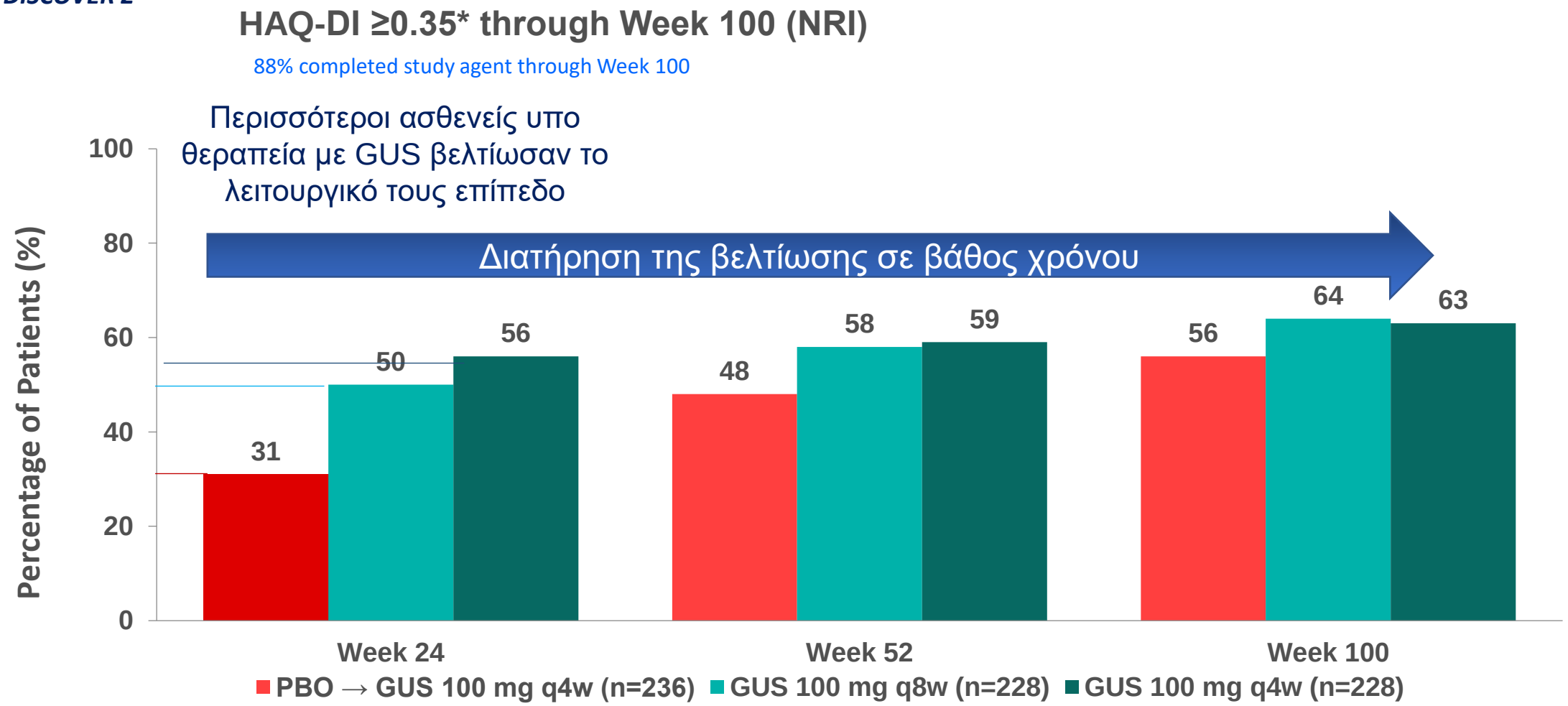
*Based on observed data, FAS3 which includes all randomized subjects still on study treatment at Week 52
FAS: Full Analysis Set, all randomly assigned and treated patients. GUS: Guselkumab;

1. Mease P, et al. *Lancet* 2020;395:1126–1136.

Δεδομένα για το λειτουργικό επίπεδο των ασθενών

- **GUS Maintained Physical Function through Week 100 (NRI)**

DISCOVER 2

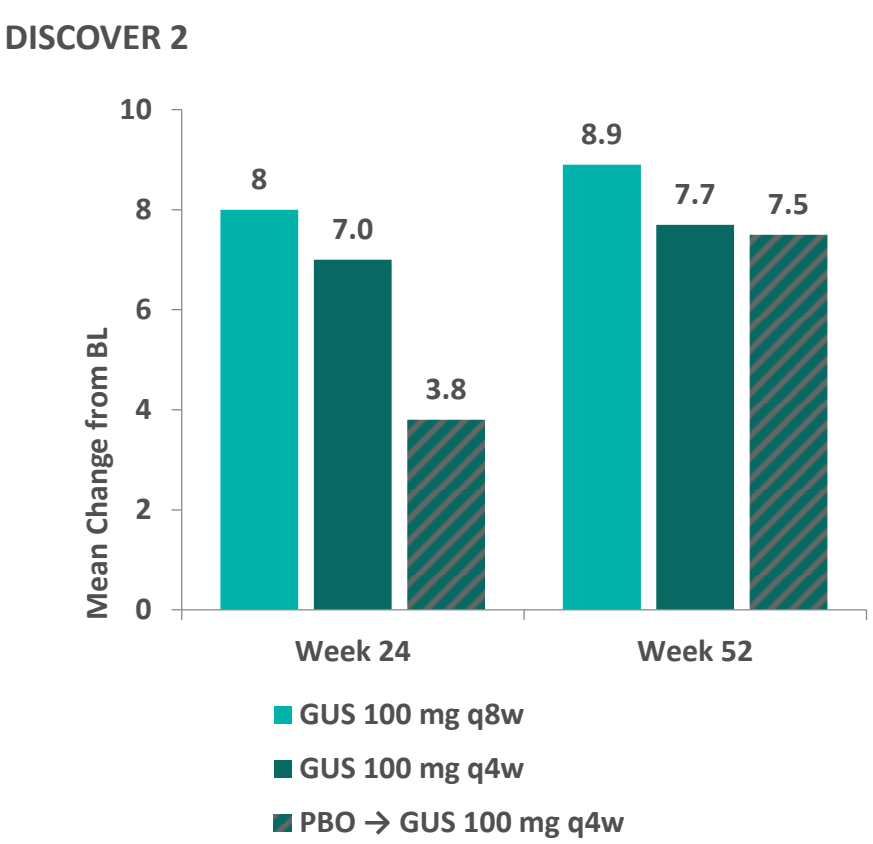


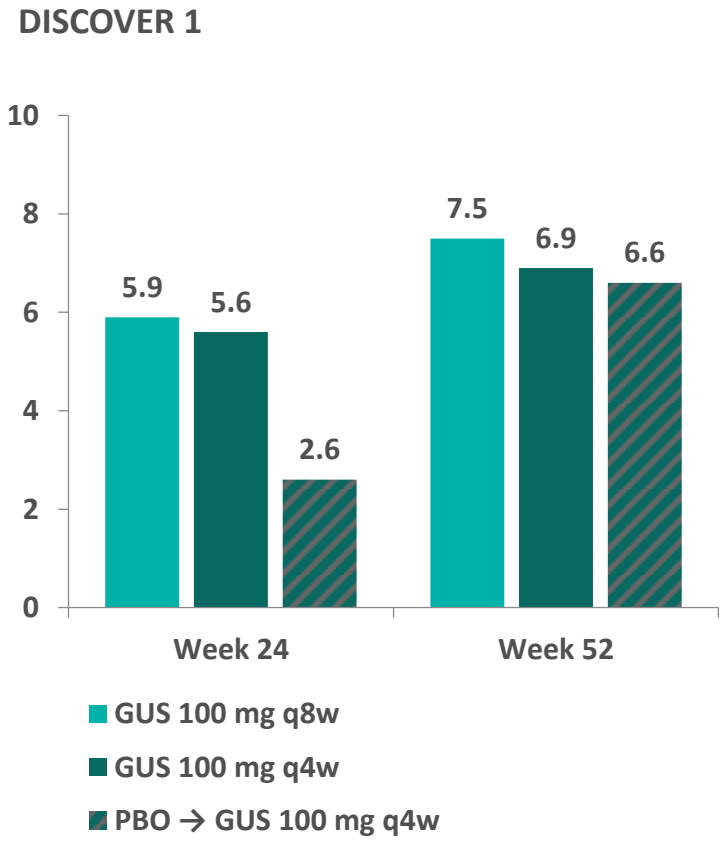
*In pts with BL HAQ-DI ≥0.35; GUS: Guselkumab; NRI: Non-responder imputation

McInnes et al. EULAR 2021 #POS1027.

Δεδομένα για την «κόπωση» των ασθενών

Βελτίωση της κόπωσης σε ένα έτος θεραπείας





Mediation analysis (ACR20)

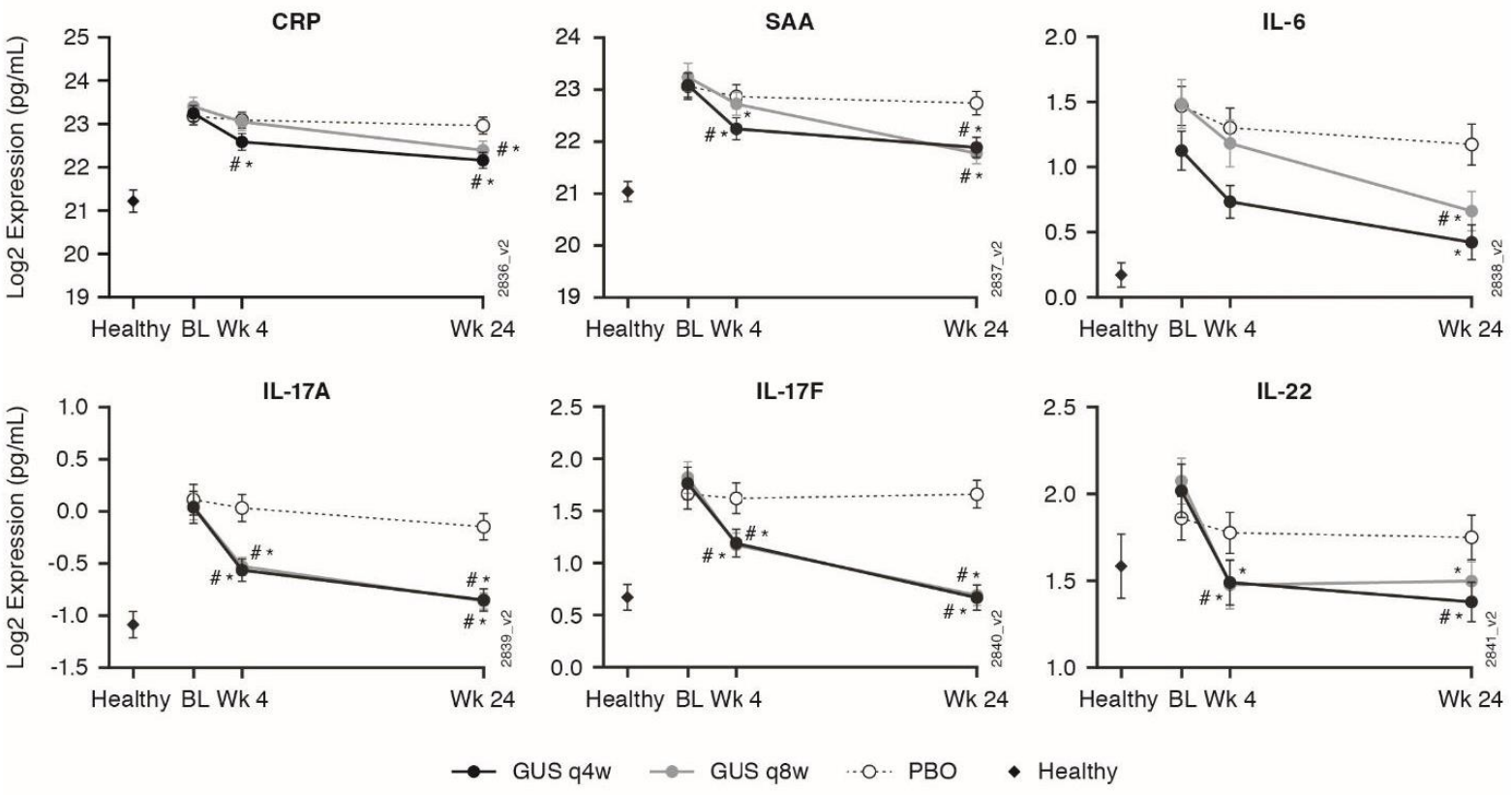
	Effect	GUS q8w vs PBO	GUS q4w vs PBO
DISCOVER 1	Total effect	3.1	3.8
	% Direct Effect	11.7	68.5
	% Indirect Effect (ACR20)	88.3	31.5
DISCOVER 2	Total effect	4.0	3.6
	% Direct Effect	36.3	69.7
	% Indirect Effect (ACR20)	63.7	30.3

Change in FACIT-Fatigue scores at Week 24 and 52 (as observed)

GUS treatment improved fatigue when compared to PBO during PBO-controlled periods and maintained improvements through 1 year of active treatment. Substantial proportions of those effects were independent of the effects on ACR20, especially for the q4w dosing group

Μείωση στα επίπεδα δεικτών φλεγμονής και κυτταροκίνων στους ασθενείς με GUS

Pooled DISCOVER 1 and DISCOVER 2



21 serum biomarkers‡ measured at Weeks 0, 4 and 24 in a random subset of 300 patients with PsA from the DISCOVER trials and in 34 healthy controls matched for age, sex and ethnicity

BL IL-17A, IL-17F, IL-22, and CCL22 were significantly associated with BL PsO disease activity (BSA, PASI)

BL CRP, SAA, IL-6, and YKL40 were significantly associated with BL joint disease activity (DAS28-CRP)

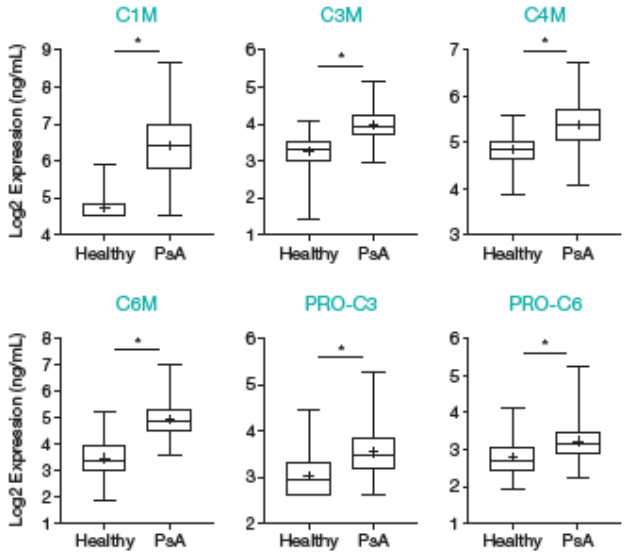
BL SAA, IL-6, IL-17A and IL-17F were significantly higher in patients with prior TNFi exposure

ACR Convergence 2020, November 5-9. Abstract 0367.

Μείωση στα επίπεδα βιοδεικτών του κολλαγόνου στους ασθενείς υπό θεραπεία με GUS

DISCOVER 2

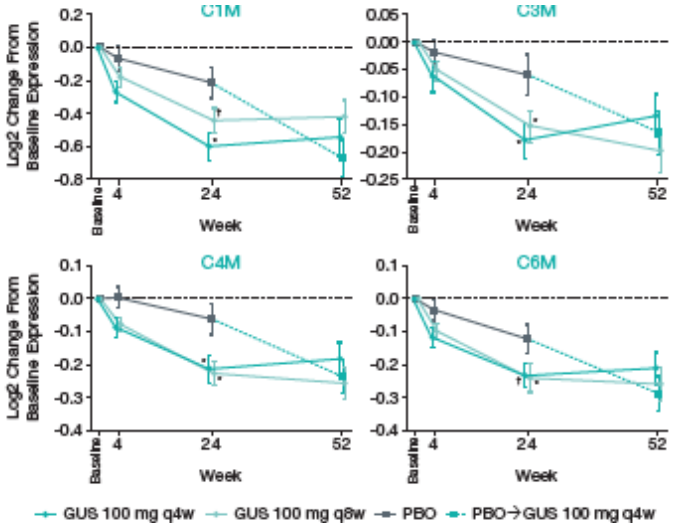
Upregulation of collagen degradation/formation biomarkers among patients with PsA



*Indicates significance defined by FDR adjusted p<0.05.

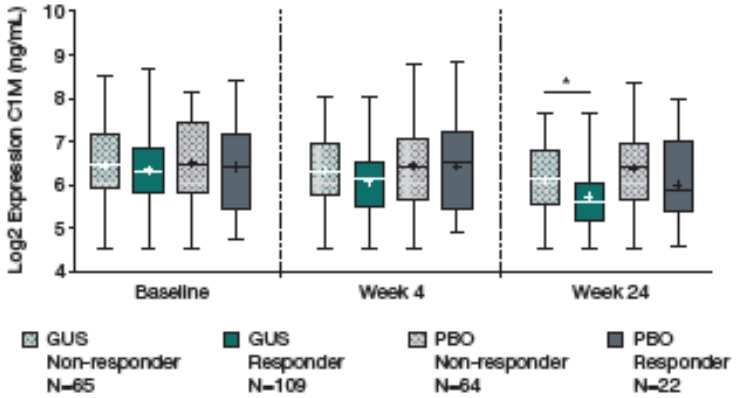
PsA n=260† Healthy n=76

Collagen degradation markers (C1M, C3M, C4M, C6M) ↓ with GUS



*p<0.05 GUS vs. PBO; †p<0.07 GUS vs. PBO.

C1M reductions by ACR20 response‡



Combined analysis of GUS q4w and q8w. Response defined by ACR20 at Week 24. Median values (+ marks mean). Boxes represent the interquartile range, whiskers the minimum and maximum.
*p=0.0065, significance between responder and non-responder defined by p<0.05.

- This study demonstrates that collagen biomarkers in serum are dysregulated in patients with PsA compared to healthy controls, and that GUS decreases levels of these proteins, with GUS causing a decrease in C1M, C3M, C4M, and C6M
- Patients achieving ACR 20 at Week 24 had a greater reduction in C1M compared to non-responders, further emphasising the association of this bone degradation marker with clinical disease activity and providing insight into how GUS may be working to protect from degradation of bone in PsA

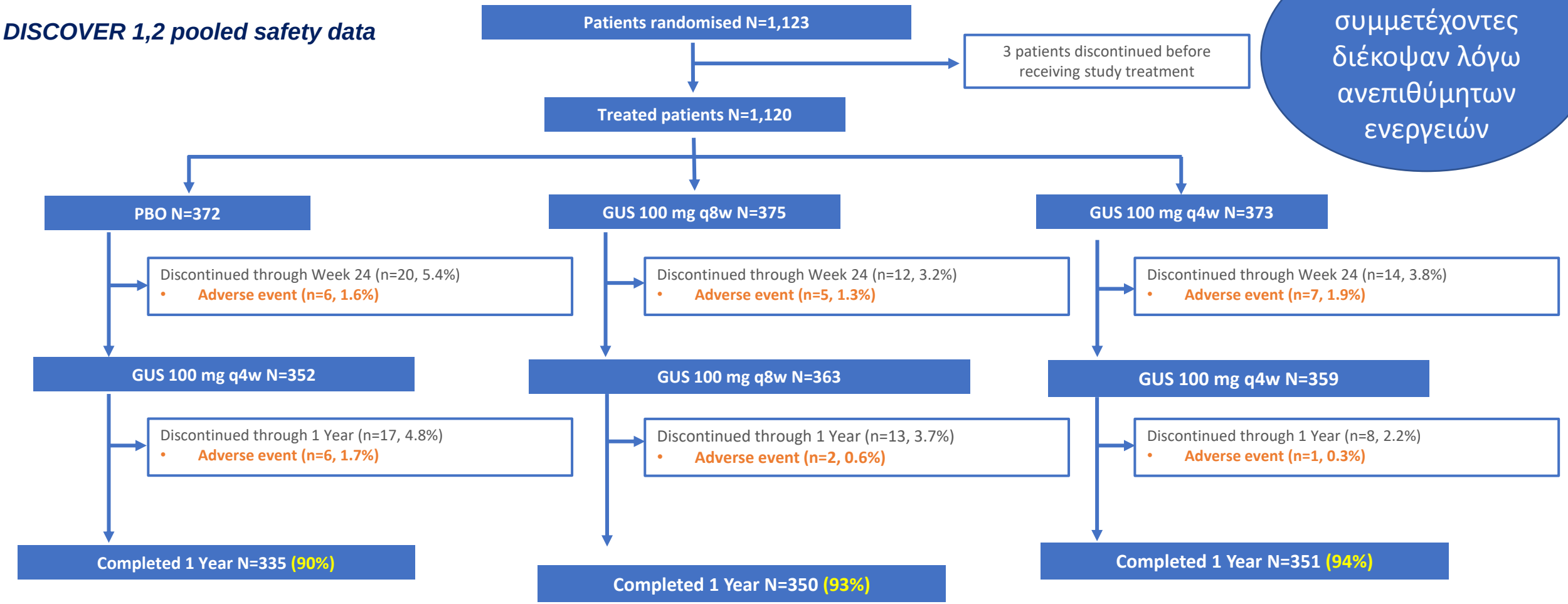
†A subset of DISCOVER 2 patients (n=260) and healthy controls matched for age, sex, ethnicity.

ACR, American College of Rheumatology; BL, baseline; GUS, guselkumab; PsA, psoriatic arthritis.

- **Schett et al. EULAR 2021 POS1036**.

Δεδομένα ασφάλειας

DISCOVER 1,2 pooled safety data



27 από 1120 συμμετέχοντες διέκοψαν λόγω ανεπιθύμητων ενεργειών

η κατανομή των ασθενών ένα έτος μετά την έναρξη του κλινικού προγράμματος

Δεδομένα ασφάλειας

- **Ανεπιθύμητες ενέργειες «ειδικού» ενδιαφέροντος**

Time period	Week 0-24				1 Year[a]			
Treatment group	**PBO[b]**	**GUS 100 mg q8w**	**GUS 100 mg q4w**	**GUS all[c]**	**PBO → GUS 100 mg q4w[d]**	**GUS 100 mg q8w**	**GUS 100 mg q4w**	**GUS all[c]**
Patients, N	372	375	373	748	352	375	373	1100
Death, %	0.5	0	0	0	0	0	0	0
Malignancy, %	0.3	0.5	0	0.3	0.3	0.5	0	0.3
MACE, %	0.3	0	0.3	0.1	0	0	0.3	0.1
Opportunistic infections, %	0	0	0	0	0	0	0	0
Tuberculosis, %	0	0	0	0	0	0	0	0
IBD, %	0.3	0	0	0	0	0	0	0
Injection-site reaction, %	0.3	1.3	1.1	1.2	1.1	1.6	2.4	1.7
Anti-GUS antibody positive*, %	NA	1.6 (n=373)	2.4 (n=371)	2.0 (n=744)	4.0 (n=350)	4.8 (n=373)	4.6 (n=371)	4.5 (n=1094)

*Presence of antibodies to GUS in serum samples of GUS-treated patients was assessed using a validated immunoassay method; [a]Through Week 60 for DISCOVER 1 and Week 52 for DISCOVER 2. [b]For pts who switched from PBO to GUS, only data prior to first GUS administration were included in this group; [c]Combined GUS q8w and q4w treatment groups (incl. pts who crossed over from PBO for 1-year results). [d]For pts who switched from PBO to GUS, only data on and after the first GUS administration were included in this group.

GUS, guselkumab; IBD, Inflammatory bowel disease; MACE, Major adverse cardiovascular events (cardiovascular death, non-fatal myocardial infarction, or non-fatal stroke); PBO, placebo; q4w, every four weeks; q8w, every eight weeks.

Rahman et al. J Rheumatol 2021; epub 01MAY doi: 10.3899/jrheum.201532.

DISCOVER 2

Δεδομένα ασφάλειας

- **Μακροπρόθεσμα δεδομένα ασφάλειας (εβδομάδα 112)**

	Week 0-112		
	PBO→GUS 100 mg q4w	GUS 100 mg q8w	GUS 100 mg q4w
N	238	248	245
Mean weeks of FU	84.2	107.1	106.4
Patients with ≥1 SAE, %	7	9	9
Patients with ≥1 serious infection, %	3	3	2
Patients with ≥1 opportunistic infection, %	0.4	0.8	0
Death	0.4	0	0

- Opportunistic infections: Fungal esophagitis, disseminated herpes zoster (GUS 100 mg q8w), listeria meningitis (PBO → GUS 100 mg q4w)
- Death: Road traffic accident (PBO → GUS 100 mg q4w)
- No GUS-treated patient had IBD (1 PBO-randomized patient had suspected IBD prior to Week 24)
- No active TB; no anaphylactic or serum sickness reactions

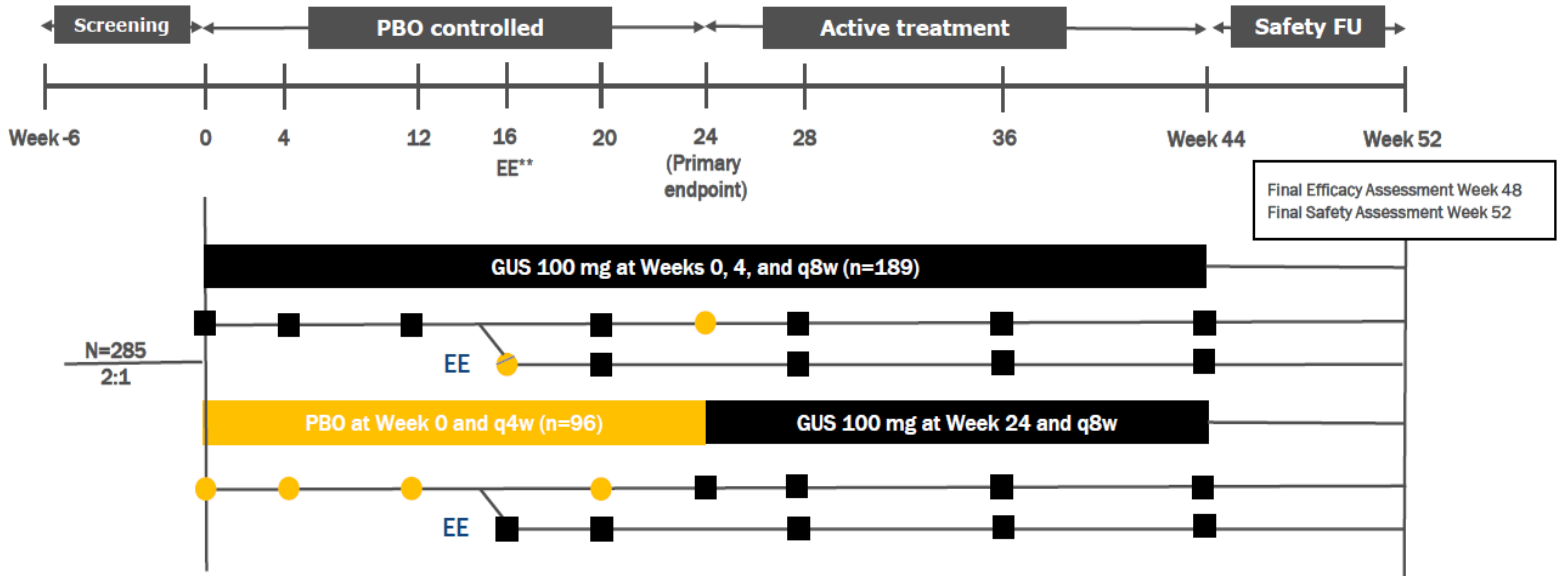
GUS: Guselkumab

McInnes et al. EULAR 2021 #POS1027.

COSMOS

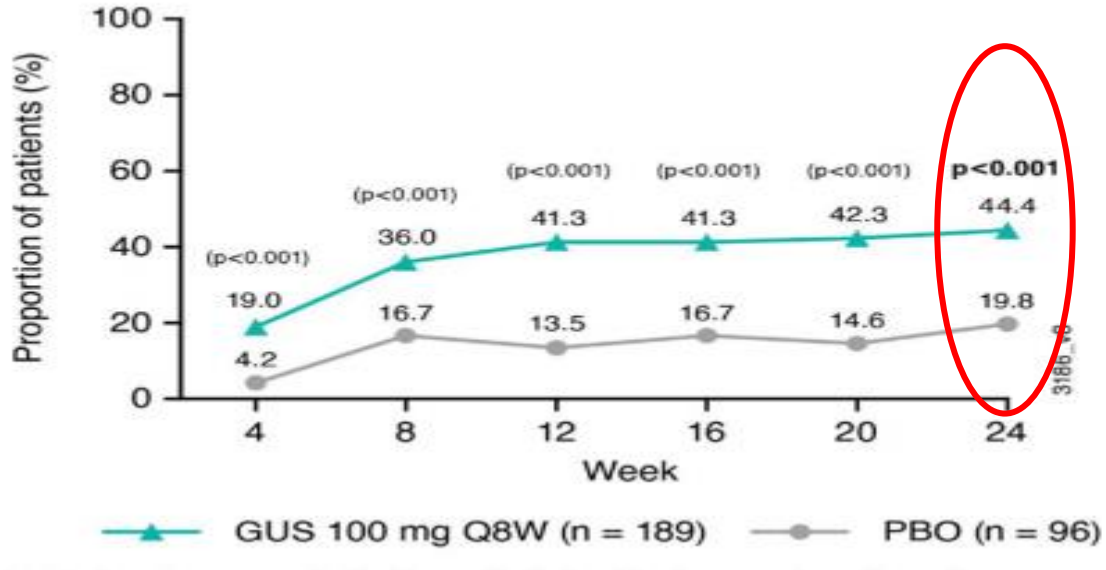
Coming soon …

Phase 3b, Multicenter, Randomized, Double-blind, Placebo-controlled Study to Evaluate the **Efficacy and Safety of Guselkumab** Administered Subcutaneously in Participants with **Active Psoriatic Arthritis** and an **Inadequate Response to Anti-Tumor Necrosis Factor Alpha (Anti-TNFα) Therapy**
CNT01959PSA3003



- **Adult**s ≥18 years of age
- Diagnosis of **PsA for at least 6 month** and meet **CASPAR** criteria at screening
- Active arthritis defined as **≥3 swollen joints,**
- **≥3 tender joints**
- **At least one PsA subset**: DIP involvement, polyarticular arthritis with absence of rheumatoid nodules, arthritis mutilans, asymmetric peripheral arthritis, or spondylitis with peripheral arthritis
- Currently active or history of **plaque psoriasis**
- **Inadequate response or intolerance to 1 or 2 anti-TNFα agents**
- DMARDs limited to 1 of the following: MTX, SSZ, HCQ, or LEF

Figure. ACR 20 Response through Week 24 of COSMOS.



Guselkumab- κλινικό πρόγραμμα … σύνοψη

- Δεδομένα αποτελεσματικότητας σε ασθενείς με υψηλή ενεργότητα νόσου
- Διατήρηση του θεραπευτικού αποτελέσματος σε βάθος χρόνου
- Βελτίωση στις περισσότερες εκδηλώσεις τις Ψωριασικής Αρθρίτιδας (ενθεσίτιδα, δακτυλίτιδα, Ψωρίαση, αρθρίτιδα)
- Βελτίωση στο συνολικό επίπεδο ζωής των πάσχοντων (λειτουργικό επίπεδο , κόπωση)
- Καλό προφίλ ασφάλειας
- Καλύπτει μεγαλύτερο θεραπευτικό κενό ; (αξονική προσβολή ; , μετά από αποτυχία tnf (i) ;)

Σας ευχαριστώ !!