



# «Κατανοώντας τον ρόλο της IL-17 στην αποτελεσματική θεραπεία της Αγκυλοποιητικής Σπονδυλαρθρίτιδας



Δαούσης Δημήτρης  
Επίκουρος καθηγητής  
Παθολογίας/Ρευματολογίας  
Ιατρική Σχολή Πανεπιστημίου  
Πατρών

10<sup>ο</sup> Συνέδριο ΕΠΕΜΥ  
Πόρτο Χέλι, Απρίλιος 2018

## Σύγκρουση συμφερόντων

- Τιμητική αμοιβή για ομιλίες και συμμετοχή σε advisory boards από τις εταιρείες UCB, Pfizer, Novartis, BMS, MSD, Jansen, Abbvie

## Διευκρινίσεις

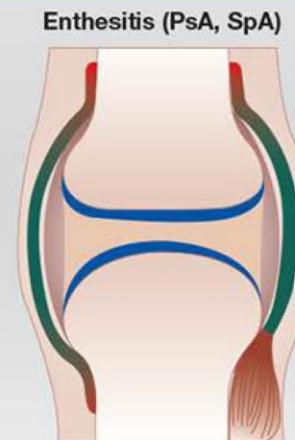
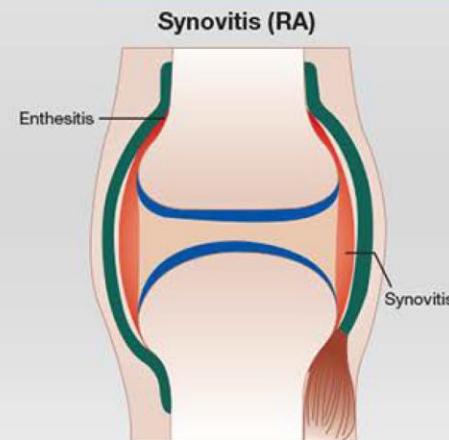
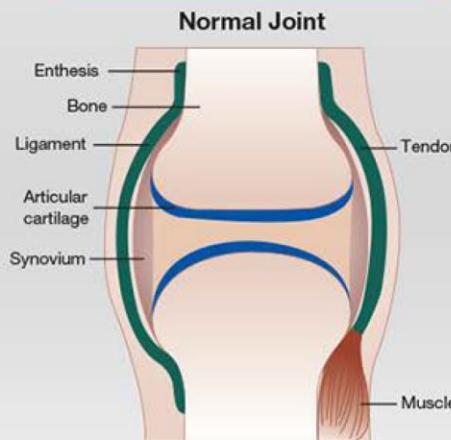
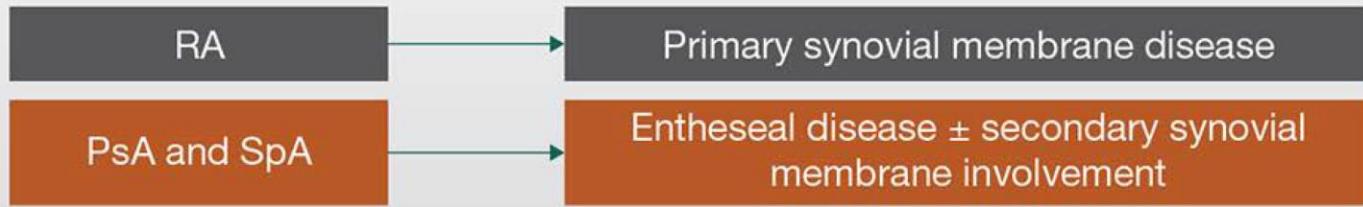
- Η παρουσίαση αυτή προορίζεται μόνο για μη-πρωθητικό επιστημονικό σκοπό και μπορεί να περιέχει πληροφορίες σχετικά με τα προϊόντα ή τις ενδείξεις τους, που επί του παρόντος μπορεί να είναι υπό διερεύνηση ή/και που δεν έχουν εγκριθεί από τις ρυθμιστικές αρχές.
- Η παρουσίαση αυτή εκφράζει αποκλειστικά τις απόψεις του ομιλητή.
- Οι πληροφορίες που περιέχονται είναι ακριβείς κατά τη δημιουργία της παρουσίασης.
- Τυχόν δεδομένα σχετικά με προϊόντα τα οποία δεν ανήκουν στη Novartis βασίζονται σε δημόσια διαθέσιμες πληροφορίες κατά τη δημιουργία της παρουσίασης.

## Classification of inflammatory arthritis by enthesitis

Dennis McGonagle, Wayne Gibbon, Paul Emery

## Enthesitis Is the Anchoring Pathologic Lesion in PsA and SpA

Enthesitis differentiates PsA and SpA from RA



- Η πρώτη επίσημη διατύπωση της θεωρίας ότι η ενθεσοπάθεια είναι το πρωτοπαθές φαινόμενο στις ΣΠΑ έγινε μόλις το 1998!!
- Σήμερα οι ΣΠΑ θεωρούνται αυτοφλεγμονώδη νοσήματα

# Τα πειραματικά μοντέλα επιβεβαίωσαν την θεωρία...



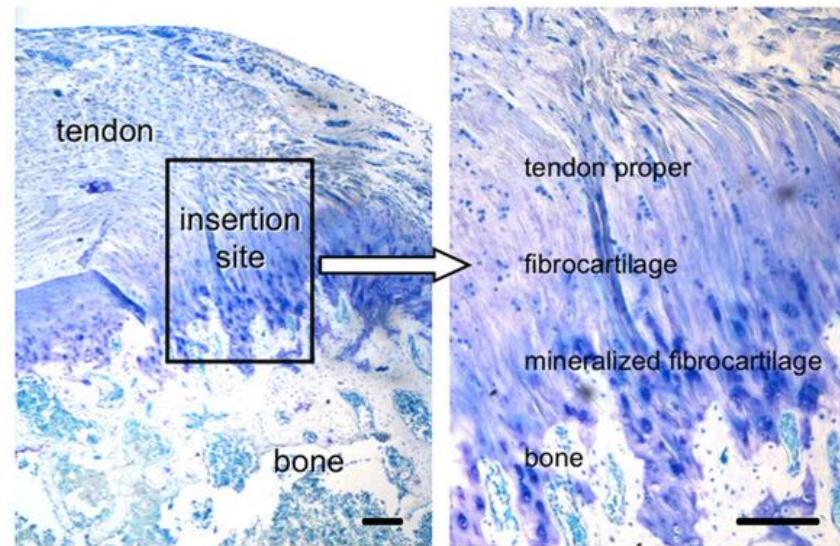
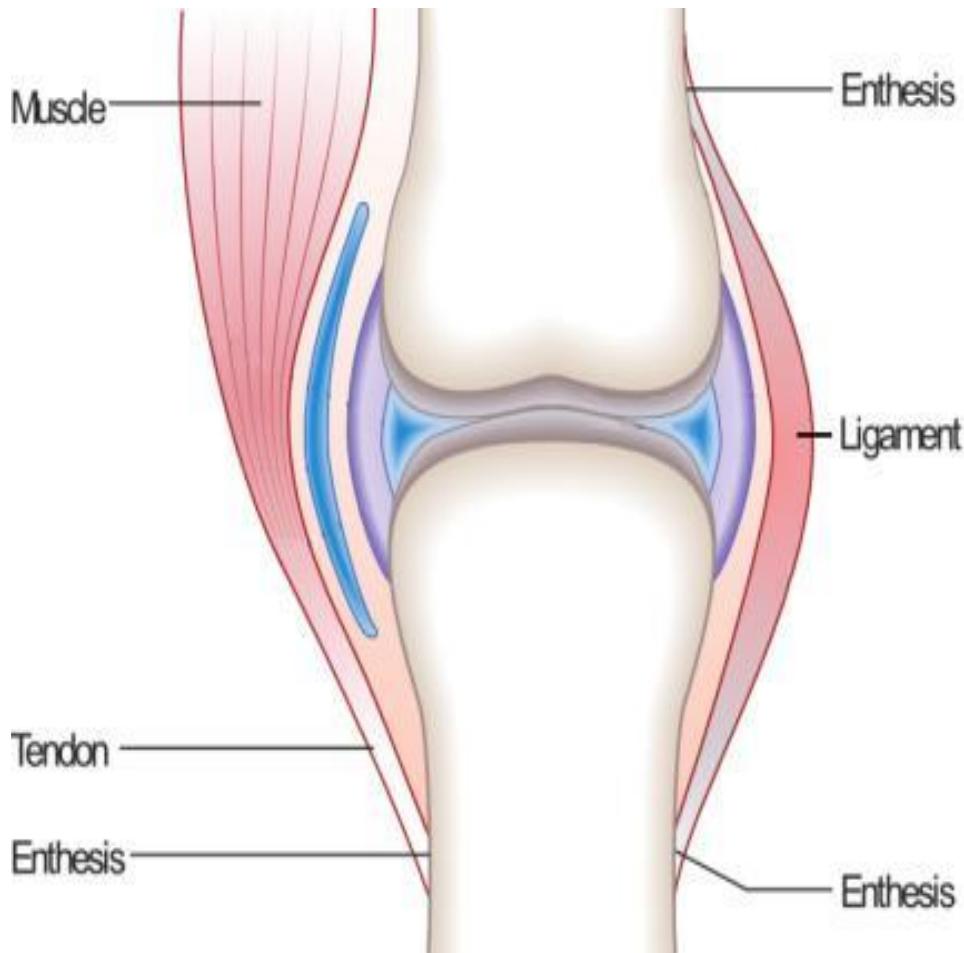
- Η ενθεσοπάθεια προηγείται της αρθρίτιδας

## EXTENDED REPORT

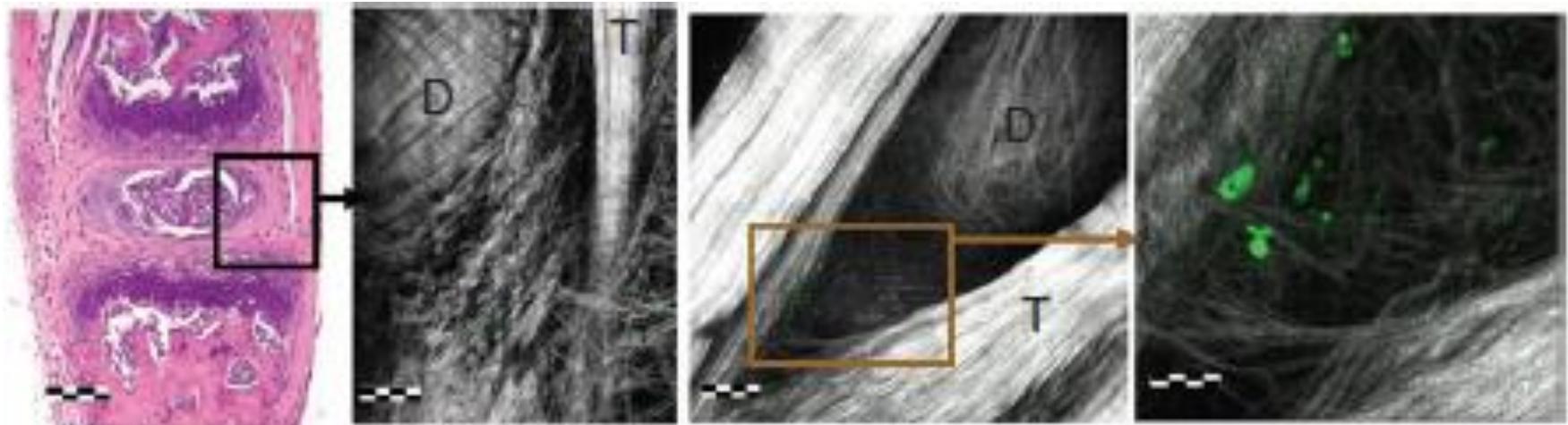
Proof of concept: enthesitis and new bone formation in spondyloarthritis are driven by mechanical strain and stromal cells

Peggy Jacques,<sup>1</sup> Stijn Lambrecht,<sup>1</sup> Eveline Verheugen,<sup>1</sup> Elin Pauwels,<sup>2</sup> George Kollias,<sup>3</sup> Maria Armaca,<sup>3</sup> Marleen Verhoye,<sup>4</sup> Annemie Van der Linden,<sup>4</sup> Rik Achter,<sup>5</sup> Rik J Lories,<sup>6</sup> Dirk Elewaut<sup>1</sup>

# Η ένθεση Ένα πιο πολύπλοκο όργανο από ότι φαίνεται....



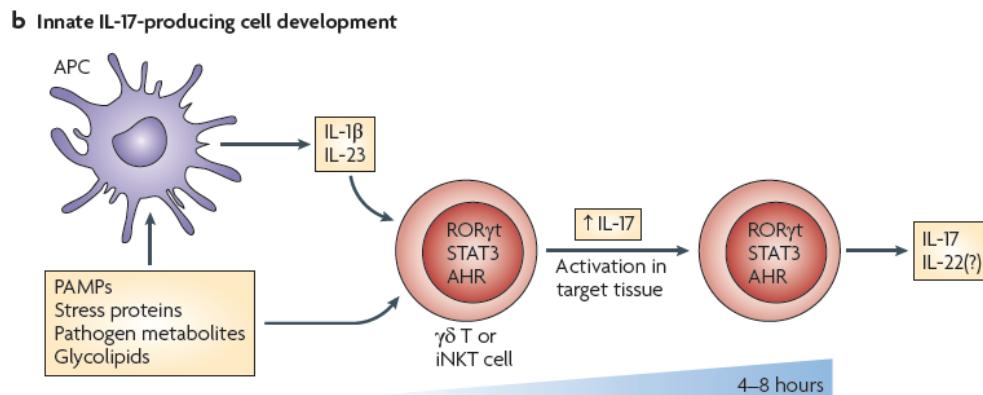
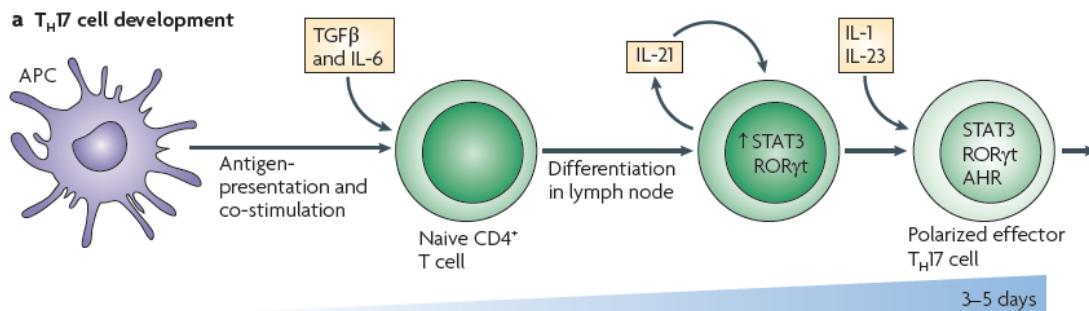
Η ένθεση διαθέτει ανοσολογικά κύτταρα....



- Innate lymphoid cells (ILC) type 3
- Τα κύτταρα αυτά απαντούν στην IL-23....
- Παράγουν μεγάλες ποσότητες IL-17

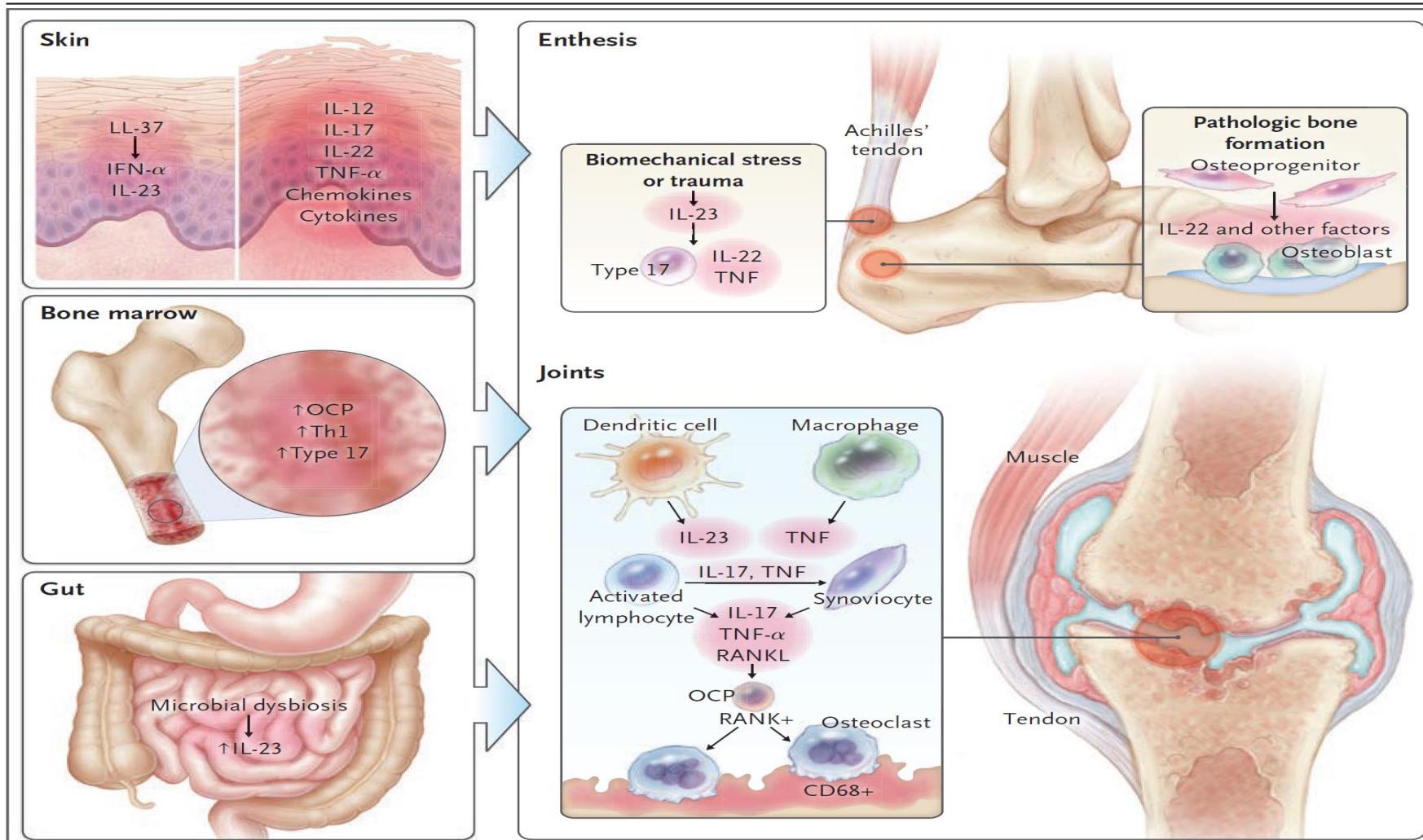
# Innate IL-17-producing cells: the sentinels of the immune system

Daniel J. Cua and Cristina M. Tato



Τα ILC βρίσκονται σε σημεία που δέχονται ένοτονο stress  
Τα κύτταρα αυτά απαντούν στην IL-23

# Οι σπονδυλοαρθροπάθειες χαρακτηρίζονται από φλεγμονή σε σημεία που δέχονται stress



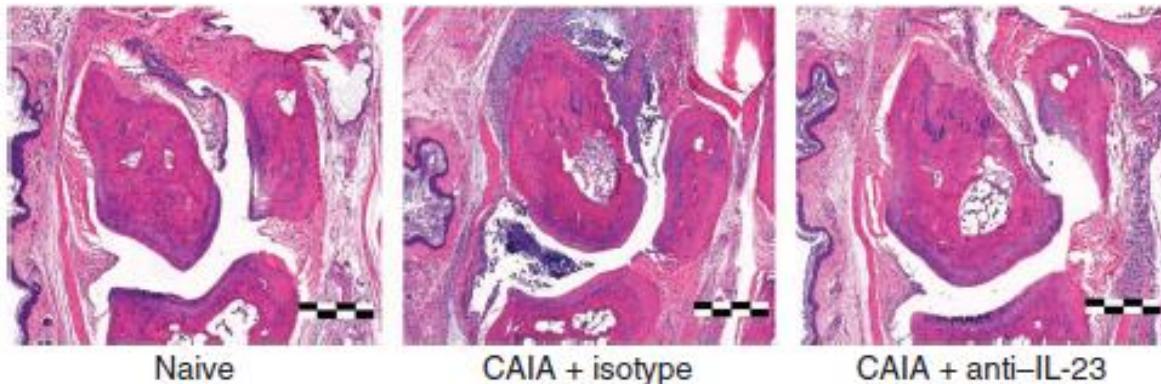
# Ο κομβικός ρόλος του άξονα IL-23/IL-17 σε πτειραματικά μοντέλα ΣΠΑ...

ARTICLES

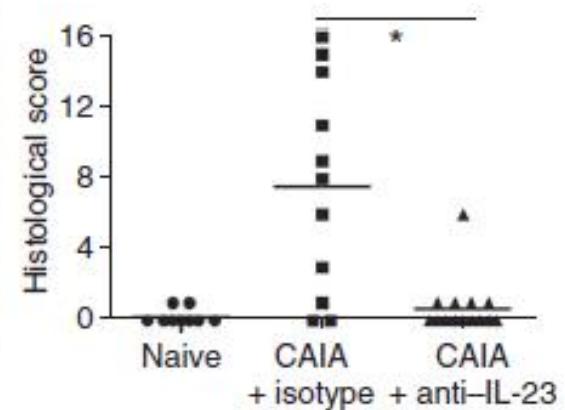
nature  
medicine

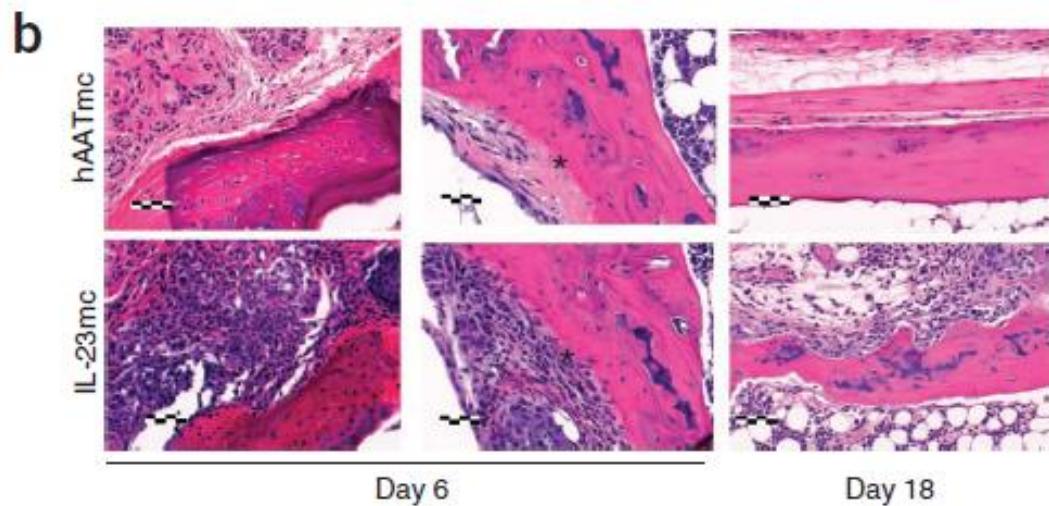
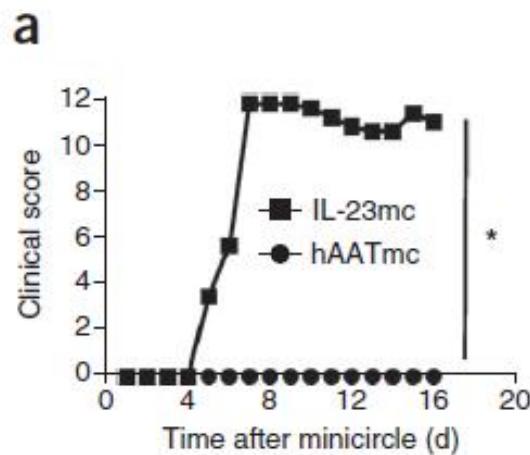
## IL-23 induces spondyloarthropathy by acting on ROR- $\gamma$ <sup>+</sup> CD3<sup>+</sup>CD4<sup>-</sup>CD8<sup>-</sup> enthesal resident T cells

Jonathan P Sherlock<sup>1-3,5</sup>, Barbara Joyce-Shaikh<sup>1,5</sup>, Scott P Turner<sup>1</sup>, Cheng-Chi Chao<sup>1</sup>, Manjiri Sathe<sup>1</sup>, Jeff Grein<sup>1</sup>, Daniel M Gorman<sup>1</sup>, Edward P Bowman<sup>1</sup>, Terrill K McClanahan<sup>1</sup>, Jennifer H Yearley<sup>1</sup>, Gérard Eberl<sup>4</sup>, Christopher D Buckley<sup>3</sup>, Robert A Kastelein<sup>1</sup>, Robert H Pierce<sup>1</sup>, Drake M LaFace<sup>1,5</sup> & Daniel J Cua<sup>1,5</sup>



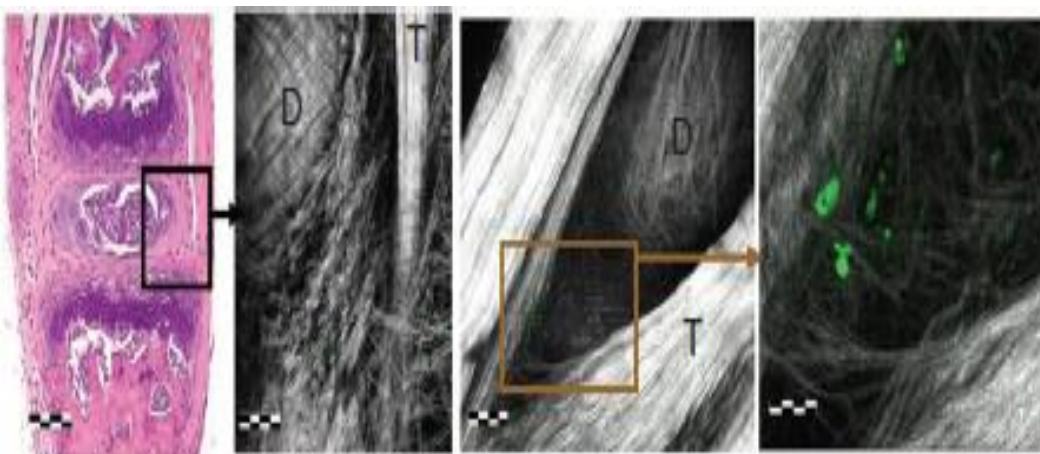
## ■ Μία σημαντική ανακάλυψη





- Η υπερέφραση IL-23 προκαλεί φαινότυπο σπονδυλοαρθροπάθειας σε ποντίκια
  - Ενθεσοπάθεια
  - Αορτίτιδα
  - Ψωρίαση
  - Οστεοπαραγωγή

## H IL-23 δρα σε innate-like lymphocytes στις ενθέσεις

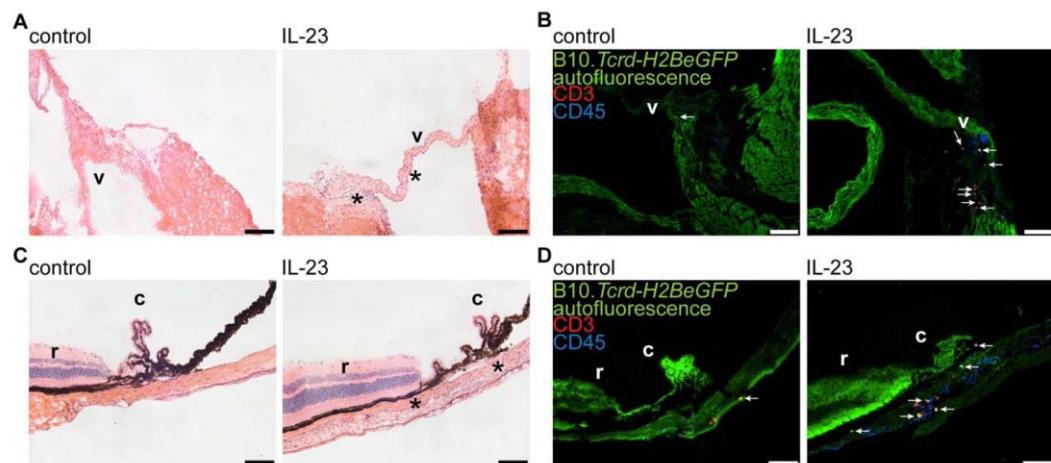
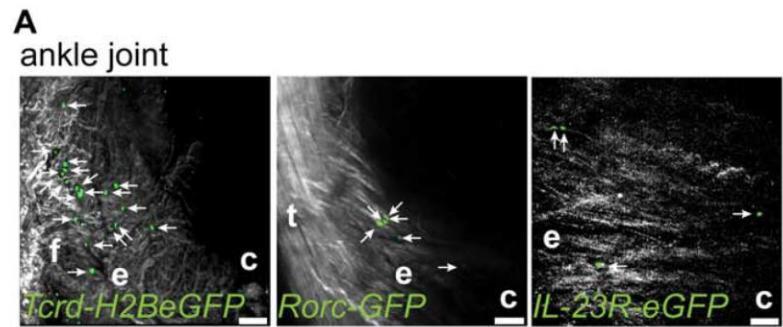


### ■ Τα κύτταρα αυτά

- Είναι λίγα
- Απαντούν ταχύτατα στην IL-23 και παράγουν IL-22 και IL-17
- Η IL-22 είναι υπεύθυνη για την οστεοπαραγωγή και IL-17 για τις φλεγμονώδεις εκδηλώσεις

## Interleukin-23-Dependent $\gamma/\delta$ T Cells Produce Interleukin-17 and Accumulate in the Enthesis, Aortic Valve, and Ciliary Body in Mice

# Η επιβεβαίωση.....

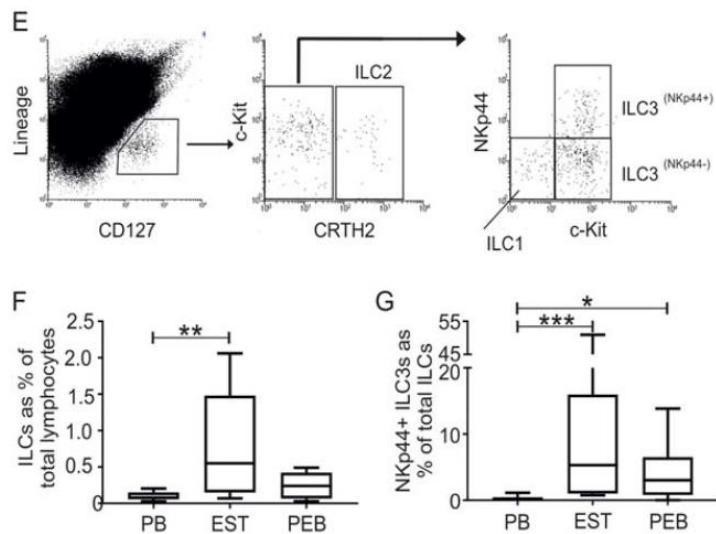
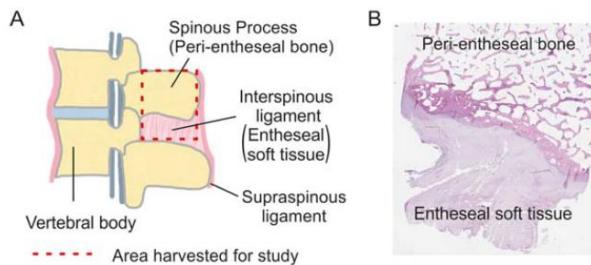


- Στις ενθέσεις βρίσκεται ένας «μόνιμος» πληθυσμός γδ-Τ λεμφοκυττάρων με ικανότητα παραγωγής IL-17
- Πολλά από αυτά τα κύτταρα είναι ROR $\gamma$ t+ IL-23R+

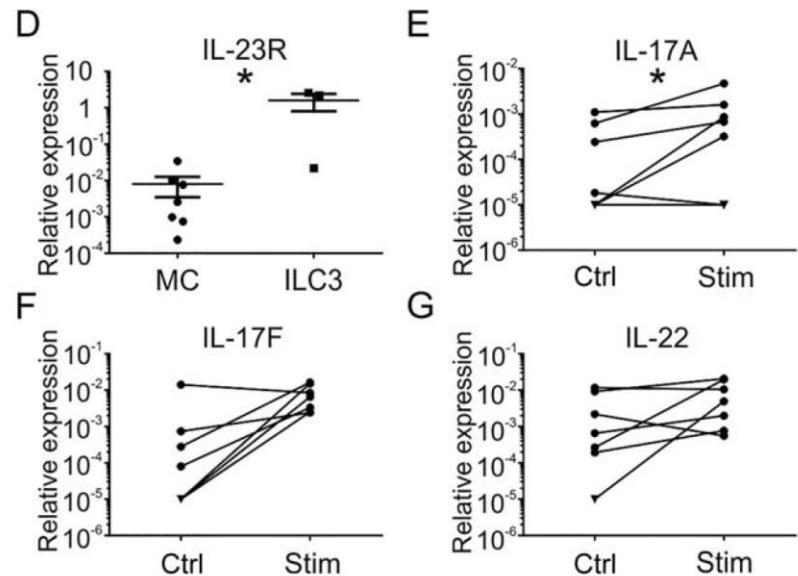
BRIEF REPORT

Group 3 Innate Lymphoid Cells in Human Enthesis

Richard J. Cuthbert,<sup>1</sup> Evangelos M. Fragkakis,<sup>2</sup> Robert Dunsmuir,<sup>3</sup> Zhi Li,<sup>4</sup> Mark Coles,<sup>4</sup> Helena Marzo-Ortega,<sup>5</sup> Peter V. Giannoudis,<sup>1</sup> Elena Jones,<sup>1</sup> Yasser M. El-Sherbiny,<sup>6</sup> and Dennis McGonagle<sup>5</sup>

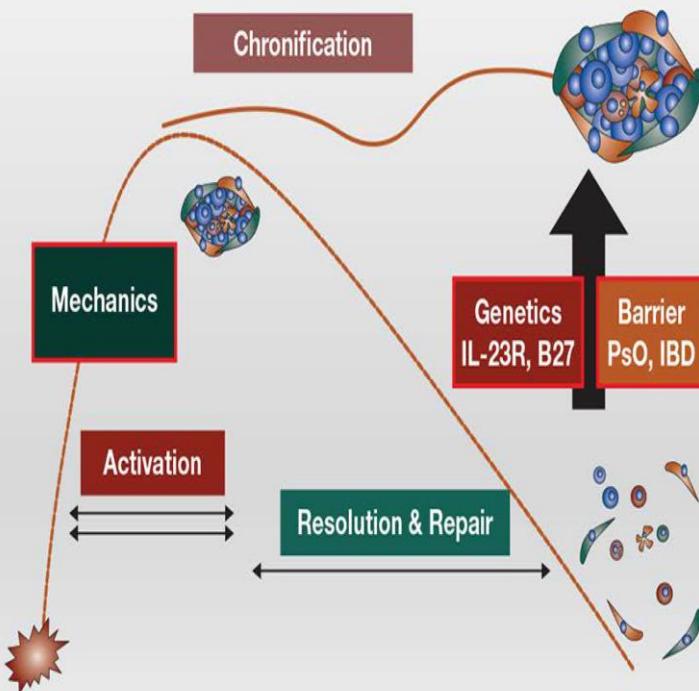


■ Η πρώτη ισχυρή ένδειξη ότι τα κύτταρα αυτά υπάρχουν και στον άνθρωπο

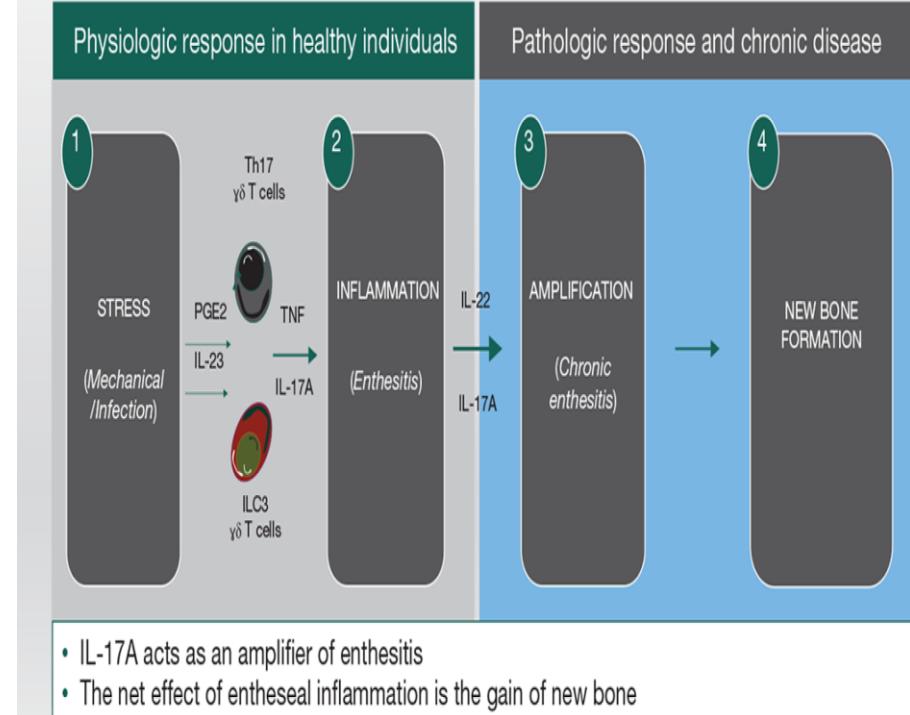


# Τα λεμφοκύτταρα αυτά δεν βρίσκοντα στις ενθέσεις για να δημιουργούν προβλήματα... Λειτουργούν ως αισθητήρες stress....

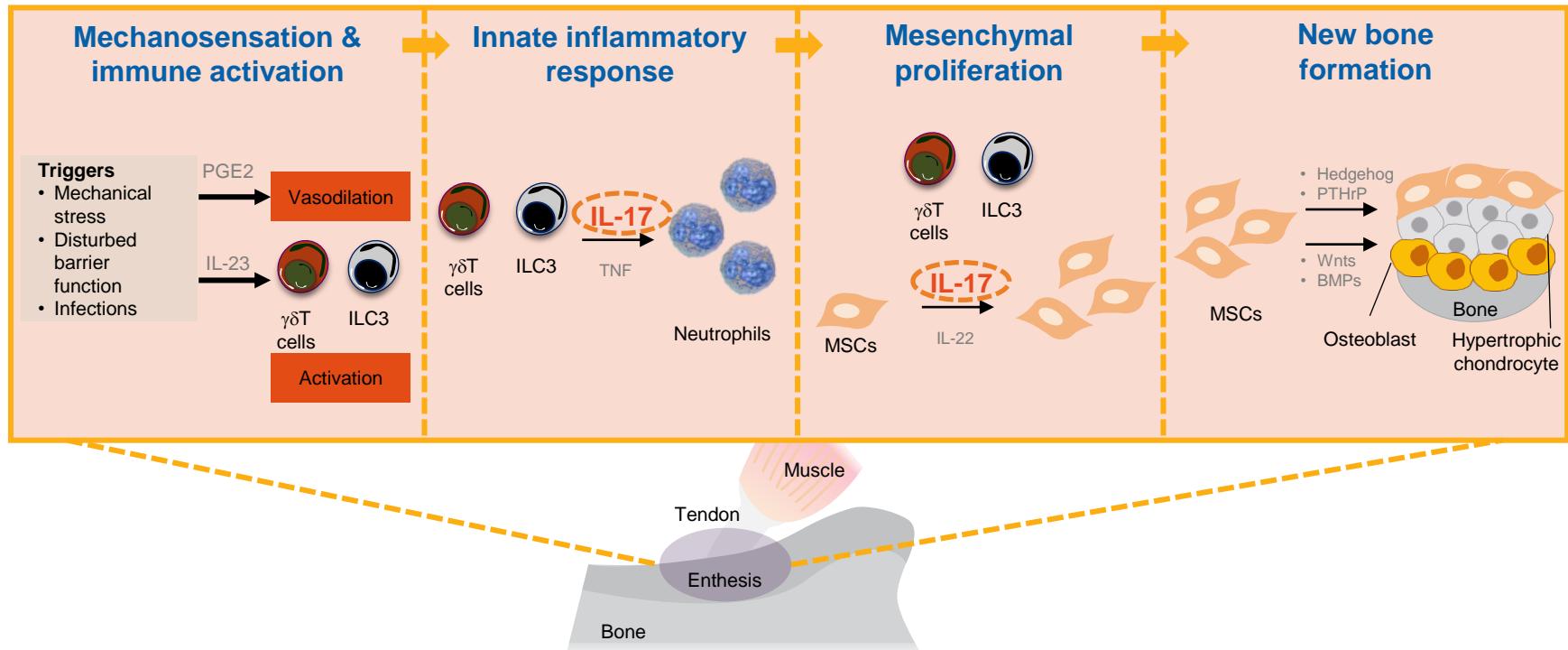
Self-Limiting vs Chronic Inflammation as a Feature of PsA and SpA



Mechanosensation and Inflammatory Response

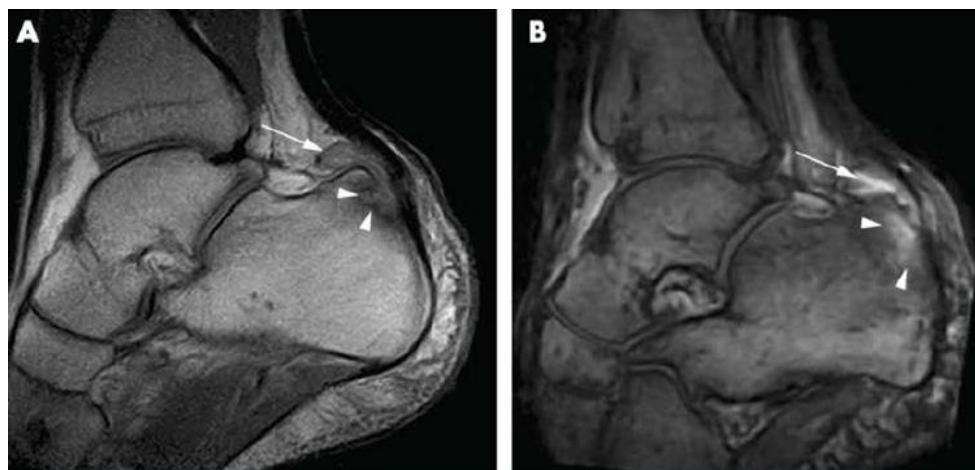
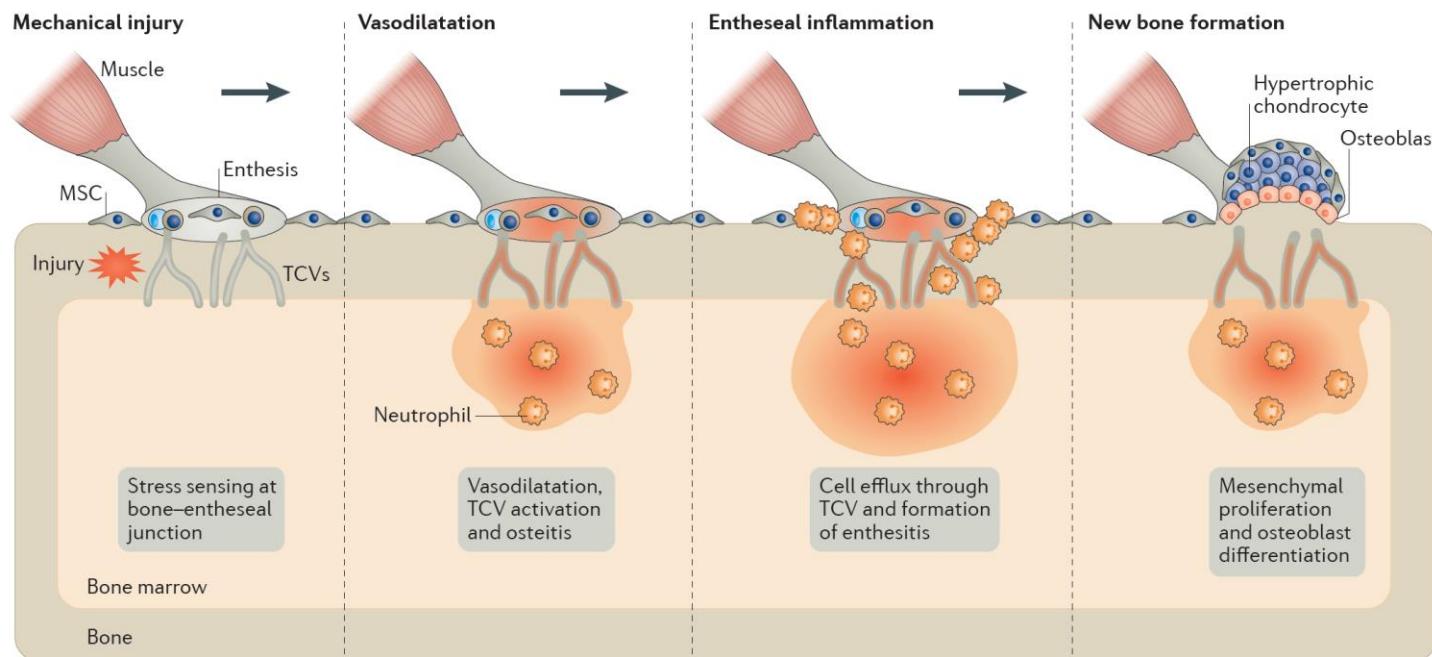


# Η IL-17A είναι ένας ενισχυτής της ενθεσίτιδας, η οποία οδηγεί σε μη αναστρέψιμη δομική βλάβη

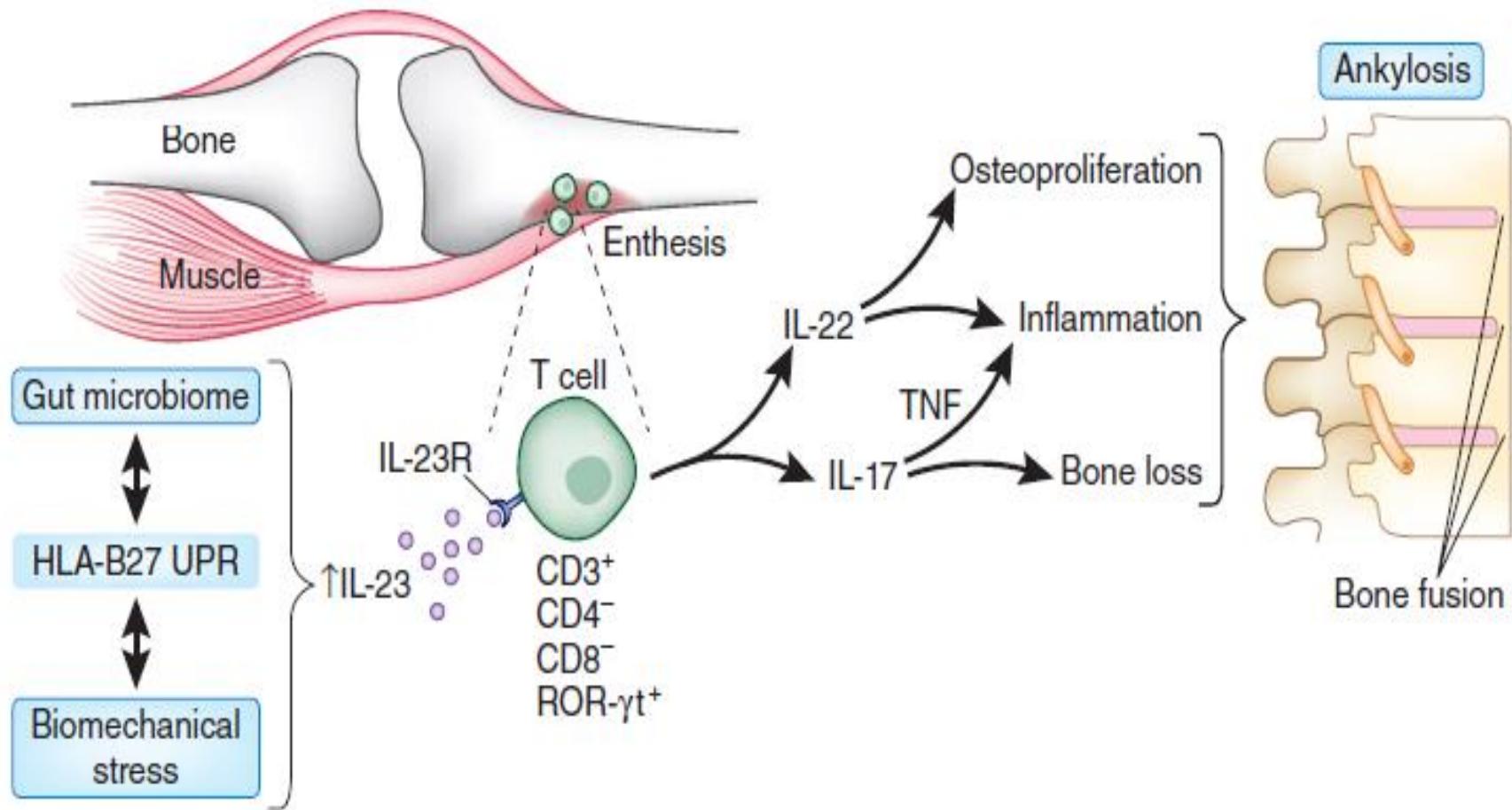


BMP, bone morphogenic protein; IL-22, interleukin 22; PTHrP, parathyroid hormone related-peptide; MSC, mesenchymal stem cell  
Adapted from Schett G, et al. *Nat Rev Rheumatol*. 2017;13:731–41.

# Ενθεσίτιδα-οστείτιδα. Μια αμφίδρομη σχέση...



# Η συνολική εικόνα



# Το κλινικό πρόγραμμα MEASURE : Αξιολόγηση του Secukinumab στην ΑΣ

2013				2014				2015				2016				2017			
Q1	Q2	Q3	Q4																

## MEASURE 1 – N = 371<sup>1</sup>

i.v. loading (10 mg/kg) →  
s.c. maintenance dosing (75 or 150 mg)

Extension Study

## MEASURE 2 – N = 219<sup>1</sup>

s.c. loading (75 or 150 mg) → s.c. maintenance dosing (75 or 150 mg)  
Pre-filled syringe

## MEASURE 3 – N = 222\*

i.v. loading (10 mg/kg) → s.c. maintenance dosing (150 or 300 mg)

## MEASURE 4 – N = 324\*†

s.c. 150 mg with or without  
s.c. loading (Pre-filled syringe)

\*Estimated enrolment; †Not yet recruiting

MEASURE 1 is a 2-year study with 3 year extension study; MEASURE 2 is a 5 year study;

MEASURE 3 is a 3 year study; MEASURE 4 is a 2 year study. The primary endpoint for all studies is at Week 16. AS, ankylosing spondylitis; i.v., intravenous; s.c., subcutaneous

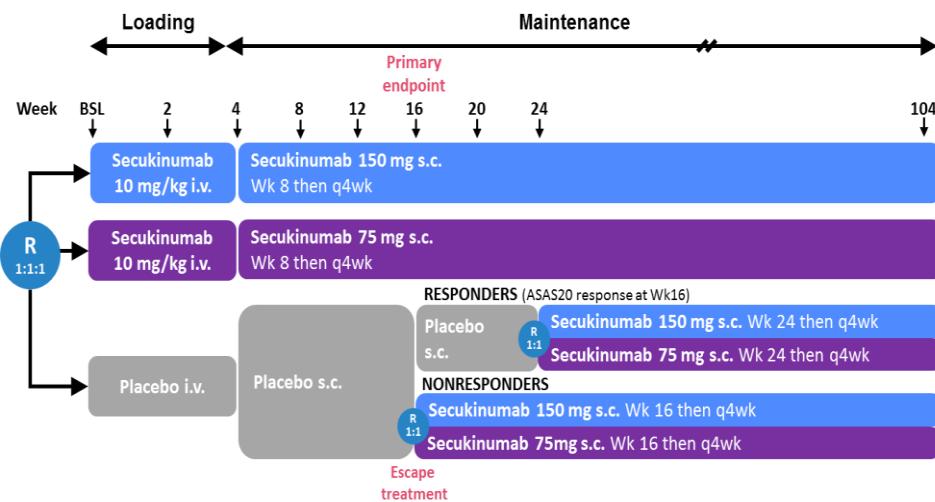
1. Baeten D & Sieper J, et al. N Engl J Med 2015;373:2534–48;  
Clinicaltrials.gov: NCT01358175 (MEASURE 1)  
NCT01649275 (MEASURE 2)  
NCT02008916 (MEASURE 3)  
NCT02159053 (MEASURE 4)

# Secukinumab Demonstrates Low Radiographic Progression and Sustained Efficacy Through 4 years in Patients with Active Ankylosing Spondylitis

ACR Late-breaking Abstract 3L

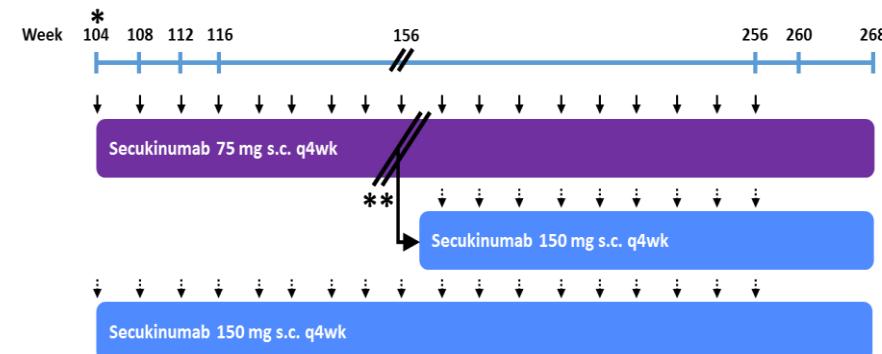
Jürgen Braun , Xenofon Baraliakos , Atul A. Deodhar , Denis Poddubnyy  
, Paul Emery , Evie Maria Delicha , Zsolt Talloczy and Brian Porter

## MEASURE 1: Σχεδιασμός κύριας μελέτης και μελέτης επέκτασης



Randomization was stratified according to whether patients were anti-TNF-naïve or had previous intolerance or inadequate response to anti-TNF therapy  
Baeten D, et al. *N Engl J Med* 2015;373:2534–48

■ Εκ των 371 ασθενών που εντάχθηκαν στην κύρια μελέτη, οι 274 (74%) συνέχισαν στην φάση επέκτασης

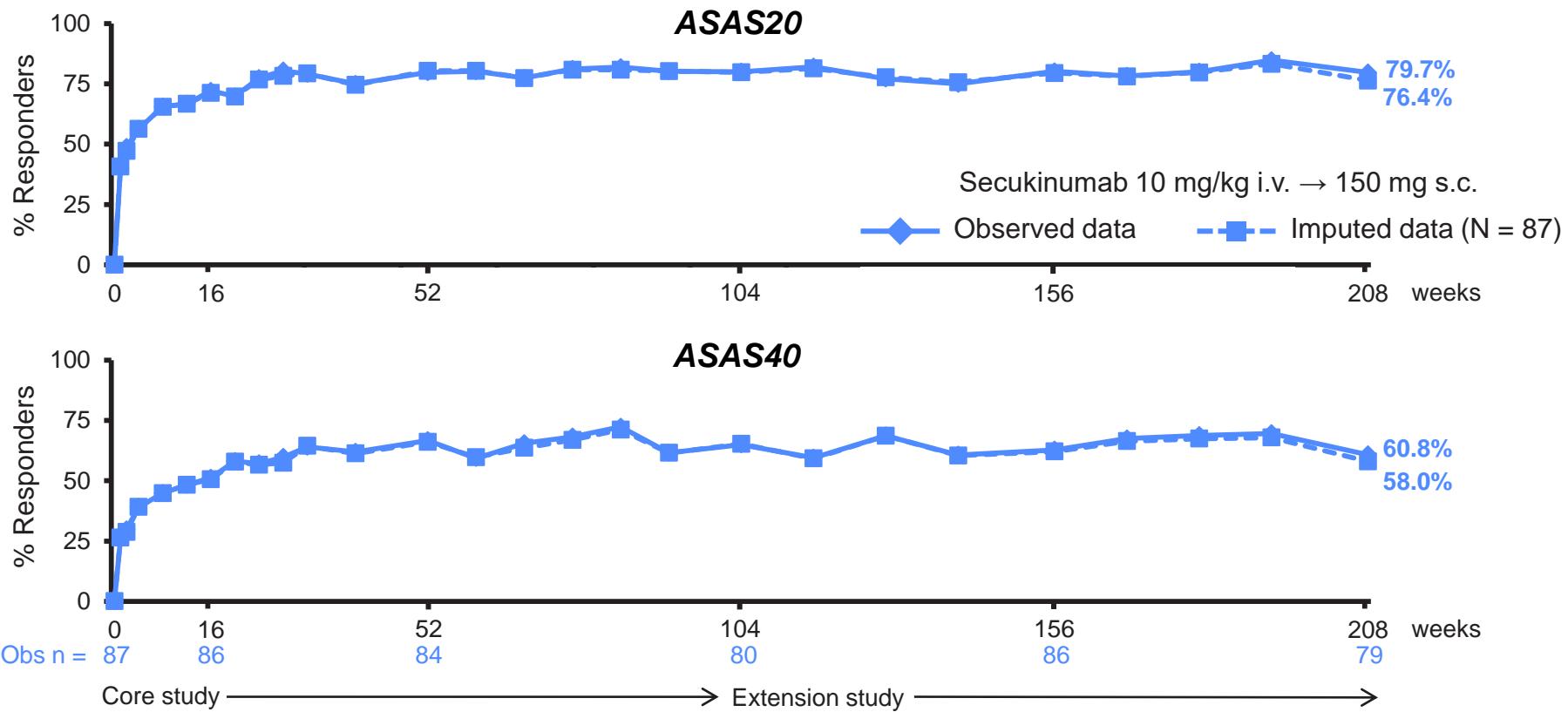


PFS, prefilled syringe

<sup>a</sup>Patients in the 75 mg group not achieving sufficient therapeutic response could have their dose escalated to 150 mg at the discretion of principal investigators, following a protocol amendment

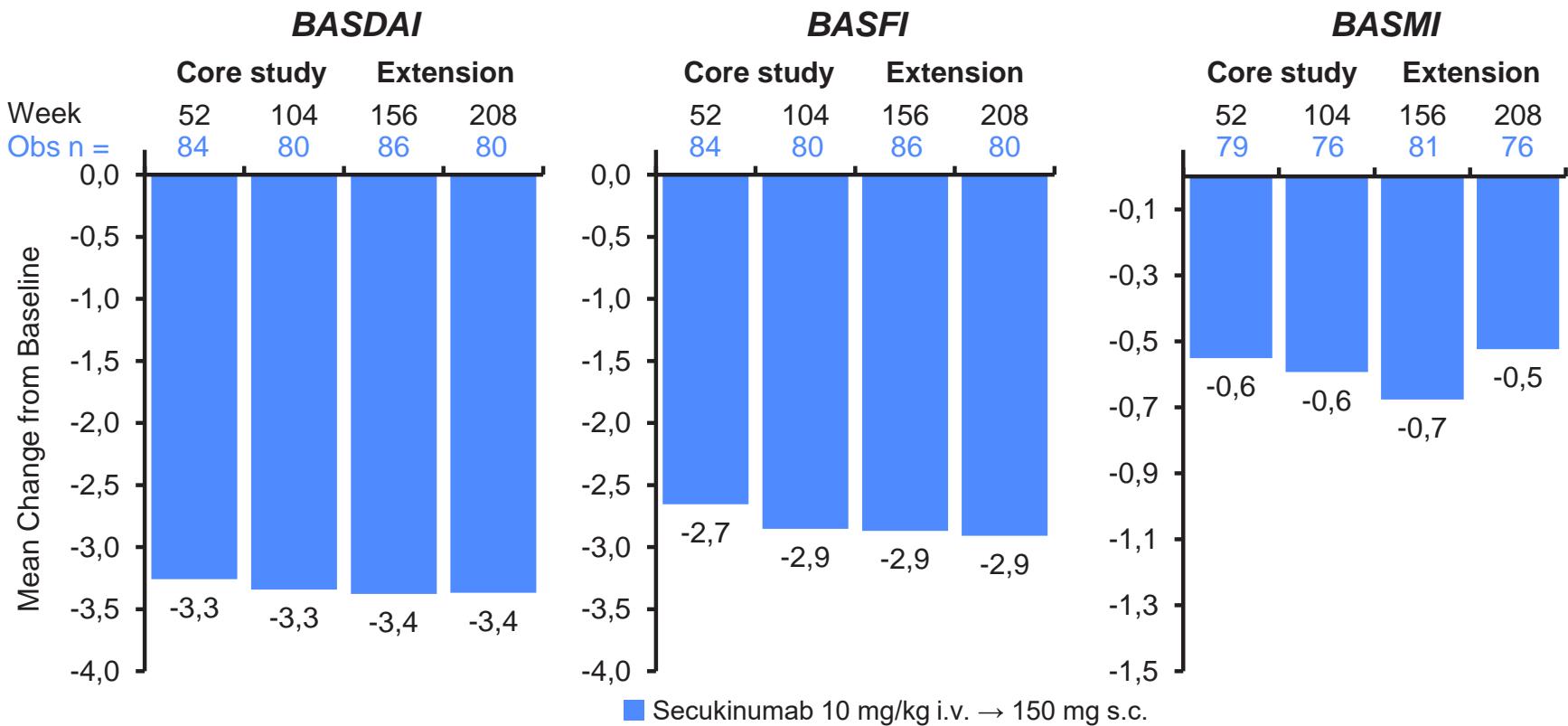
Baraliakos X, et al. *Clin Exp Rheumatol* 2017 [Epub ahead of print]

# Ταχεία έναρξη δράσης & Διατήρηση αποκρίσεων ASAS έως τα 4 έτη θεραπείας.-



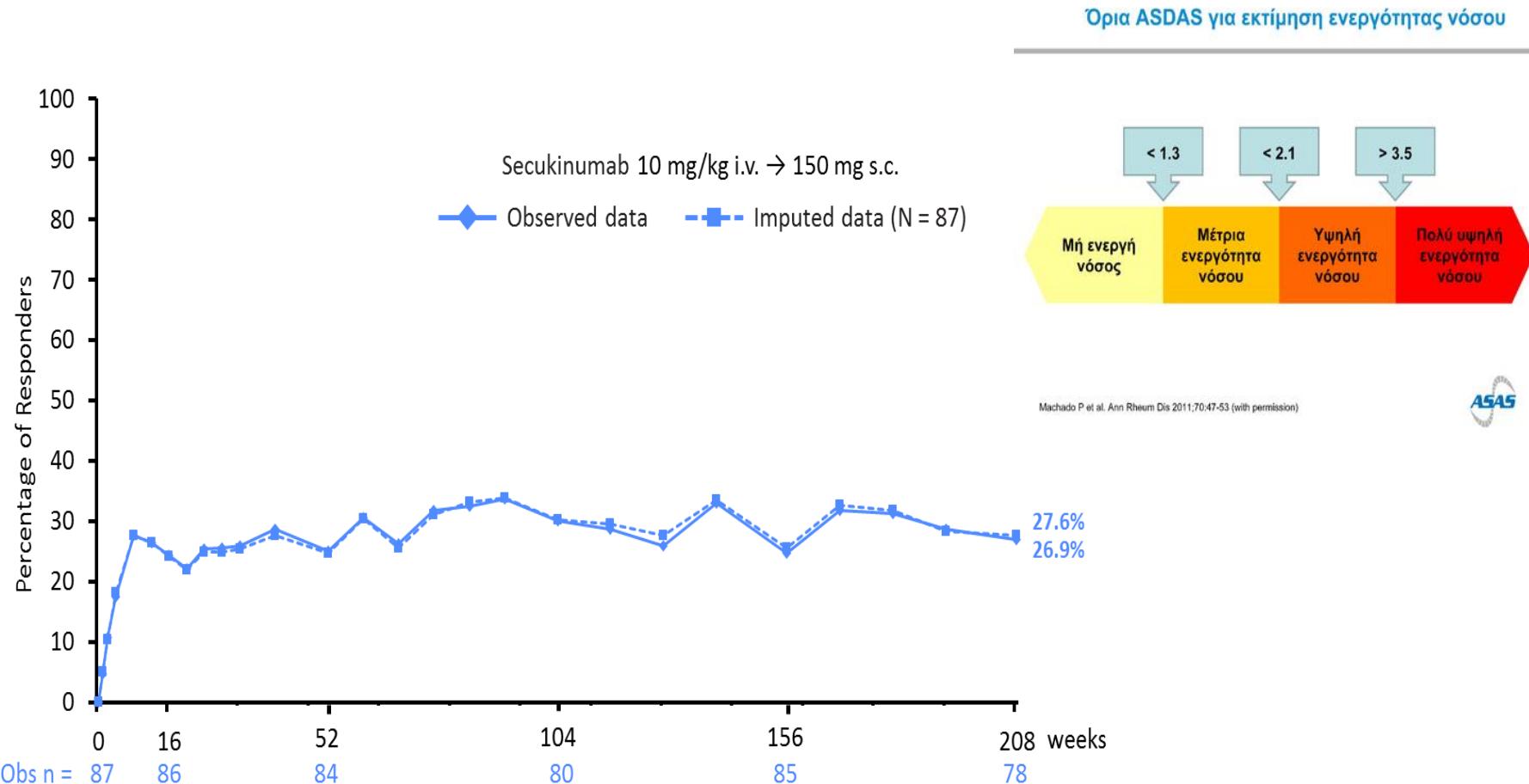
ASAS, Assessment of Spondyloarthritis International Society; n, number of pts evaluated in the treatment group; N, total number of pts in the extension trial; Obs, observed data. Solid lines represent observed data through Week 208. Dashed lines represent multiple imputation data through Week 208

# Διατήρηση αποτελεσματικότητας έως τα 4 έτη θεραπείας



BASDAI, Bath Ankylosing Spondylitis Disease Activity Index; BASFI, Bath Ankylosing Spondylitis Functional Index; BASMI, Bath Ankylosing Spondylitis Metrology Index; n, number of pts evaluated in the treatment group; Obs, observed data. Observed data through Week 208

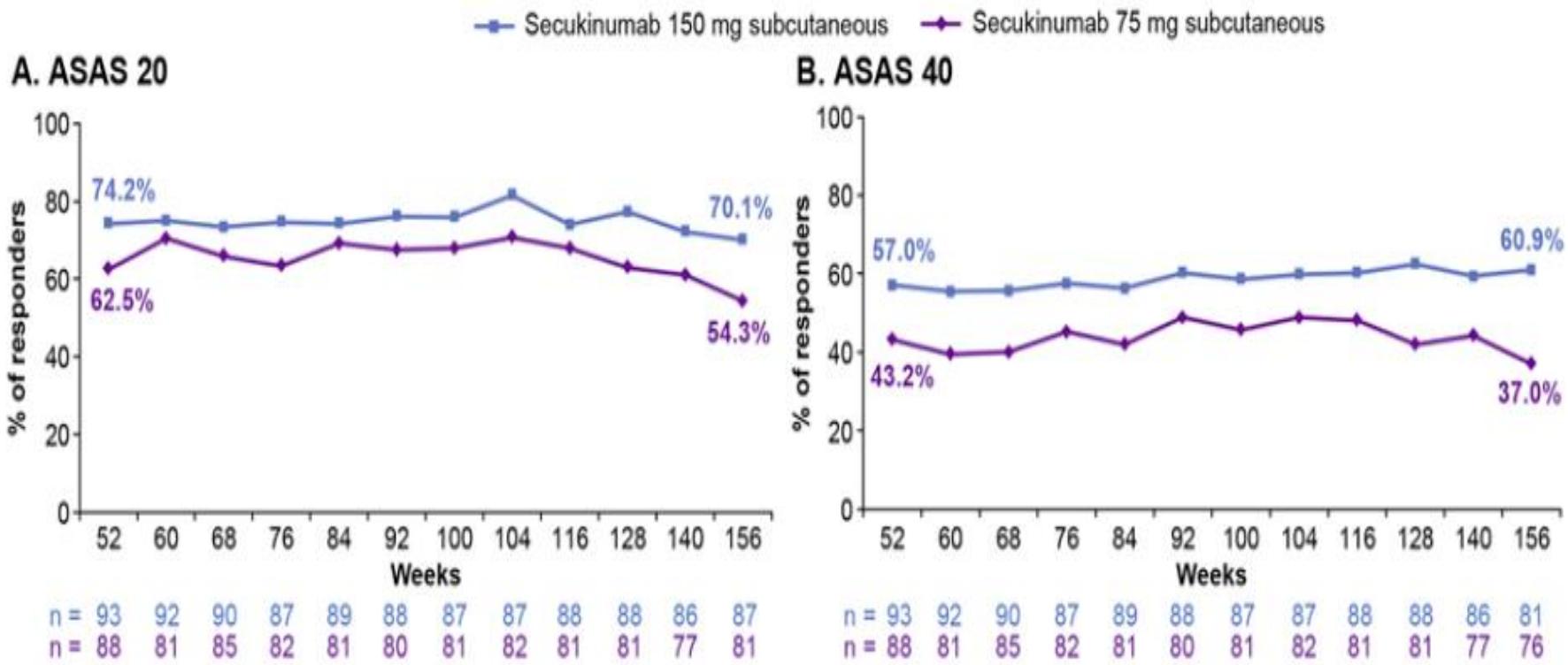
# Απόκριση κατά ASDAS-ανενεργή νόσος στα 4 έτη θεραπείας



Braun J et al. Arthritis Rheumatol. 2017; 69 (suppl 10).

ASDAS, Ankylosing Spondylitis Disease Activity Score; n, number of evaluable patients (observed); N, number of patients randomized  
Solid lines represent observed data through Week 208  
Dashed lines represent multiple imputation data through Week 208

## MEASURE 2: ταχεία έναρξη δράσης & διατήρηση απόκρισης ASAS έως τα 3 έτη θεραπείας.

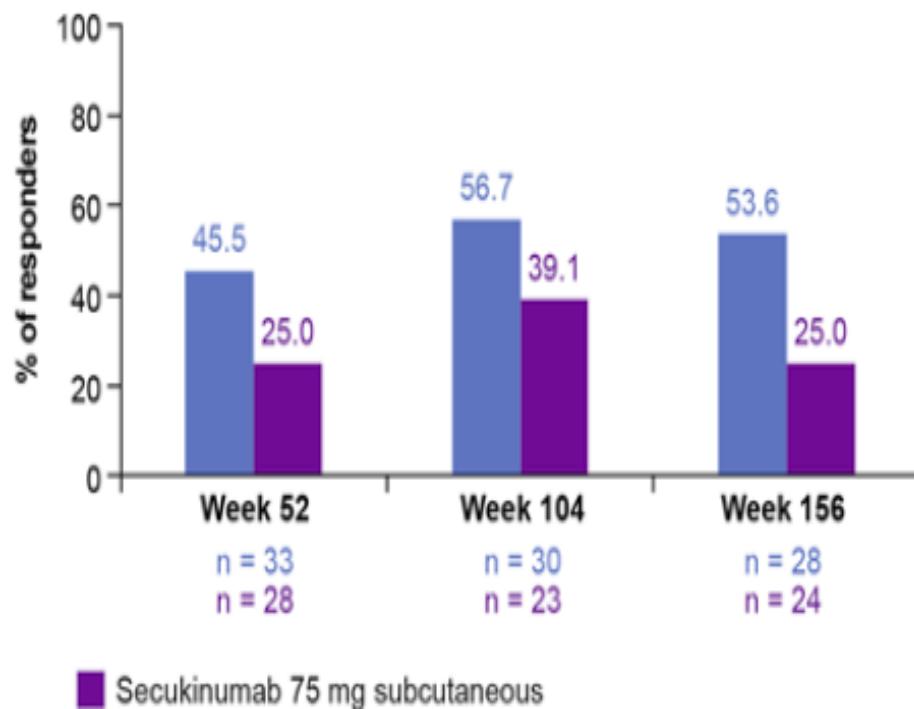
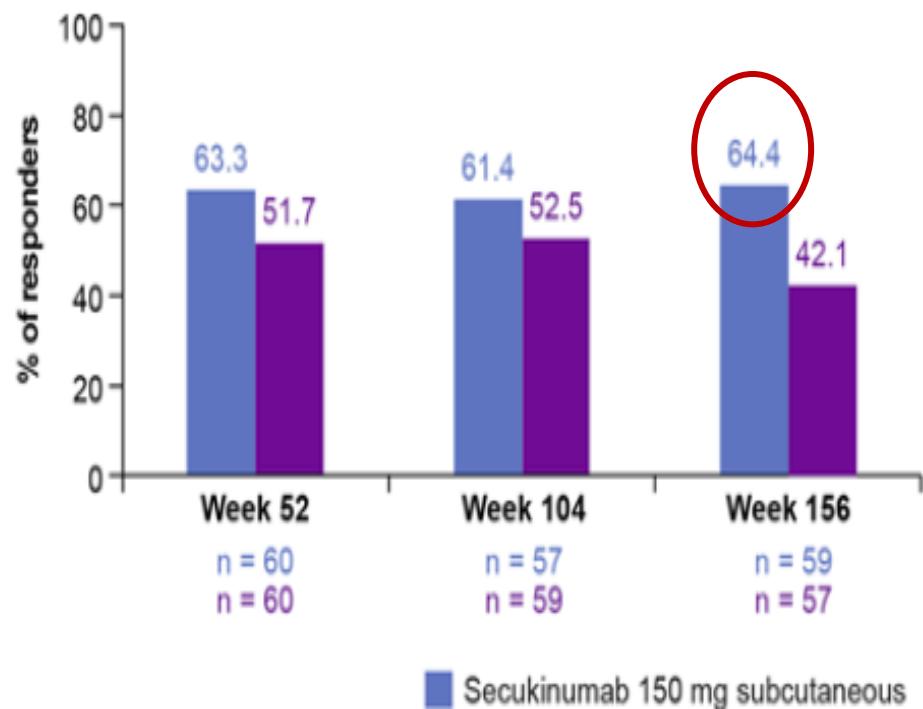


## MEASURE 2: διατήρηση απόκρισης ASAS 40 έως τα 3 έτη θεραπείας ανά κατάσταση θεραπείας με αντί-TNF

αντί-TNF naive

αντί-TNF - IR

### B. ASAS 40

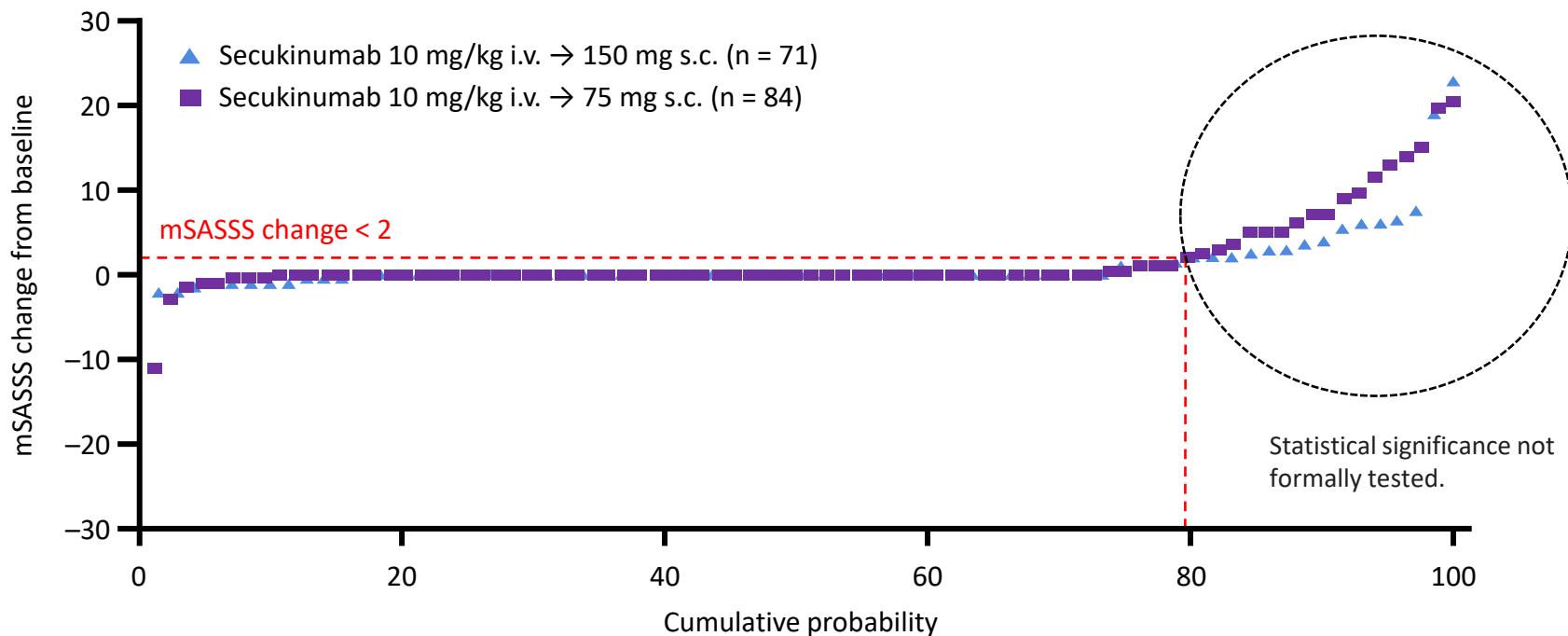


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## Secukinumab 100 mg s.c. vs Secukinumab 150 mg s.c.

Secukinumab\*

Radiographic Outcome Measure (definition of mSASSS progression)	Secukinumab, IV→150 mg (N = 71)
mSASSS change from baseline < 2	<u>78.9%</u>
mSASSS change from baseline ≤ 0.5	<u>73.2%</u>
mSASSS change from baseline ≤ 0	<u>73.2%</u>

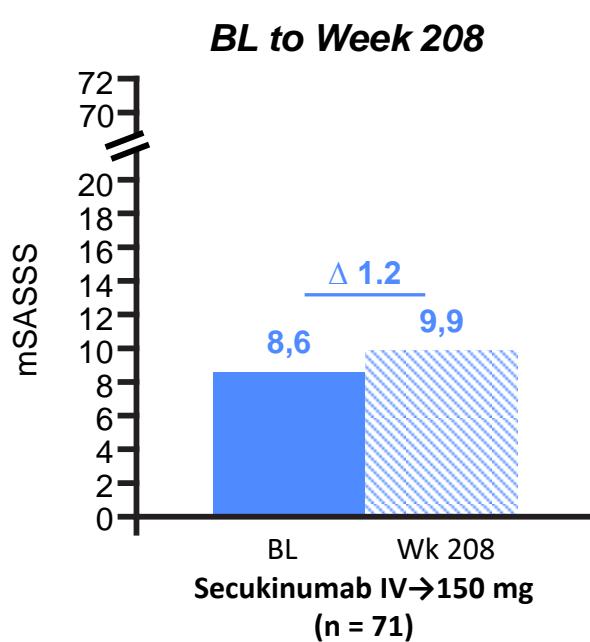
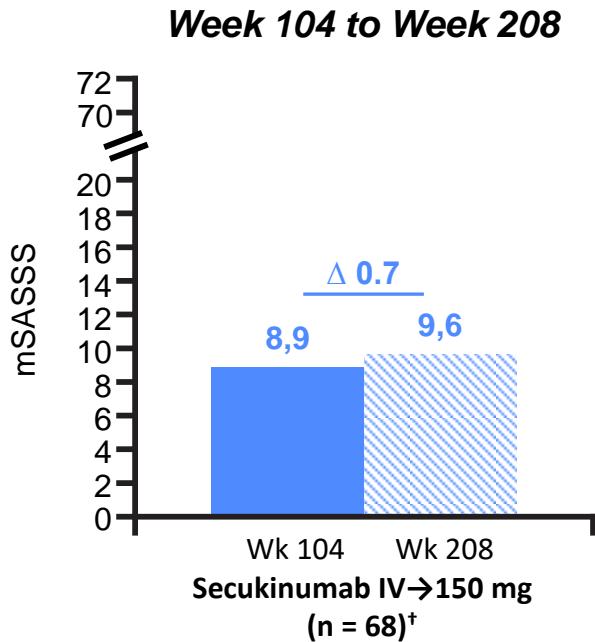
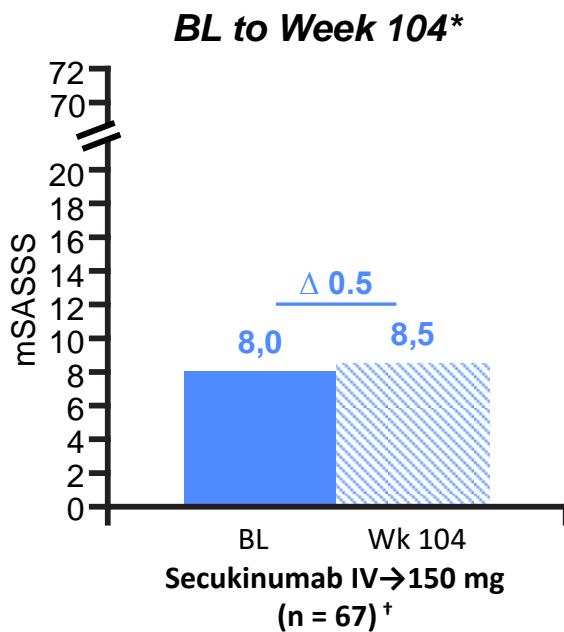


mSASSS, modified Stoke Ankylosing Spondylitis Spine Score; n, number of patients with assessments at Baseline and Week 208

\*No progression was defined as a mSASSS change < 2 from Baseline to Week 208

# Secukinumab 150 mg : χαμηλή μέση μεταβολή στην κλίμακα mSASSS έως 4 έτη θεραπείας

## Observed Data

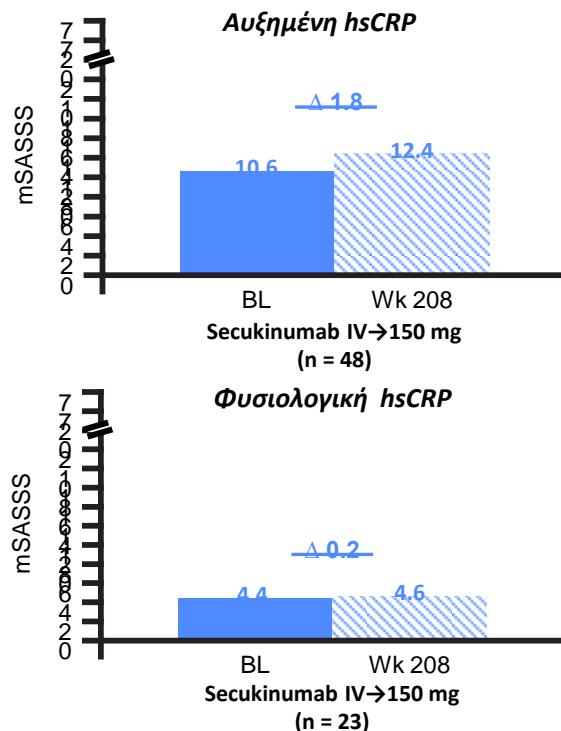


\*BL and Week 104 X-rays for these patients were re-read with Week 208 X-rays, per Imaging Charter. mSASSS range: 0–72; Δ represents mean difference in mSASSS between time points. <sup>†</sup>Includes out of window assessments at Week 104 for 10 patients in the 150 mg group.

BL, baseline; mSASSS, modified Stoke Ankylosing Spondylitis Spine Score; n, number of patients with assessments at both timepoints

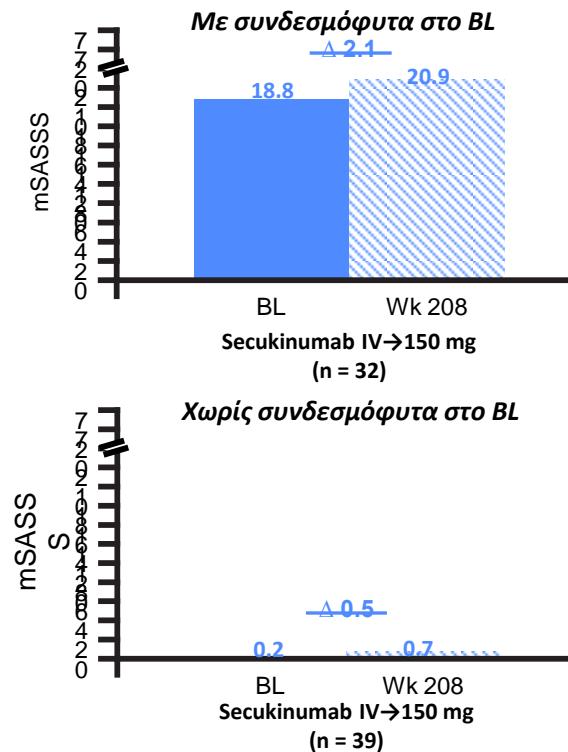
# Ακτινολογική εξέλιξη mSASSS στα 4 έτη θεραπείας

Μέση μεταβολή mSASSS ώς 4 έτη θεραπείας ως προς  
**hsCRP** κατά την έναρξη



mSASSS range: 0–72; Δ represents mean difference in mSASSS between time points  
Elevated hsCRP: >5 mg/L; normal hsCRP: ≤5 mg/L  
BL, baseline; hsCRP, high-sensitivity C-reactive protein; mSASSS, modified Stoke Ankylosing Spondylitis Spine Score; n, number of patients with both BL and Wk 208 assessments; wk, week

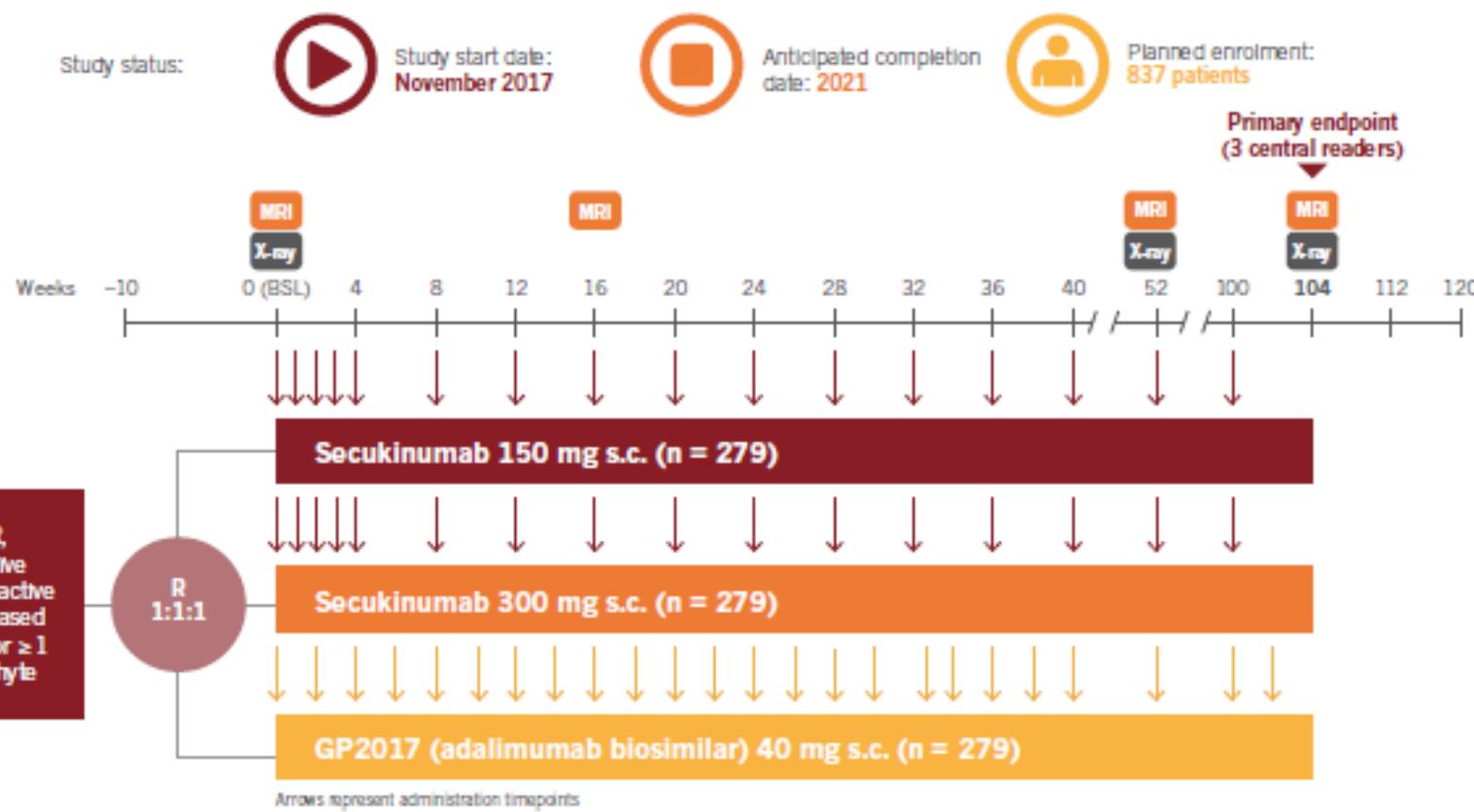
Μέση μεταβολή mSASSS ώς 4 έτη θεραπείας ως προς  
την παρουσία **συνδεσμοφύτων** κατά την έναρξη



# SURPASS

The largest randomized, active-controlled study of a biologic in AS

A Phase 3b randomized, partially blinded, active-controlled, multicenter study to evaluate radiographic progression with secukinumab versus the adalimumab biosimilar, GP2017, at 104 weeks in subjects with active AS

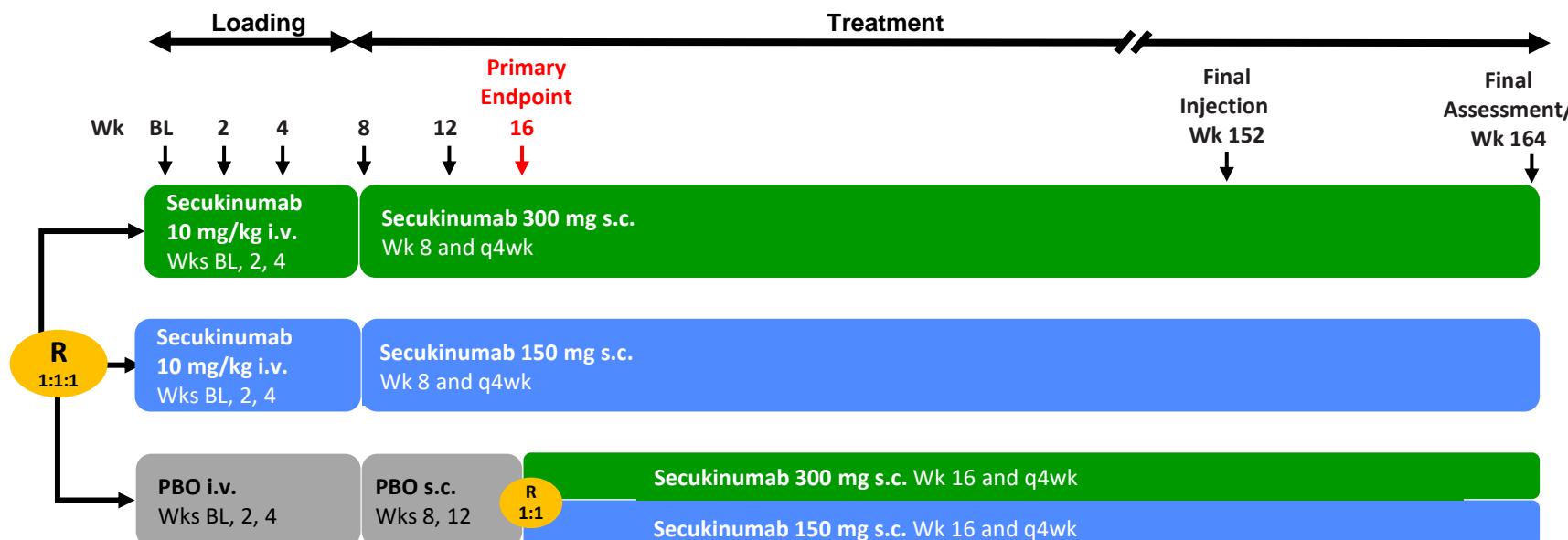


# Secukinumab Provides Sustained Improvements in the Signs and Symptoms of Active Ankylosing Spondylitis: 2-year Results from a Phase 3 Study

Karel Pavelka , Alan J. Kivitz , Eva Dokoupilova , Ricardo Blanco , Marco Maradiaga , Hasan Tahir , Alan Slade , Yi Wang , Susanne Rohrer & Brian Porter

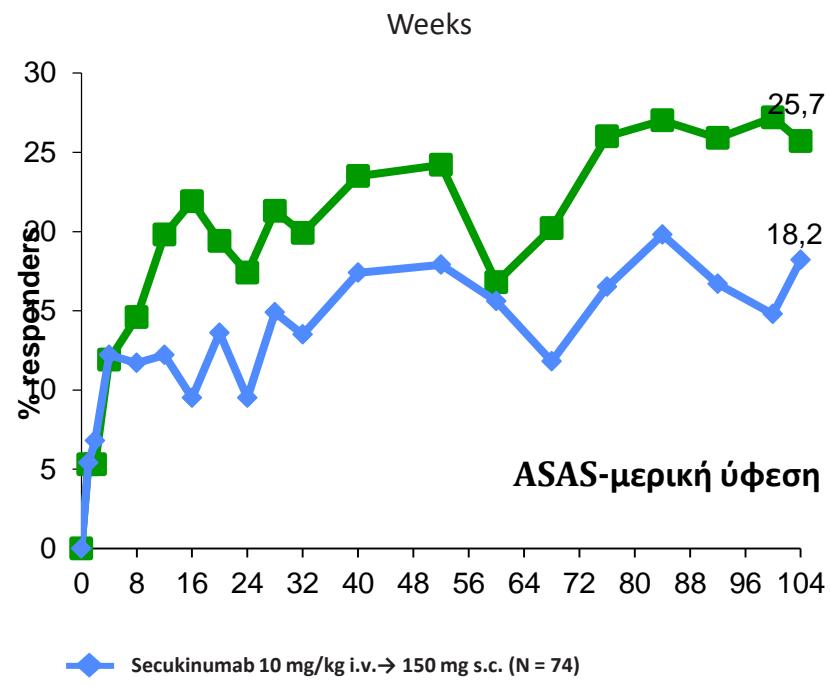
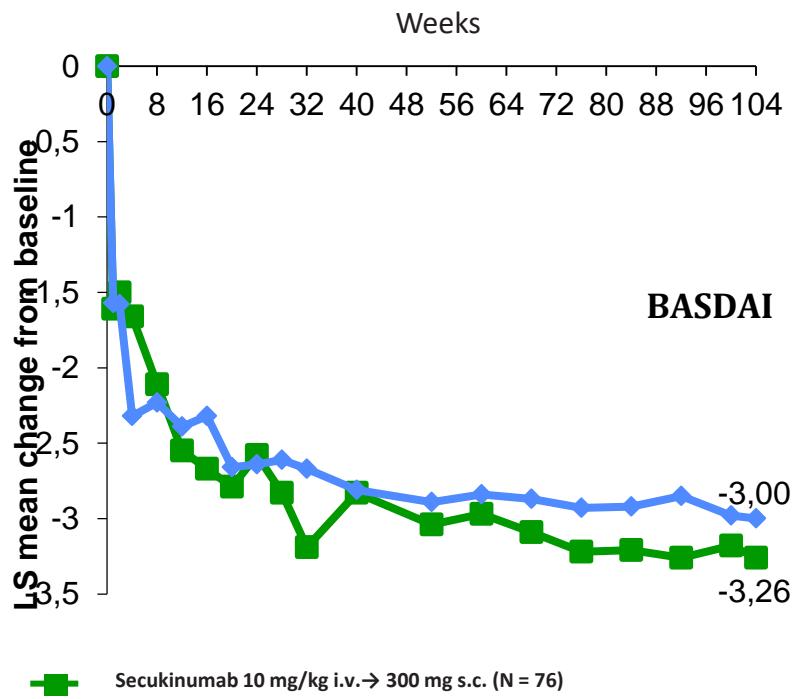
ACR Concurrent Abstract Session (1828)

## MEASURE 3: Σχεδιασμός μελέτης



BL, baseline; i.v., intravenous; PBO, placebo; q4wk, every 4 weeks; R, randomization; s.c., subcutaneous; Wk, Week

# Ταχεία και παρατεταμένη βελτίωση κατά BASDAI και ASAS-μερική ύφεση στα 2 έτη θεραπείας

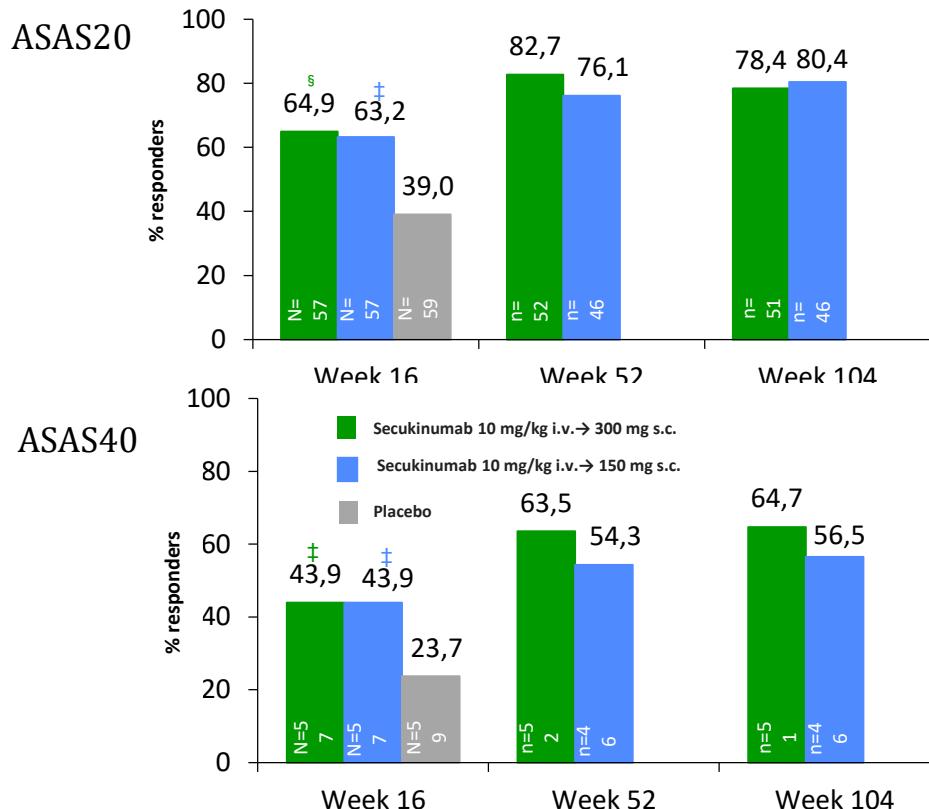


LS mean change from mixed-effect model repeated measure through Week 104. N, number of patients randomized  
 BASDAI, Bath Ankylosing Spondylitis Disease Activity Index; i.v., intravenous; LS, least squares; s.c., subcutaneous  
 Multiple imputation through Week 104. N, number of patients randomized  
 ASAS, Assessment of Spondyloarthritis International Society; i.v., intravenous; s.c., subcutaneous  
 Pavelka K, et al. *Arthritis Rheumatol.* 2017; 69 (suppl 10).

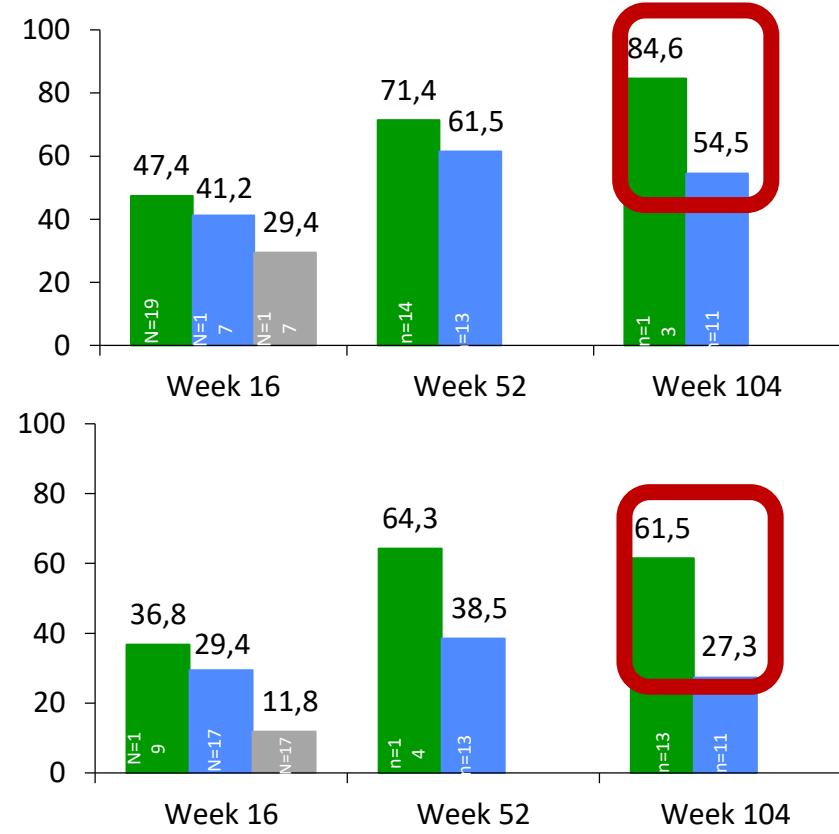
# Διατήρηση αποκρίσεων κατά ASAS 20/40 στα 2 έτη

## Θεραπείας

Anti-TNF-naïve



Anti-TNF-IR



<sup>§</sup>P < 0.01; <sup>†</sup>P < 0.05 versus placebo at Week 16 (P-values are un-adjusted). Non-responder imputation at Week 16 and observed data at Weeks 52 and 104. N, number of randomized patients; n, number of evaluable patients at Weeks 52 and 104. ASAS, Assessment of Spondyloarthritis International Society; i.v., intravenous; IR, inadequate response or intolerance; TNF, tumor necrosis factor; s.c., subcutaneous

# Secukinumab Demonstrates Consistent Safety over Long-term Exposure (up to 4 years) in Patients with Active Ankylosing Spondylitis: Pooled Analysis of Three Phase 3 Trials

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American College of Rheumatology Annual Meeting (ACR),  
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**Poster # 1529**

Item code: GLDEIM/AIN457/0115  
Date: 31 October 2017

# Περίληψη συγκεντρωτικών αποτελεσμάτων ασφάλειας στα 4 έτη: ΑΣ, ΣΑΣ & συχνά ΑΣ

Criterion	Any secukinumab N = 794
Total exposure, patient-years	1943.1
Minimum–maximum exposure (days)	1–1530
Death, n (%) <sup>a</sup>	5 (0.6)
Discontinuation due to AE, n (%) <sup>a</sup>	58 (7.3)
<b>EAIR per 100 Patient-years (95% CI)</b>	
Any AE	140.1 (129.8, 151.0)
Any SAE	6.3 (5.2, 7.6)
<b>Most Common AEs<sup>b</sup></b>	
Viral upper respiratory tract infection	9.8 (8.4, 11.5)
Headache	5.3 (4.3, 6.5)
Diarrhea	5.2 (4.2, 6.4)
Upper respiratory tract infection	5.2 (4.2, 6.4)

ACR 2017:  
**Pooled secukinumab safety**  
 Deodhar AA, et al.  
*Arthritis Rheumatol.* 2017; 69  
 (suppl 10) [poster #1529]

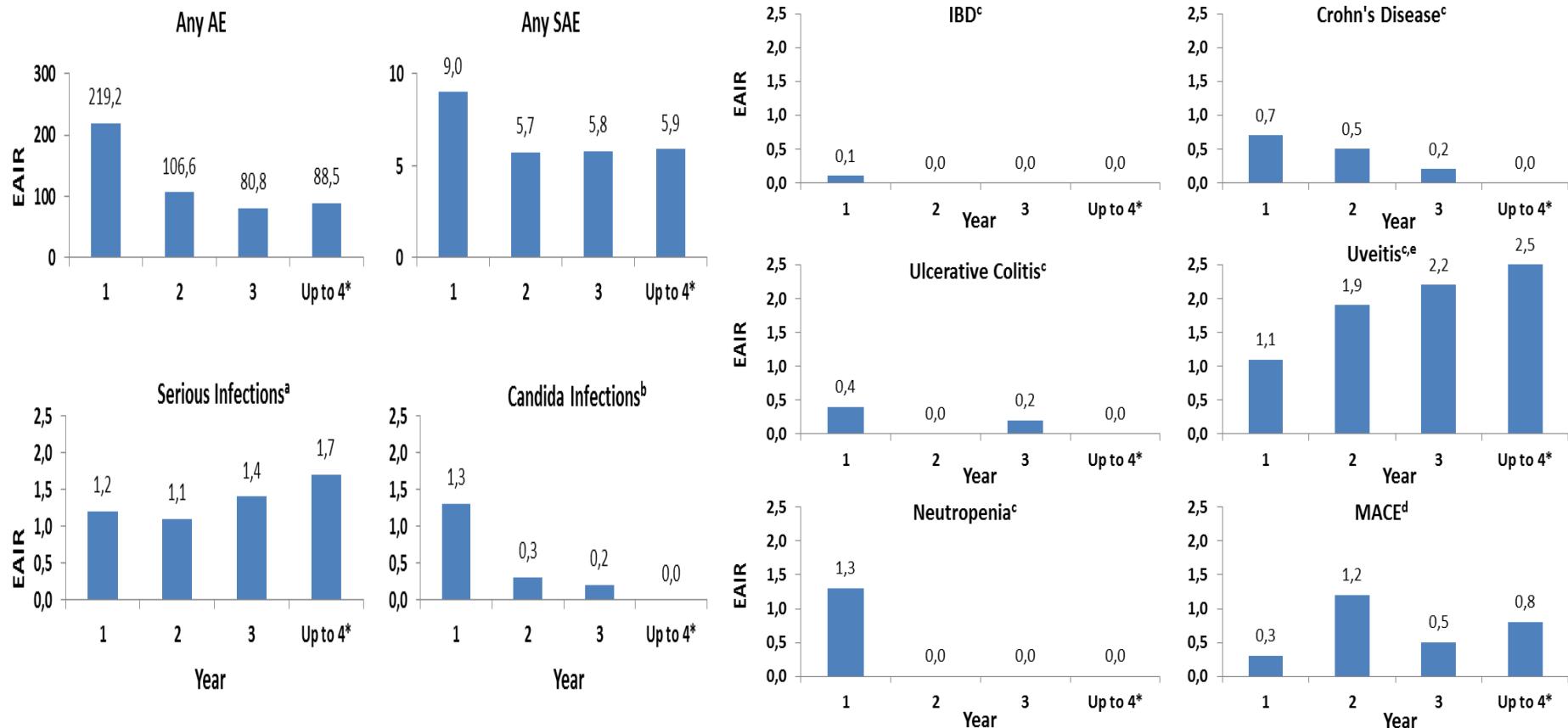
# Περίληψη συγκεντρωτικών αποτελεσμάτων ασφάλειας στα 4 έτη: ΑΣ ειδικού ενδιαφέροντος

Criterion	Any secukinumab N = 794
<b>AEs of selected interest with Secukinumab</b>	
Serious infections and infestations <sup>c</sup>	1.2 (0.8, 1.8)
<i>Candida</i> infections <sup>d</sup>	0.7 (0.4, 1.2)
Inflammatory Bowel Disease <sup>e</sup>	0.1 (0.0, 0.3)
Crohn's disease <sup>e</sup>	0.4 (0.2, 0.8)
Ulcerative colitis <sup>e</sup>	0.2 (0.1, 0.5)
Uveitis <sup>e,g</sup>	1.4 (0.9, 2.0)
Neutropenia <sup>e</sup>	0.5 (0.3, 1.0)
MACE <sup>f</sup>	0.6 (0.3, 1.1)

<sup>a</sup>Rate are n (%) as EAIR was not calculated for death and discontinuations  
<sup>b</sup>AEs that occurred with an EAIR  $\geq$ 5.0 patients per 100 patient-years during the entire safety period  
<sup>c</sup>Rates are for system organ class which includes multiple associated preferred terms (PT)  
<sup>d</sup>Rates are for candida infections high level term which includes multiple associated PTs  
<sup>e</sup>Rates are for PT (IBD PT data are reported for unspecified IBD)  
<sup>f</sup>Rates are for Novartis MedDRA Query term which includes multiple associated PTs  
<sup>g</sup>Amongst all cases of uveitis (n=26), 14 were flares in patients with a history of uveitis at baseline  
N, number of patients in the analysis  
CI, confidence interval; EAIR, exposure adjusted incidence rates; MACE, major adverse cardiac events

ACR 2017:  
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(suppl 10) [poster #1529]

# Συγκεντρωτικά EAIR των ΑΣ ανά έτος υπό Secukinumab



Patients included in the analysis: Year 1 (N = 794), Year 2 (N = 700), Year 3 (N = 557), Up to Year 4 (N = 332)

\*Data shown for patients (N = 332) with data beyond the Week 156 calendar date (Up to 4 years); <sup>a</sup>Rates are for system organ class which includes multiple associated preferred terms (PT); <sup>b</sup>Rates are for candida infections high level term which includes multiple associated PTs; <sup>c</sup>Rates are for PT (IBD PT data are reported for unspecified IBD); <sup>d</sup>Rates are for Novartis MedDRA Query term which includes multiple associated PTs; \*Amongst all cases of uveitis (n=26), 14 were flares in patients with a history of uveitis at baseline  
EAIR, exposure adjusted incidence rates; IBD, inflammatory bowel disease; MACE, major adverse cardiac events

# PREVENT: Phase 3 study to evaluate the efficacy and safety of secukinumab in nr-axSpA

A Phase 3, randomized, double-blind, placebo-controlled, multicenter study to evaluate the efficacy and safety of secukinumab in patients with non-radiographic axial spondyloarthritis



Planned  
enrolment:  
**555 patients**



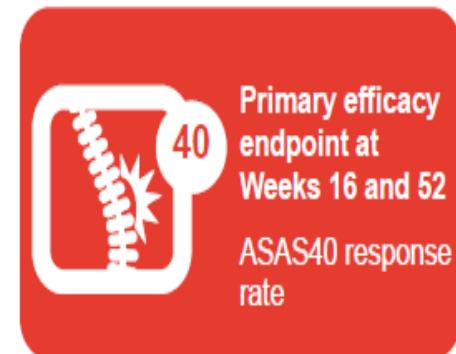
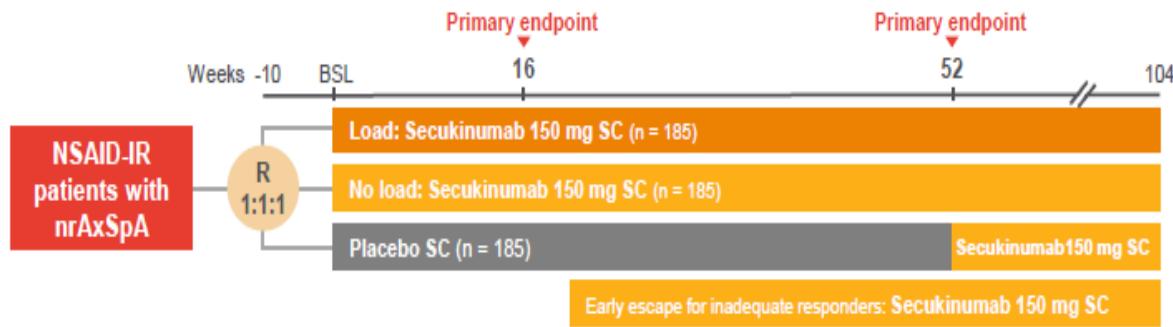
Population:  
NSAID-IR,  
bx-IR or  
DMARD-IR



Study  
start date:  
**April 2016**



Anticipated  
Completion date:  
**November 2019**



biologic-IR, biologic inadequate responders; BSL, baseline; bx, biologic; DMARD-IR, disease-modifying anti-rheumatic drug inadequate responders; nrAxSpA, non-radiographic axial spondyloarthritis; NSAID-IR, non-steroidal anti-inflammatory drug inadequate responders; SC, subcutaneous; R, randomization

Single-lined arrow represents secukinumab 150 mg SC; double-lined arrow represents placebo to secukinumab administration SC

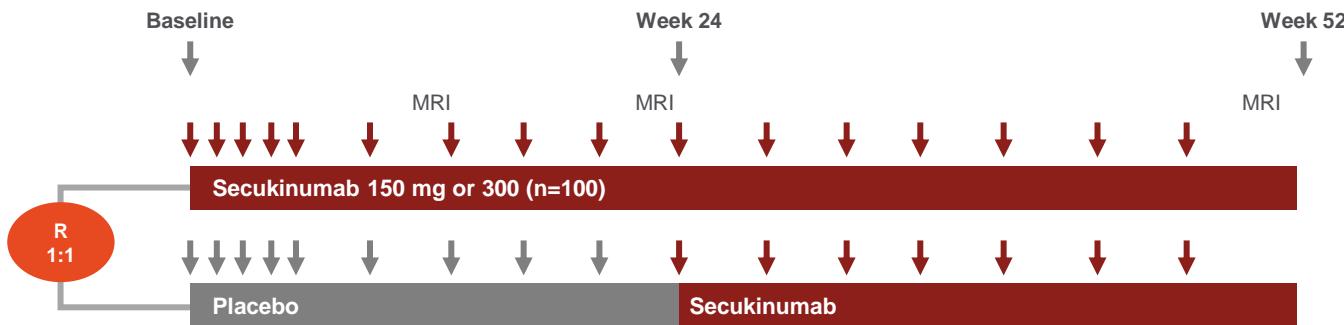
Biologic-IR patients are patients who have had an inadequate response to not more than 1 anti-TNF agent

nr-axSpA; non-radiographic axial spondyloarthritis

Clinicaltrials.gov – Identifier NCT02696031

# ACHILLES

## *Achilles tendon enthesitis resolution in PsA and axial SpA*



### Study population

- Male and female adult patients
- Active PsA or axSpA
- Active enthesitis including one clinically diagnosed (MRI+) Achilles tendon site refractory to standard treatment



### Purpose

- Demonstrate efficacy of secukinumab on enthesitis, including effects on inflammation (MRI) in Achilles tendon



### Objective

- Primary:* Superiority of secukinumab vs. placebo based on the percentage of patients with resolution of Achilles tendon enthesitis (LEI) at Week 24

An aerial photograph of the Rio-Antirrio cable-stayed bridge in Greece. The bridge spans a deep blue sea, connecting two landmasses. In the background, a range of mountains is visible under a clear blue sky.

Ευχαριστώ!

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