

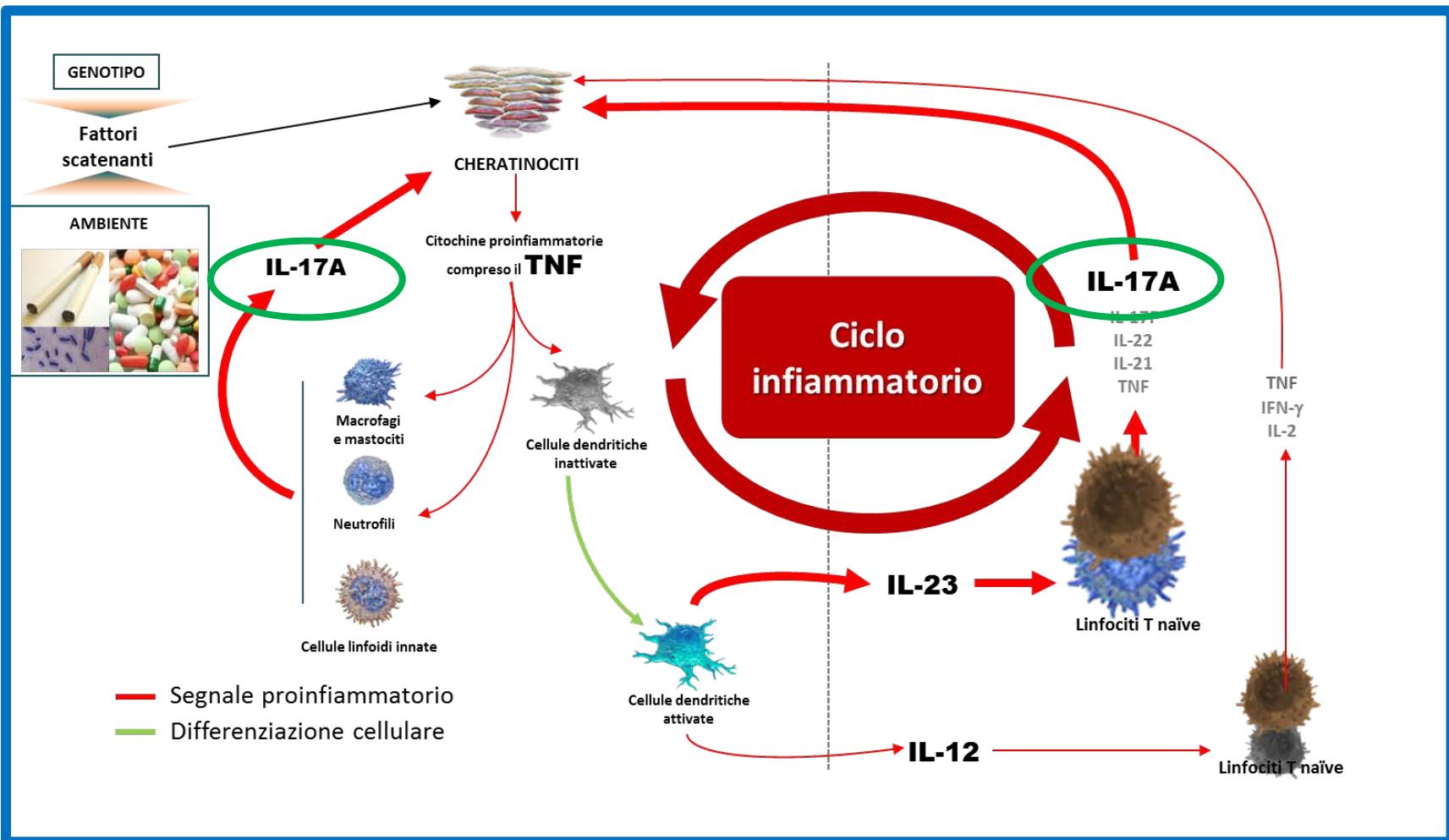
Secukinumab : studi clinici

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Secukinumab

Anticorpo monoclonale IgG1κ interamente umano
che si lega selettivamente e neutralizza l'IL 17A



EMA Approval of Secukinumab



EUROPEAN MEDICINES AGENCY
SCIENCE MEDICINES HEALTH

20 November 2014
EMA/CHMP/489954/2014
Committee for Medicinal Products for Human Use (CHMP)

Summary of opinion¹ (initial authorisation)

Cosentyx
secukinumab

The approved indication is: “Cosentyx is indicated for the treatment of moderate-severe plaque psoriasis in adults who are candidates for systemic therapy”. The recommended dose is 300 mg.

The CHMP, on the basis of quality, safety and efficacy data submitted, considers there to be a favourable benefit-to-risk balance for Cosentyx and therefore recommends the granting of the marketing authorisation.



Determina dell'Agenzia Italiana del Farmaco, 26 gennaio 2016

- **COSENTYX**

secukinumab

Indicazioni terapeutiche

- **Psoriasi a placche**

Cosentyx è indicato per il trattamento della psoriasi a placche di grado da moderato a severo in adulti che sono candidati alla terapia sistemica.

- **Artrite psoriasica**

Cosentyx, da solo o in associazione con metotressato (MTX), è indicato per il trattamento dell'artrite psoriasica attiva in pazienti adulti quando la risposta a precedente terapia con farmaci antireumatici in grado di modificare il decorso della malattia (DMARD) è risultata inadeguata

- Spondilite anchilosante

Cosentyx è indicato per il trattamento della spondilite anchilosante attiva in adulti con risposta inadeguata alla terapia convenzionale.

Secukinumab: risultati di fase III

The NEW ENGLAND JOURNAL of MEDICINE

ORIGINAL ARTICLE

Secukinumab in Plaque Psoriasis — Results of Two Phase Three Trials

ERASURE

FIXTURE

Scopo: Valutare l'efficacia di secukinumab alla Settimana 12, nonché la sicurezza, la tollerabilità e l'efficacia a lungo termine (fino a 52 settimane)

Endpoint coprimari: risposta PASI 75 e IGA 0/1 alla Settimana 12

Endpoint secondari: risposte PASI 90 e PASI 100 alla Settimana 12
e PASI 75, 90, 100 e IGA 0/1 fino a 52 settimane

Numero di pazienti = 738

Secukinumab 150 mg (n = 245)
Secukinumab 300 mg (n = 245)
Placebo (n = 248)*

Numero di pazienti = 1306

Secukinumab 150 mg (n = 327)
Secukinumab 300 mg (n = 327)
Placebo (n = 326)*
Etanercept 50 mg (n = 326)

IGA, valutazione globale dello sperimentatore.

*I non responder PASI 75 con placebo alla Settimana 12 sono stati riandomizzati a secukinumab 150 mg o 300 mg.

ERASURE and FIXTURE: Criteri di Inclusione

Soggetti adulti con psoriasi a placche moderata-severa diagnosticata da ≥ 6 mesi

Definiti al momento della randomizzazione da:

- PASI ≥ 12 , e
- IGA ≥ 3 (scala 0–4), e
- Body surface area (BSA) $\geq 10\%$

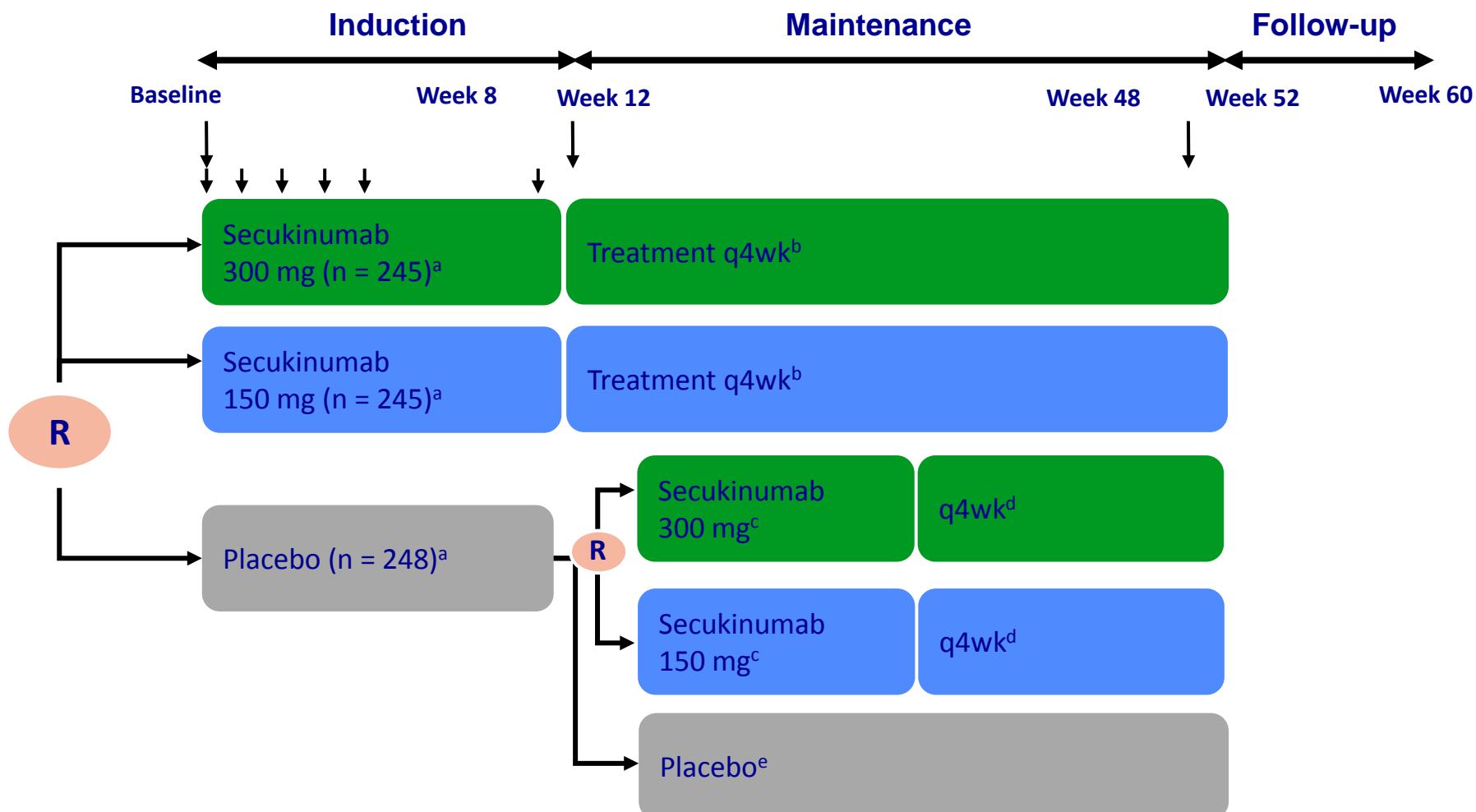
Malattia non controllata da:

- Terapia topica e/o
- Fototerapia e/o
- Precedenti terapie sistemiche

IGA, investigator's global assessment; PASI, Psoriasis Area and Severity Index.

*IGA mod 2011; static 5-point scale.

ERASURE Study Design: A Randomized, Double-Blind, Placebo-Controlled Phase III Study

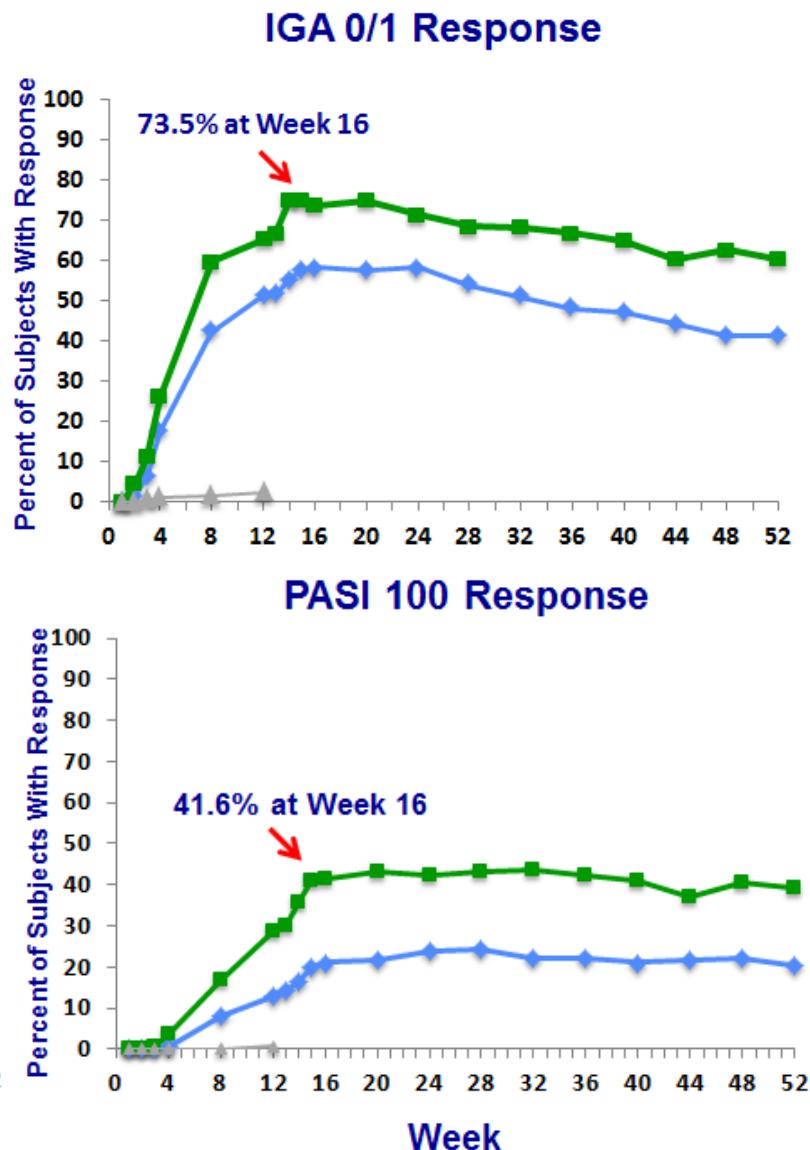
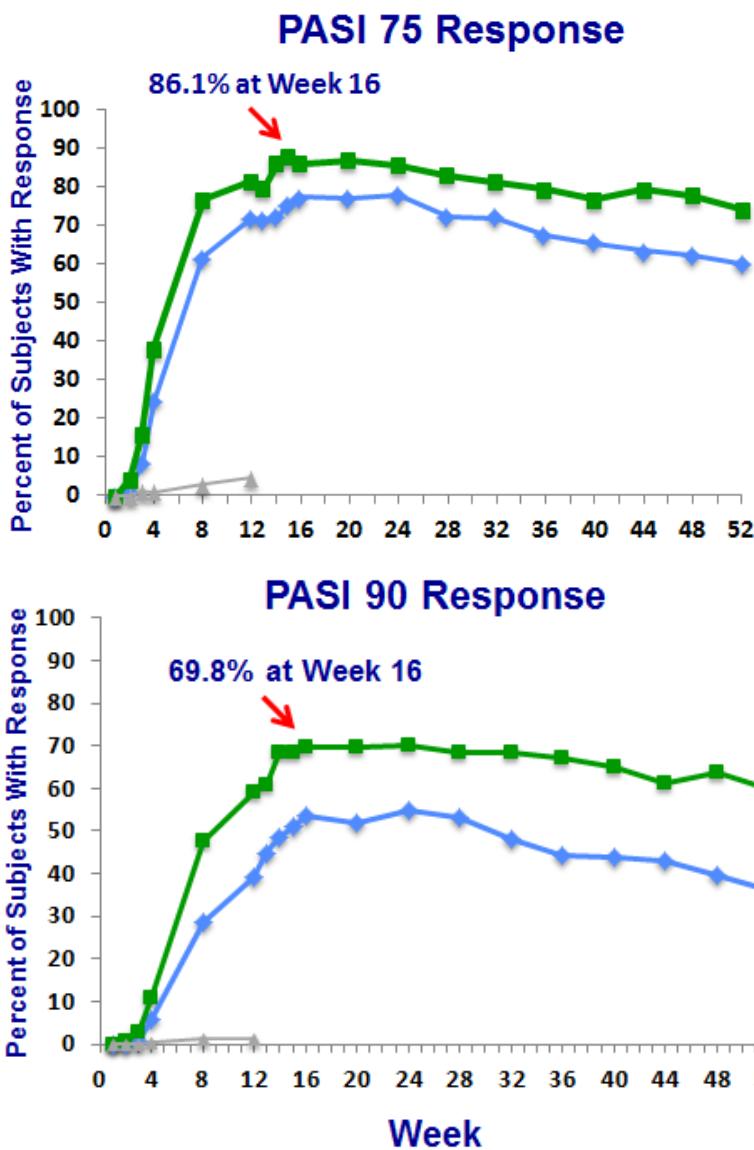


q4wk, every 4 weeks; R, randomization.

^aTreatment at baseline and Weeks 1, 2, 3, 4, and 8; ^bTreatment starts at Week 12 (+ placebo for blinding); ^cTreatment at Weeks 12, 13, 14, 15, and 16; ^dTreatment starts at Week 20, then q4wk to Week 48; ^eTreatment at Weeks 12, 13, 14, 15, 16, and 20, then q4wk to Week 48.

ERASURE: Secukinumab Sustained High Response Rates Through 52 Weeks (1/2)

Secukinumab 300 mg (n = 245^a) Secukinumab 150 mg (n = 243^{ab}) Placebo (n = 246^a)



ORIGINAL ARTICLE

Dramatic impact of a Psoriasis Area and Severity Index 90 response on the quality of life in patients with psoriasis: An analysis of Japanese clinical trials of infliximab

Hideshi TORII,¹ Noriko SATO,² Toru YOSHINARI,² Hidemi NAKAGAWA,³ The Japanese Infliximab Study Investigators*

¹Division of Dermatology, Social Insurance Central General Hospital Tokyo, ²Department of Dermatology, The Jikei University School of Medicine, Tokyo, and ³Mitsubishi Tanabe Pharma, Osaka, Japan

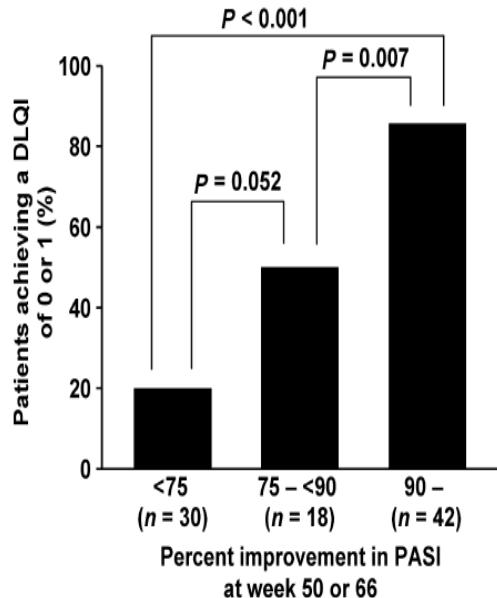
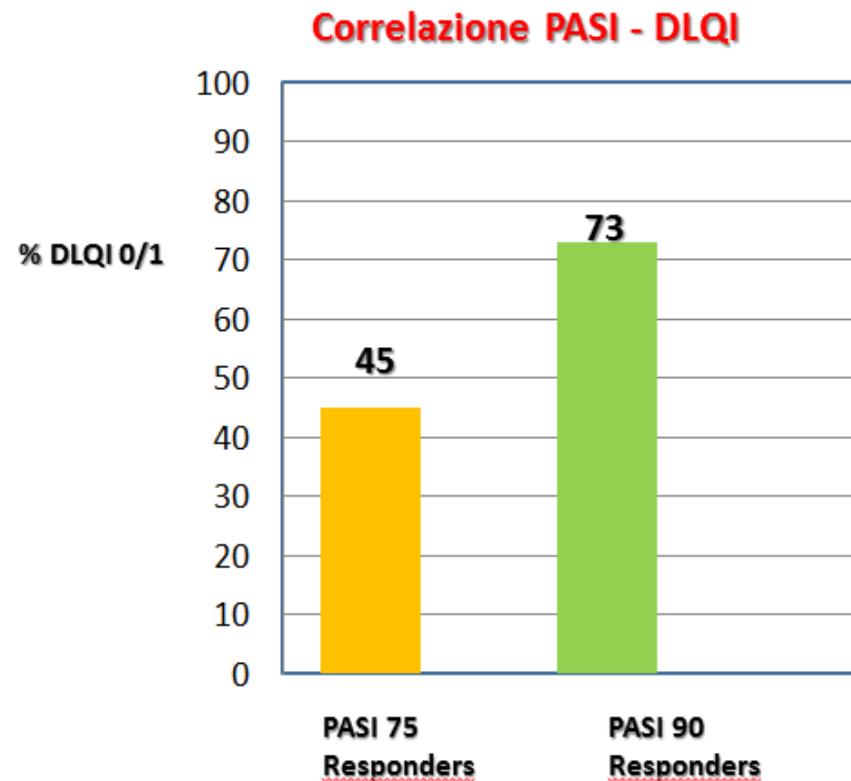


Figure 5. Percentage of patients achieving a Dermatology Life Quality Index (DLQI) of 0 or 1 according to percent improvement in Psoriasis Area and Severity Index (PASI) at the complete assessment (week 50 or 66).

Clear or almost clear skin improves the quality of life in patients with moderate to severe psoriasis: a systematic review and meta-analysis.

Puig L¹, Thom H², Mollon P³, Tian H⁴, Ramakrishna GS⁵.





ELSEVIER

ACTAS Dermo-Sifiliográficas

Full English text available at
www.actasdermo.org



OPINION ARTICLE

Treatment goals for psoriasis: Should PASI 90 become the standard of care?

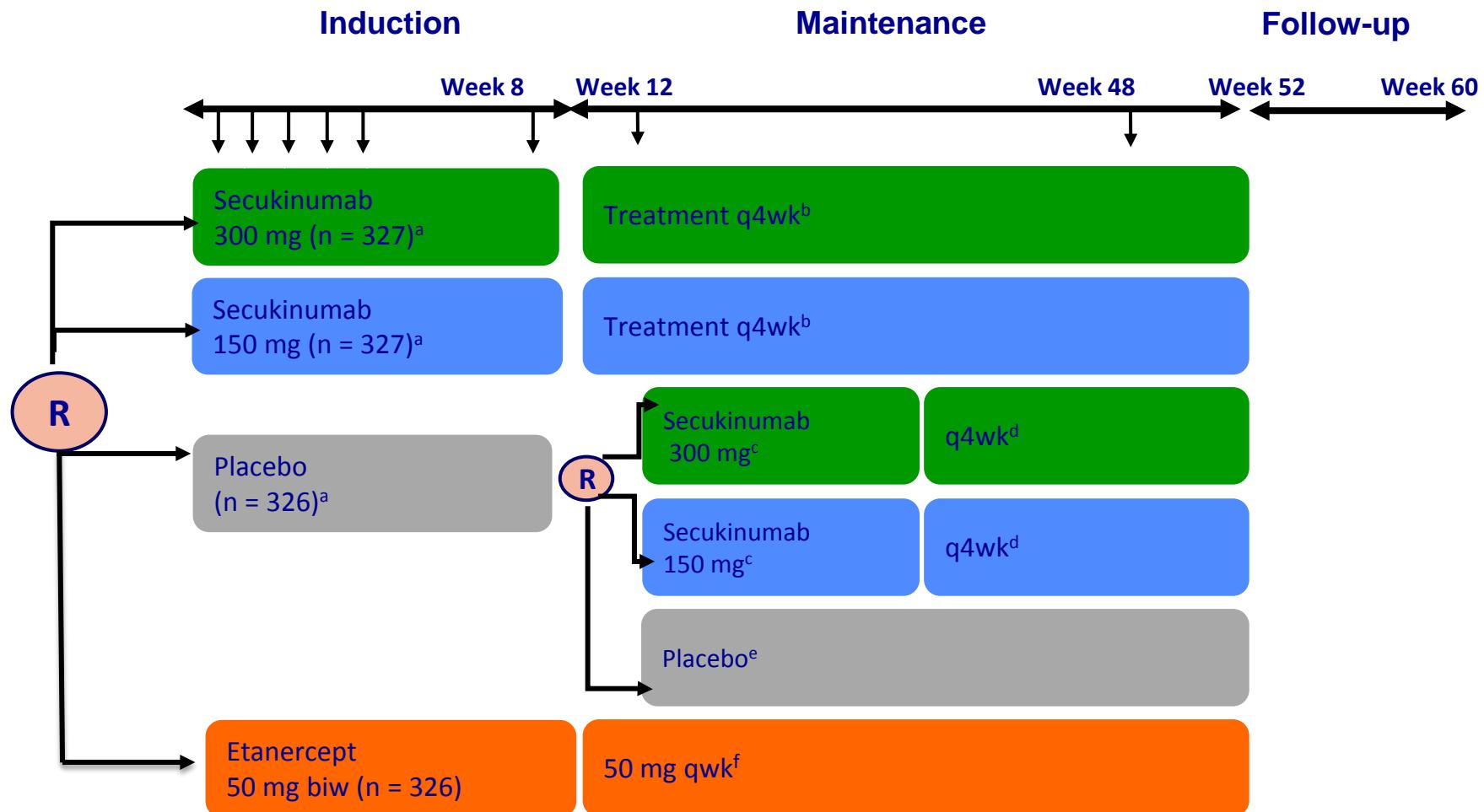


Objetivos terapéuticos en la psoriasis: ¿debería ser la respuesta PASI90 la norma asistencial?

T. Torres^{a,b,*}, L. Puig^{c,d}

I farmaci anti IL 17 negli studi di Fase II e III hanno mostrato percentuali di raggiungimento del **PASI 90** superiori al 50% pertanto il PASI 90 potrebbe diventare il *nuovo endpoint primario di efficacia*

Fixture Design: A Randomized, Double-Blind, Double-Dummy, Active Comparator, Placebo-Controlled, Phase III Study

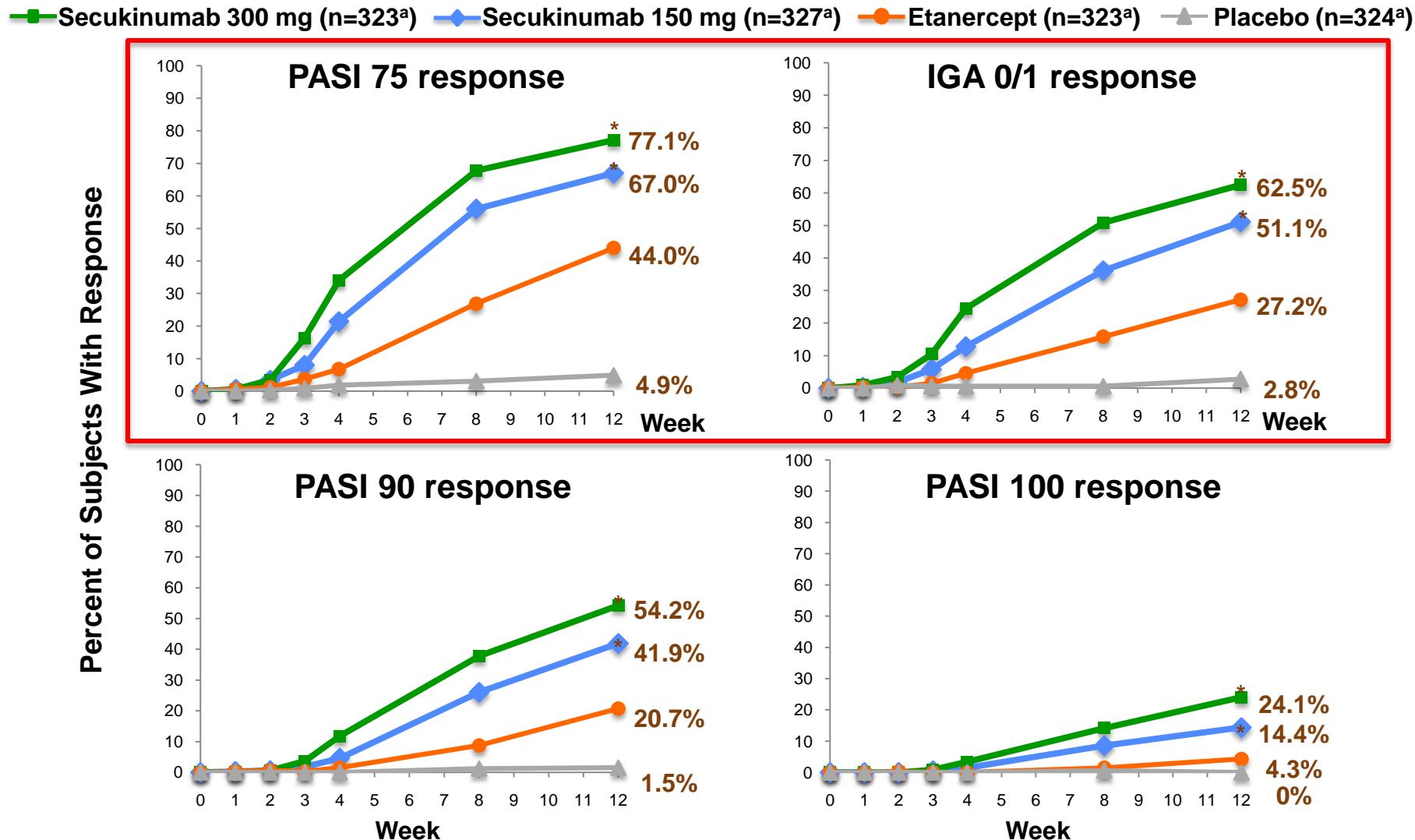


Secukinumab 300 mg s.c.: at randomization and Weeks 1, 2, and 3, and every 4 weeks for Weeks 4 to 48, except for Weeks 13, 14, and 15 when subjects receive weekly doses of PBO

^abiw, twice weekly; ^bqwk, every week; ^cq4wk, every 4 weeks; ^dR, randomization.

^eTreatment or placebo at baseline and Weeks 1, 2, 3, 4, and 8. Short arrows indicate time points when doses were given during induction period. ^fMaintenance treatment starts at Week 12 and continues q4wk until Week 48. ^gTreatment at Weeks 12, 13, 14, and 15. ^hTreatment q4wk from Week 16 until Week 48. ⁱPlacebo at Weeks 12, 13, 14, and 15, then q4wk from Week 16 until Week 48. ^jTreatment qwk from Week 12 until Week 51.

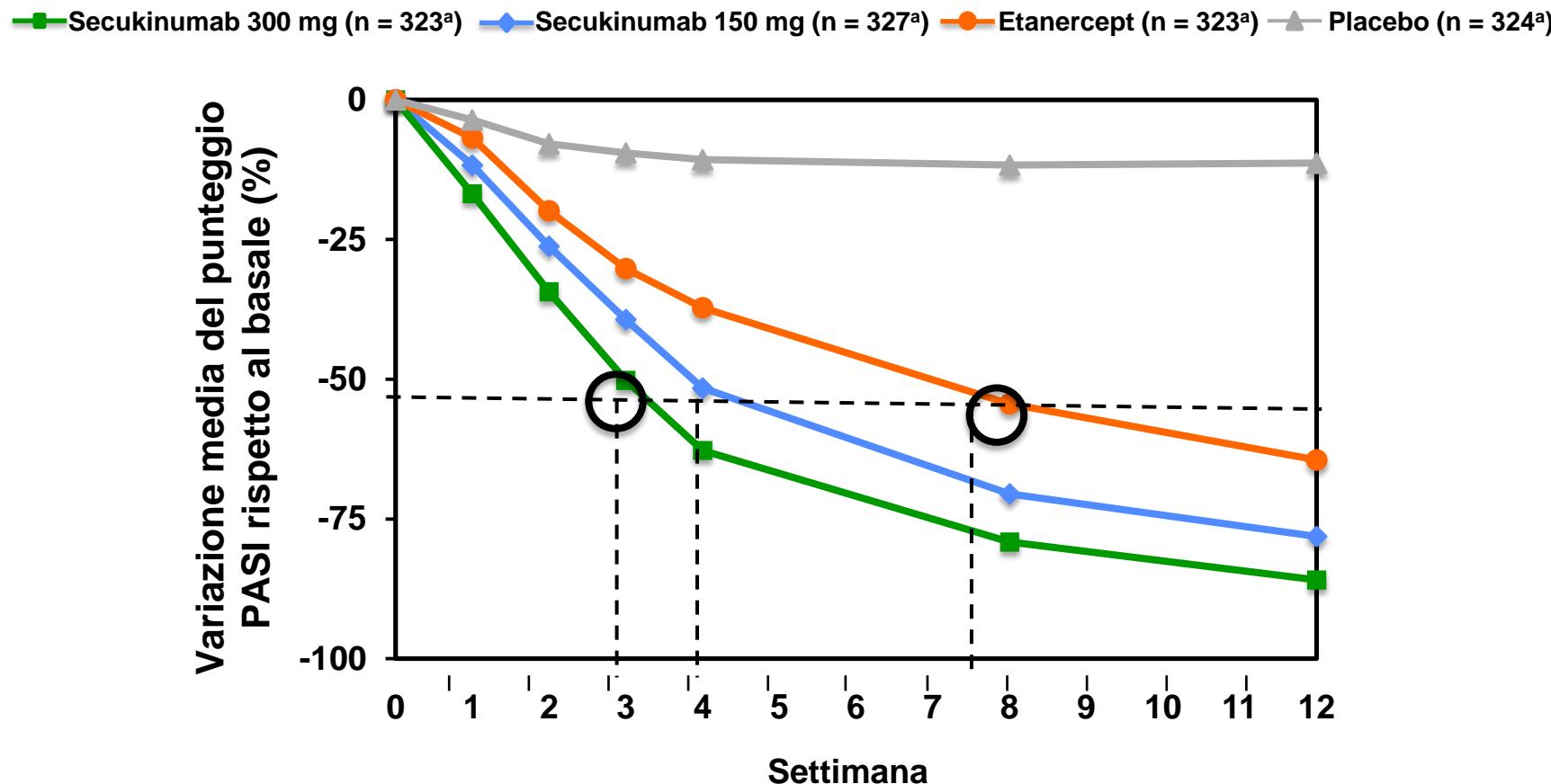
FIXTURE: Efficacia superiore di secukinumab vs. placebo e vs etanercept alla Settimana 12



^aNumber of evaluable subjects. *P < 0.0001 for comparisons of secukinumab vs. etanercept.

Studio FIXTURE: secukinumab ha migliorato rapidamente la psoriasi a placche

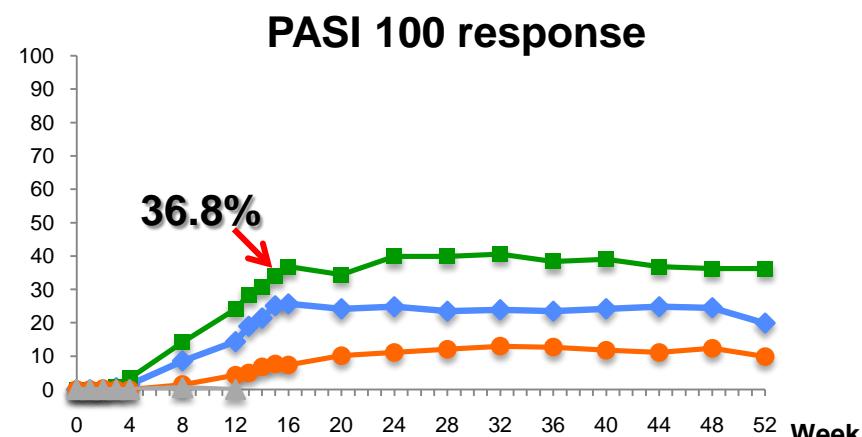
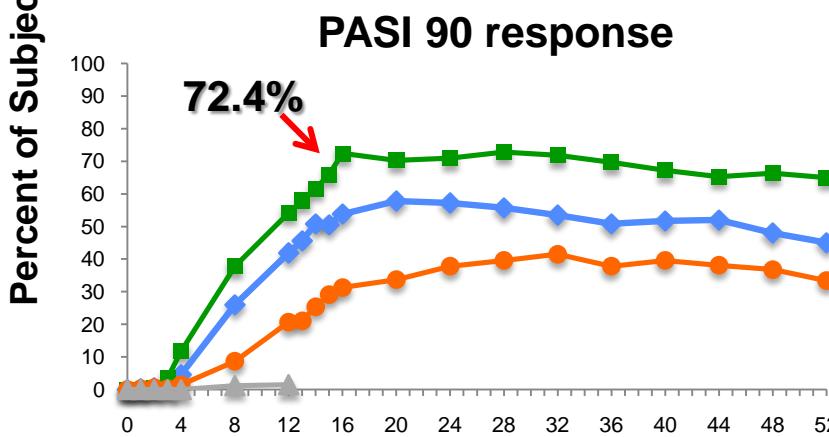
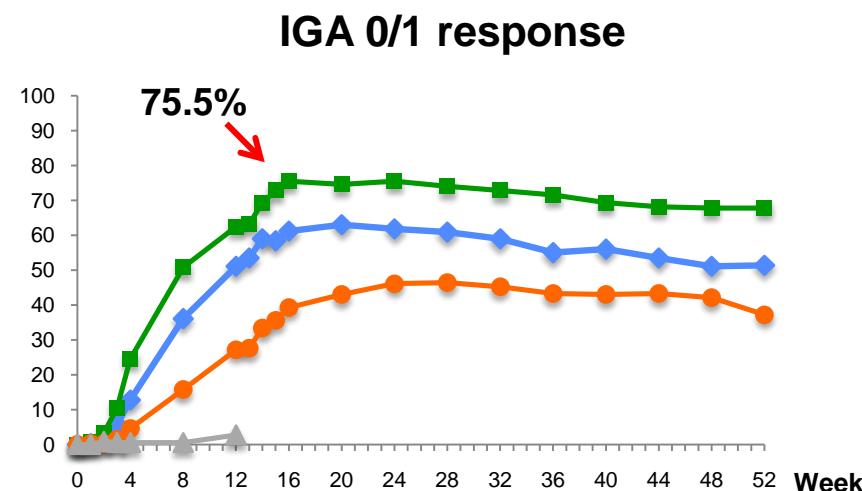
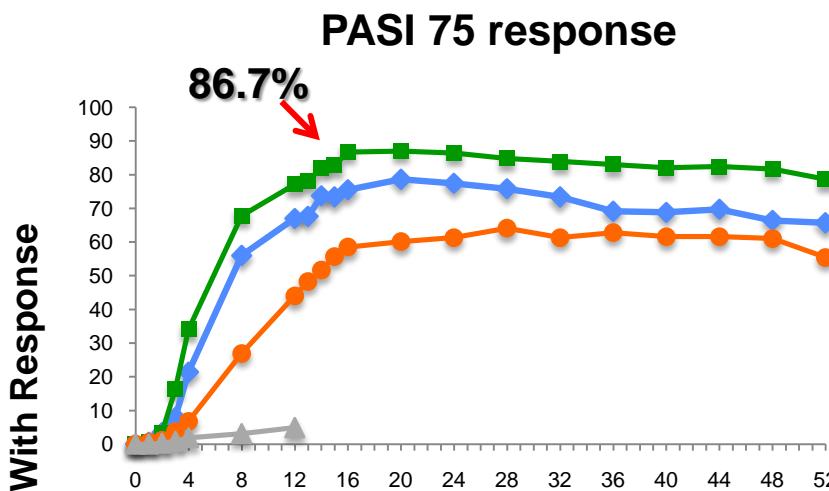
Secukinumab 300 mg ha ottenuto una riduzione del 50% circa del punteggio PASI *dopo 3 settimane di trattamento* rispetto a 8 settimane di etanercept



^aNumero di soggetti valutabili. Notare che il grafico è solo osservazionale, non è stata effettuata alcuna analisi statistica.

Studio FIXTURE: l'efficacia di secukinumab aumenta fino alla 16° settimana e si mantiene alla 52°

■ Secukinumab 300 mg (n=323^a) ■ Secukinumab 150 mg (n=327^a) ■ Etanercept (n=323^a) ■ Placebo (n=324^a)



^aNumber of evaluable subjects. Red arrows indicate peak response around week 16

Secukinumab is superior to ustekinumab in clearing skin of subjects with moderate to severe plaque psoriasis: CLEAR, a randomized controlled trial

J AM ACAD DERMATOL
Thaci et al VOLUME 73, NUMBER 3

Studio CLEAR (A2317)

Obiettivo primario

- Studio multicentrico, randomizzato in doppio cieco della durata di 52 settimane, con secukinumab sottocute per dimostrare l'efficacia, valutata mediante Psoriasis Area and Severity Index a 16 settimane di trattamento rispetto a ustekinumab e valutare sicurezza, tollerabilità ed efficacia a lungo termine in soggetti con psoriasi a placche da moderata a grave
- Dimostrare la **superiorità** di secukinumab 300 mg rispetto a ustekinumab in soggetti con psoriasi a placche da moderata a grave in base alla **proporzione di risposte PASI 90 alla Settimana 16**

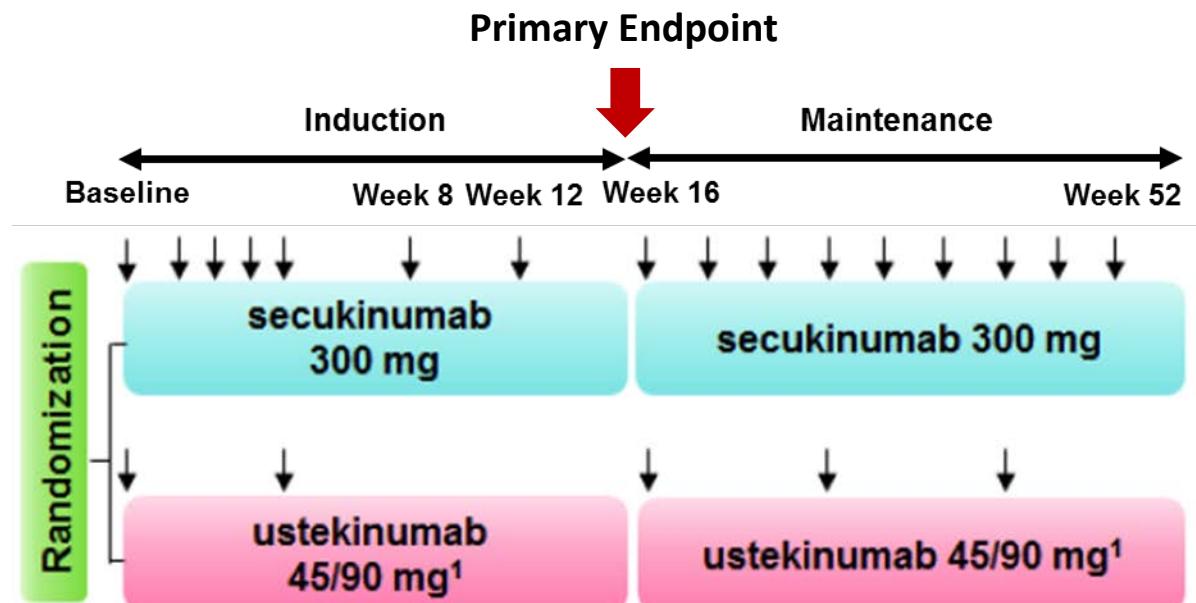
Endpoint di efficacia

Primario:

- Risposta PASI 90 alla Settimana 16

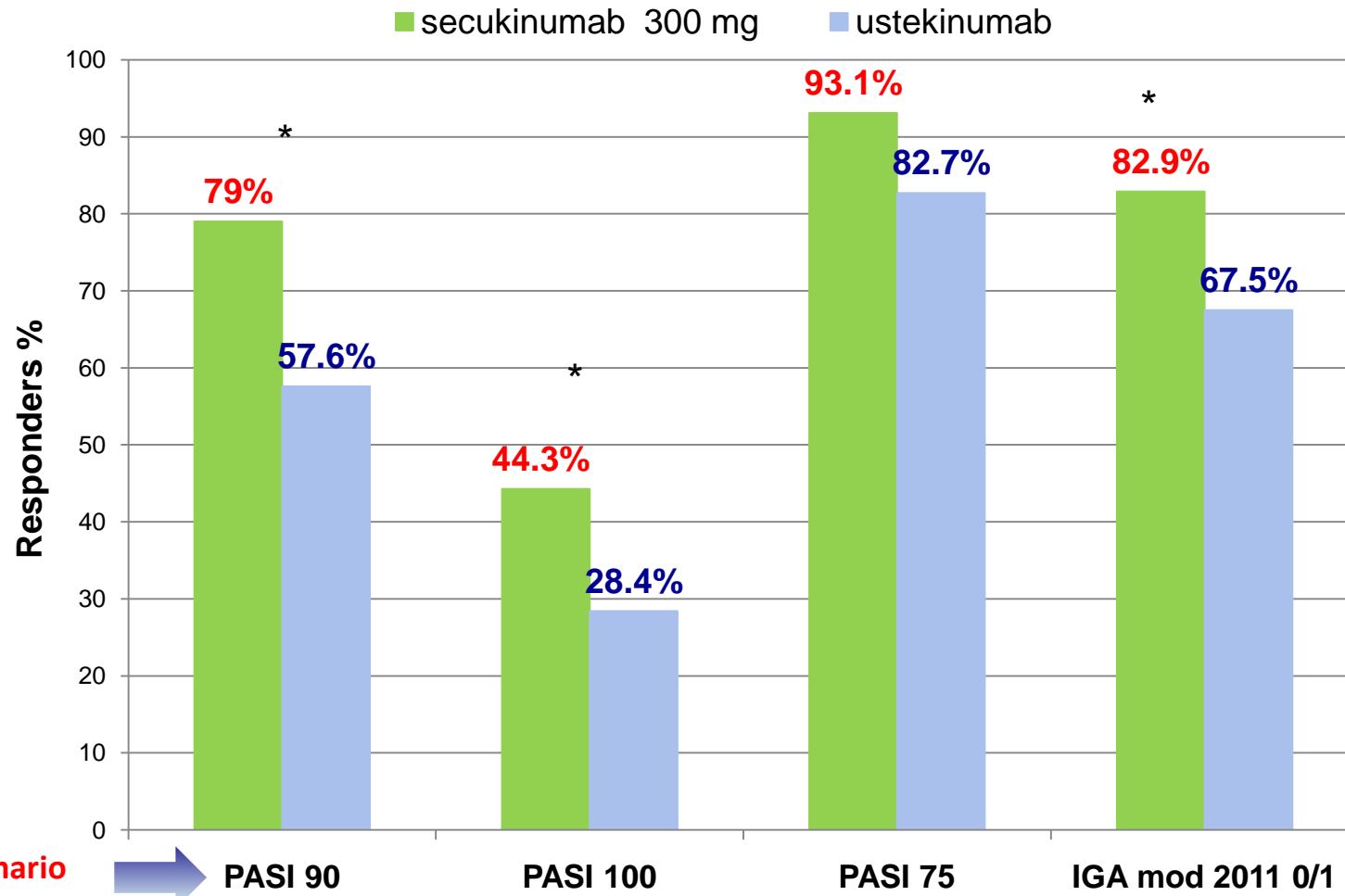
Secondari:

- Risposta PASI 75 alla Settimana 4
- Risposta PASI 90 alla Settimana 52



Secukinumab is superior to ustekinumab in clearing skin of subjects with moderate to severe plaque psoriasis: CLEAR, a randomized controlled trial

Thaçi et al J Am Acad Dermatol
VOLUME 73, NUMBER 3



Endpoint primario
raggiunto

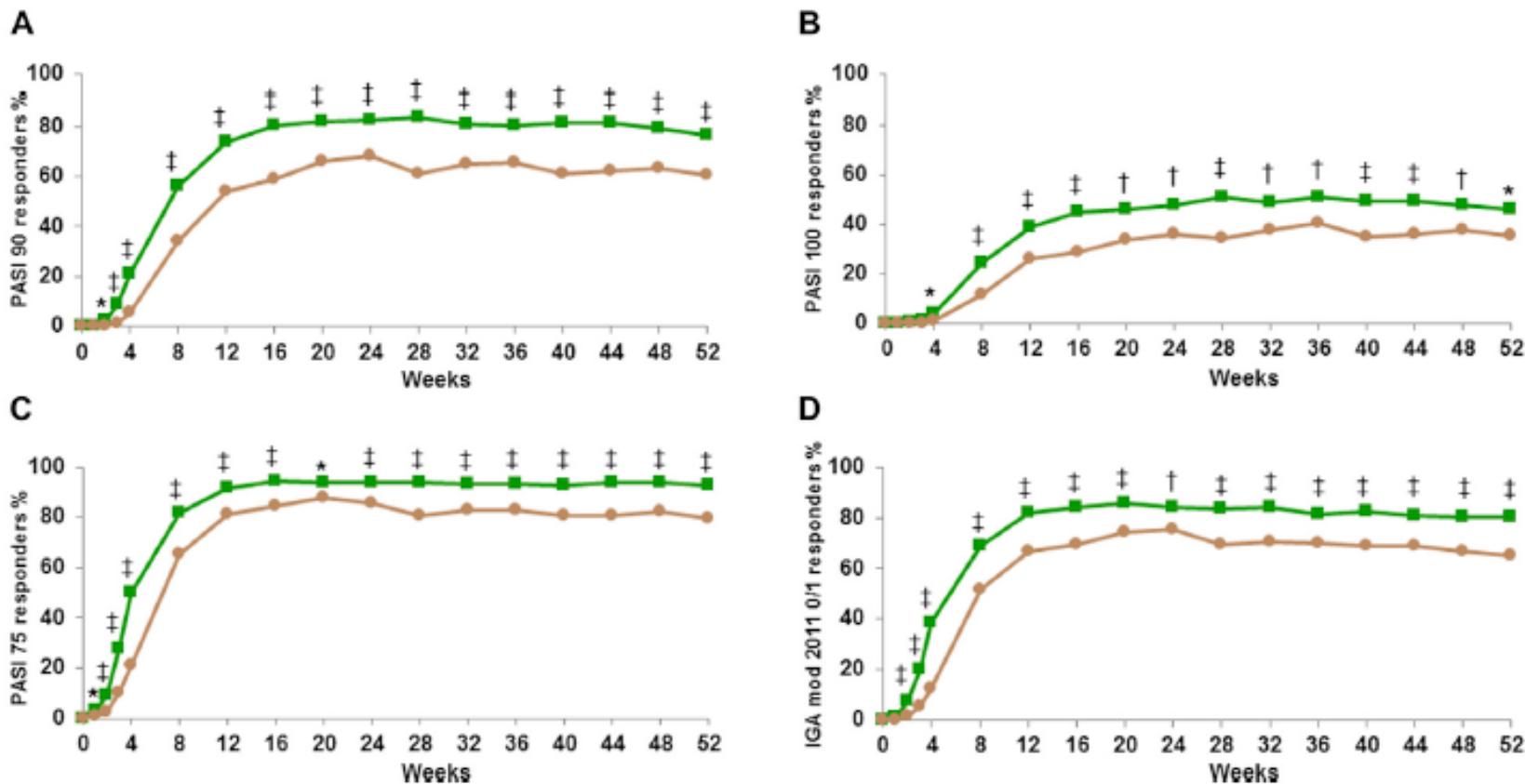
p values ≤0.0001

Alla week 16 Secukinumab è più efficace di Ustekinumab

Secukinumab is superior to ustekinumab in clearing skin of subjects with moderate-to-severe plaque psoriasis up to 1 year: Results from the CLEAR study

Blauvelt et al J AM ACAD DERMATOL VOLUME 76, NUMBER 1

■ Secukinumab 300 mg (n = 334) ■ Ustekinumab (n = 335)

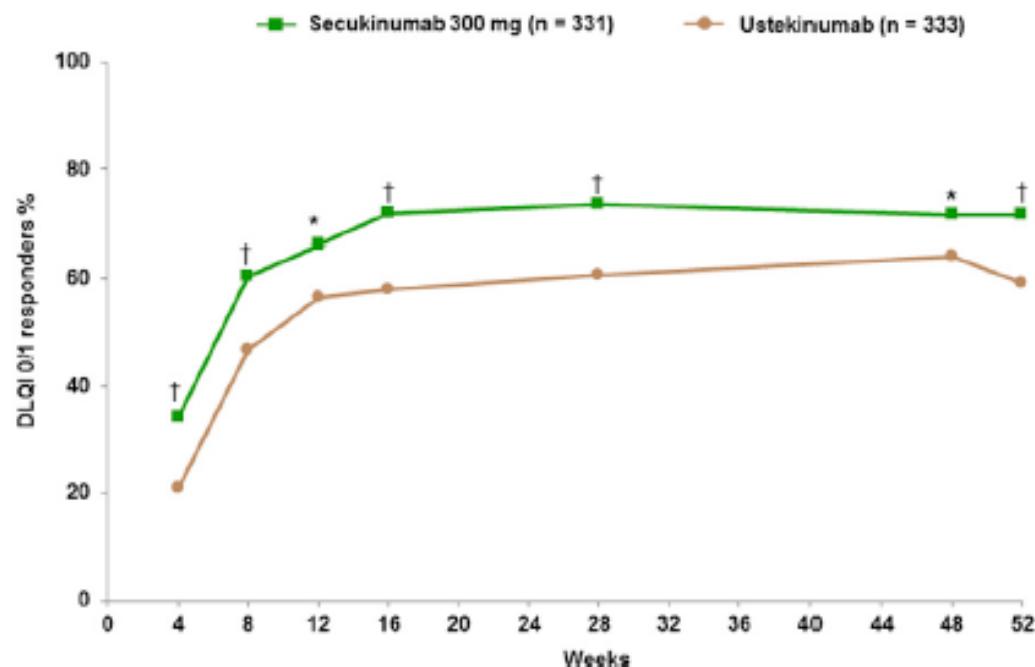


Secukinumab is superior to ustekinumab in clearing skin of subjects with moderate-to-severe plaque psoriasis up to 1 year: Results from the CLEAR study

J AM ACAD DERMATOL
Blauvelt et al VOLUME 76, NUMBER 1

CAPSULE SUMMARY

- Secukinumab has demonstrated superior efficacy to ustekinumab at weeks 4 and 16 in subjects with plaque psoriasis (CLEAR study).
- This superior efficacy is sustained over 52 weeks, with greater improvement in health-related quality of life and comparable safety.
- This study provides head-to-head data that will inform clinical decisions on long-term management of psoriasis.

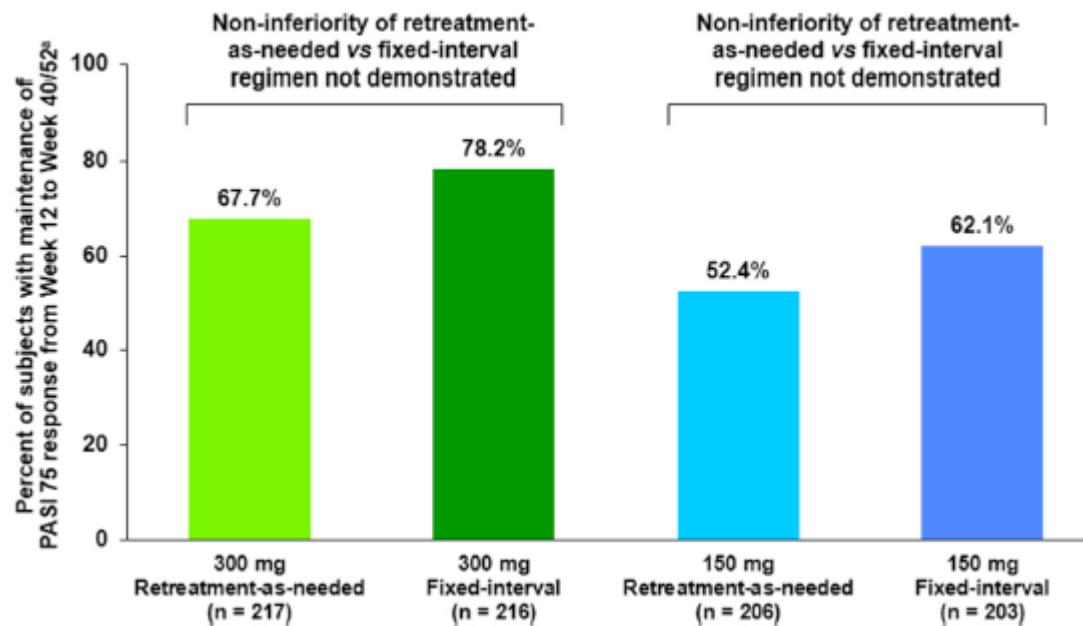


Sintesi dei dati di efficacia

- Il regime terapeutico di secukinumab 300 mg mostra un'efficacia più elevata **rispetto a placebo, etanercept e ustekinumab** sugli endpoint co-primari rispettivamente alla 12° e 16° settimana
- Efficacia è **dose-dipendente** ($300\text{ mg} > 150\text{ mg}$)
- Beneficio clinico osservabile già alla week 3 nel gruppo 300 mg
- La risposta clinica raggiunge un plateau alla Week 16, e viene mantenuta fino alla Week 52

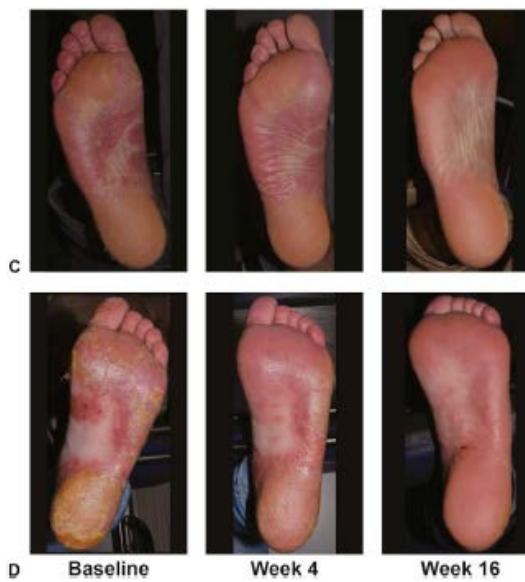
Secukinumab retreatment-as-needed versus fixed-interval maintenance regimen for moderate to severe plaque psoriasis: A randomized, double-blind, noninferiority trial (SCULPTURE)

Mrowietz et al J AM ACAD DERMATOL
VOLUME 73, NUMBER 1



Conclusion: Secukinumab fixed interval showed clear benefit versus the study-specified retreatment-as-needed regimen for maintaining efficacy. Both regimens exhibited safety consistent with previous trials. The potential of retreatment as needed with secukinumab warrants further investigation.

Secukinumab shows significant efficacy in palmoplantar psoriasis: Results from GESTURE, a randomized controlled trial



CAPSULE SUMMARY

- Palmoplantar psoriasis is difficult-to-treat and significantly impacts quality of life.
- At 16 weeks, one-third of subjects treated with secukinumab 300 mg showed clear or almost clear palms and soles with a significant improvement in quality of life.
- Secukinumab represents a new therapeutic option for the treatment of palmoplantar psoriasis.

Gottlieb et al J AM ACAD DERMATOL
JANUARY 2017

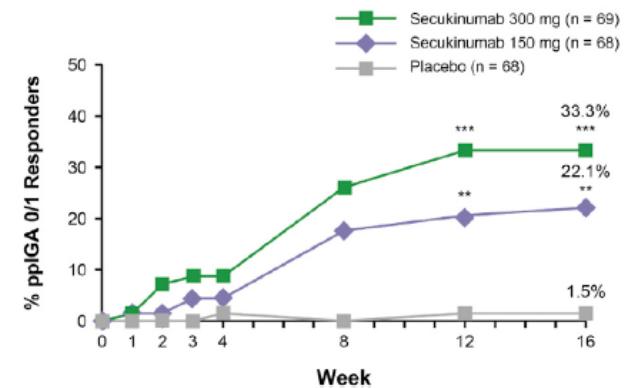


Fig 3. ppIGA 0/1 responders over time. The percentage of subjects with moderate-to-severe palmoplantar psoriasis who achieved a ppIGA 0/1 and a reduction of at least 2 points from baseline on the ppIGA scale over 16 weeks of treatment by nonresponder imputation. ** $P < .001$ vs placebo; *** $P < .0001$ vs placebo. ppIGA, Palmoplantar Investigator's Global Assessment.

Conclusion: In GESTURE, the largest randomized controlled trial in palmoplantar psoriasis, secukinumab demonstrated the greatest efficacy to date for treating difficult-to-treat psoriasis. *J Am Acad Dermatol*

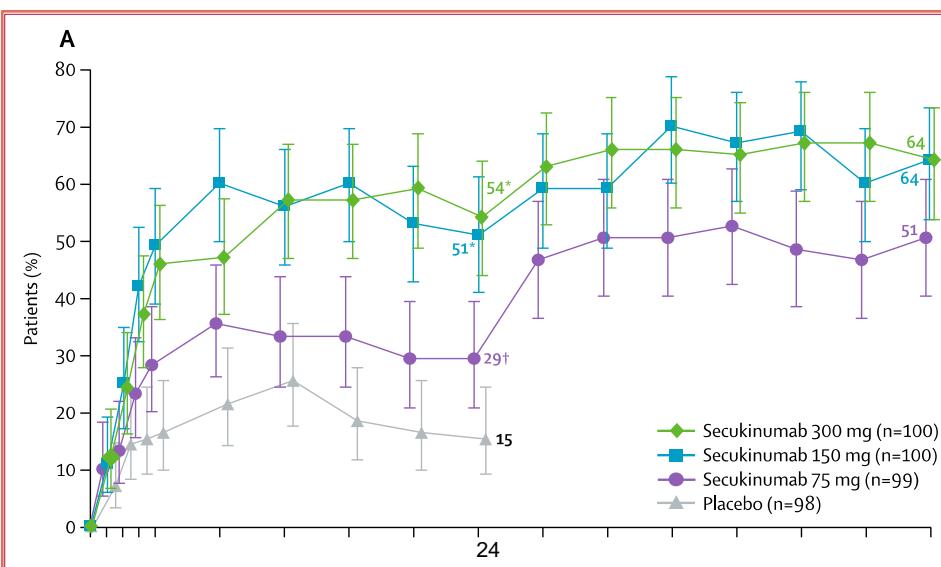
SECUKINUMAB E' EFFICACE NELLA PSORIASI ARTROPATICA

Secukinumab, a human anti-interleukin-17A monoclonal antibody, in patients with psoriatic arthritis (FUTURE 2): a randomised, double-blind, placebo-controlled, phase 3 trial

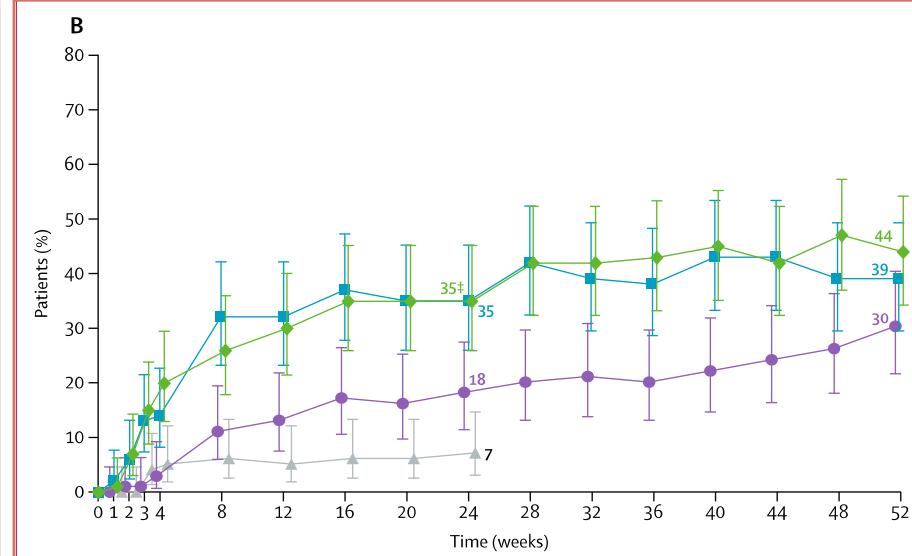
Iain B McInnes, Philip J Mease, Bruce Kirkham, Arthur Kavanaugh, Christopher T Ritchlin, Proton Rahman, Désirée van der Heijde, Robert Landewé, Philip G Conaghan, Alice B Gottlieb, Hanno Richards, Luminita Pricop, Gregory Ligozio, Manmath Patekar, Shephard Mpofu, on behalf of the FUTURE 2 Study Group

Lancet 2015; 386: 1137-46

ACR 20



ACR 50



Most Common AE

Placebo-controlled period (12 weeks)

Most frequent (>3%) AEs by preferred term

	Secukinumab 300 mg (n=690) n (%)	Secukinumab 150 mg (n=692) n (%)	Placebo (n=694) n (%)	Etanercept (n=323) n (%)
Any AE	388 (56.2)	412 (59.5)	340 (49.0)	186 (57.6)
Nasopharyngitis	79 (11.4)	85 (12.3)	60 (8.6)	36 (11.1)
Headache	45 (6.5)	38 (5.5)	36 (5.2)	23 (7.1)
Diarrhea	28 (4.1)	18 (2.6)	10 (1.4)	11 (3.4)
Pruritus	23 (3.3)	21 (3.0)	18 (2.6)	8 (2.5)
Upper respiratory tract infection	17 (2.5)	22 (3.2)	5 (0.7)	7 (2.2)
Arthralgia	9 (1.3)	20 (2.9)	17 (2.4)	12 (3.7)
Hypertension	7 (1.0)	22 (3.2)	12 (1.7)	5 (1.5)
Injection site erythema	1 (0.1)	0 (0.0)	0 (0.0)	16 (5.0)

Highlighted cells indicate the highest event rate between groups

Treatment-emergent AEs are summarized.



Most Frequent SAEs

Entire treatment period – exposure adjusted (52 weeks)

	Secukinumab 300 mg (n=1410) n (IR)	Secukinumab 150 mg (n=1395) n (IR)	Placebo (n=793) n (IR)	Etanercept (n=323) n (IR)
Any SAE	85 (7.42)	76 (6.80)	15 (7.54)	20 (7.01)
Pneumonia	3 (0.25)	3 (0.26)	0 (0.00)	0 (0.00)
Angina pectoris	1 (0.08)	2 (0.18)	0 (0.00)	0 (0.00)
Cellulitis	1 (0.08)	2 (0.18)	2 (0.99)	1 (0.34)
Abscess bacterial	0 (0.00)	3 (0.26)	0 (0.00)	0 (0.00)
Appendicitis	2 (0.17)	1 (0.09)	0 (0.00)	0 (0.00)
Coronary artery disease	1 (0.08)	1 (0.09)	0 (0.00)	0 (0.00)
Hypertensive crisis	2 (0.17)	1 (0.09)	0 (0.00)	0 (0.00)
Psoriasis	1 (0.08)	1 (0.09)	4 (1.99)	1 (0.34)
Sciatica	2 (0.17)	2 (0.18)	0 (0.00)	0 (0.00)

*Treatment-emergent SAEs are summarized in this table. IR = incidence rate per 100 patient years.
For patients with event, exposure time is censored at time of first event.*

MECHANISMS OF DISEASE

Interleukin-17 and Type 17 Helper T Cells

Pierre Miossec, M.D., Ph.D., Thomas Korn, M.D., and Vijay K. Kuchroo, Ph.D.

A number of pathogens induce mainly Th17 responses (Fig. 1). They include gram-positive *Propionibacterium acnes*, gram-negative *Citrobacter rodentium*, *Klebsiella pneumoniae*, *bacteroides* species and *borrelia* species, *Mycobacterium tuberculosis*, and **fungi such as *Candida albicans***. To rid the body of fungi and certain extracellular bacteria requires inflammation of the type engendered by Th17 cells. The role of interleukin-17 and Th17 cells in clearing infections has been shown in the hyper-IgE syndrome, in which a mutation in *STAT3*, one of a family of transcription activators, nullifies the ability to mount Th17 responses. Patients with this disorder have recurrent *C. albicans* and *Staphylococcus aureus* infections in the skin and lungs.

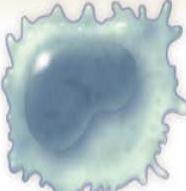
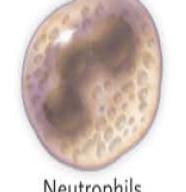
Th Group	Cell Products	Cell Target	Infectious Agents
Th1	 Interleukin-12R	 Macrophages Dendritic cells	Intracellular bacteria Fungi Viruses
Th17	 Interleukin-23R	 Neutrophils	Extracellular bacteria Fungi
Th2	 Interleukin-4R	 Eosinophils Basophils	Parasites

Figure 1. Helper T-Cell (Th) Subgroups and Effector Functions.

The cytokine profile (including key cytokine receptors as denoted by R), the effector cell type that is activated, and the corresponding types of infections are shown for each Th subgroup.

Sintesi dati di sicurezza

- Secukinumab 300 mg mostra un favorevole profilo di sicurezza nei pazienti con psoriasi moderata-severa
- Gli effetti collaterali sono facilmente controllabili
- Infezioni prevalentemente lievi delle vie respiratorie superiori
Infezioni da Candida superficiali
- Sicurezza del dosaggio di 300 mg e 150 mg paragonabili
- Assenza di differenze clinicamente significative nelle infezioni serie in 52 settimane di trattamento
- Incidenza di neoplasie ed eventi cardiovascolari maggiori comparabili al placebo ed etanercept in 52 settimane
- Rapporto rischio/beneficio complessivamente favorevole al dosaggio di 300 mg

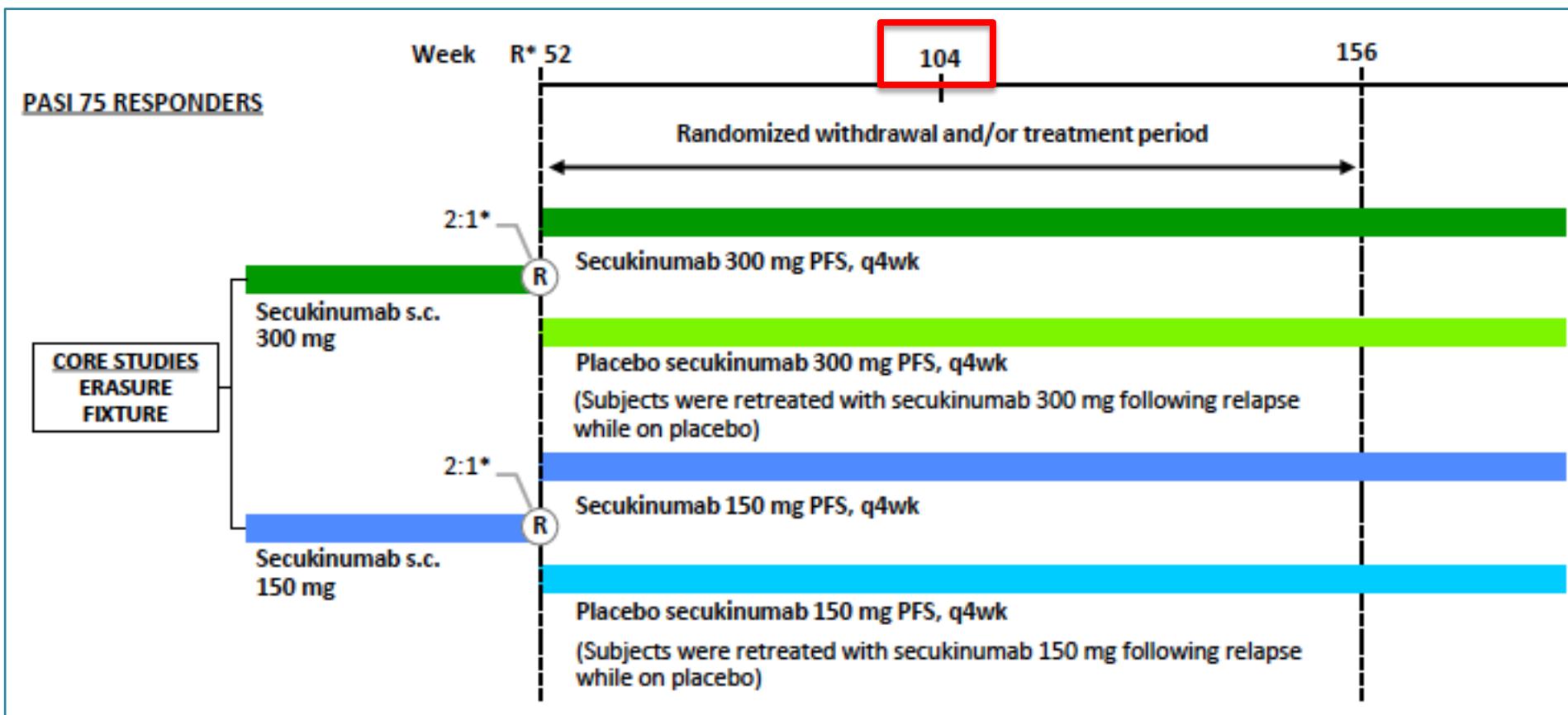
Secukinumab: dati di efficacia a 2 anni

- Estensione FIXTURE ed ERASURE
- 995 pazienti che avevano ottenuto una risposta PASI 75 dopo un anno di terapia (settimana 52) hanno ricevuto secukinumab 300 mg, secukinumab 150 mg o placebo per un altro anno (settimana 104)¹⁰. Dopo due anni di terapia, 7 pazienti su 10 (71%) trattati con secukinumab 300 mg hanno ottenuto una risoluzione PASI 90; 4 su 10 (44%) una risoluzione PASI 100 e quasi 9 su 10 (88%) hanno mantenuto una risposta PASI 75.

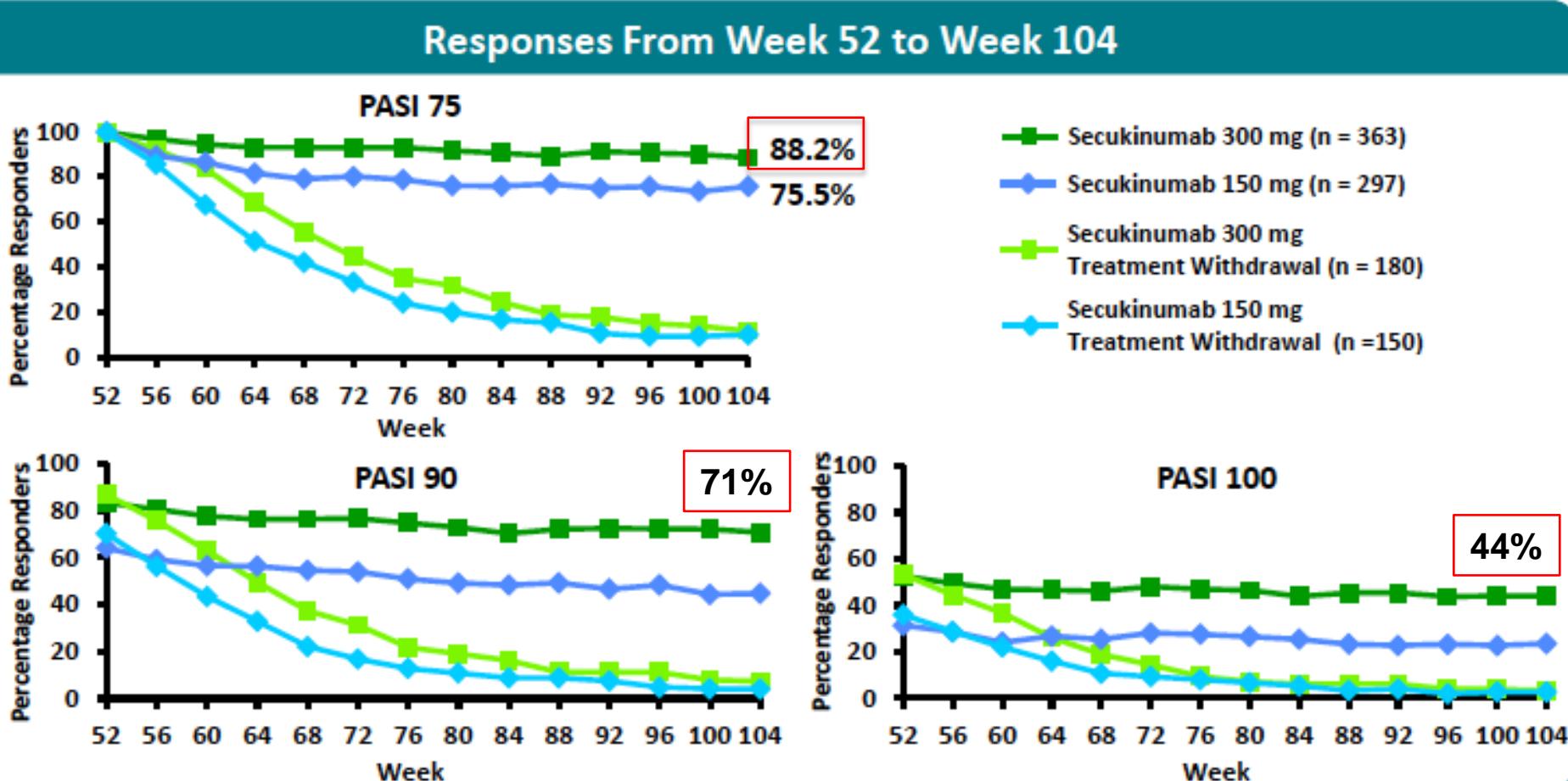
EXTENSION STUDY DESIGN - 2-year analysis

Objective of the 2-year analysis

To assess efficacy and safety/tolerability to week 104 in patients with PASI75 response at week 52 of the ERASURE AND FIXTURE studies



Secukinumab sustained efficacy to 2 years



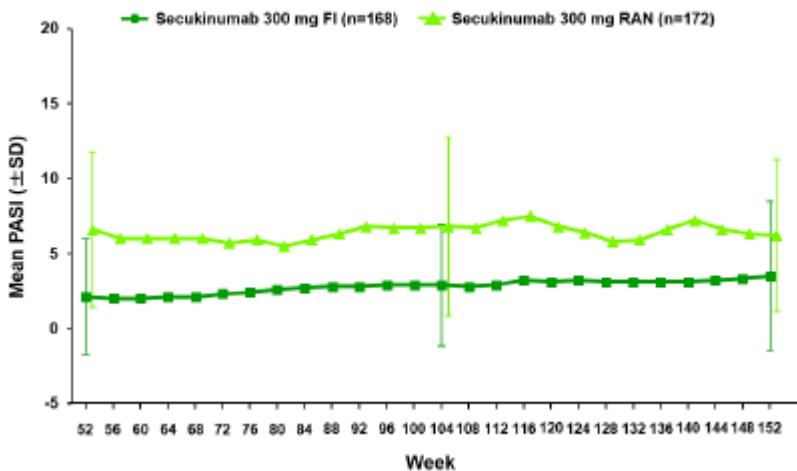
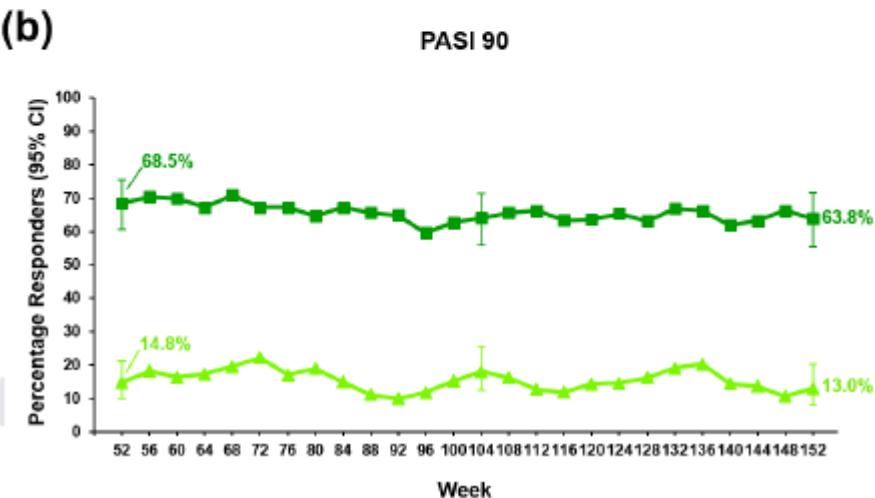
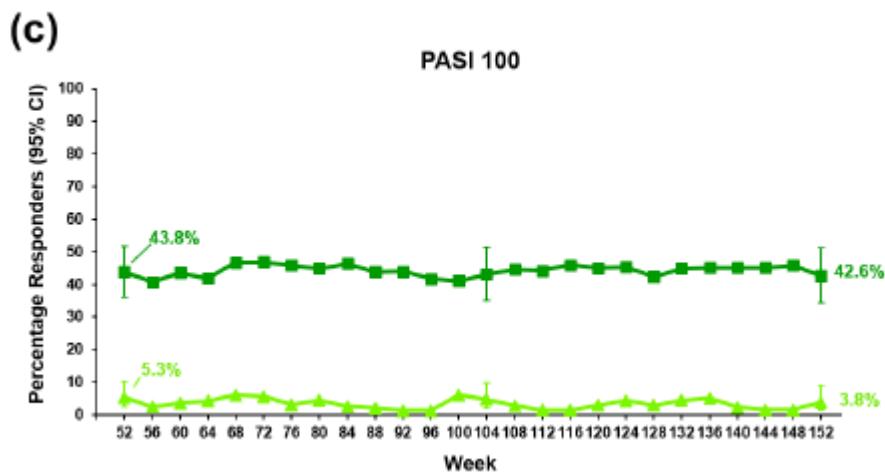
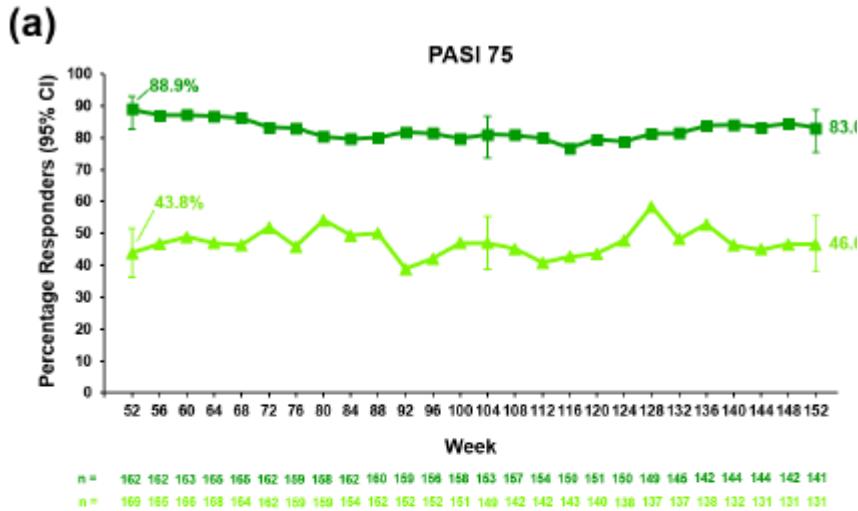
Multiple imputation was used to handle missing data in the treatment groups that continued secukinumab every four weeks; in the treatment-withdrawal groups non-responder imputation was used.

n, number of evaluable subjects; PASI, Psoriasis Area and Severity Index; PASI 75/90/100, $\geq 75\%/\geq 90\%/100\%$ improvement in Baseline PASI score.

*A loss of >50% of the maximum PASI gain compared to the baseline of the core studies.

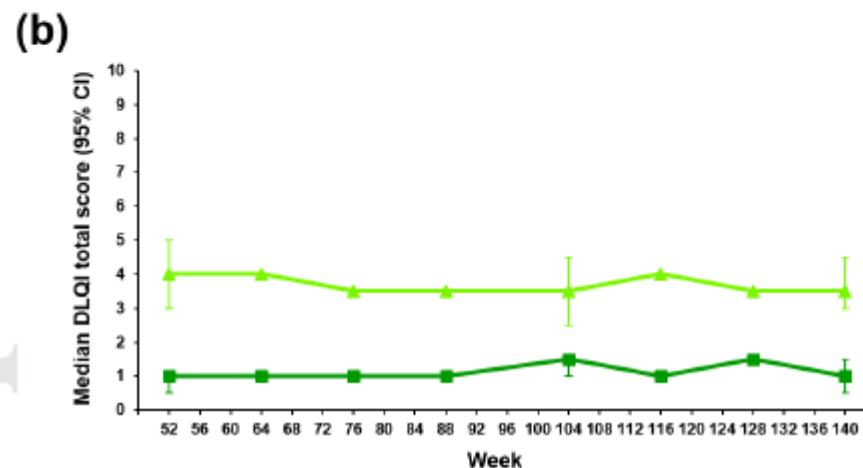
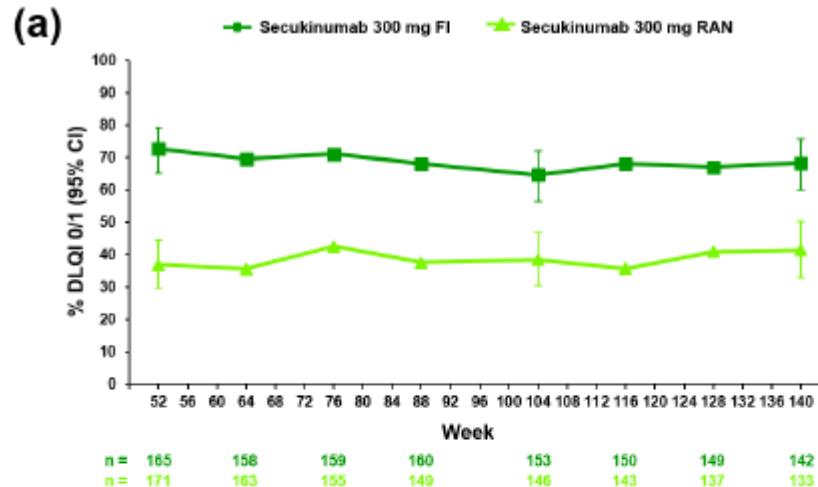
Secukinumab Sustains Good Efficacy and Favourable Safety in Moderate to Severe Psoriasis up to 3 Years of Treatment: Results from A Double-Blind Extension Study

R. Bissonnette,¹ T. Luger,² D. Thaçi,³ D. Toth,⁴ I. Messina,⁵ R. You,⁶ A. Guana,⁵ T. Fox,⁷ C. Papavassilis,⁷ I. Gilloteau,⁷ U. Mrowietz⁸



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Ambulatorio Psoriasis Policlinico «A.Gemelli»

Totale pazienti	42 pazienti
Sesso M/F	29/13
Età media (anni)	50 ± 11
BMI medio (Kg/m²)	27,5 ± 3,8
Artrite Psoriasica	15/42 (35%)
Pazienti naive/non naive	13/29

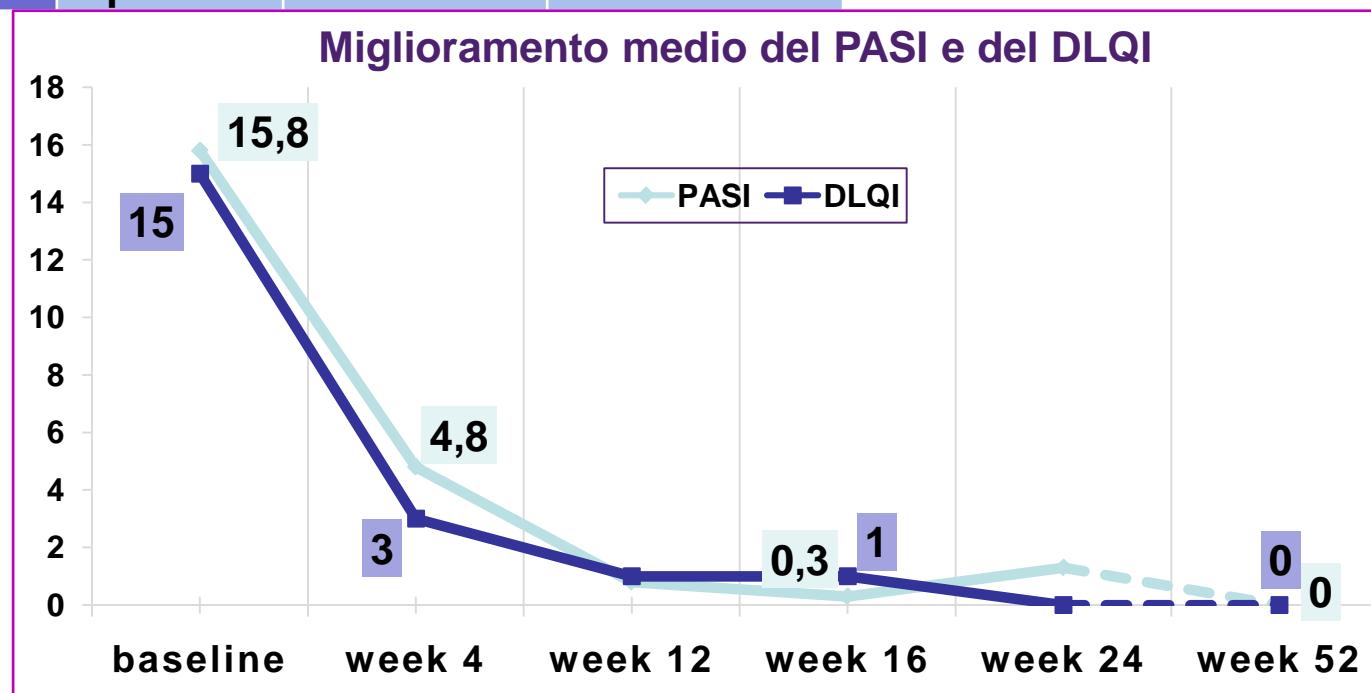
COMORBIDITA'	
Totale pazienti	20/42 (47%)
Ipertensione e/o pat. cardiovascolari	9
Dislipidemia	9
Diabete	2
Epatite B (pregressa /cronica)	2
Altro (tireopatia, s. ansioso-depressiva)	9

PASI medio al baseline	15,8
DLQI medio al baseline	15

	Totale pazienti	PASI medio	PASI ≥ 90
Baseline		15,8 \pm 14,1	-
week 4	42 pz	4,8 \pm 1,4	35%
week 12	31 pz	0,8 \pm 0,1	67%
week 16	23 pz	0,3 \pm 0,9	82%
week 24	13 pz	1,3 \pm 0,1	77%
week 52	6 pz	0	100%

4 pazienti hanno sospeso il farmaco:

- 1° paziente a 5 settimane per evento avverso
- 2° paziente a 8 settimane per inefficacia primaria
- 3° paziente a 20 settimane per riscontro di nodulo tiroideo
- 4° paziente a 32 settimane per perdita di efficacia





Conclusioni

- Nella nostra esperienza secukinumab ha mostrato **un'efficacia elevata**, caratterizzata da una risposta **PASI 90 nel 67% dei pazienti a 12 settimane e nell'82% dei pazienti a 16 settimane**, raggiunta rapidamente e persistente nel tempo.
- La **rapidità di risposta** è stata osservata sia nei pazienti naive che nei pazienti precedentemente trattati con farmaci biologici
- Il farmaco si è dimostrato efficace e ben tollerato anche nei **pazienti con comorbidità multiple** (47% dei pazienti trattati) e nei pazienti **con BMI elevato**.
- Tra gli effetti collaterali osservati è stata osservata **l'aumentata incidenza di candidosi mucocutanee**, tuttavia solo in un caso è stata necessaria la sospensione del farmaco.