# L'era degli anti-IL17/23

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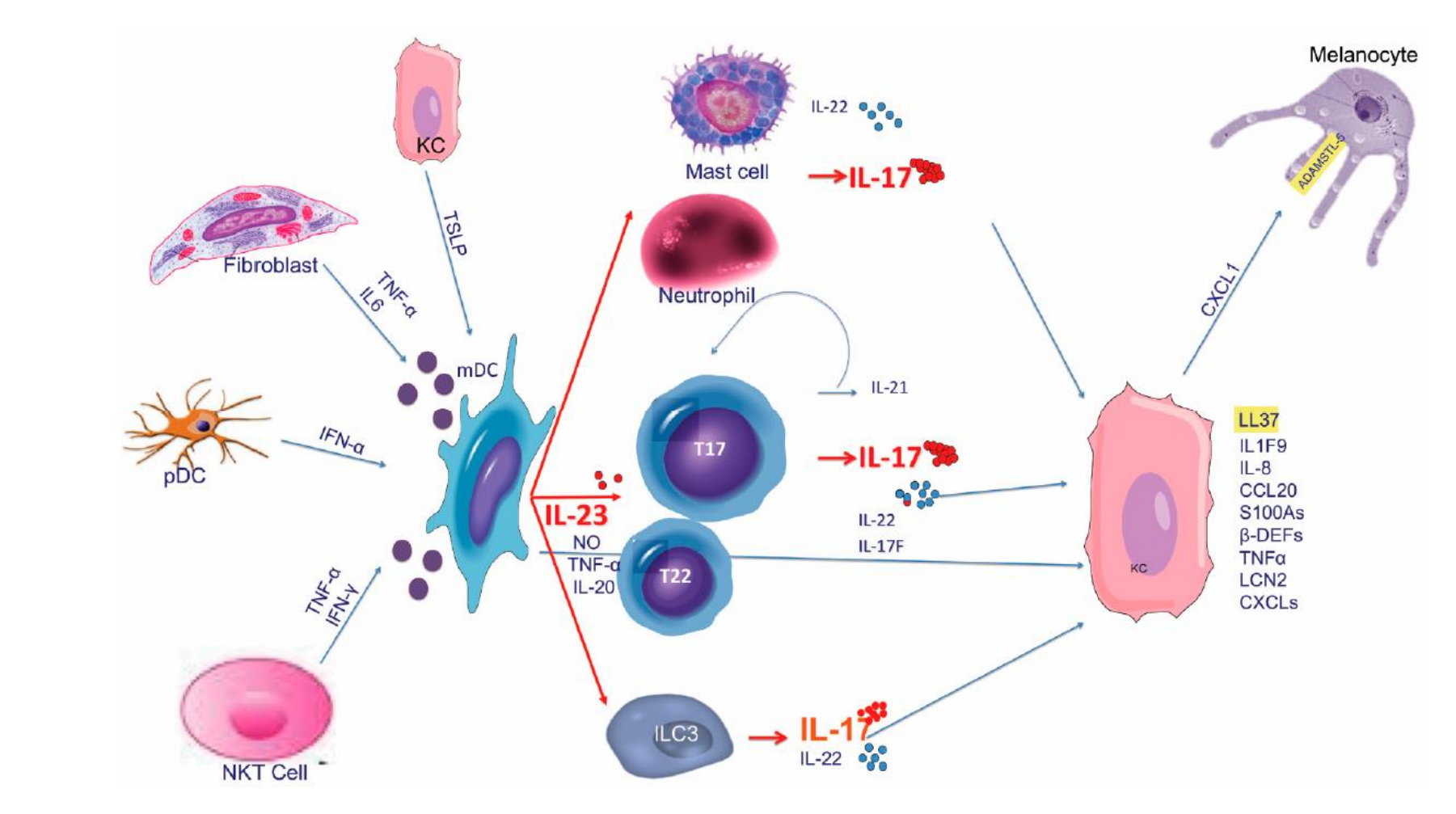
# The pathogenic model of psoriasis based on the IL-23/IL-17 axis

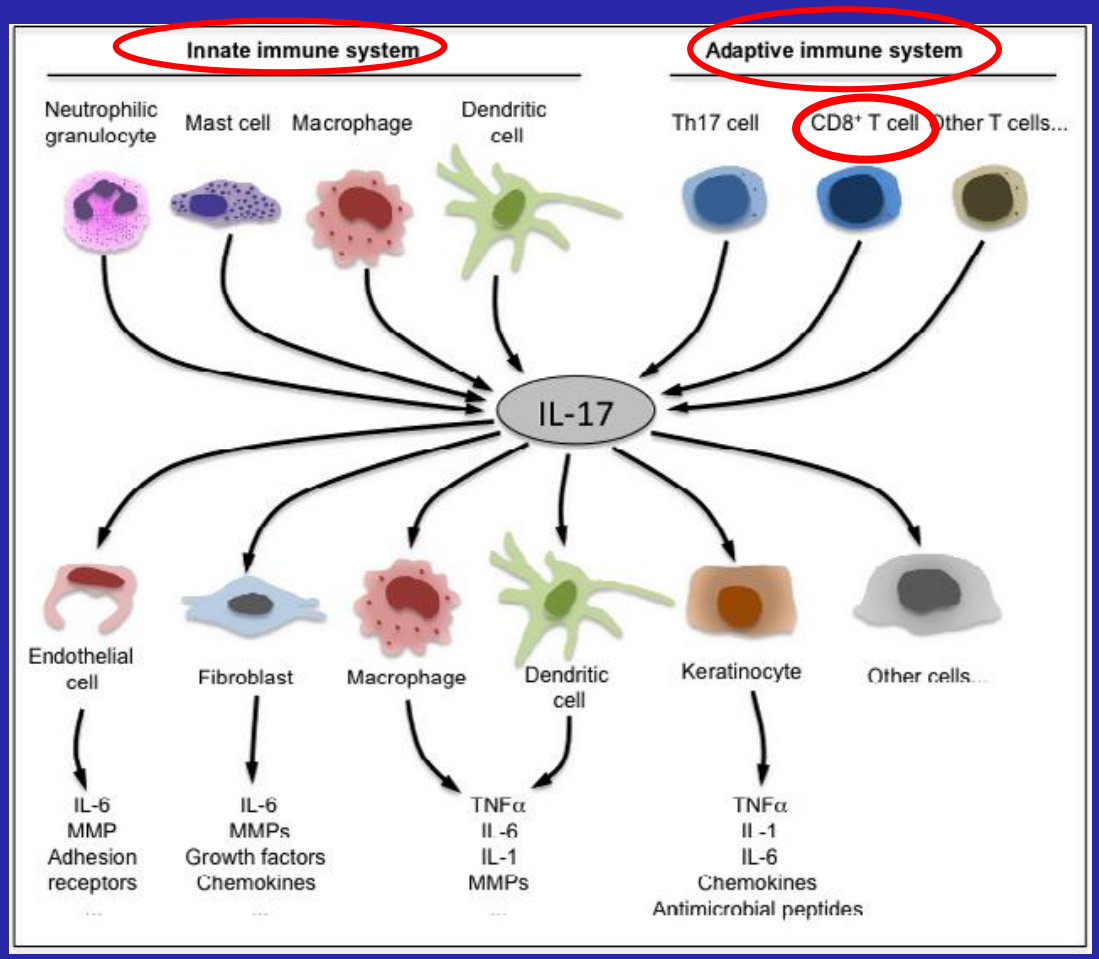



Chiricozzi, Int. J. Mol. Sci. 2018, 19, 179

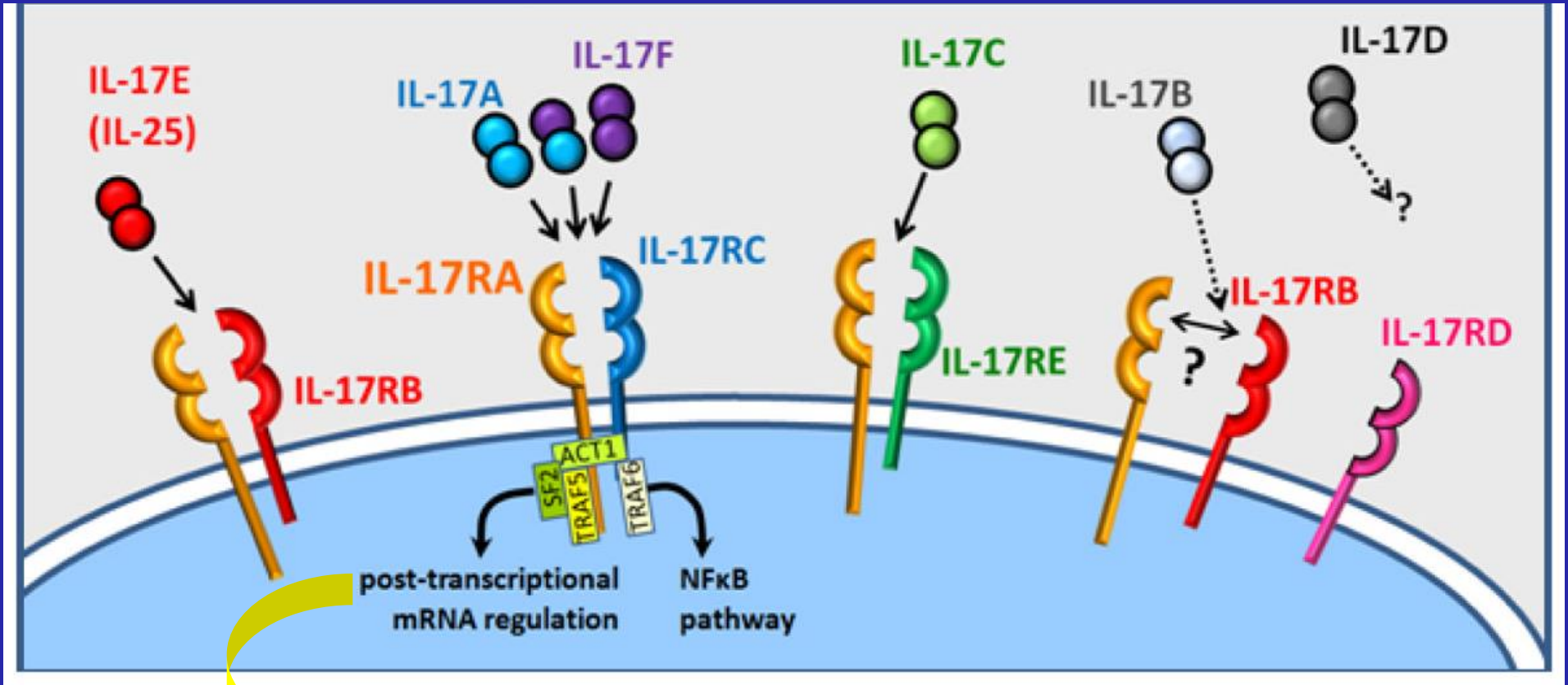
# InterLeuchine 17 (IL-17)

| Ligand | Source | | Receptor |
|---|---|---|---|
| IL-17A | •**Th17 cells**<br>•CD8+ T cells<br>•γδ T cells<br>•NK cells | •NKT cells<br>•LTi cells<br>•Neutrophils | IL-17RA<br>IL-17RC |
| IL-17F | | | |
| IL-17A/IL-17F heterodimer | | | |
| IL-17C | •**Keratinocytes**<br>•Lung epithelial cells | •Colon epithelial cells | IL-17RA<br>IL-17RE |
| IL-17E (IL-25) | •T cells<br>•Intraepithelial lymphocytes<br>•Lung epithelial cells<br>•Cells of the GI tract and uterus | •Eosinophils<br>•Basophils<br>•Mast cells<br>•Alveolar MΦs | IL-17RA<br>IL-17RB |
| IL-17B | Expression and function remain under investigation | | IL-17RB |
| IL-17D | | | Unknown |

# InterLeuchine 17 (IL-17)



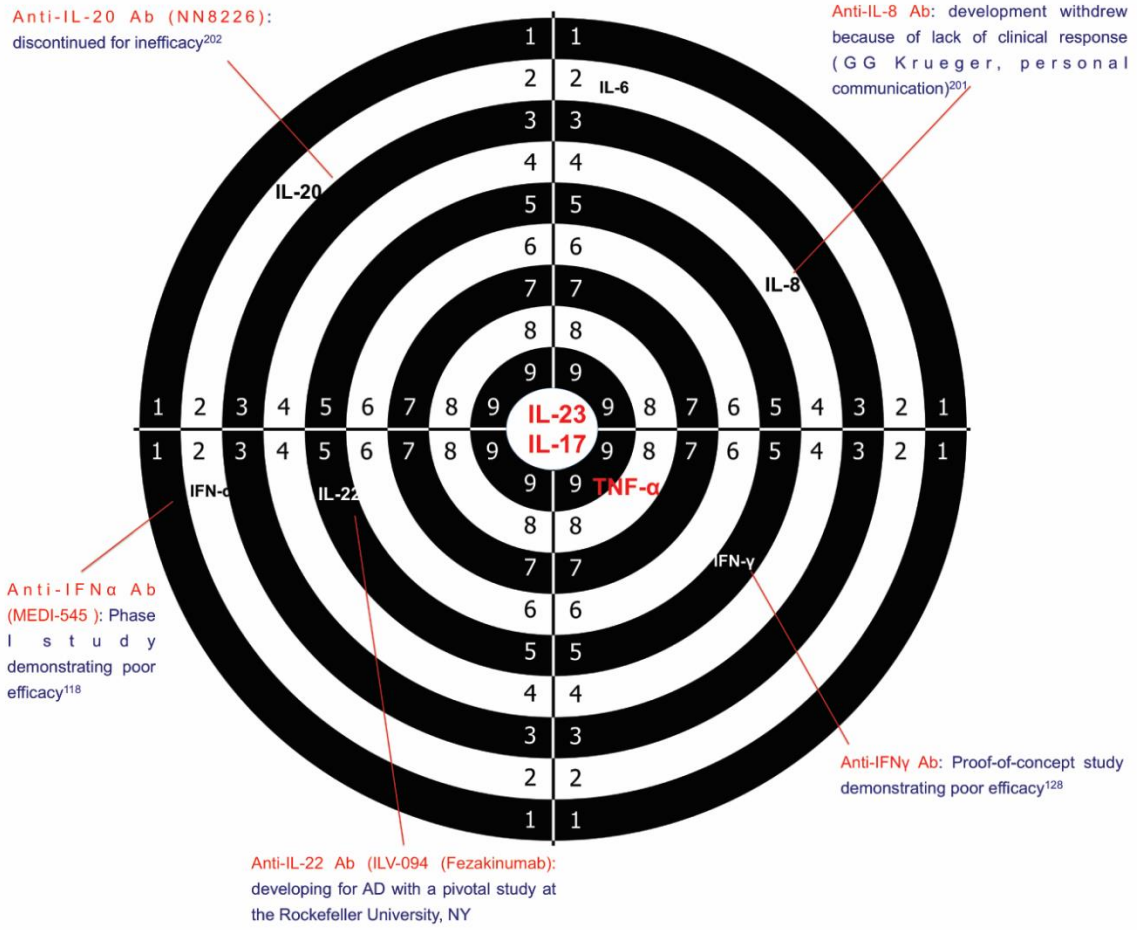
# InterLeuchine 17 (IL-17)




Attivazione del pathway trascrizionale di NF-KB
Attivazione di fattori post-trascrizionali pro-infiammatori

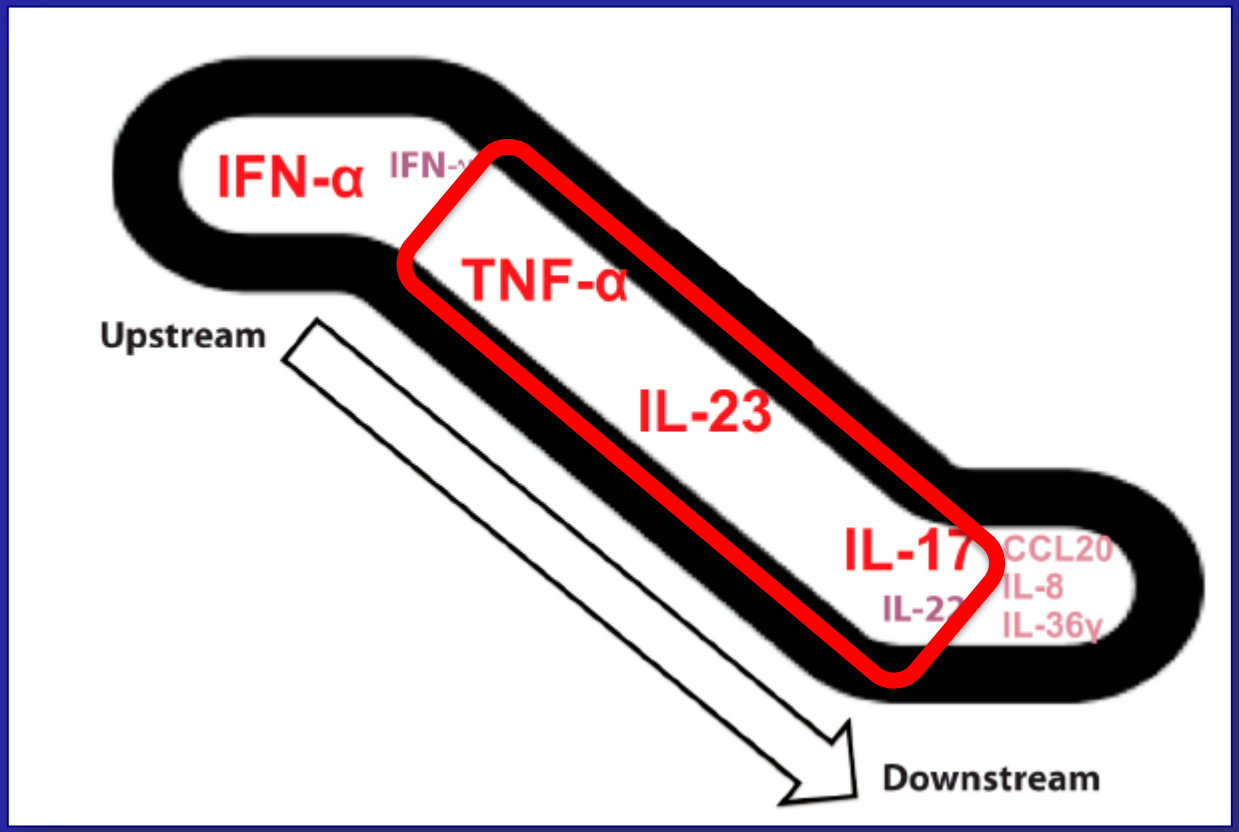
Martin et al., 2013

# Rilevanza terapeutica




Chiricozzi A, et al. Int J Mol Sci 2018

# Target terapeutici nella psoriasi




Chiricozzi A, et al. Int J Mol Sci 2018

# Vantaggio blocco IL-17 over IL-23

- Tanti pathways confluiscono verso un unico effettore che è IL-17.

- Bloccando IL-17 siamo in grado di neutralizzare anche l'IL-17 indotta non da IL-23 ma da IL-1β, per esempio

- Bloccando IL-17, si inibisce la produzione di autoantigeni proteici e di AMP che attivano pDCs a monte di IL-17 (loop amplificatori)

# Agenti bloccanti IL-17 e IL-17R

| Farmaco | Struttura | Meccanismo d'azione | Azienda |
|---|---|---|---|
| Secukinumab | Anticorpo monoclonale IgG1κ completamente umano | Si lega selettivamente a IL-17A neutralizzandola | Novartis |
| Ixekizumab | Anticorpo monoclonale IgG4 umanizzato | Si lega selettivamente a IL-17A neutralizzandola | Eli Lilly |
| Brodalumab | Anticorpo monoclonale IgG2 completamente umano anti-IL-17RA | Inibisce l'attività di IL-17A, IL-17F, IL-17A/F ed IL-17E (IL-25) bloccando il recettore (IL-17RA) | Valeant (USA) LEO Pharma (Europa) Kyowa Hakko Kirin (Giappone) |

# Secukinumab

***Cosentyx®***

EUROPEAN MEDICINES AGENCY
SCIENCE MEDICINES HEALTH

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

Summary of opinion[1] (initial authorisation)

Cosentyx
secukinumab

Indicazioni terapeutiche:

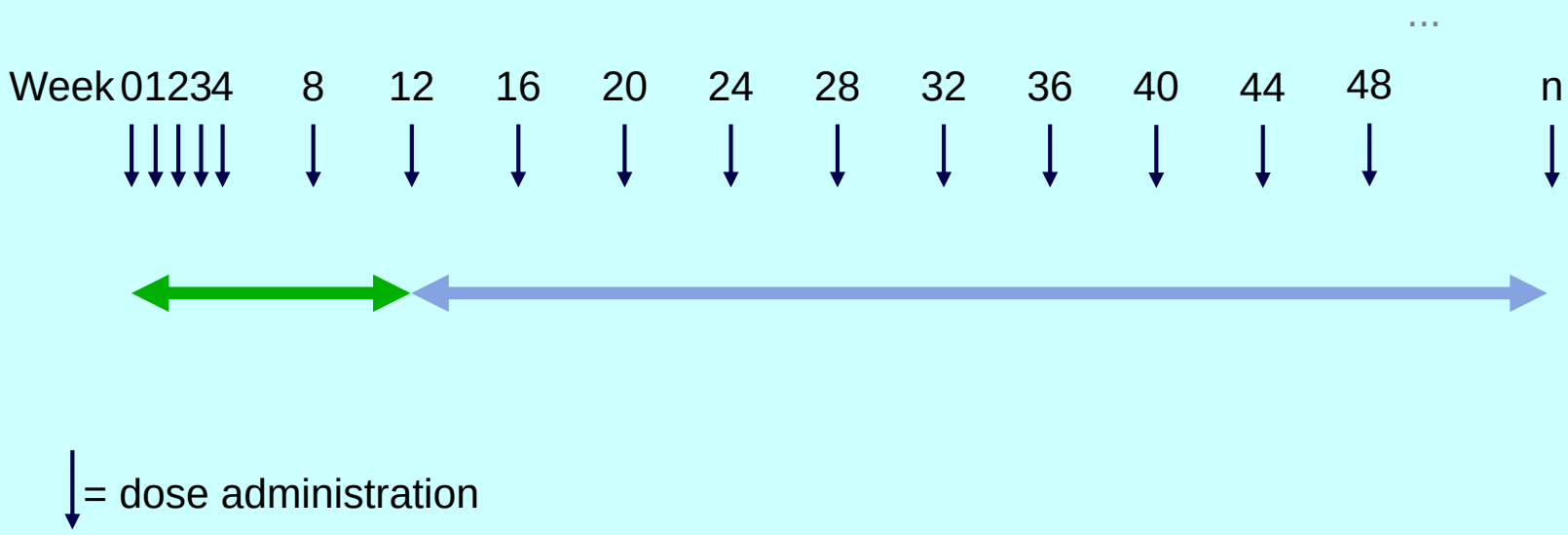
1. *Psoriasi a placche di grado moderato-severo* in pazienti adulti che sono candidati alla terapia sistemica

2. *Artrite psoriasica*: da solo o in associazione con MTX in pazienti adulti quando la risposta a precedente terapia con DMARDs e' risultata inadeguata

3. *Spondilite anchilosante* in adulti con risposta inadeguata alla terapia convenzionale.

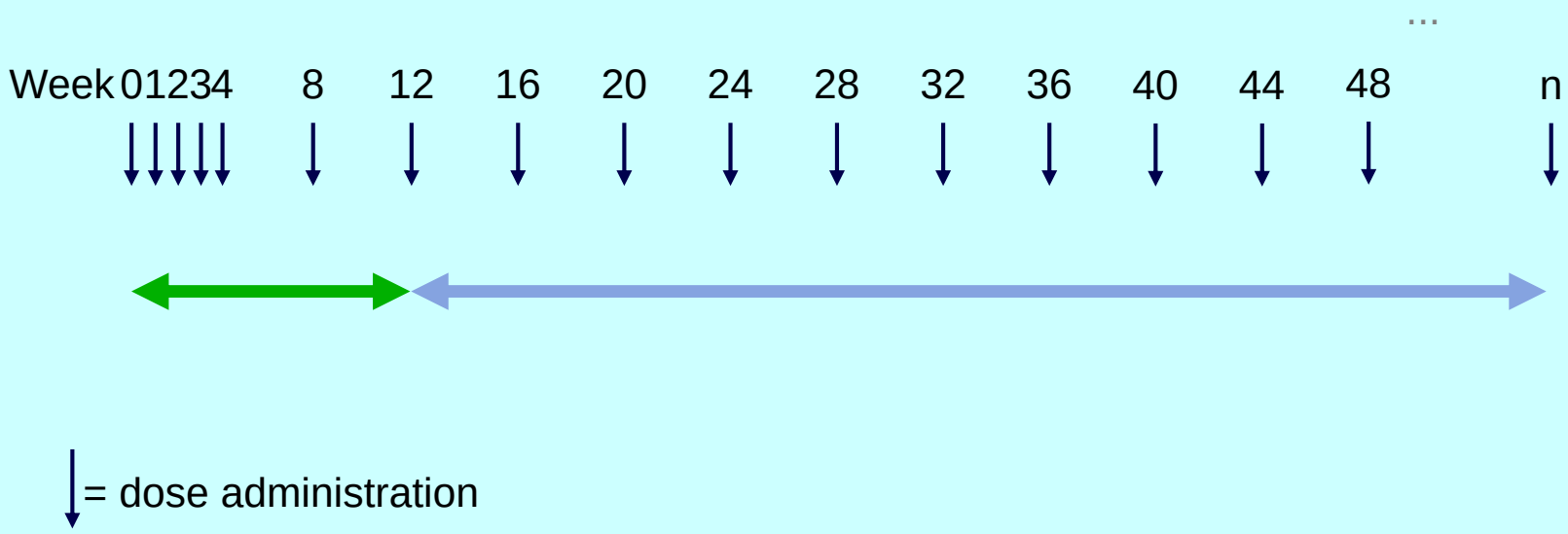
# Secukinumab:
## dosaggio e regime di somministrazione nella psoriasi cronica a placche

**Secukinumab 300 mg s.c**

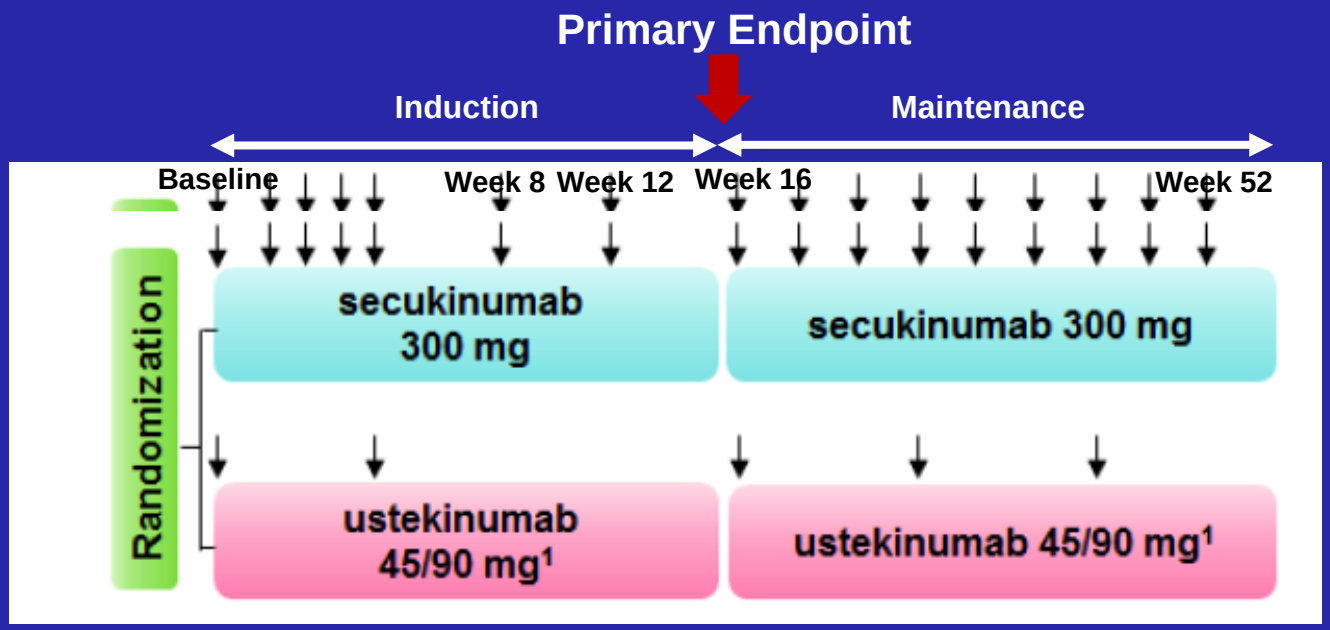


# Secukinumab:
## dosaggio e regime di somministrazione nell'artrite psoriasica

**Secukinumab 300 mg s.c** in pazienti con concomitante PSO mod./sev. o non responder agli anti -TNF
**Secukinumab 150mg s.c**. in tutti gli altri pazienti



# Studio CLEAR
# secukinumab head-to-head versus ustekinumab



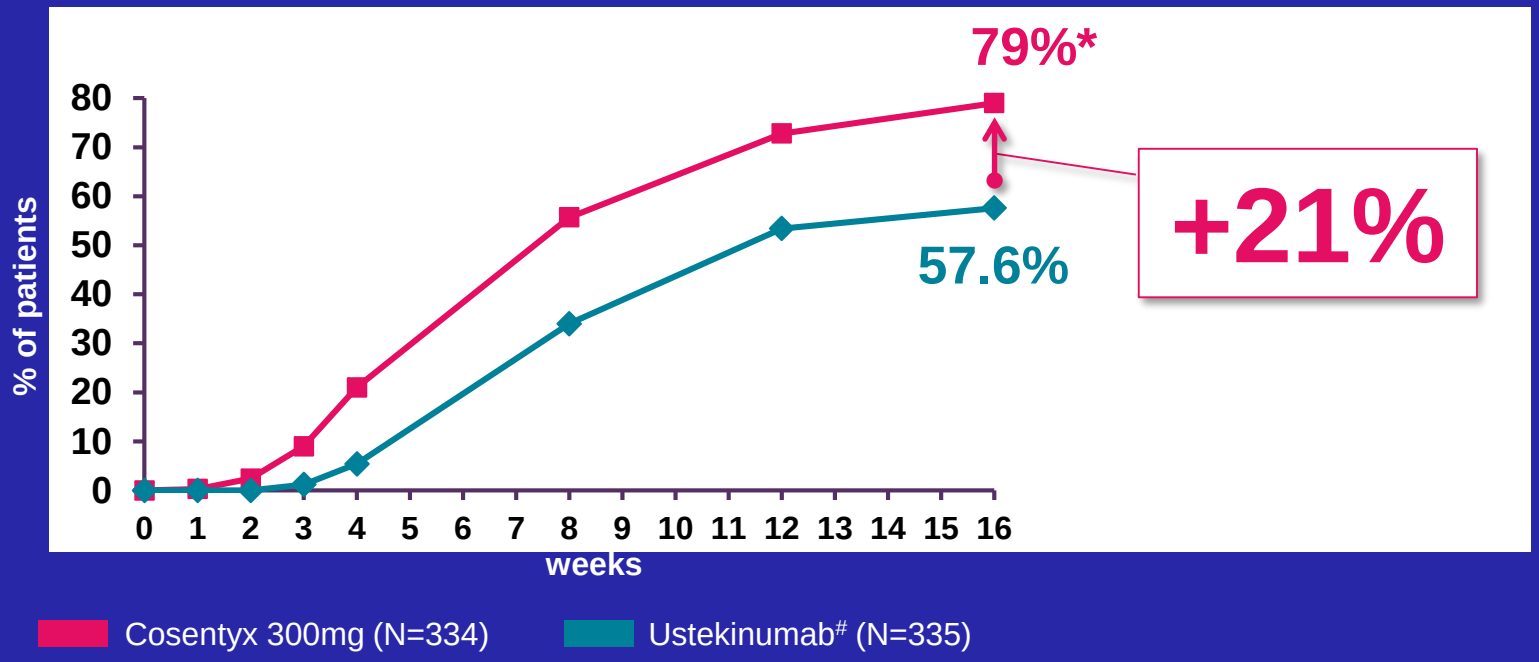

- **Endpoint primario**
  - Superiorità di SEC *vs* UST sul **PASI 90** alla settimana 16
- **Endpoint secondari**
  - Superiorità di SEC *vs* UST sul **PASI 75** alla settimana 4
  - Superiorità di SEC *vs* UST sul **PASI 90** alla settimana 52

1. 45 mg for subjects ≤100 kg at Baseline; 90 mg for subjects >100 kg at Baseline. To maintain blinding, placebo injections matching the secukinumab regimen were given to subjects in the ustekinumab group.

Thaci D et al. J Am Acad Dermatol. 2015 Sep;73(3):400-9.

# Studio CLEAR: a 16 week Secukinumab è più efficace di Ustekinumab

**8 pazienti su 10 raggiungono il PASI 90 a 16 settimana:**

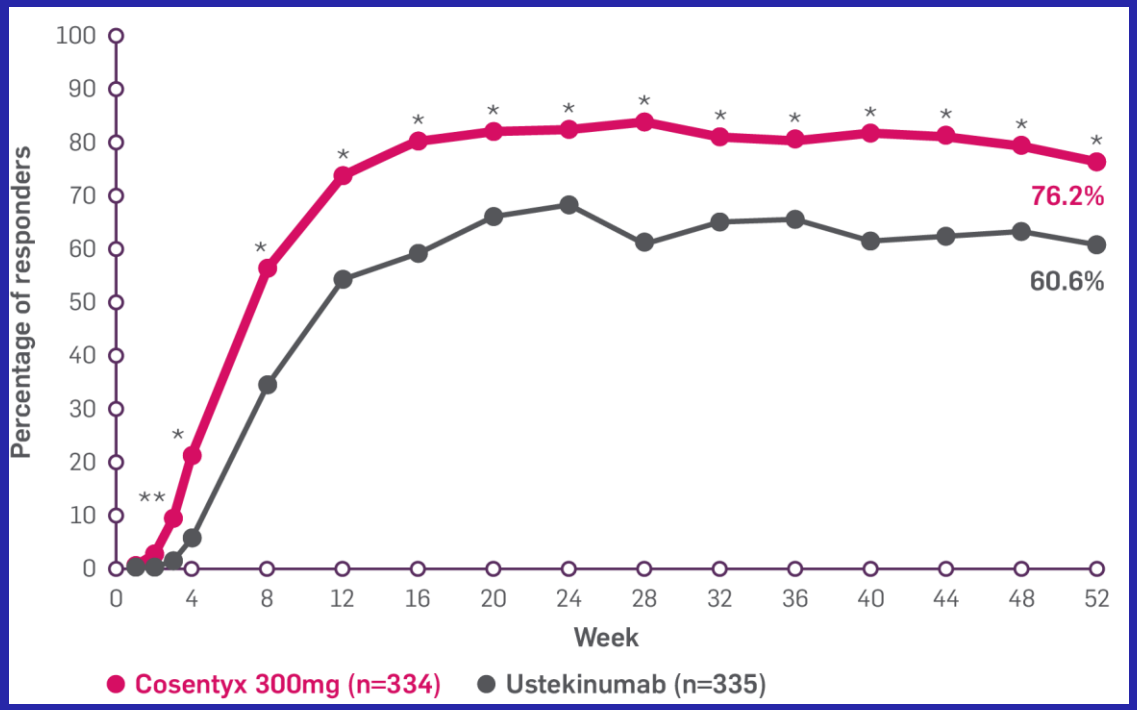



* ***p*<0.0001** Missing data were imputed as nonresponse. Only subjects who could be evaluated for a response were included (subjects who had missed all post-baseline values were excluded for that response variable). # ustekinumab administered with weight based dosing according to label

Thaci D et al. J Am Acad Dermatol. 2015 Sep;73(3):400-9.

# Sustained superior efficacy versus Ustekinumab up to 52 weeks

**CLEAR: PASI 90 response at 52 weeks**




Adapted from Blauvelt A et al. 2016.

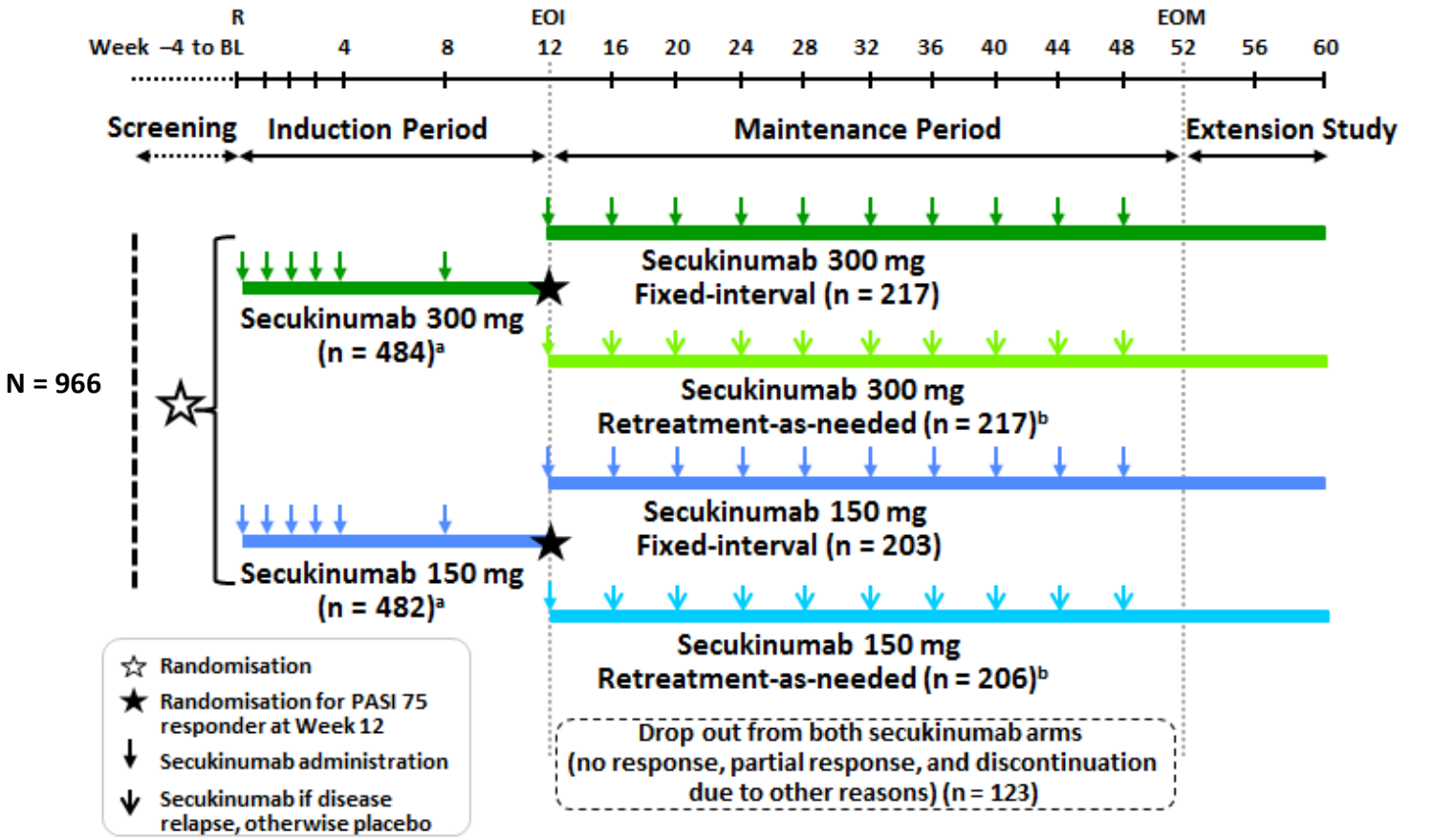
With Secukinumab 300mg at week 52:

- 76.2% of patients achieved PASI 90

- * p<0.0001 vs ustekinumab.
- ** p=0.0001 vs ustekinumab.
- Data from multiple imputation (MI) analysis.

# Studio SCULPTURE

Dimostrare la non inferiorità di un regime di mantenimento “al bisogno” rispetto ad un regime “fisso”




BL, baseline; EOI, end of induction period; EOM, end of maintenance period; PASI 75, ≥75% improvement in Baseline Psoriasis Area and Severity Index score; q4wk, every 4 weeks; R, randomisation. [a]At Baseline and Weeks 1, 2, 3, 4, and 8; [b]Subjects were treated with secukinumab at Week 12 and then at the start of relapse q4wk until they achieved PASI 75 response again.

Fixed-interval dosing occurred once every 4 weeks.

Mrowietz U et al. *J Am Acad Dermatol*. 2015;73:27-36.

# Studio SCULPTURE

48% potenziale perdita di risposta PASI75

77% potenziale perdita di risposta PASI90

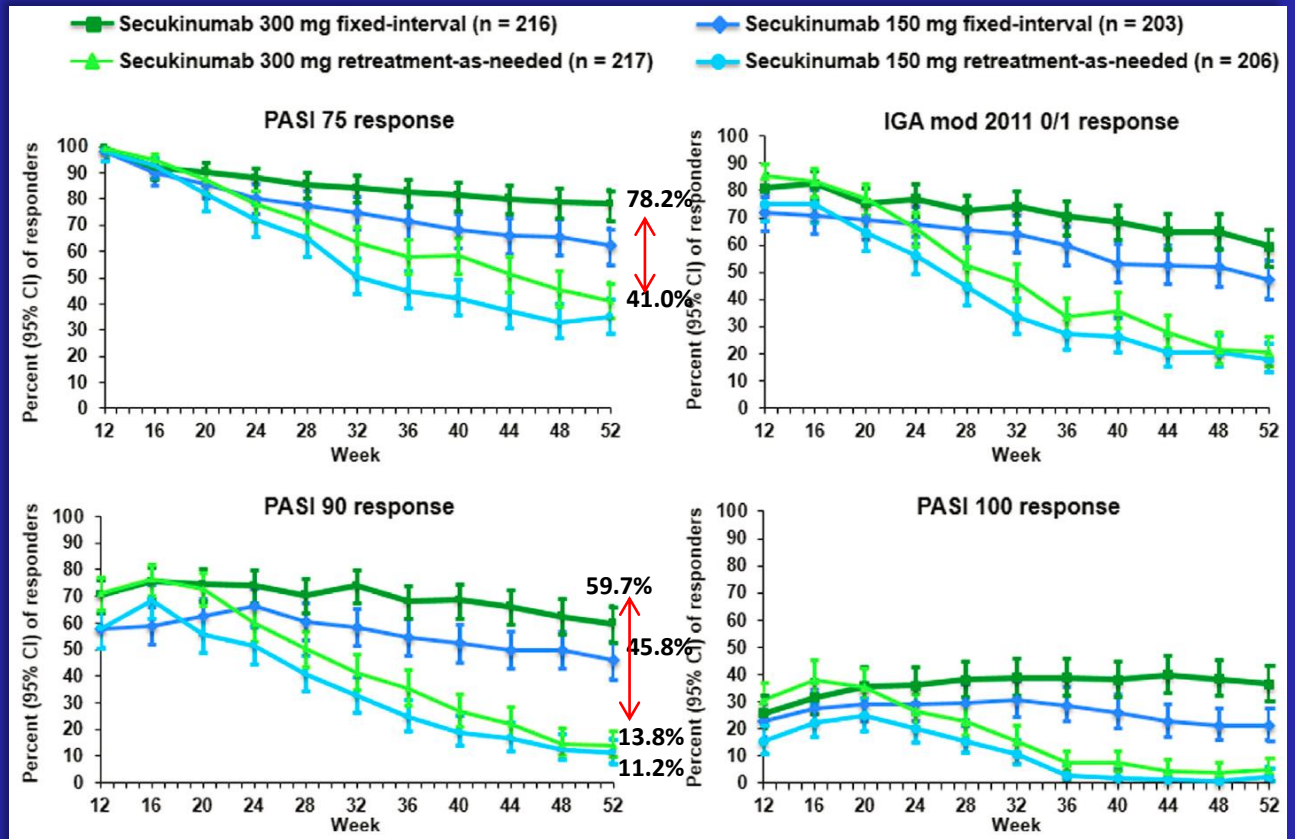
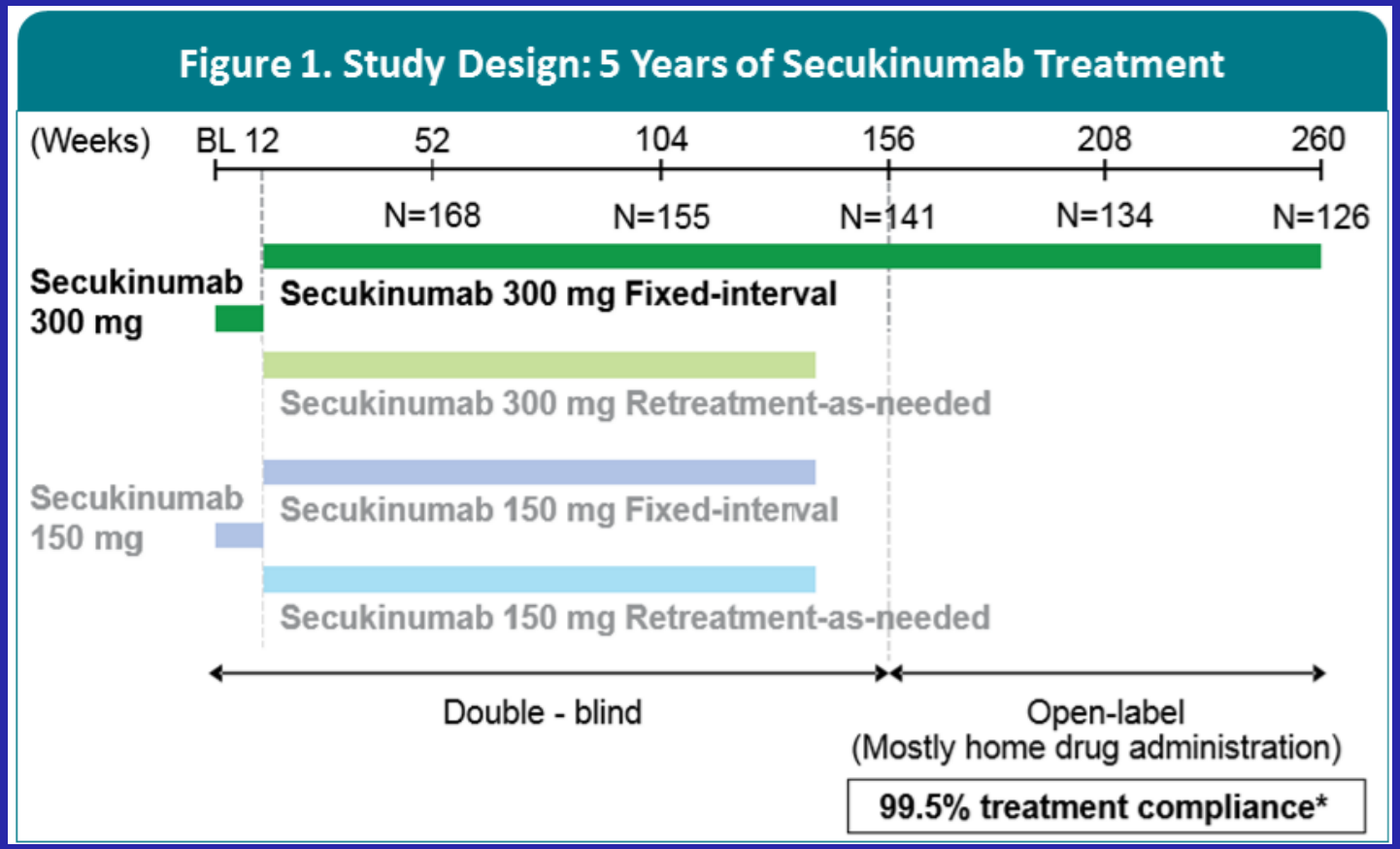



**Fig 5.** Clinical response rates from weeks 12 to 52. Among patients who achieved 75% or more improvement from baseline Psoriasis Area and Severity Index (PASI) score (*PASI 75* response) at week 12, the proportions (95% confidence interval [*CI*]) of patients with PASI 75, investigator global assessment 2011 modified version (*IGA mod 2011*) 0/1, 90% or more improvement from baseline PASI score (*PASI 90*), and 100% improvement from baseline PASI score (*PASI 100*) response during the maintenance period (weeks 12-52) are shown. n = number of evaluable patients.

Mrowietz U, et al., J Am Acad Dermatol, July 2015, Vol 73, N.1

# Secukinumab efficacia mantenuta a 5 anni – Studio SCULPTURE




PASI 75 responders at Wk 12 were re-randomized to either "Fixed-interval" or "Re-treatment as needed" regimens. Fixed-interval dosing occurred once every 4 weeks. Re-treatment-as-needed dosing was at the start of relapse until patients achieved PASI 75 response again.

At Wk 52 all patients rolled over to the extension study. Here we report results of the 300 mg fixed-interval arm. BL, baseline; PASI 75, ≥75% improvement in Baseline Psoriasis Area and Severity Index score; N, number of subjects evaluated at the visit. *% of non-missed self-administrations

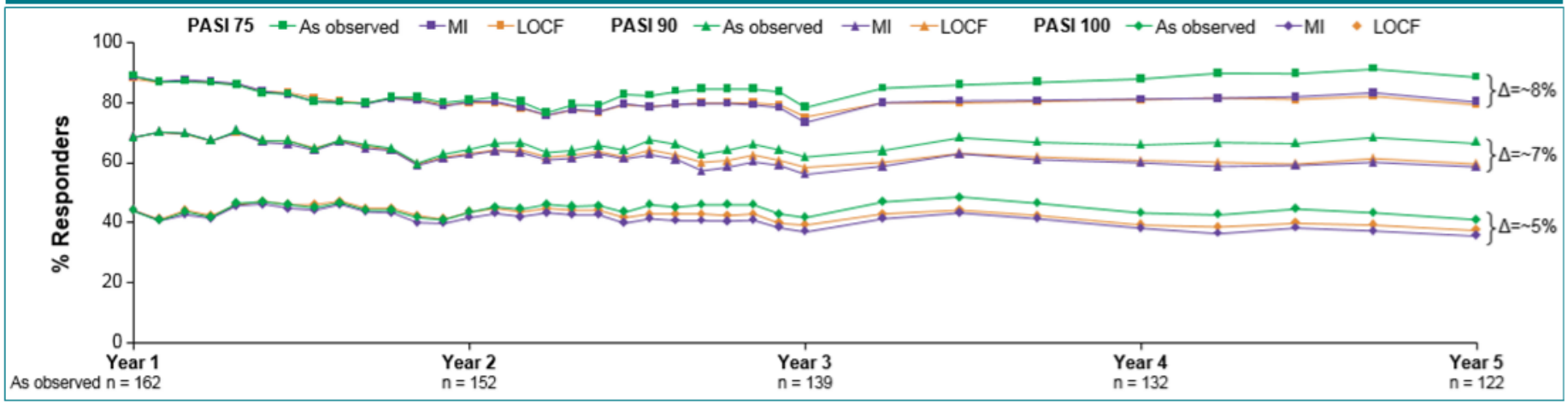
Bissonnette R, et al., J Eur Acad Dermatol Venereol 2018 Feb 14

# Secukinumab efficacia mantenuta a 5 anni – Studio SCULPTURE

Tassi di risposta PASI 75, 90 e 100 sostenuti da 1 anno a 5 anni:

- As observed → 1 anno: 88.9%, 68.5% e 43.8%; a 5 anni:88.5%, 66.4% e 41%
- MI → 1 anno: 88.9%, 68.5% e 43.8%; 5 anni: 80.1%, 58.6% e 35.6%
- LOCF → 1 anno: 88.9%, 68.5% e 43.8%; 5 anni: 79.2%, 59.2% e 37.5%

**Figure 2. Secukinumab Delivers High and Long Lasting Skin Improvement Through 5 Years**




LOCF, last observation carried forward; MI, multiple imputation; n, number of evaluable patients in the as observed analysis (the number of evaluable patients in the MI and LOCF analyses was 168 at each time point); PASI, Psoriasis Area and Severity Index score

Bissonnette R, et al., J Eur Acad Dermatol Venereol 2018 Feb 14

| Treatment emergent AEs[a] | Year 1<br>N = 168<br>168 PY<br>n (IR) | Year 2<br>N = 168<br>162.8 PY<br>n (IR) | Year 3<br>N = 157<br>148.8 PY<br>n (IR) | Year 4<br>N = 142<br>136.5 PY<br>n (IR) | Year 5<br>N = 134<br>142 PY<br>n (IR) |
|---|---|---|---|---|---|
| Any AE(s) | 131 (204.6) | 126 (166.3) | 109 (139.2) | 91 (118.5) | 77 (87.2) |
| Death | 0 (0.0) | 0 (0.0) | 0 (0.0) | 0 (0.0) | 1 (0.7)[b] |
| Non-fatal SAEs | 14 (8.8) | 11 (6.9) | 13 (9.1) | 13 (10.1) | 11 (8.0) |
| Most frequent AEs | | | | | |
| Nasopharyngitis | 30 (20.1) | 27 (18.1) | 25 (18.8) | 17 (13.5) | 15 (11.1) |
| Hypertension | 11 (6.8) | 8 (5.1) | 3 (2.0) | 7 (5.3) | 5 (3.6) |
| Back pain | 7 (4.3) | 9 (5.7) | 9 (6.2) | 3 (2.2) | 3 (2.1) |
| URTI | 12 (7.5) | 11 (7.1) | 5 (3.5) | 5 (3.8) | 5 (3.6) |
| Headache | 10 (6.2) | 7 (4.4) | 4 (2.7) | 3 (2.2) | 1 (0.7) |
| Selected AEs | | | | | |
| Opportunistic infections (other than TB and candidiasis) | 0 (0.0) | 0 (0.0) | 0 (0.0) | 0 (0.0) | 0 (0) |
| Tuberculosis | 0 (0.0) | 0 (0.0) | 0 (0.0) | 0 (0.0) | 0 (0) |
| *Candida* infections | | | | | |
| - Vulvovaginal candidiasis | 3 (1.8) | 3 (1.9) | 1 (0.7) | 0 (0.0) | 0 (0) |
| - Oral candidiasis | 0 (0.0) | 1 (0.6) | 0 (0.0) | 1 (0.7) | 0 (0.0) |
| Neutropenia | 0 (0.0) | 0 (0.0) | 0 (0.0) | 0 (0.0) | 0 (0.0) |
| MACE | 0 (0.0) | 0 (0.0) | 0 (0.0) | 1 (0.7) | 1 (0.7)[b] |
| Inflammatory bowel disease | | | | | |
| Crohn's disease | 0 (0.0) | 0 (0.0) | 0 (0.0) | 0 (0.0) | 0 (0.0) |
| Ulcerative colitis | 0 (0.0) | 2 (1.2)[c] | 1 (0.7) | 0 (0.0) | 0 (0.0) |
| Malignant or unspecified tumors (excl. NMSC) | 0 (0.0) | 2 (1.2)[d] | 0 (0.0) | 0 (0.0) | 1 (0.7)[e] |

# Safety

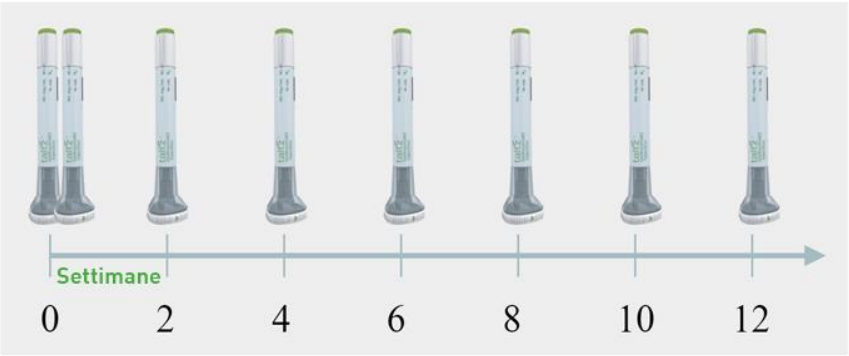
Profilo di efficacia favorevole a 5 anni, senza aumento dell'incidenza di AE negli anni successivi al primo.

9 infezioni da candida in 5 anni

3 casi di colite ulcerosa, di cui 1 esacerbazione di colite ulcerosa presistente

No infezioni opportunistiche, no infezioni tubercolari (nuove o riattivazioni) riportate nel corso dei 5 anni

# Ixekizumab (Taltz)




Dose iniziale:
2 iniezioni (80mg ciascuna)
Prime 12 settimane:
1 iniezione (80mg) ogni 2 settimane

Dopo le prime **12 settimane** di trattamento

1 iniezione (80mg) ogni 4 settimane
Dalla settimana 12, utilizzerà una dose da 80mg (una iniezione) ogni 4 settimane.

Taltz® is indicated for the treatment of moderate to severe plaque psoriasis in adults who are candidates for systemic therapy.

Taltz, alone or in combination with methotrexate, is indicated for the treatment of active psoriatic arthritis in adult patients who have responded inadequately to, or who are intolerant to one or more disease-modifying anti-rheumatic drug (DMARD) therapies.”

# Ixekizumab

## UNCOVER-2 and UNCOVER-3

- Due studi multicentrici di fase III, hanno valutato la sicurezza e l'efficacia di ixekizumab rispetto a etanercept e placebo.
- I pazienti (1224 pazienti UNCOVER-2 e 1346 a UNCOVER-3) sono stati randomizzati a ricevere:

✓ placebo

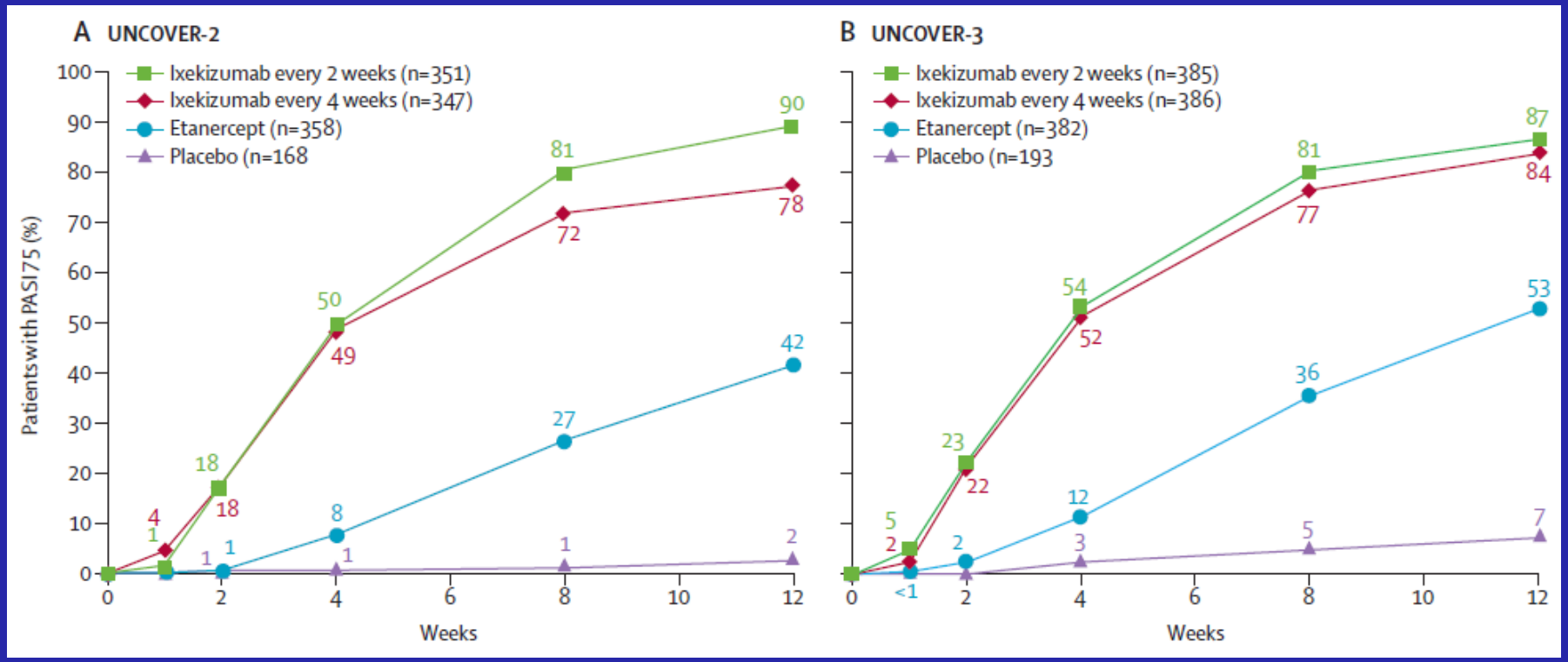
✓ etanercept 50 mg due volte a settimana

✓ ixekizumab 80 mg ogni 2 settimane
✓ ixekizumab 80 mg ogni 4 settimane

dopo una dose iniziale di 160 mg

*Griffiths CE et al. Lancet. 2015 Aug*

# Ixekizumab: UNCOVER-2 and UNCOVER-3 PASI-75 a week 12

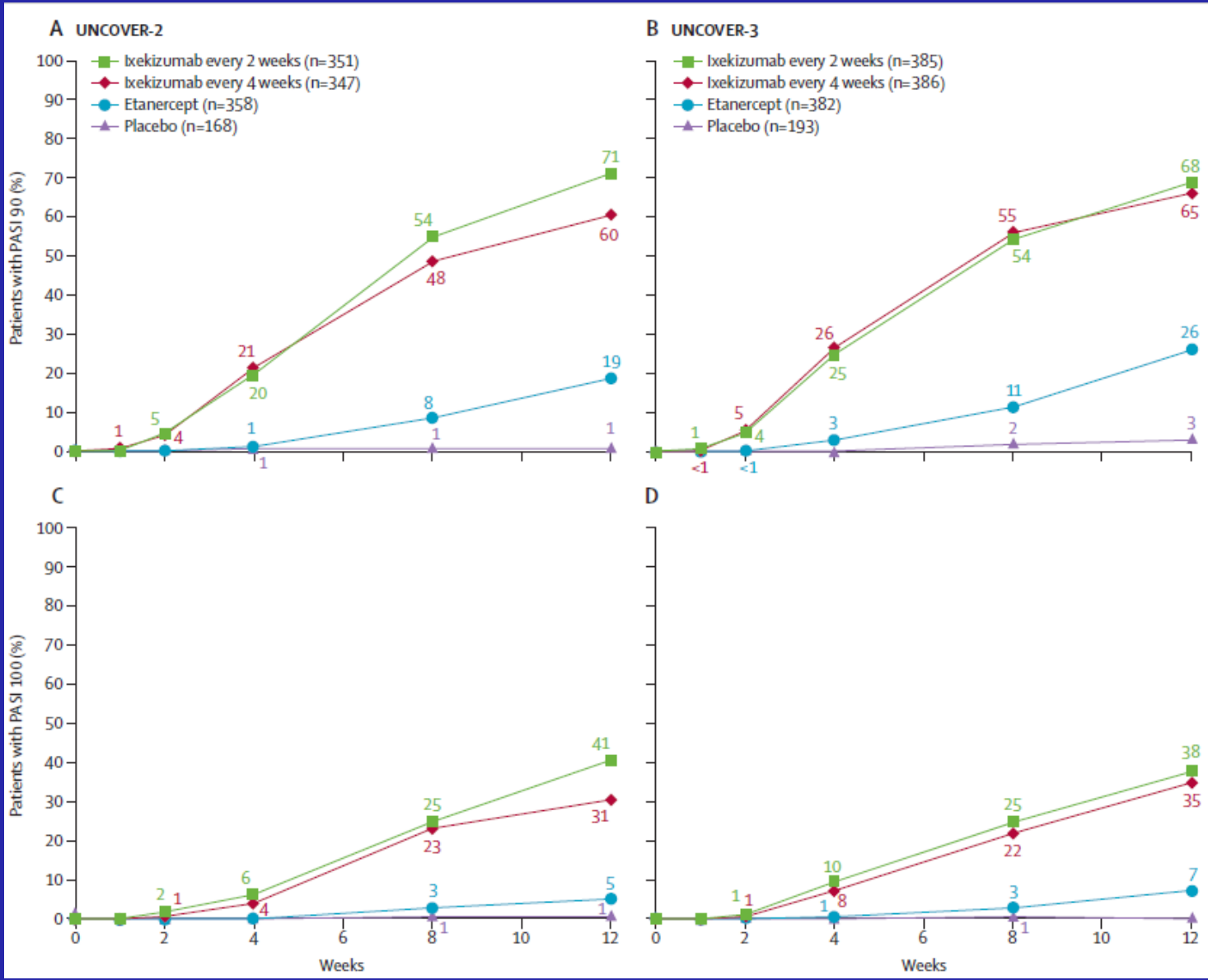



- 89.7% (ixekizumab 80 mg Q2W)
- 77.5% (ixekizumab 80 mg Q4W)
- 41.6% etanercept
- 2.4% (placebo)

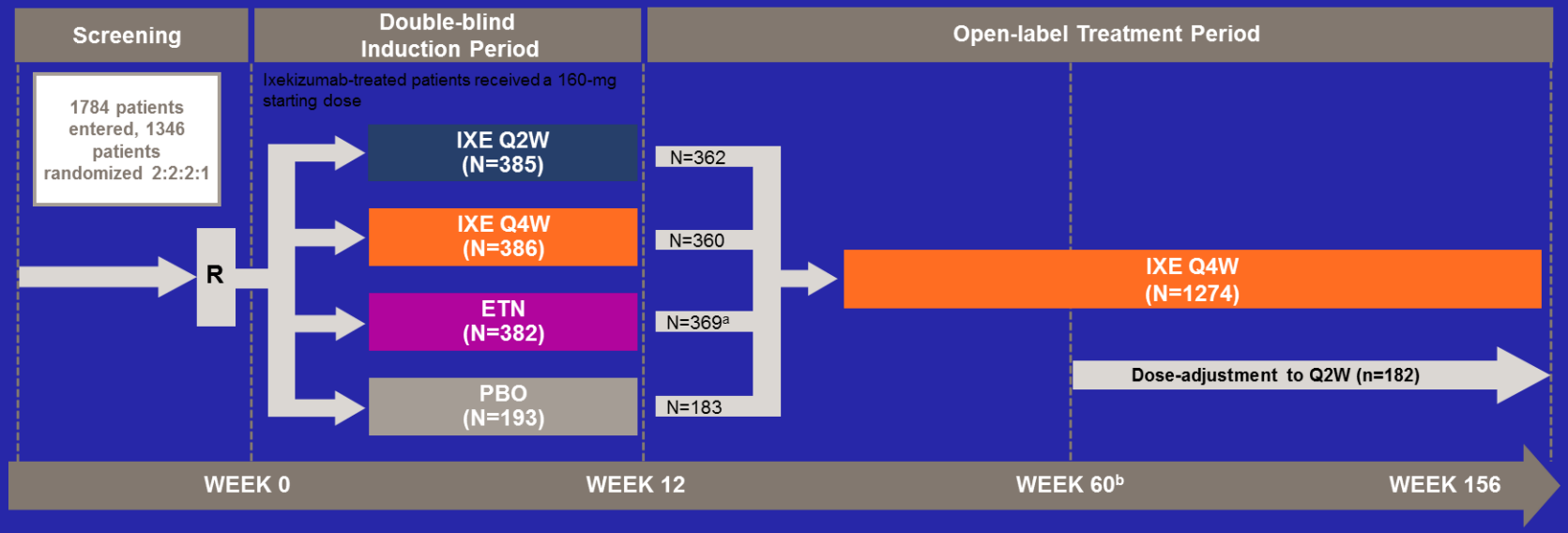
- 87.3% (ixekizumab 80 mg Q2 W)
- 84.2% (ixekizumab 80 mg Q4 W)
- 53.4% etanercept
- 7.3% (placebo)

*Griffiths CE et al. Lancet. 2015 Aug*

# Ixekizumab: UNCOVER-2 and UNCOVER-3
## PASI-90 e PASI-100 a week 12



# UNCOVER-3




**IXE Q2W:** 80 mg IXE every 2 weeks

**IXE Q4W:** 80 mg IXE every 4 weeks

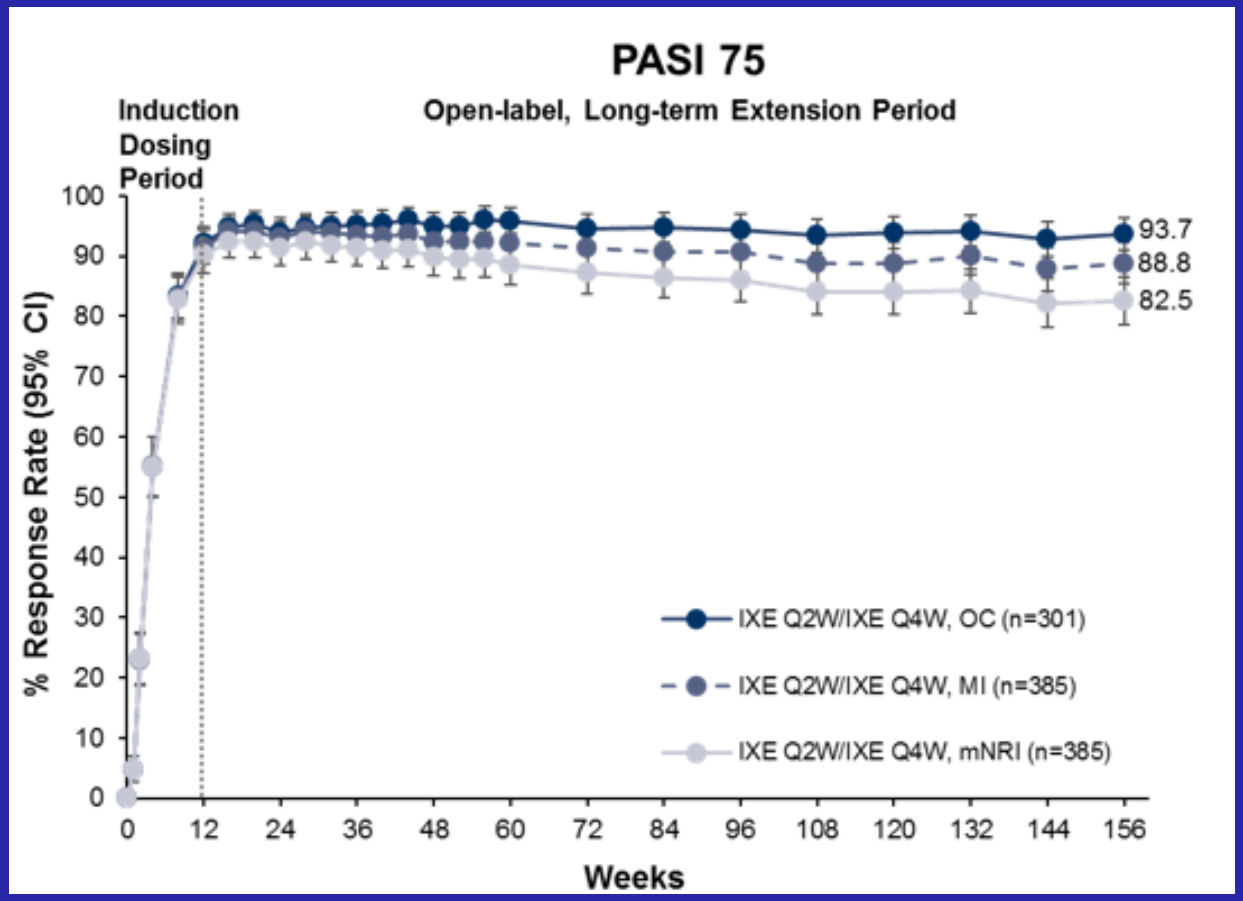
**ETN:** 50 mg ETN twice weekly

**PBO:** Placebo

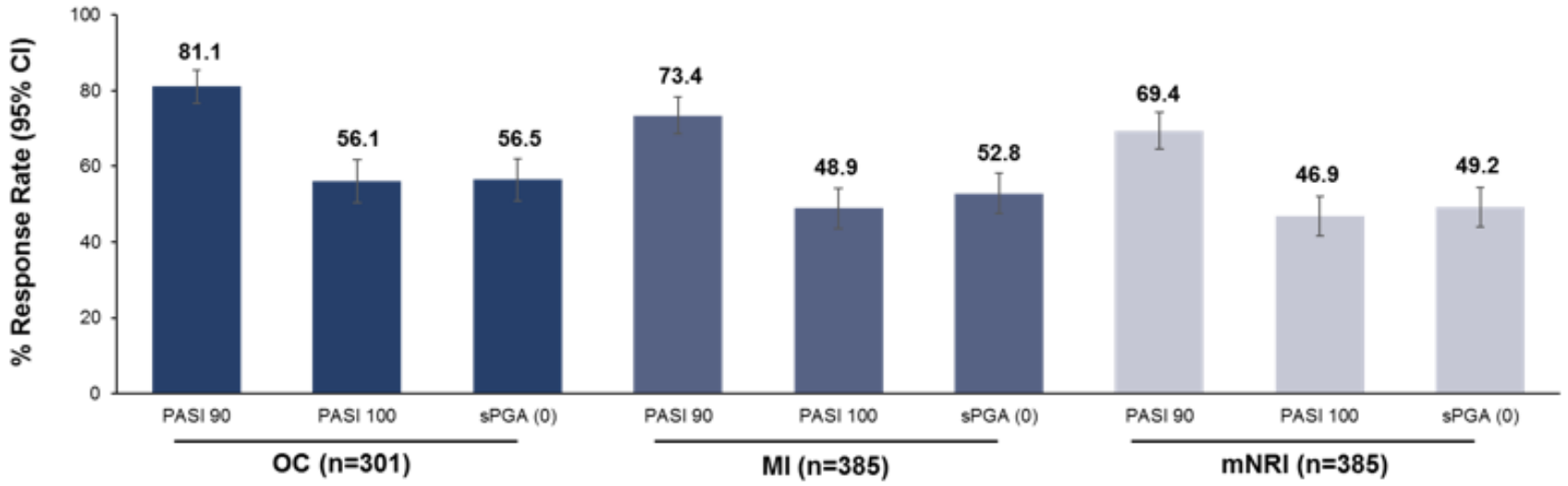
[a] Patients who were administered etanercept during the induction period did not receive IXE until Week 16 to allow for washout; [b] At Week 60, dose could be adjusted to IXE Q2W until the end-of-study at the investigator's discretion

*ETN=etanercept; IXE=ixekizumab; PBO=placebo; R=randomization*

# UNCOVER-3 EFFICACIA A 3 ANNI



# UNCOVER-3 EFFICACIA A 3 ANNI




PASI and sPGA and response rates at Week 156 for the IXE Q2W/IXE Q4W dosing regimen. Error bars represent 95% CI

*CI=confidence interval; IXE Q2W=80 mg ixekizumab every 2 weeks; IXE Q4W=80 mg ixekizumab every 4 weeks; IXE Q2W/IXE Q4W=IXE Q2W during induction then IXE QW4 during LTE; LTE=long-term extension; MI=multiple imputation; mNRI=modified non-responder imputation; OC=observed cases; PASI=Psoriasis Area and Severity Index; PASI 90=Psoriasis Area and Severity Index 90% Response; PASI 100=Psoriasis Area and Severity Index 100% Response; sPGA=static Physician's Global Assessment*

# UNCOVER-3 SAFETY

| n, (%) | PBO/IXE Q4W (N=183) | ETN/IXE Q4W (N=369) | IXE Q4W/IXE Q4W (N=360) | IXE Q2W/IXE Q4W (N=362) |
|---|---|---|---|---|
| Patients with ≥1 treatment-emergent AE | 162 (88.5) | 321 (87.0) | 311 (86.4) | 318 (87.8) |
| Mild | 38 (20.8) | 100 (27.1) | 86 (23.9) | 95 (26.2) |
| Moderate | 88 (48.1) | 159 (43.1) | 164 (45.6) | 181 (50.0) |
| Severe | 36 (19.7) | 62 (16.8) | 61 (16.9) | 42 (11.6) |
| Serious AEs | 35 (19.1) | 57 (15.4) | 57 (15.8) | 39 (10.8) |
| Discontinuation due to AEs | 15 (8.2) | 29 (7.9) | 30 (8.3) | 23 (6.4) |
| Death | 2 (1.1) | 2 (0.5) | 1 (0.3) | 2 (0.6) |
| Most common AEs | | | | |
| Viral upper respiratory tract infection | 53 (29.0) | 104 (28.2) | 91 (25.3) | 103 (28.5) |
| Upper respiratory tract infection | 16 (8.7) | 29 (7.9) | 40 (11.1) | 32 (8.8) |
| Injection-site reaction | 17 (9.3) | 24 (6.5) | 32 (8.9) | 23 (6.4) |
| Candida infection | 9 (4.9) | 15 (4.1) | 22 (6.1) | 13 (3.6) |
| Crohn's disease | 1 (0.5) | 1 (0.3) | 2 (0.6) | 0 |
| Ulcerative colitis | 1 (0.5) | 1 (0.3) | 1 (0.3) | 1 (0.3) |
| Neutropenia, grade 3 or worse[a] | 1 (0.5) | 3 (0.8) | 4 (1.1) | 0 |

- Infections remained the most commonly observed adverse events (AEs), and the majority of treatment-emergent AEs during the extension period continued to be mild or moderate in severity

[a] Percentages for neutropenia were calculated based on the number of patients with a baseline and at least 1 post-baseline neutrophil count (PBO/IXE Q4W=182, ETN/IXE Q4W=368, IXE Q4W/IXE Q4W=357, IXE Q2W/Q4W=362)

*AE=adverse event; ETN=etanercept; IXE Q2W=80 mg ixekizumab every 2 weeks; IXE Q4W=80 mg ixekizumab every 4 weeks; LTE=long-term extension; PBO=placebo*

The NEW ENGLAND JOURNAL of MEDICINE

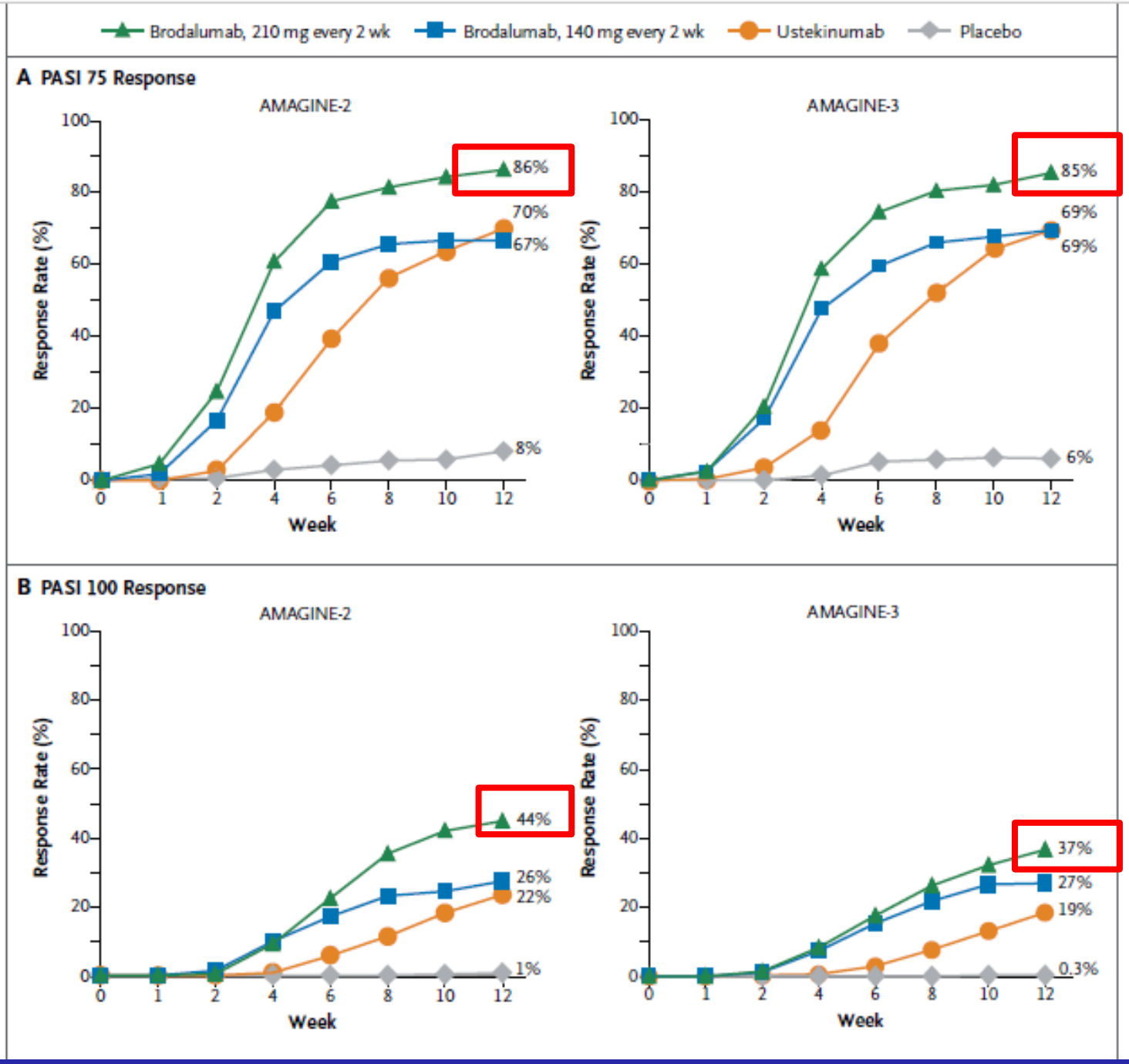
ORIGINAL ARTICLE

# Phase 3 Studies Comparing Brodalumab with Ustekinumab in Psoriasis

M. Lebwohl, B. Strober, A. Menter, K. Gordon, J. Weglowska, L. Puig, K. Papp, L. Spelman, D. Toth, F. Kerdel, A.W. Armstrong, G. Stingl, A.B. Kimball, H. Bachelez, J.J. Wu, J. Crowley, R.G. Langley, T. Blicharski, C. Paul, J.-P. Lacour, S. Tyring, L. Kircik, S. Chimenti, K.C. Duffin, J. Bagel, J. Koo, G. Aras, J. Li, W. Song, C.E. Milmont, Y. Shi, N. Erondu, P. Klekotka, B. Kotzin, and A. Nirula

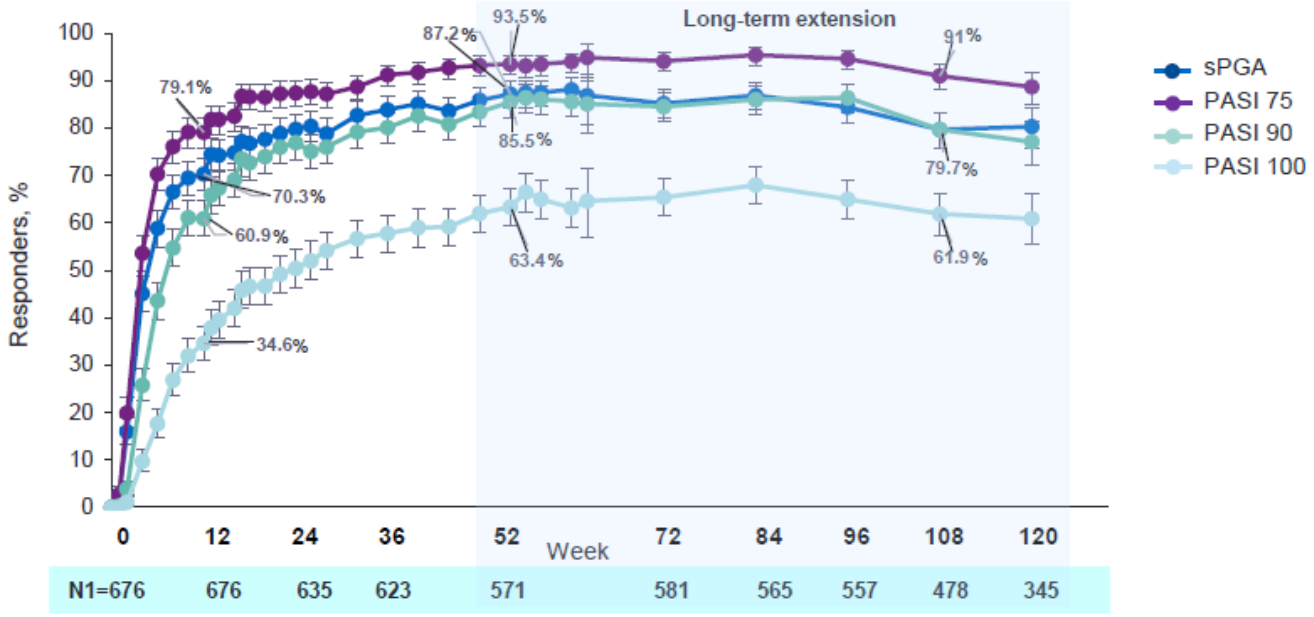
N ENGL J MED 373;14 NEJM.ORG OCTOBER 1, 2015

**1831 pazienti studio AMAGINE 2**
**1881 pazienti studio AMAGINE 3**
**Pazienti randomizzati con rapporto 2:2:1:1 a ricevere Brodalumab 140 mg, Brodalumab 210 mg, Ustekinumab (45 mg o 90 mg a seconda del peso) e placebo al baseline, alle settimane 1, 2 e successivamente ogni 2 settimane.**


Brodalumab, 210 mg every 2 wk
Brodalumab, 140 mg every 2 wk
Ustekinumab
Placebo
A PASI 75 Response
AMAGINE-2
AMAGINE-3
Response Rate (%)
Week
86%
70%
67%
8%
85%
69%
69%
6%
B PASI 100 Response
44%
26%
22%
1%
37%
27%
19%
0.3%

# Treatment With Brodalumab Resulted in Substantial Psoriatic Lesion Clearing for >2 Years (AMAGINE-2/-3)

**Figure 2.** PASI and sPGA rates in patients who received any dose of brodalumab in the induction phase and brodalumab 210 mg Q2W (the US FDA–approved dose) during the maintenance and long-term extension phases (n=676).




- Among patients who received brodalumab 210 mg Q2W, rates of achieving sPGA 0/1, PASI 75, PASI 90, and PASI 100 were maintained from weeks 52 to 108

FDA, Food and Drug Administration; N1, number of patients who were randomized to brodalumab 210 mg Q2W after week 12 and had a valid measurement value at the specified week; PASI 75, 90, and 100, psoriasis area and severity index 75%, 90%, and 100% improvement; Q2W, every 2 weeks; sPGA 0/1, static physician's global assessment score of 0 or 1. Error bars are the 95% confidence interval. As observed analysis.
Data on file, Valeant Pharmaceuticals North America LLC.

# Treatment-Emergent Adverse Events

**Table 1.** Overall Summary of Exposure-Adjusted Treatment-Emergent AEs for Years 1 and 3, From First Dose of Brodalumab Through End of Study (AMAGINE-2/-3)

| | Year 1, n (r) (n=3625; 3360.6 patient-years) | Year 3, n (r) (n=1753; 589.3 patient-years) |
|---|---|---|
| All TEAEs | 12986 (386.4) | 1022 (173.4) |
| Grade ≥2 | 6444 (191.8) | 641 (108.8) |
| Grade ≥3 | 508 (15.1) | 53 (9.0) |
| Serious AE | 278 (8.3) | 37 (6.3) |
| Fatal AEs | 3 (0.1) | 0 (0.0) |
| AEs leading to discontinuation of treatment | 118 (3.5) | 3 (0.5) |
| Serious | 41 (1.2) | 2 (0.3) |
| Nonserious | 77 (2.3) | 1 (0.2) |
| Frequently occurring TEAEs | | |
| Arthralgia | 431 (12.8) | 33 (5.6) |
| Headache | 383 (11.4) | 19 (3.2) |
| Fatigue | 174 (5.2) | 5 (0.8) |
| Diarrhea | 164 (4.9) | 12 (2.0) |
| Oropharyngeal pain | 168 (5.0) | 13 (2.2) |
| Nausea | 105 (3.1) | 1 (0.2) |
| Myalgia | 101 (3.0) | 1 (0.2) |
| Injection site reactions | 171 (5.1) | 2 (0.3) |
| Influenza | 121 (3.6) | 13 (2.2) |
| Neutropenia | 74 (2.2) | 1 (0.2) |
| *Tinea* infections | 56 (1.7) | 8 (1.4) |
| Conjunctivitis | 57 (1.7) | 6 (1.0) |
| *Candida* infections | 125 (3.7) | 16 (2.7) |

## CONCLUSION

Brodalumab demonstrated consistent safety and sustained efficacy for >2 years (108 weeks), with >60% of patients achieving PASI 100 and >79% of patients achieving sPGA 0/1

AE, adverse event; n, number of AEs; r, exposure-adjusted event rate per 100 patient-years (n/total patient-years of exposure through week 52 × 100); patient-year, total patient-years of exposure through end of study; TEAE, treatment-emergent AE.

# Brodalumab: ideazione suicidaria e suicidi

ORIGINAL ARTICLE

## Psychiatric adverse events during treatment with brodalumab: Analysis of psoriasis clinical trials

Mark G. Lebwohl, MD,[a] Kim A. Papp, MD, PhD, FRCPC,[b] Lauren B. Marangell, MD,[c,d] John Koo, MD,[e] Andrew Blauvelt, MD, MBA,[f] Melinda Gooderham, MD,[g] Jashin J. Wu, MD,[h] Shipra Rastogi, PhD,[i] Susan Harris, MS,[i] Radhakrishnan Pillai, PhD,[j] and Robert J. Israel, MD[i]
*New York, New York; Waterloo and Peterborough, Ontario, Canada; Houston, Texas; San Francisco, Los Angeles, and Petaluma, California; Portland, Oregon; and Bridgewater, New Jersey*

**CAPSULE SUMMARY**

- Patients with psoriasis are at increased risk for psychiatric comorbidities, including suicidal ideation and behavior.
- This study compared the incidence of psychiatric adverse events in patients treated with brodalumab, placebo, and ustekinumab.
- Data from 5 clinical trials did not reveal a causal relationship between suicidality and brodalumab treatment.

22 episodi di ideazione suicidaria e
4 suicidi completati

# Brodalumab: ideazione suicidaria e suicidi

COMMENTARY

**Brodalumab and suicidal ideation in the context of a recent economic crisis in the United States**

Melissa J. Danesh, BS,[a] and Alexa B. Kimball, MD, MPH[b]
*San Francisco, California, and Boston, Massachusetts*

- Un gruppo di esperti della FDA ha revisionato i dati provenienti dagli studi clinici e non ha evidenziato alcuna associazione casuale tra brodalumab e suicidi.
- Per tali motivi tutti i 18 membri hanno votato in favore di un'approvazione da parte dell'FDA che ha poi approvato il farmaco il 15 Febbraio 2017 (SILIQ®) – Valeant
- Il 4 Luglio 2016 il brodalumab è stato approvato in Giappone (*LUMICEF*®) per il trattamento della psoriasi cronica a placche, l'artrite psoriasica, la psoriasi pustolosa e la psoriasi eritrodermica. (Kyowa Hakko Kirin )

Suicidal ideation and behavior, including completed suicides, have occurred in patients treated with Siliq during clinical trials. Siliq users with a history of suicidality or depression had an increased incidence of suicidal ideation and behavior compared to users without this history. A causal association between treatment with Siliq and increased risk of suicidal ideation and behavior has not been established.

Because of the observed risk of suicidal ideation and behavior, the labeling for Siliq includes a Boxed Warning and the drug is only available through a restricted program under a Risk Evaluation and Mitigation Strategy (REMS) called the Siliq REMS Program. Notable requirements of the Siliq REMS Program include the following:

- Prescribers must be certified with the program and counsel patients about this risk. Patients with new or worsening symptoms of depression or suicidality should be referred to a mental health professional, as appropriate.
- Patients must sign a Patient-Prescriber Agreement Form and be made aware of

# LEO Pharma Receives Marketing Authorisation for Kyntheum® (Brodalumab), a New Biologic for the Treatment of Moderate-to-Severe Plaque Psoriasis in the European Union

20 luglio 2017

in patients being treated with Siliq.

# Vantaggio blocco p19 over p40 (ustekinumab)

- Si evitano immunosoppressioni inutili: vedi blocco del pathway Th1 che media risposte immunitarie contro infezioni virali e neoplasie
- Th1 ed IFN-ɣ rappresentano un freno contro il segnale IL-17, in quanto riducono l'effetto dell'IL-23 attraverso una down-regulation del recettore dell'IL-23 e di conseguenza riducono la differenziazione dei Th17
- Maggiore specificità perchè si blocca solo ciò che risulta essere upregolato (IL-12 non è aumentata in psoriasi)
- Non sono stati riportati (almeno finora) MACEs negli anti-p19

MJ Gooderham et al. 2018

# Vantaggio riduzione dell’espansione clonale dei Th17 attraverso il blocco di IL-23

- Un potenziale beneficio è rappresentato dalla bassa frequenza di somministrazione dei farmaci anti-IL23 rispetto ai farmaci anti-IL17.

- Si ipotizza che il blocco dell'IL-23 possa essere più efficace e che gli effetti durino più a lungo a causa di un effetto a monte che include ridotta espressione di diverse citochine pro-infiammatorie secrete dalle cellule Th17 (ad es. IL-17A, IL-17F, IL-21 e IL-22).

- Ciò potrebbe essere dovuto a una compromissione della sopravvivenza o ad un cambiamento fenotipico nelle cellule Th17 patogene o ad un ripristino della funzione T-reg alterata: importante poiché le cellule Th17 sono longeve e metabolicamente attive, anche dopo la risoluzione della placca.

- Prevenire la produzione iniziale di queste cellule potrebbe rivelarsi utile.

MJ Gooderham et al. 2018

# Anti-IL23 (p19)

| | Guselkumab[1] | Tildrakizumab[2] | Risankizumab[3] |
|---|---|---|---|
| **Description** | • Human IgG1 mAb | • Humanized IgG1/κ mAb | • Humanized IgG1 mAb |
| **Intended Indications** | • Ps<br>• PsA | • Ps | • Crohn's disease<br>• Psoriasis<br>• AS<br>• PsA<br>• Asthma |
| **Status** | • Approved | • Approved | • To be submitted |
| **Manufacturer** | janssen | SUN PHARMA | abbvie |

Tremfya® Ilumya®

# Efficacy and safety of guselkumab, an anti-interleukin-23 monoclonal antibody, compared with adalimumab for the continuous treatment of patients with moderate to severe psoriasis: Results from the phase III, double-blinded, placebo- and active comparator–controlled VOYAGE 1 trial

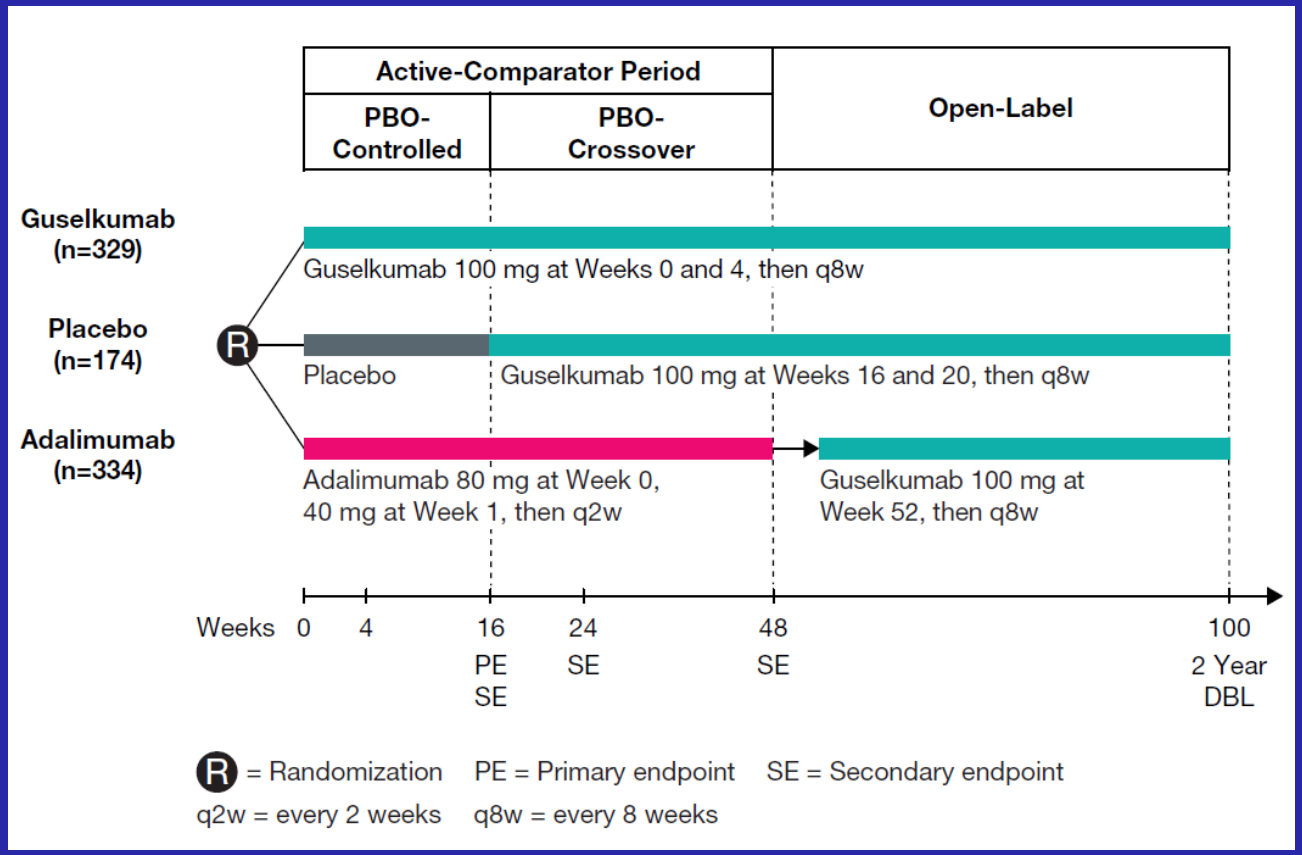
Andrew Blauvelt, MD, MBA,[a] Kim A. Papp, MD, PhD,[b] Christopher E. M. Griffiths, MD,[c] Bruce Randazzo, MD, PhD,[d,e] Yasmine Wasfi, MD, PhD,[d] Yaung-Kaung Shen, PhD,[d] Shu Li, PhD,[d] and Alexa B. Kimball, MPH, MD[f]

*Portland, Oregon; Waterloo, Ontario, Canada; Manchester, United Kingdom; Spring House and Philadelphia, Pennsylvania; and Boston, Massachusetts*

J Am Acad Dermatol
March 2017

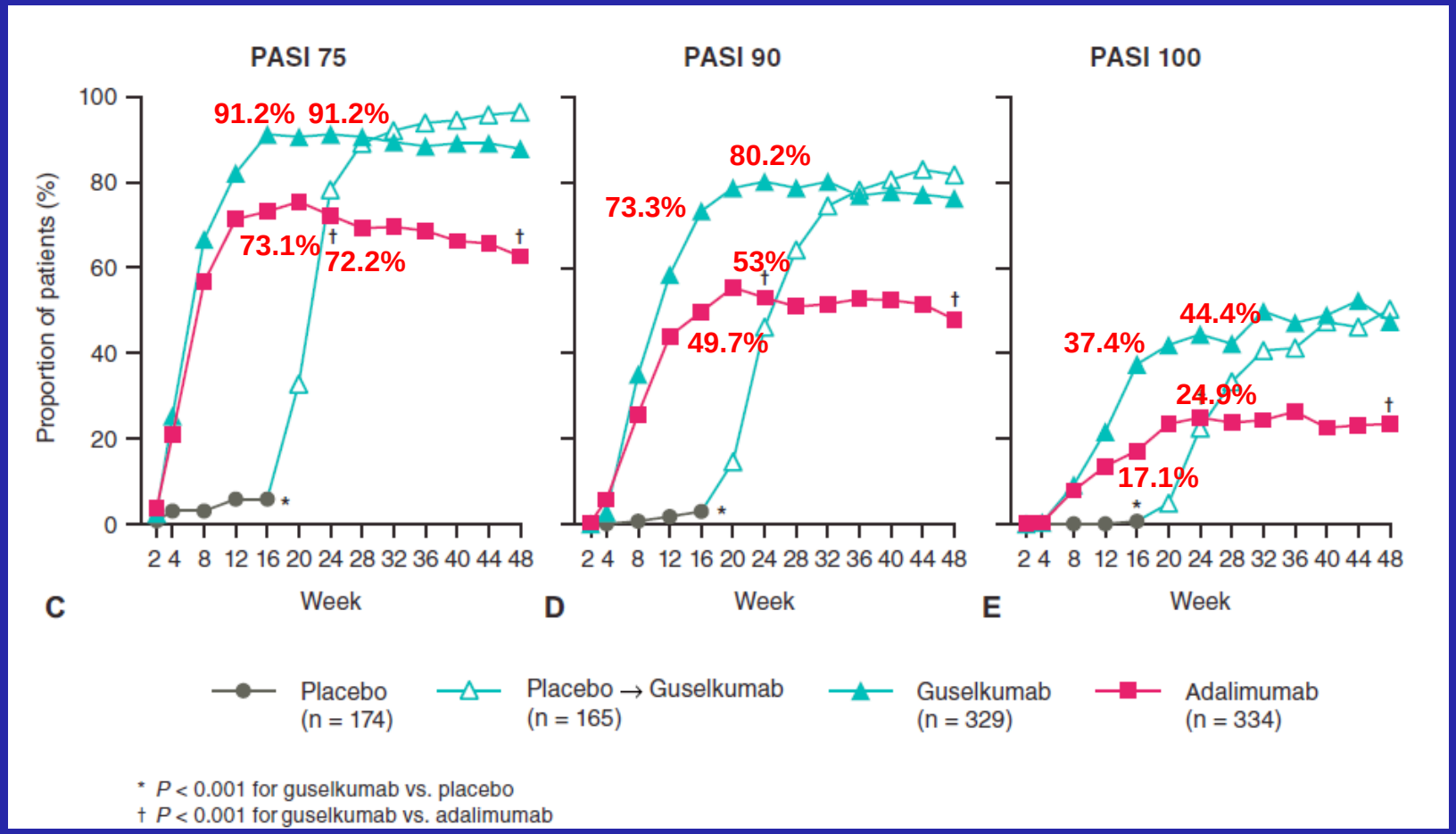
**Anticorpo monoclonale completamente umano IgG1λ anti IL-23 p19 (emivita 15-17 giorni)**
**837 pazienti randomizzati con rapporto 2:1:2; studio di fase III**

# VOYAGE 1 Study Design Through Week 100

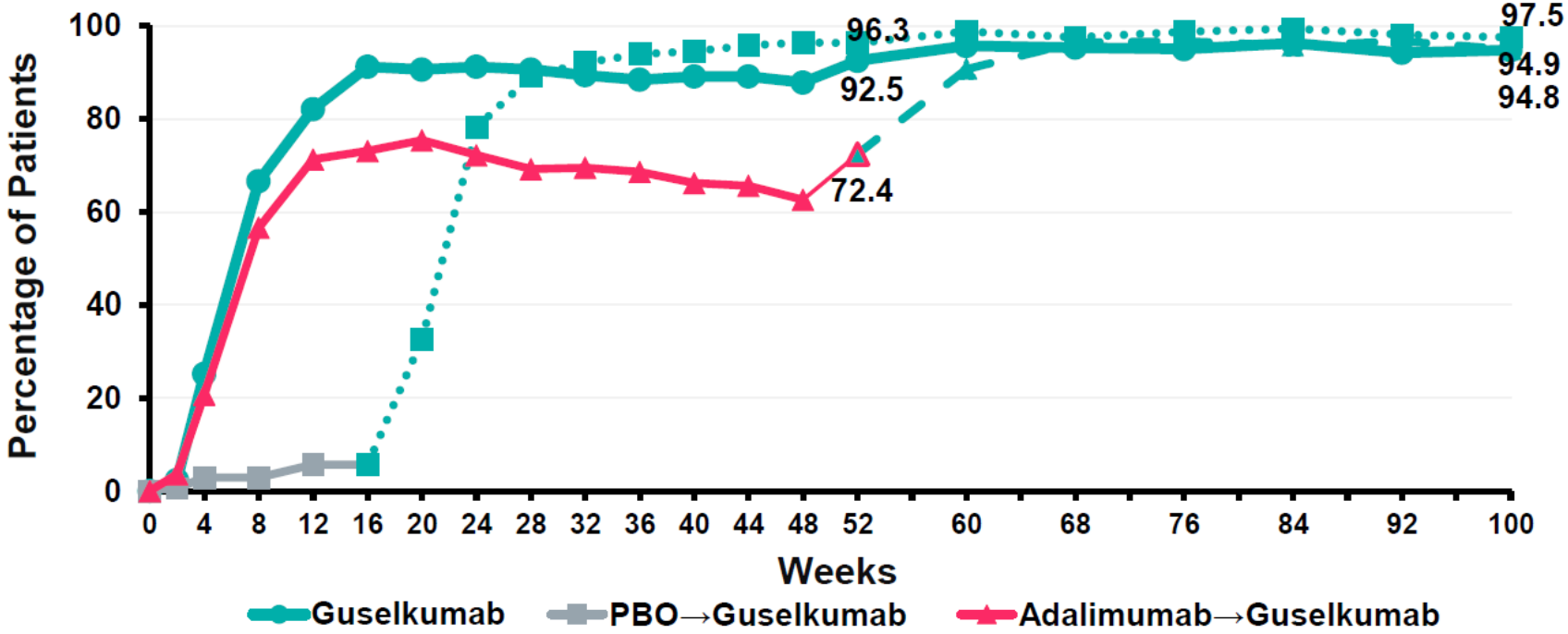



**End point primario: raggiungimento PASI 90 e IGA score di 0/1 alla settimana 16**

# VOYAGE 1: efficacy studio core



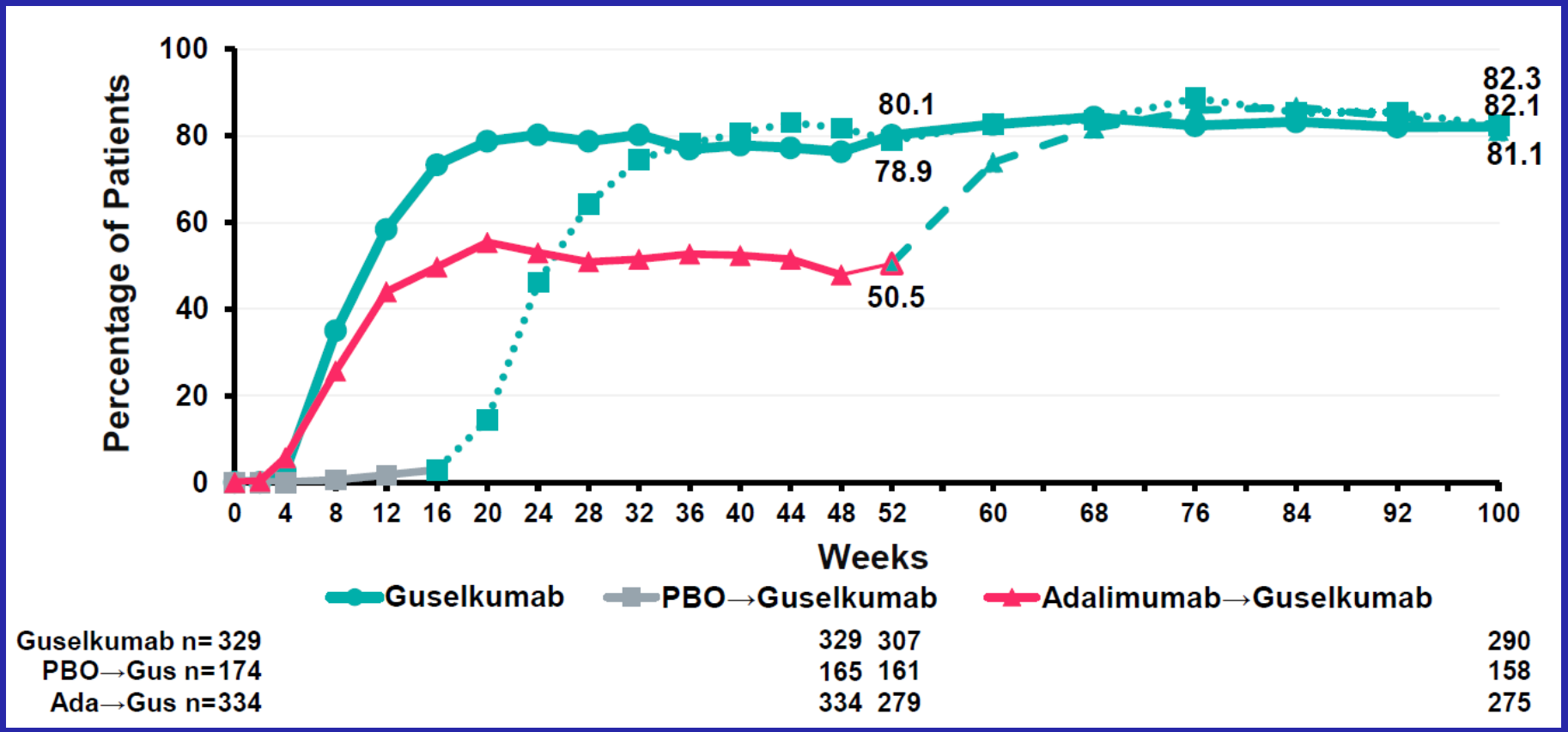
# Proportion of Patients Who Achieved PASI 75 Response (Week 0-100), *Prespecified*




| | | | |
|---|---|---|---|
| Guselkumab n= 329 | 329 | 307 | 290 |
| PBO→Gus n=174 | 165 | 161 | 158 |
| Ada→Gus n=334 | 334 | 279 | 275 |

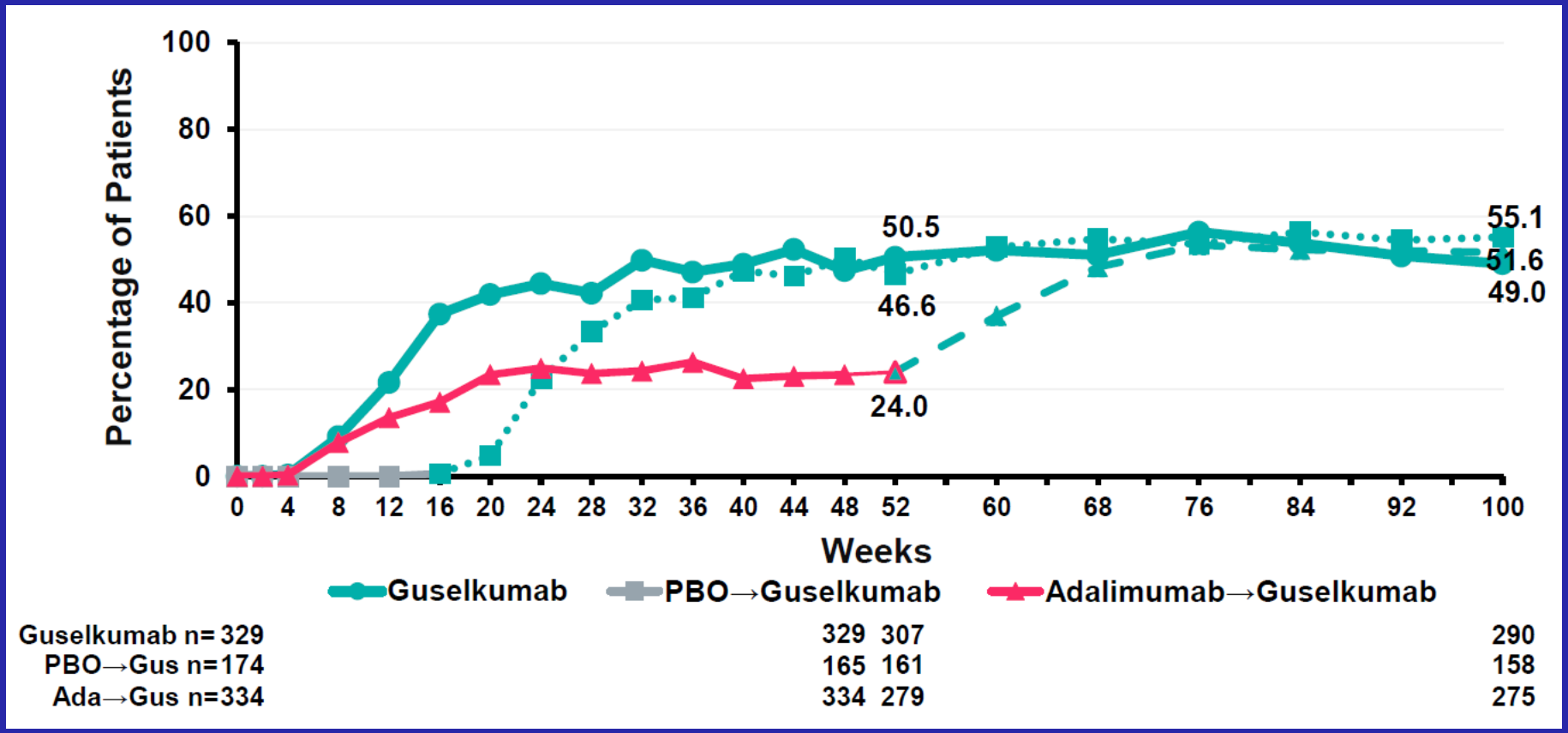
C.E.M. Griffiths, et al. EADV 2017

# Proportion of Patients Who Achieved PASI 90 Response (Week 0-100), *Prespecified*




C.E.M. Griffiths, et al. EADV 2017

# Proportion of Patients Who Achieved PASI 100 Response (Week 0-100), *Prespecified*




C.E.M. Griffiths, et al. EADV 2017

# Safety

**Table VI.** Cumulative rates of key safety events; treated patients

| | Wk 0-16 Placebo-controlled period | | | Wk 0-48 Active comparator—controlled period | | Wk 16-48 |
|---|---|---|---|---|---|---|
| | Placebo | Guselkumab | Adalimumab | Guselkumab | Adalimumab | Placebo → guselkumab |
| Patients treated, n | 174 | 329 | 333 | 329 | 333 | 165 |
| Mean duration of follow-up, wk | 15.88 | 16.27 | 16.14 | 46.47 | 45.56 | 31.88 |
| At least 1 AE | 86 (49.4) | 170 (51.7) | 170 (51.1) | 243 (73.9) | 248 (74.5) | 107 (64.8) |
| Common AEs* | | | | | | |
| Nasopharyngitis | 17 (9.8) | 30 (9.1) | 35 (10.5) | 83 (25.2) | 74 (22.2) | 34 (20.6) |
| Upper respiratory tract infection | 9 (5.2) | 25 (7.6) | 16 (4.8) | 47 (14.3) | 42 (12.6) | 17 (10.3) |
| Injection-site erythema | 1 (0.6) | 6 (1.8) | 15 (4.5) | 8 (2.4) | 22 (6.6) | 3 (1.8) |
| Headache | 7 (4.0) | 12 (3.6) | 13 (3.9) | 18 (5.5) | 25 (7.5) | 1 (0.6) |
| Arthralgia | 3 (1.7) | 11 (3.3) | 9 (2.7) | 18 (5.5) | 16 (4.8) | 2 (1.2) |
| Pruritus | 10 (5.7) | 5 (1.5) | 7 (2.1) | 8 (2.4) | 12 (3.6) | 0 |
| Back pain | 2 (1.1) | 6 (1.8) | 4 (1.2) | 12 (3.6) | 17 (5.1) | 1 (0.6) |
| Discontinued study agent because of AE | 2 (1.1) | 4 (1.2) | 3 (0.9) | 9 (2.7) | 12 (3.6) | 1 (0.6) |
| At least 1 SAE | 3 (1.7) | 8 (2.4) | 6 (1.8) | 16 (4.9) | 15 (4.5) | 5 (3.0) |
| Infections | 44 (25.3) | 85 (25.8) | 85 (25.5) | 172 (52.3) | 167 (50.2) | 76 (46.1) |
| Requiring treatment | 13 (7.5) | 20 (6.1) | 24 (7.2) | 54 (16.4) | 60 (18.0) | 25 (15.2) |
| Serious infections | 0 | 0 | 2 (0.6) | 2 (0.6) | 3 (0.9) | 1 (0.6) |
| Malignancies† | 0 | 0 | 0 | 2 (0.6) | 0 | 0 |
| NMSC‡ | 0 | 1 (0.3) | 0 | 2 (0.6) | 1 (0.3) | 0 |
| MACE§ | 0 | 1 (0.3) | 1 (0.3) | 1 (0.3) | 1 (0.3) | 0 |

Values are reported as n (%).

*AE*, Adverse event; *MACE*, major adverse cardiovascular events; *NMSC*, nonmelanoma skin cancers; *SAE*, serious adverse event.

*Occurred in at least 5% of patients in any treatment group through wk 48.

†Includes malignancies other than NMSC (ie, prostate and breast cancer).

‡Includes 3 basal cell carcinomas.

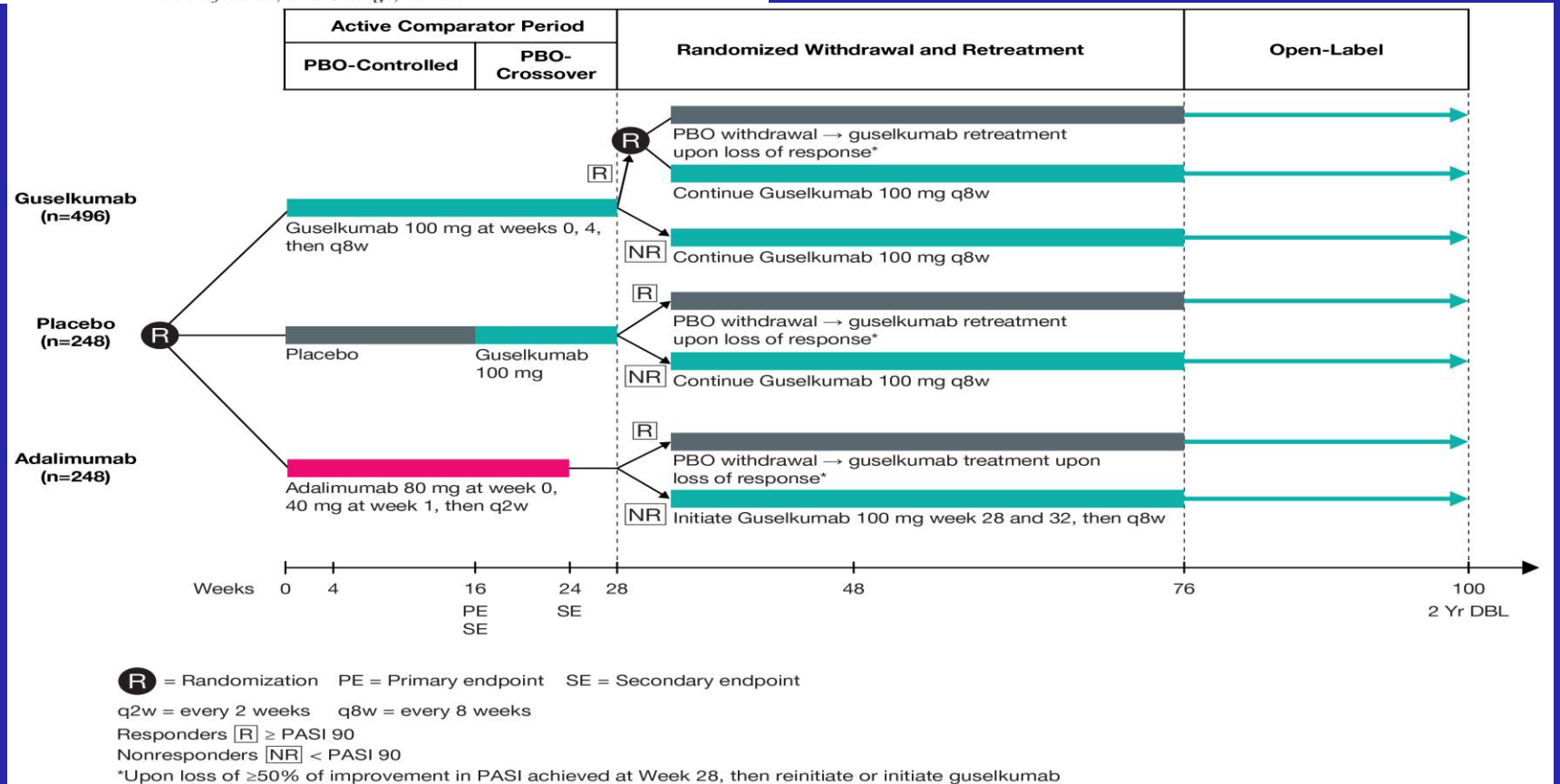
§Includes sudden cardiac death, myocardial infarction, and stroke.

# Efficacy and safety of guselkumab, an anti-interleukin-23 monoclonal antibody, compared with adalimumab for the treatment of patients with moderate to severe psoriasis with randomized withdrawal and retreatment: Results from the phase III, double-blind, placebo- and active comparator–controlled VOYAGE 2 trial

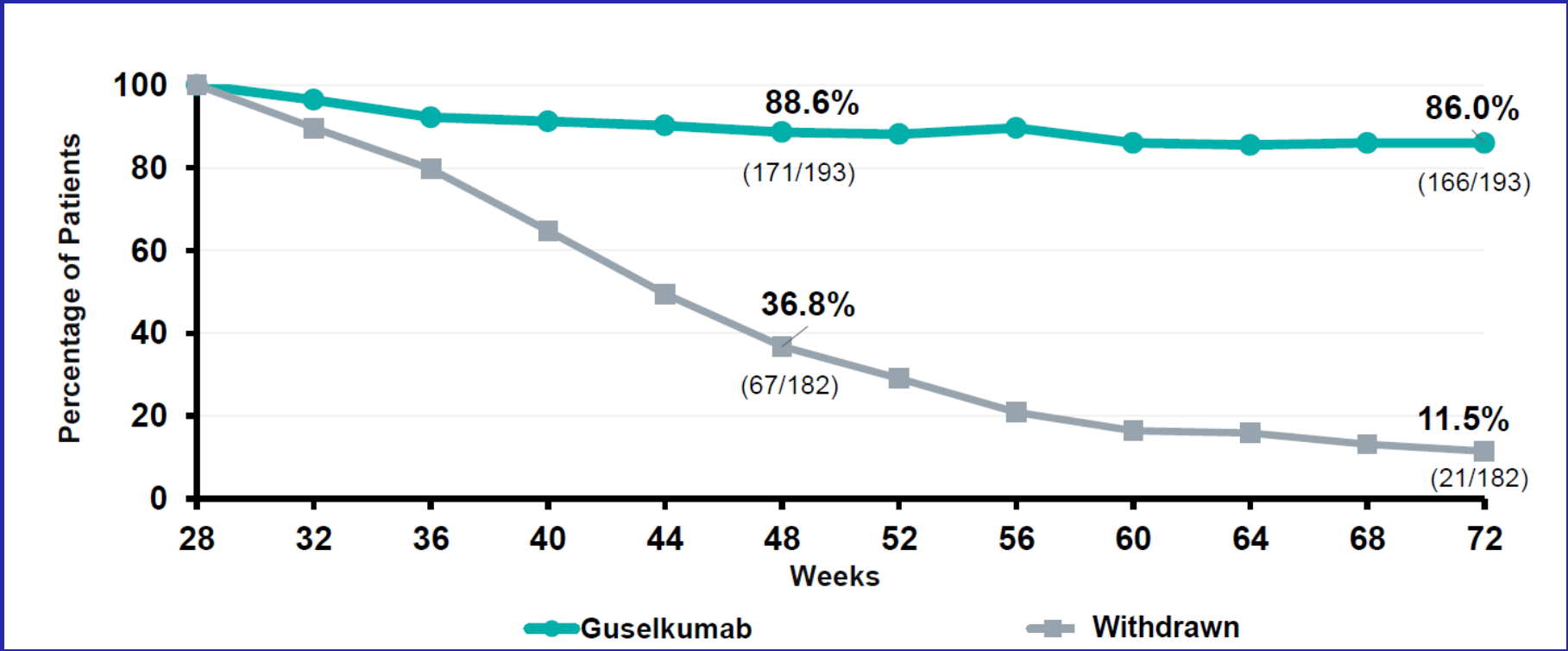
J Am Acad Dermatol
March 2017

Kristian Reich, MD,[a] April W. Armstrong, MD, MPH,[b] Peter Foley, MD,[c,d]
Michael Song, MD,[e] Yasmine Wasfi, MD, PhD,[e] Bruce Randazzo, MD, PhD,[e]
Shu Li, PhD,[e] Y.-K. Shen, PhD,[e] and Kenneth B. Gordon, MD[f]
*Hamburg, Germany; Los Angeles, California; Melbourne and Carlton, Australia; Spring House, Pennsylvania; and Chicago, Illinois*

**992 pazienti randomizzati, con rapporto 2:1:1, studio di fase III**



# PASI 90 Response From Week 28 Through Week 72, Among Patients Who Were Originally Randomized to Guselkumab and Achieved a PASI 90 Response at Week 28*




Gordon K., et al. Late-Breaker AAD 2018. 6748.

*Non-responder Imputation (NRI)

# Tildrakizumab versus placebo or etanercept for chronic plaque psoriasis (reSURFACE 1 and reSURFACE 2): results from two randomised controlled, phase 3 trials

*Kristian Reich, Kim A Papp, Andrew Blauvelt, Stephen K Tyring, Rodney Sinclair, Diamant Thaçi, Kristine Nograles, Anish Mehta, Nicole Cichanowitz, Qing Li, Kenneth Liu, Carmen La Rosa, Stuart Green, Alexa B Kimball*

www.thelancet.com Published online June 5, 2017 http://dx.doi.org/10.1016/S0140-6736(17)31279-5

**Anticorpo monoclonale umanizzato IgG1 κ anti IL-23 p19 (emivita 20-27 giorni)**

**772 pazienti (reSURFACE 1), 1090 pazienti (reSURFACE 2)**

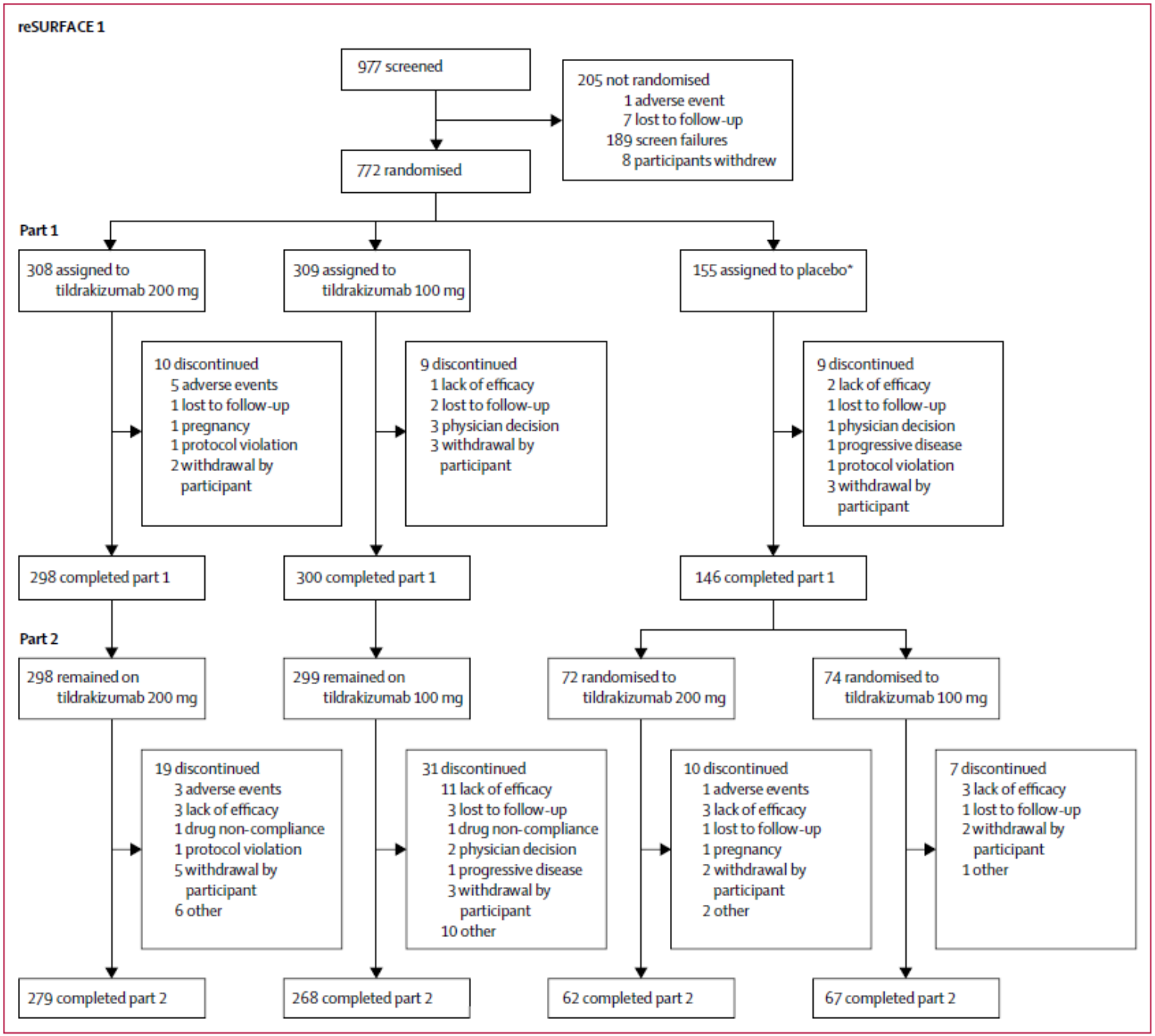
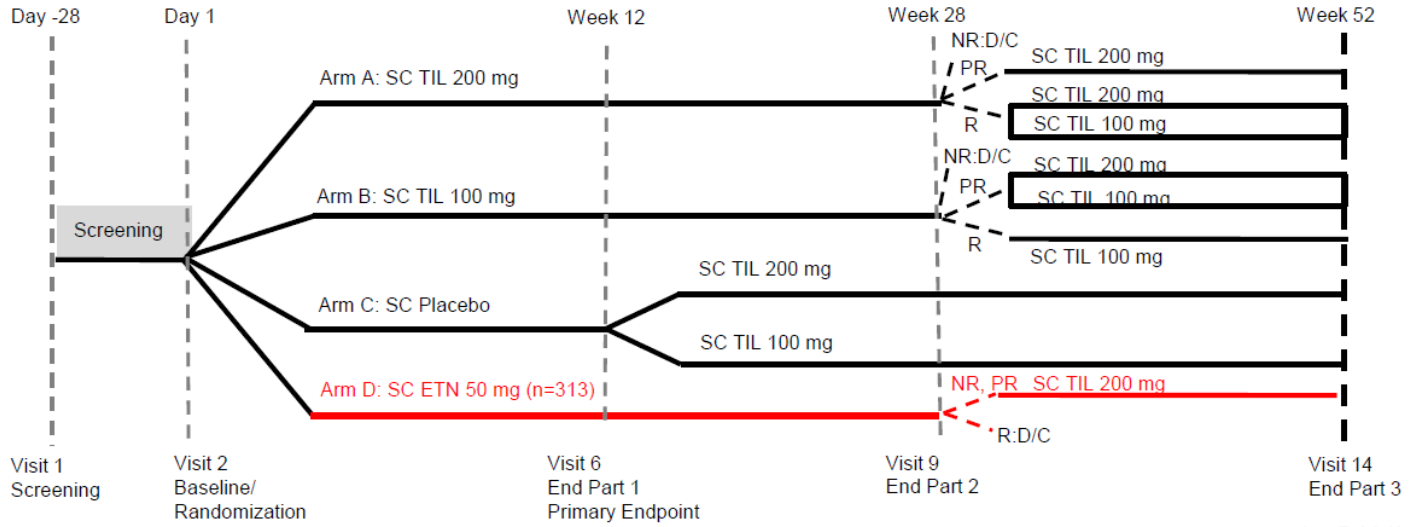



*Figure 1:* reSURFACE 1 trial profile

## reSURFACE 2[1]




D/C, discontinued; NR, nonresponder; PR, partial responder; R, responder; SC, subcutaneous

1. Reich K et al. *Lancet*.2017;390:276-288.

Patients that achieved at least a PASI 50 response by the end of Part 3 of the study started the optional long-term extension study, until week 244.

# Efficacy at week 12

| | Tildrakizumab 200 mg (n=314) | Tildrakizumab 100 mg (n=307) | Placebo (n=156) | Etanercept (n=313) |
|---|---|---|---|---|
| **PASI 75** | | | | |
| n (%) | 206 (66%) | 188 (61%) | 9 (6%) | 151 (48%) |
| % difference from placebo (95% CI; p value) | 59·8% (52·9 to 65·9; p<0·0001) | 55·5% (48·3 to 61·8; p<0·0001) | N/A | N/A |
| % difference from etanercept (95% CI; p value) | 17·4% (9·7 to 24·9; p<0·0001) | 13·1 (5·3 to 20·7; p=0·001) | N/A | N/A |
| **Clear or minimal PGA** | | | | |
| n (%) | 186 (59%) | 168 (55%) | 7 (4%) | 149 (48%) |
| % difference from placebo (95% CI; p value) | 54·7 (47·9 to 60·8; p<0·0001) | 50·2 (43·2 to 56·5; p<0·0001) | N/A | N/A |
| % difference from etanercept (95% CI; p value) | 11·7 (4·0 to 19·3; p=0·0031) | 7·3 (−0·5 to 15·0; p=0·0663) | N/A | N/A |
| **PASI 90** | | | | |
| n (%) | 115 (37%) | 119 (39%) | 2 (1%) | 67 (21%) |
| % difference from placebo (95% CI; p value) | 35·3% (29·2 to 41·1; p<0·0001) | 37·5% (31·1 to 43·4; p<0·0001) | N/A | N/A |
| % difference from etanercept (95% CI; p value) | 15·2% (8·3 to 22·1; p<0·0001) | 17·4% (10·3 to 24·4; p<0·0001) | N/A | N/A |
| **PASI 100** | | | | |
| n (%) | 37 (12%) | 38 (12%) | 0 | 15 (5%) |
| % difference from placebo (95% CI; p value) | 11·7% (7·8 to 16·0; p<0·0001) | 12·4% (8·5 to 16·6; p<0·0001) | N/A | N/A |
| % difference from etanercept (95% CI; p value) | 7·0% (2·8 to 11·6; p=0·0014) | 7·6% (3·3 to 12·3; p=0·0006) | N/A | N/A |
| **DLQI** | | | | |
| n (%) | 145 (47%) | 119 (40%) | 12 (8%) | 108 (36%) |
| % difference from placebo (95% CI; p value) | 39·3% (31·8 to 46·1; p<0·0001) | 32·1% (24·5 to 39·1; p<0·0001) | N/A | N/A |
| % difference from etanercept (95% CI; p value) | 11·9% (4·1 to 19·5; p=0·0029) | 4·8% (−2·9 to 12·5; p=0·2206) | N/A | N/A |

The full-analysis-set population included all randomly assigned patients who received at least one dose of study medication. % differences and 95% CIs were calculated with the Miettinen-Nurminen method and stratified by bodyweight (≤90 kg *vs* >90 kg) and previous exposure to biologic therapy for psoriasis (yes *vs* no) with sample size weights. p values were calculated with the Cochran-Mantel-Haenszel (CMH) and stratified by bodyweight and exposure to biologic therapies; p values were not adjusted for multiplicity. Non-responder imputation was pre-specified and is shown for all data, except for DLQI, for which observed data are shown. PASI=Psoriasis Area and Severity Index. N/A=not applicable. PGA=Physician's Global Assessment. DLQI=Dermatology Life Quality Index.

***Table 3*: Primary and secondary efficacy endpoints at 12 weeks in reSURFACE2 part 1 (full analysis set)**

# Efficacy at week 28

| | Tildrakizumab 200 mg (n=299)* | Tildrakizumab 100 mg (n=294)* | Placebo→tildrakizumab 200 mg (n=72)* | Placebo→tildrakizumab 100 mg (n=69)* | Etanercept (n=289)* |
|---|---|---|---|---|---|
| **PASI 75 (NRI)** | | | | | |
| n (%) | 217 (73%) | 216 (73%) | 50 (69%) | 38 (55%) | 155 (54%) |
| % difference from etanercept (95% CI; p value) | 19·2% (11·5–26·7; p<0·0001) | 20·1% (12·4–27·6; p<0·0001) | N/A | N/A | N/A |
| **Clear or minimal PGA (NRI)** | | | | | |
| n (%) | 207 (69%) | 190 (65%) | 46 (64%) | 33 (48%) | 131 (45%) |
| % difference from etanercept (95% CI; p value) | 24·1% (16·2–31·7; p<0·0001) | 19·6% (11·7 to 27·3; p<0·0001) | N/A | N/A | N/A |
| **PASI 90 (OD)** | | | | | |
| n (%) | 169 (58%) | 161 (56%) | 33 (49%) | 26 (39%) | 85 (31%) |
| % difference from Etanercept (95% CI; p value) | 27·1% (19·1, 34·7; p<0·0001) | 24·9% (17·0–32·6; p<0·0001) | N/A | N/A | N/A |
| **PASI 90 (NRI)** | | | | | |
| n (%) | 169 (57%) | 161 (55%) | 33 (46%) | 26 (38%) | 85 (29%) |
| % difference from etanercept (95% CI; p value) | 27·3% (19·5–34·7; p<0·0001) | 25·5% (17·6–33·0; p<0·0001) | N/A | N/A | N/A |
| **PASI 100 (OD)** | | | | | |
| n (%) | 79 (27%) | 66 (23%) | 13 (19%) | 9 (14%) | 31 (11%) |
| % difference from etanercept (95% CI; p value) | 15·7% (9·4–22·1; p<0·0001) | 11·7% (5·6–17·9; p=0·0002) | N/A | N/A | N/A |
| **PASI 100 (NRI)** | | | | | |
| n (%) | 79 (26%) | 66 (22%) | 13 (18%) | 9 (13%) | 31 (11%) |
| % difference from etanercept (95% CI; p value) | 15·7% (9·6–22·0; p=0·0001) | 11·8% (5·9–17·9; p<0·0001) | N/A | N/A | N/A |
| **DLQI score 0 or 1 (OD)** | | | | | |
| n (%) | 193 (65%) | 157 (54%) | 39 (57%) | 26 (38%) | 111 (39%) |
| % difference from etanercept (95% CI; p value) | 25·7% (17·7–33·4; p<0·0001) | 15·0% (6·9–22·9; p=0·0003) | N/A | N/A | N/A |

The full-analysis-set population included all patients entering part 2 who received at least one dose of study medication. NRI was pre-specified and is shown for key secondary outcomes. OD were pre-specified for all other secondary outcomes. % differences and 95% CIs were calculated with the Miettinen-Nurminen method and stratified by bodyweight (≤90 kg *vs* >90 kg) and previous exposure to biologic therapy for psoriasis (yes *vs* no) with sample size weights. p values were calculated with the Cochran-Mantel-Haenszel and stratified by bodyweight and exposure to biologic therapies; p values were not adjusted for multiplicity. Post-hoc analyses for PASI 90 and PASI 100 at week 28 were done with NRI. PASI=Psoriasis Area and Severity Index. NRI=non-responder imputation. N/A=not applicable. PGA=Physician's Global Assessment. OD=observed data. DLQI=Dermatology Life Quality Index. *Numbers shown include participants with missing data.

***Table 5*: Secondary efficacy endpoints at 28 weeks in reSURFACE2 part 2 (full analysis set)**

# Safety

| | Part 1 | | | | Part 2 | | | | |
|---|---|---|---|---|---|---|---|---|---|
| | Tildrakizumab 200 mg (n=314) | Tildrakizumab 100 mg (n=307) | Placebo (n=156) | Etanercept (n=313) | Tildrakizumab 200 mg→ tildrakizumab 200 mg (n=299) | Tildrakizumab 100 mg→ tildrakizumab 100 mg (n=294) | Etanercept→ etanercept (n=289) | Placebo→ tildrakizumab 200 mg (n=72) | Placebo→ tildrakizumab 100 mg (n=69) |
| ≥1 adverse events* | 155 (49%) | 136 (44%) | 86 (55%) | 169 (54%) | 135 (45%) | 135 (46%) | 164 (57%) | 31 (43%) | 37 (54%) |
| Serious adverse events | 6 (2%) | 4 (1%) | 4 (3%) | 7 (2%) | 6 (2%) | 9 (3%) | 14 (5%) | 2 (3%) | 1 (1%) |
| Deaths† | 0 | 1 (<1%) | 0 | 0 | 0 | 0 | 0 | 0 | 0 |
| Discontinued because of adverse events | 3 (1%) | 3 (1%) | 2 (1%) | 6 (2%) | 1 (<1%) | 1 (<1%) | 3 (1%) | 0 | 1 (1%) |
| Most common adverse events | | | | | | | | | |
| Injection site erythema | 2 (1%) | 2 (1%) | 1 (1%) | 27 (9%) | 1 (<1%) | 3 (1%) | 3 (1%) | 0 | 0 |
| Nasopharyngitis | 35 (11%) | 41 (13%) | 12 (8%) | 36 (12%) | 43 (14%) | 23 (8%) | 34 (12%) | 3 (4%) | 8 (12%) |
| Upper respiratory tract infection | 0 | 0 | 0 | 0 | 6 (2%) | 5 (2%) | 7 (2%) | 0 | 0 |
| Adverse events of special interest | | | | | | | | | |
| Severe infections‡ | 1 (<1%) | 0 | 1 (1%) | 0 | 2 (1%) | 1 (<1%) | 3 (1%) | 0 | 0 |
| Malignancies§ | 1 (<1%) | 1 (<1%) | 0 | 1 (<1%) | 0 | 0 | 3 (1%) | 1 (1%) | 1 (1%) |
| Non-melanoma skin cancer | 1 (<1%) | 1 (<1%) | 0 | 1 (<1%) | 0 | 0 | 1 (<1%) | 1 (1%) | 1 (1%) |
| Confirmed major adverse cardiovascular events¶ | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 |
| Drug-related hypersensitivity reactions | 0 | 1 (<1%) | 1 (1%) | 0 | 0 | 0 | 0 | 0 | 2 (3%) |

Data are n (%). *Participants who took at least one dose of part 1 study drug; based on the treatment actually received. †A patient on tildrakizumab 100 mg died; the patient had alcoholic cardiomyopathy and steatohepatitis, although adjudication was unable to determine the cause of death. ‡Infection meeting the regulatory definition of a serious adverse event, or any infection requiring intravenous antibiotics, irrespective of whether it was reported as a serious adverse event, as per the regulatory definition. §Excluding carcinoma in situ of the cervix. ¶Includes non-fatal myocardial infarction, non-fatal stroke, and cardiovascular deaths that are confirmed as "cardiovascular" or "sudden".

*Table 7*: Summary of adverse events in reSURFACE 2

# Sun Pharma Announces U.S. FDA Approval of ILUMYA™ (tildrakizumab-asmn) for the Treatment of Moderate-to-Severe Plaque Psoriasis

NEWS PROVIDED BY
**Sun Pharma →**
Mar 21, 2018, 09:04 ET

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MUMBAI, India and PRINCETON, N.J., March 21, 2018 /PRNewswire/ -- Sun Pharmaceutical Industries Ltd. (Reuters: SUN.BO, Bloomberg: SUNP IN, NSE: SUNPHARMA, BSE: 524715, "Sun Pharma" and includes its subsidiaries and/or associate companies) today announced that the U.S. Food and Drug Administration (FDA) has approved ILUMYA™ (tildrakizumab-asmn) for the treatment of adults with moderate-to-severe plaque psoriasis who are candidates for systemic therapy or phototherapy. ILUMYA selectively binds to the p19 subunit of IL-23 and inhibits its interaction with the IL-23 receptor leading to inhibition of the release of pro-inflammatory cytokines and chemokines. ILUMYA is administered at a dose of 100 mg by subcutaneous injection every 12 weeks, after the completion of initial doses at weeks 0 and 4. ILUMYA is contraindicated in patients with a previous serious hypersensitivity reaction to tildrakizumab or to any of the excipients.

The NEW ENGLAND JOURNAL of MEDICINE

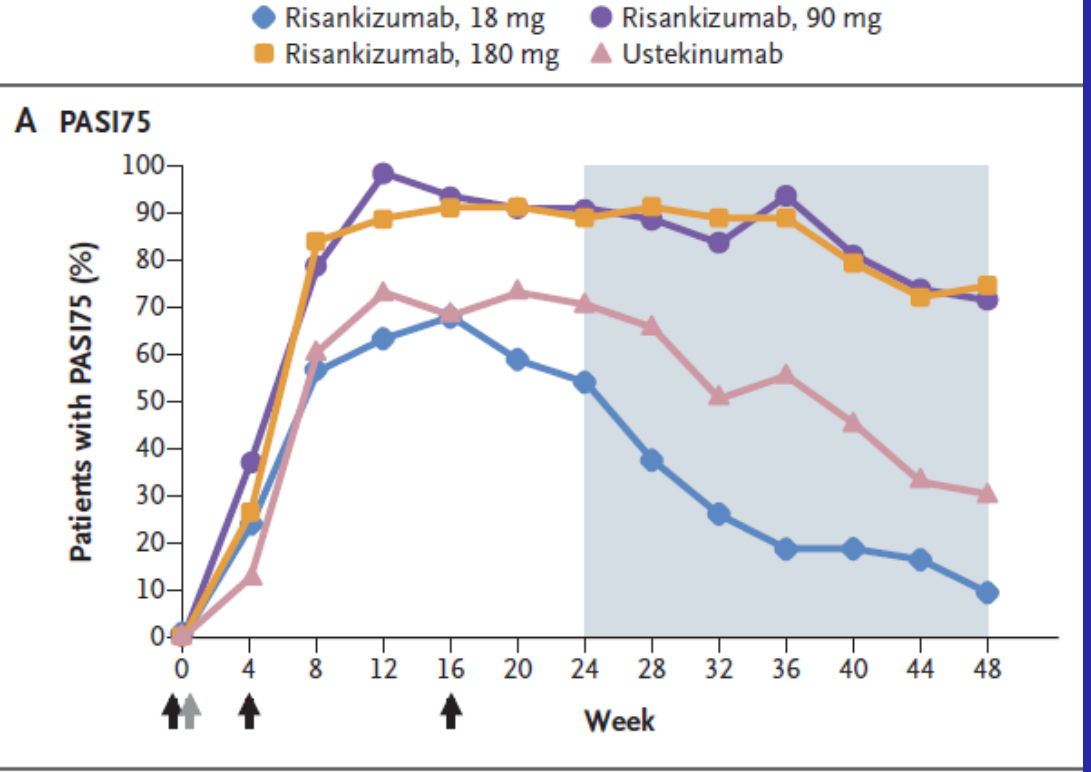
ORIGINAL ARTICLE

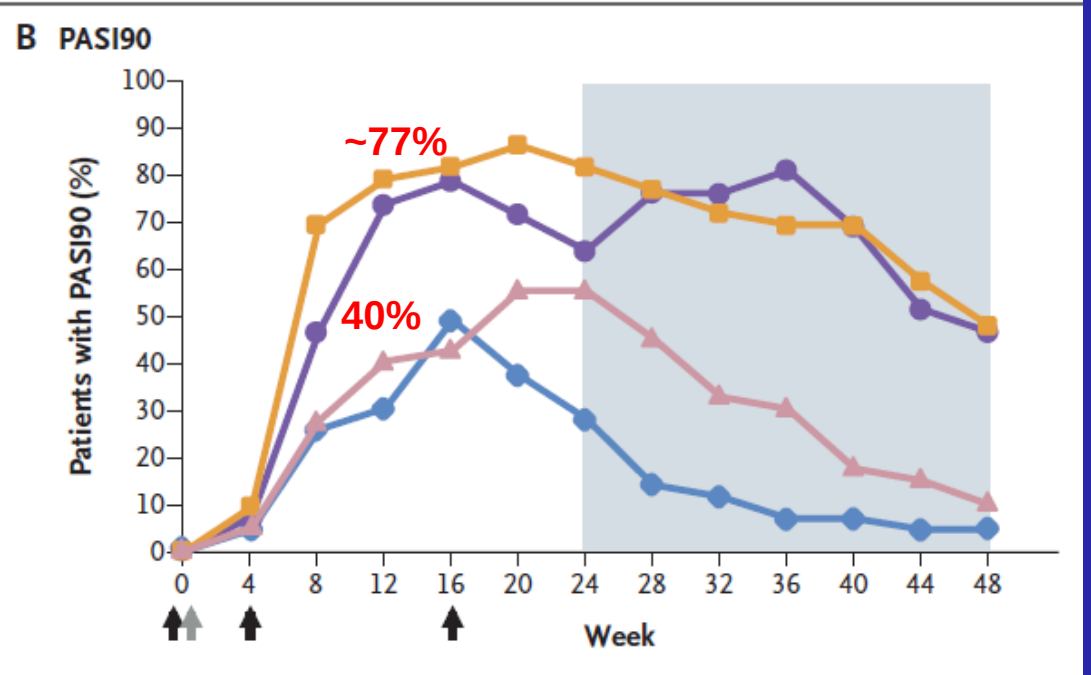
# Risankizumab versus Ustekinumab for Moderate-to-Severe Plaque Psoriasis

Kim A. Papp, M.D., Ph.D., Andrew Blauvelt, M.D., Michael Bukhalo, M.D., Melinda Gooderham, M.D., James G. Krueger, M.D., Ph.D., Jean-Philippe Lacour, M.D., Alan Menter, M.D., Sandra Philipp, M.D., Howard Sofen, M.D., Stephen Tyring, M.D., Ph.D., Beate R. Berner, M.D., Sudha Visvanathan, Ph.D., Chandrasena Pamulapati, Ph.D., Nathan Bennett, Ph.D., Mary Flack, M.D., Paul Scholl, M.B., B.Chir., and Steven J. Padula, M.D.

N ENGL J MED 376;16 NEJM.ORG APRIL 20, 2017

**Anticorpo monoclonale umanizzato IgG1 anti IL-23 (emivita 20-28 giorni)**
**166 pazienti, studio di fase II**
**Pazienti randomizzati con rapporto 1:1:1:1 a ricevere risankizumab 18 mg dose singola, risankizumab 90 mg, 180 mg, ustekinumab (45 mg o 90 mg secondo peso del paziente) al baseline, alla settimana 4 e alla settimana 16.**




# Efficacy

- Primary end point: raggiungimento PASI90 alla settimana 12
- Secondary end point: raggiungimento PASI50, PASI75, PASI100, alla settimana 12; raggiungimento PASI75 e PASI100 alla settimana 24; tempo di perdita della risposta PASI50
- Alla settimana 16, il PASI100 veniva raggiunto dal 55% dei pazienti in trattamento con risankizumab 180 mg, e dal 20% dei pazienti in trattamento con ustekinumab

# Safety

**Table 3. Adverse Events through Week 48.***

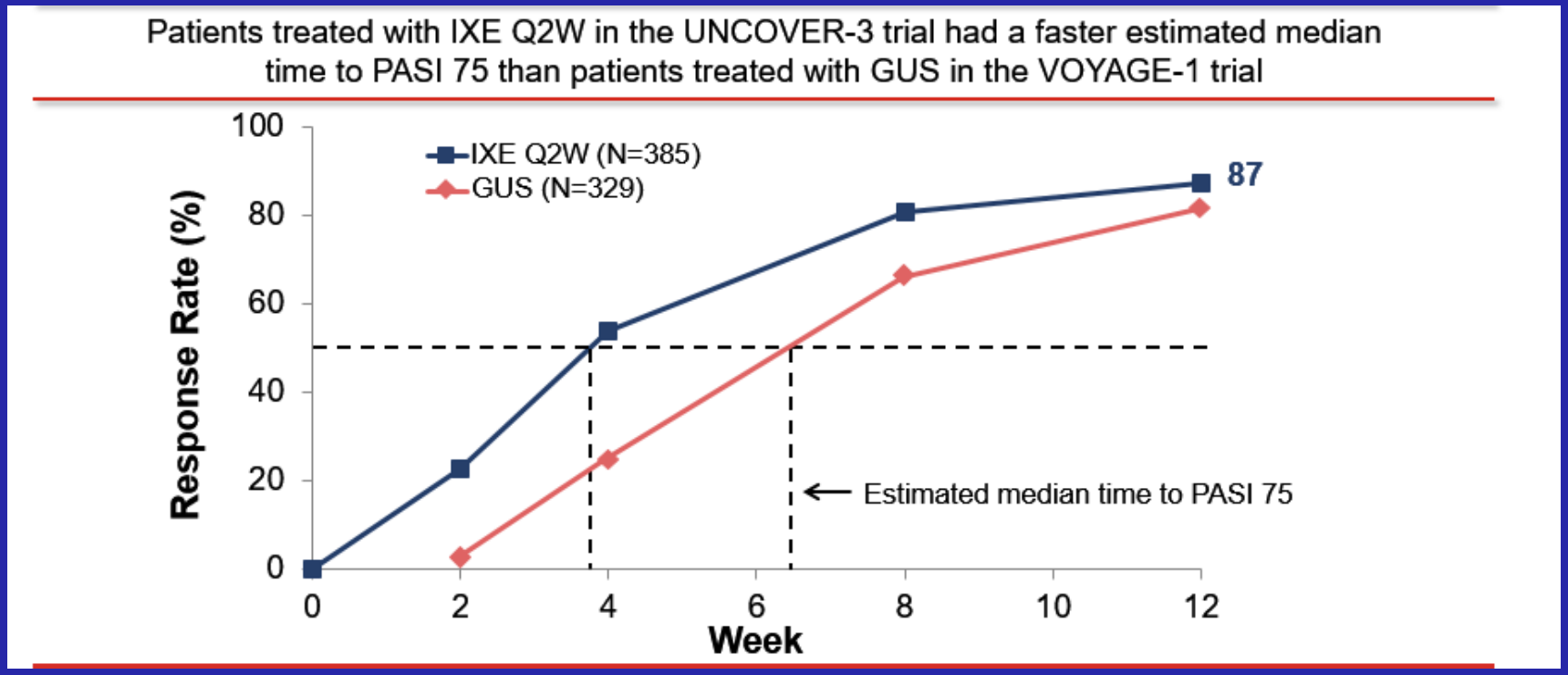
| Adverse Event | Risankizumab 18 mg (N=43) | Risankizumab 90 mg (N=41) | Risankizumab 180 mg (N=42) | Ustekinumab (N=40) |
|---|---|---|---|---|
| | *number of patients (percent)* | | | |
| Any adverse event | 35 (81) | 33 (80) | 29 (69) | 29 (72) |
| Severe adverse event | 4 (9) | 4 (10) | 1 (2) | 4 (10) |
| Investigator-defined drug-related adverse event | 7 (16) | 10 (24) | 6 (14) | 8 (20) |
| Adverse event leading to discontinuation of treatment | 1 (2) | 1 (2) | 0 | 1 (2) |
| Serious adverse event† | 5 (12) | 6 (15) | 0 | 3 (8) |
| Death | 0 | 0 | 0 | 0 |
| Common adverse events‡ | | | | |
| Nasopharyngitis | 15 (35) | 14 (34) | 11 (26) | 5 (12) |
| Headache | 6 (14) | 2 (5) | 3 (7) | 4 (10) |
| Sinusitis | 1 (2) | 0 | 1 (2) | 4 (10) |
| Gastroenteritis | 1 (2) | 4 (10) | 0 | 0 |
| Back pain | 2 (5) | 4 (10) | 1 (2) | 1 (2) |
| Serious adverse events | | | | |
| Infection or infestation | 1 (2) | 0 | 0 | 3 (8) |
| Bronchitis | 0 | 0 | 0 | 1 (2) |
| Diverticulitis | 0 | 0 | 0 | 1 (2) |
| Urinary tract infection | 0 | 0 | 0 | 1 (2) |
| Perineal abscess | 1 (2) | 0 | 0 | 0 |
| Benign, malignant, or unspecified neoplasm | 1 (2) | 2 (5) | 0 | 0 |
| Basal-cell carcinoma | 1 (2) | 1 (2) | 0 | 0 |
| Salivary gland neoplasm | 0 | 1 (2) | 0 | 0 |
| Nervous system disorder | 2 (5) | 1 (2) | 0 | 0 |
| Cerebrovascular accident§¶ | 0 | 1 (2) | 0 | 0 |
| Headache | 1 (2) | 0 | 0 | 0 |
| Transient ischemic attack | 1 (2) | 0 | 0 | 0 |
| Cardiac disorder§ | 0 | 2 (5) | 0 | 0 |
| Acute myocardial infarction | 0 | 1 (2) | 0 | 0 |
| Chronic coronary artery occlusion | 0 | 1 (2) | 0 | 0 |
| Other serious adverse event‖ | 4 (9) | 2 (5) | 0 | 0 |

# ANTI-IL17 O ANTI-IL23?

| | UNCOVER-2 and -3 IXE Q2W, Week 12,[1] NRI N=736 | VOYAGE-1 GUS Q8W, Week 16,[2] NRI N=329 | VOYAGE-2 GUS Q8W, Week 16,[3] NRI N=496 |
|---|---|---|---|
| **PASI 75 (%)** | 89% | 91% | 86% |
| **PASI 90 (%)** | 69% | 73% | 70% |
| **PASI 100 (%)** | 39% | 37% | 34% |

Dati provenienti da trials diversi; no head to head study

# ANTI-IL17 O ANTI-IL23?




Dati provenienti da trials diversi; no head to head study

# ANTI-IL17 O ANTI-IL23?

Week 48

| | UNCOVER-3<br>IXE Q2W,[1] NRI<br>N=385 | VOYAGE-1<br>GUS Q8W,[2] NRI<br>N=329 |
|---|---|---|
| **PASI 75 (%)** | 83% | 88% |
| **PASI 90 (%)** | 75% | 76% |
| **PASI 100 (%)** | 55% | 47% |

Dati provenienti da trials diversi; no head to head study

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# The potential pathogenic role of IL-17/Th17 cells in both type 1 and type 2 diabetes mellitus

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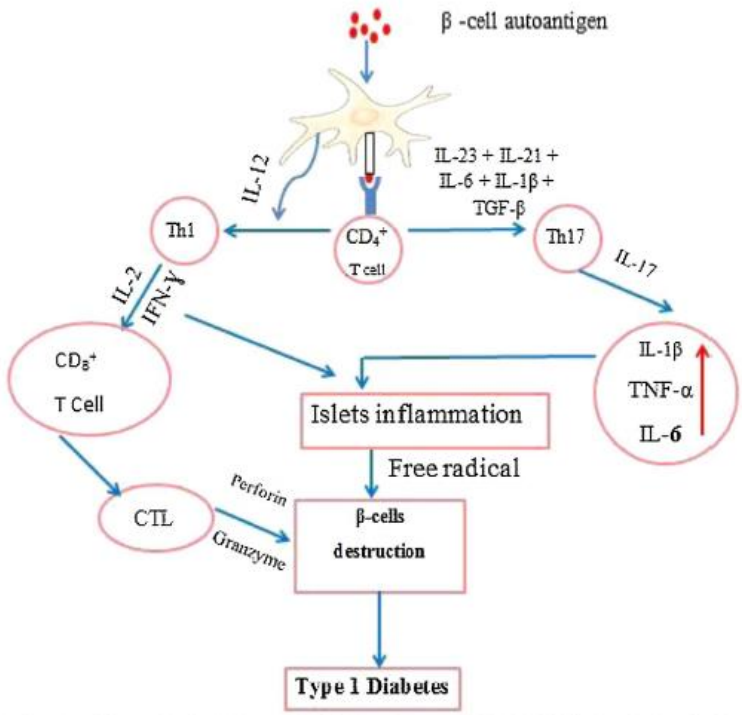
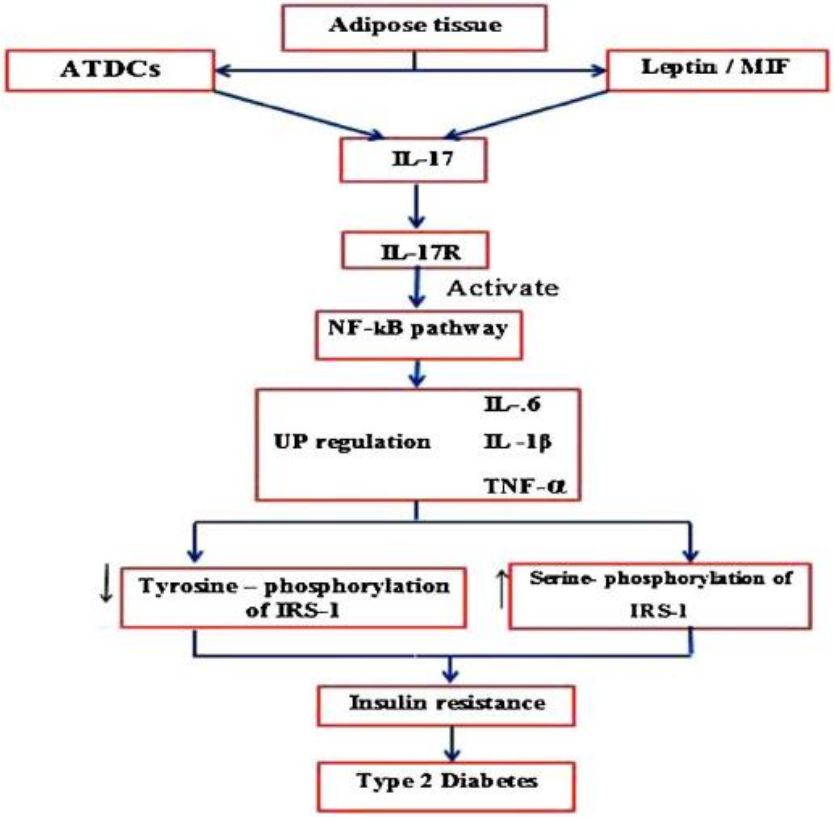



Fig. 1. Mechanism of autoimmune diabetes and role of interleukin-17. Dendritic cells (DCs) are well recognized for their role in the differentiation of naive CD4+ T cells. During antigenic stimulation, naive CD4+ T cells become effector Th1 and/or Th17 cells, based on their cytokine microenvironment. IL-12 released from APCs activates Th1 cells. Th1 cells secrete IL-2 that activates CD8+ T cells (Pre-CTL) to become cytotoxic T cells (CTL). IFN-γ-secreting Th1 cells are the key players in the destruction of β-cell, as they activate cytotoxic CD8+ T cells. These CTLs release granzyme and perforin which induce β-cells apoptosis. Simultaneously, IL-23 augmentes the differentiation of Th17 cells. IL-17 initiates inflammation by enhancing production of proinflammatory cytokines (TNF-α, IL-1β and IL-6), chemokines, and induces release of inducible nitric oxide synthase (INOS); and in turn causes an increase in free radicals which may induce β-cell destruction.



**29 Settembre 2018 – Lecce**