La via IL 12-23… ¿Contra qué diana actuar?

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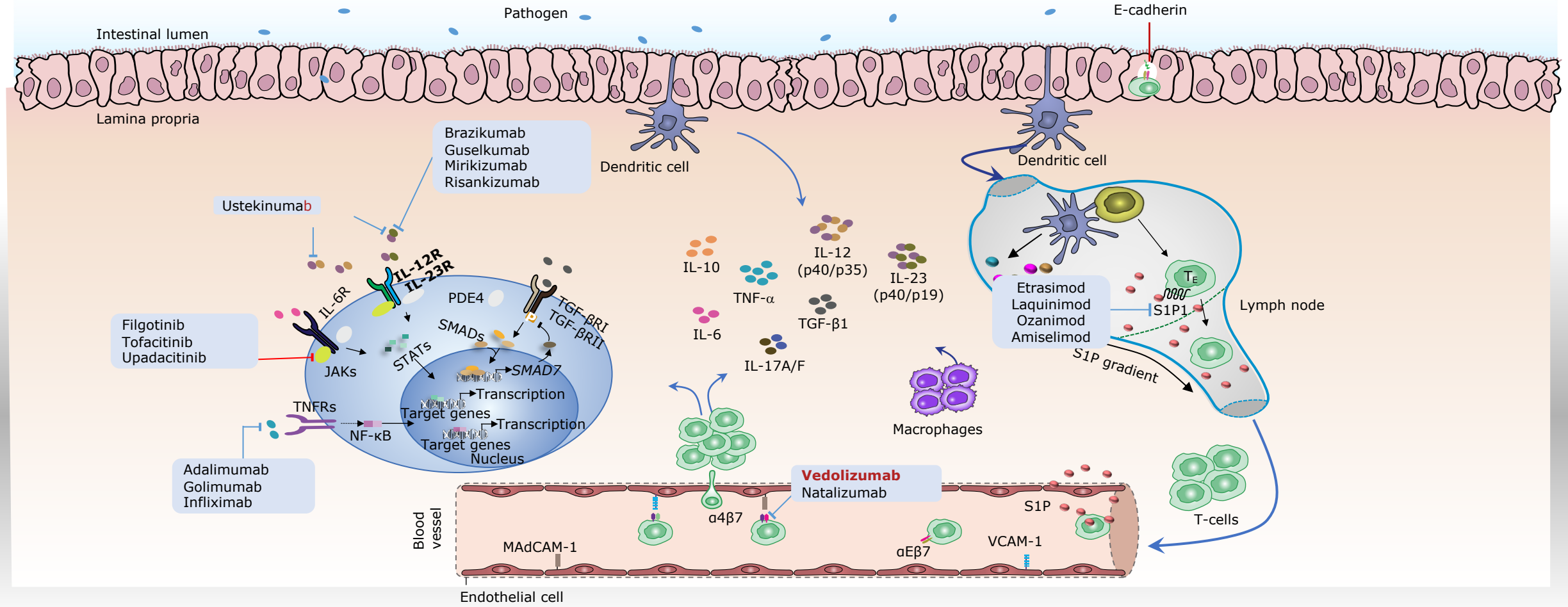
DIGESTIVO
HOSPITAL GENERAL UNIVERSITARIO DE ALICANTE

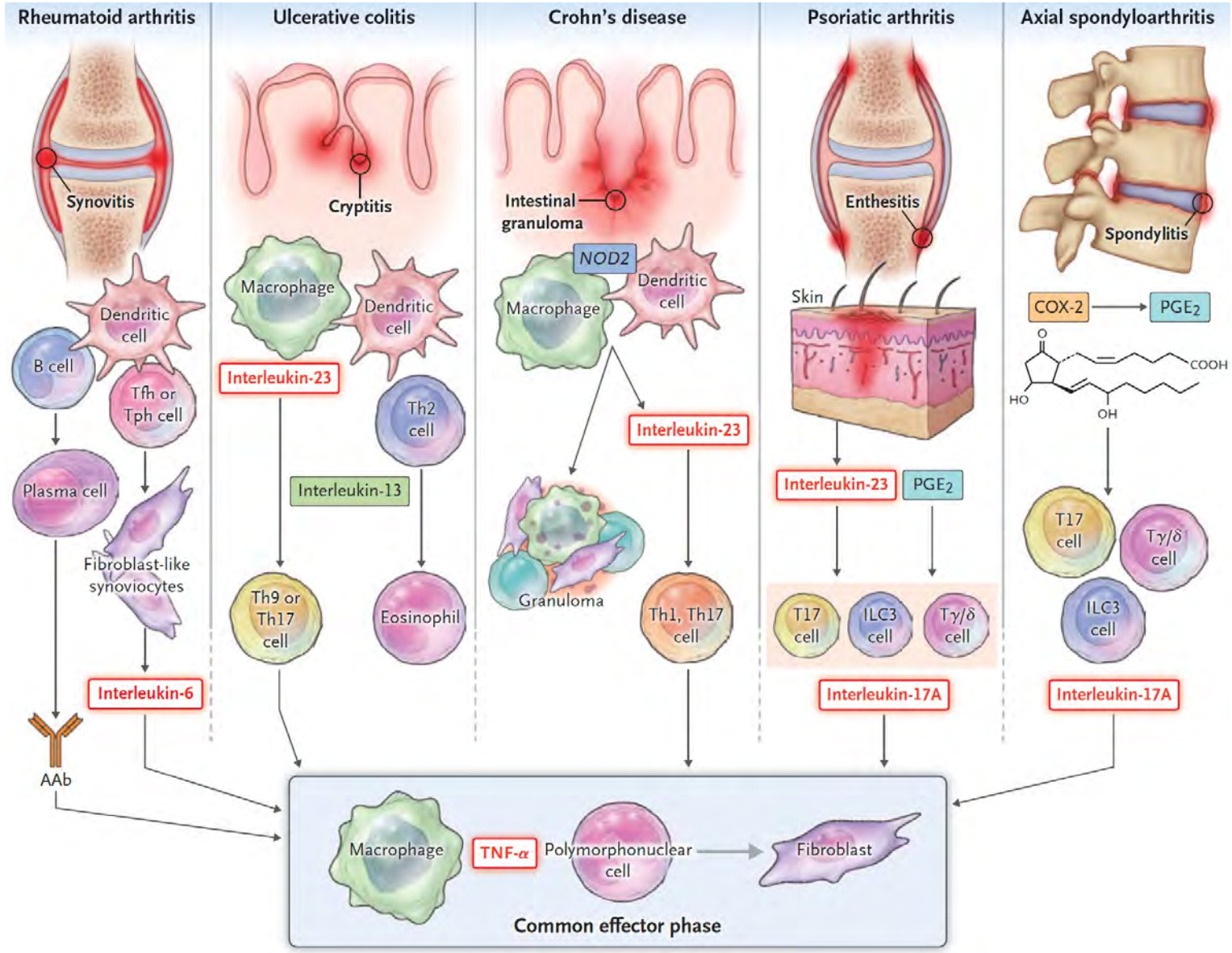
Conflicto de interés, relacionado con fármacos incluidos en esta presentación

- He recibido honorarios por conferencias, asesoría o financiación para asistencias a congresos o ayudas a investigación por Abbvie, Lilly y Janssen.


ALL YOU
NEED IS
LOVE
IMMUNOLOGY

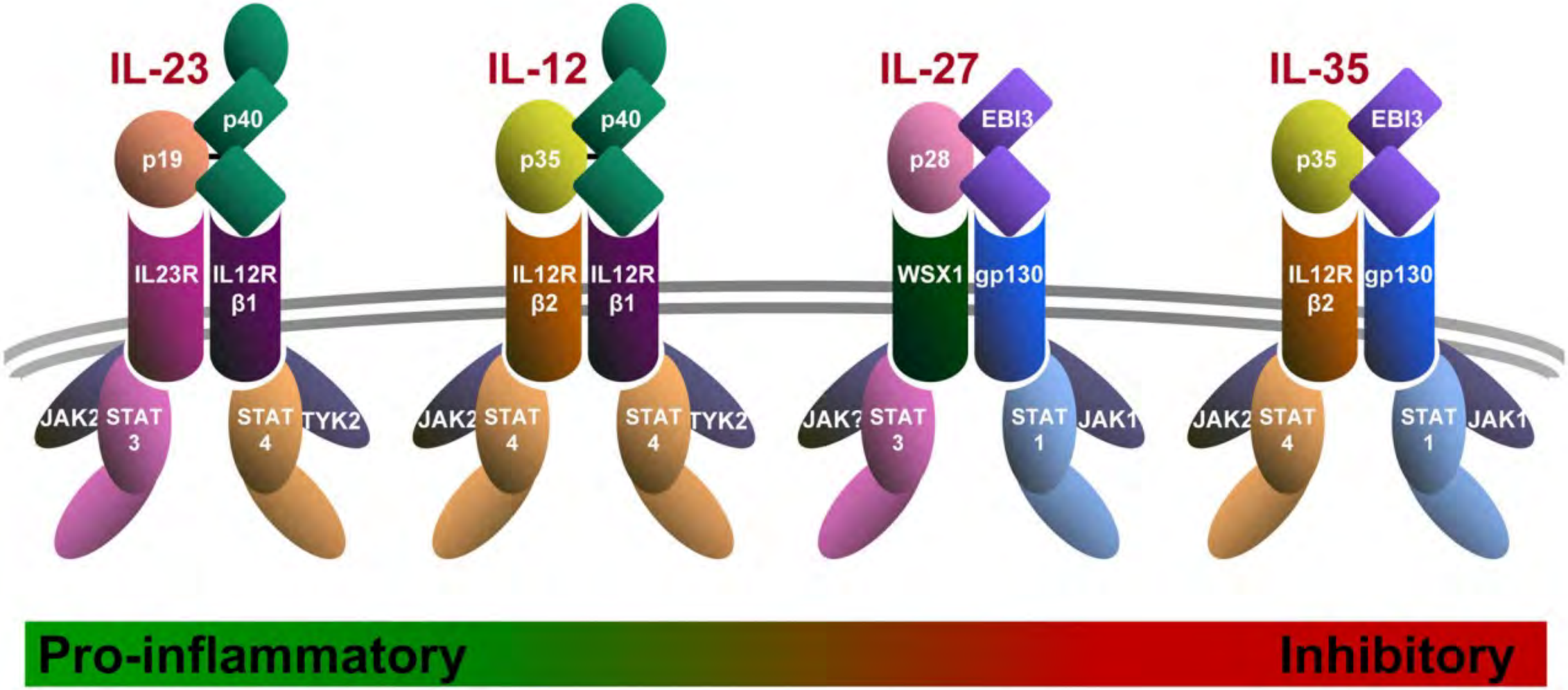


La compleja inmunología de la EII…



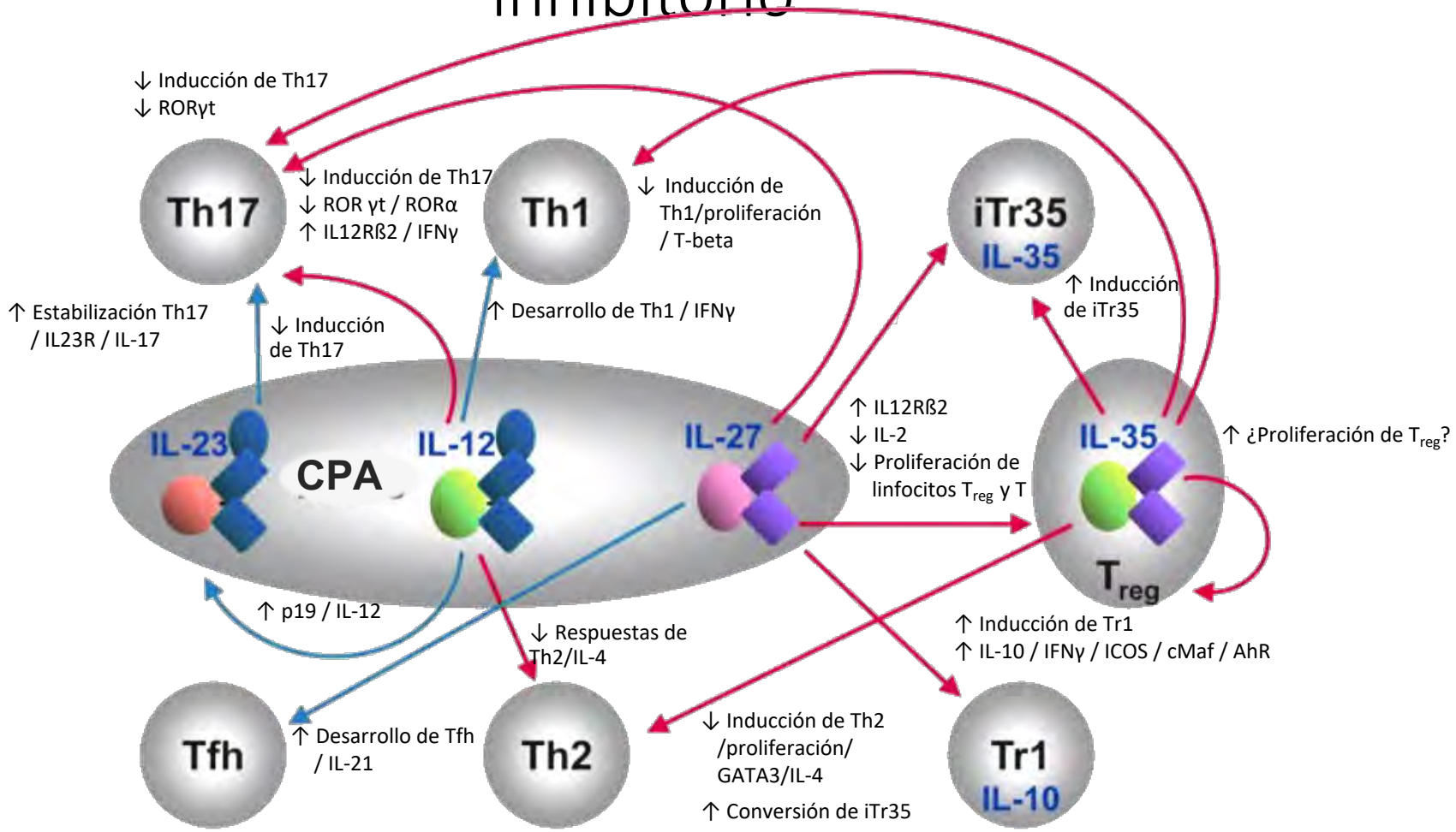
, *Schett et al, NEJM 2021*

Familia de las IL-12: una familia muy unida



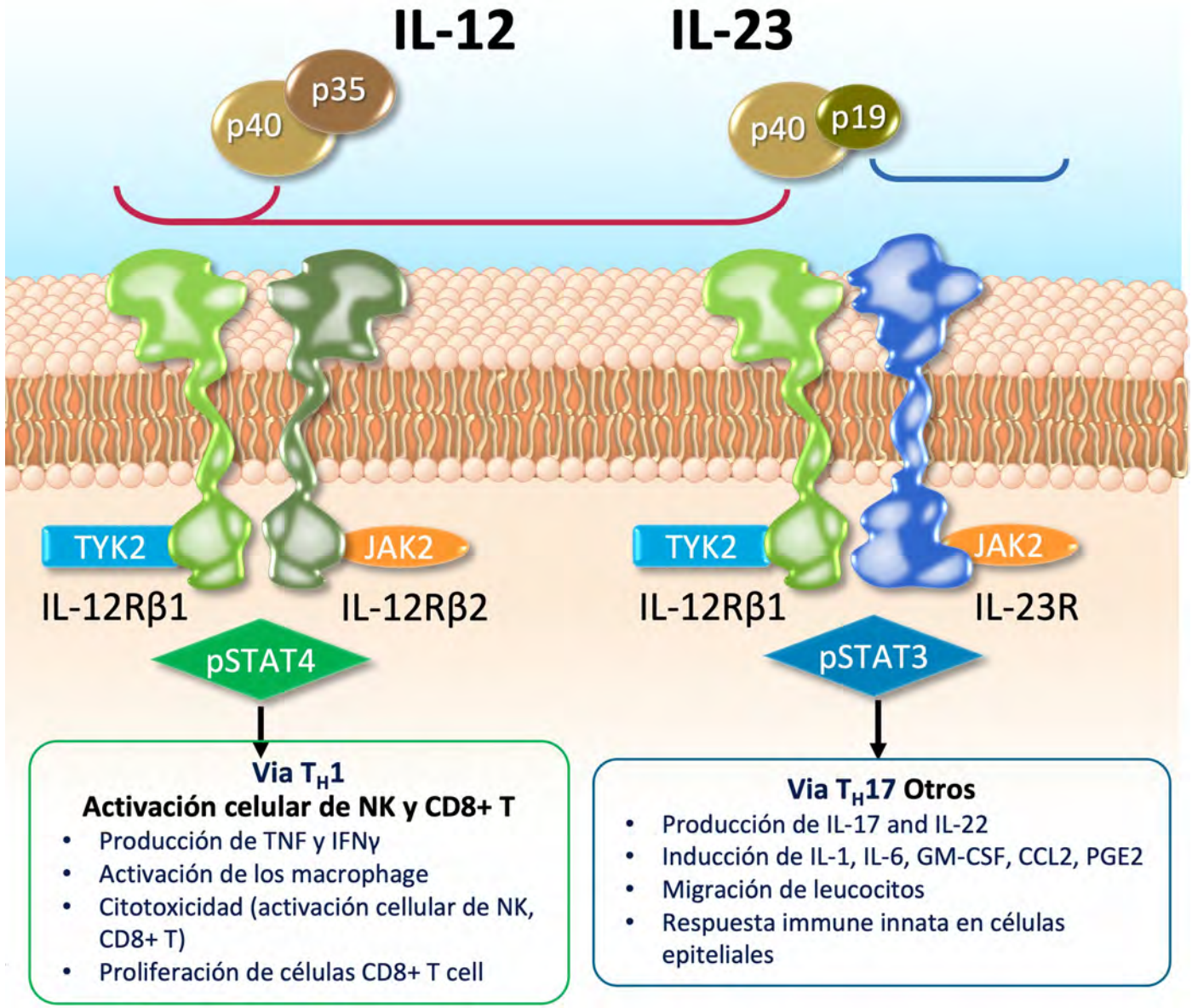
Vignali DA, et al. Nat Immunol. 2012 Jul 19;13(8):722-8.

Interleuquinas de la familia 12 y su papel proinflamatorio o inhibitorio



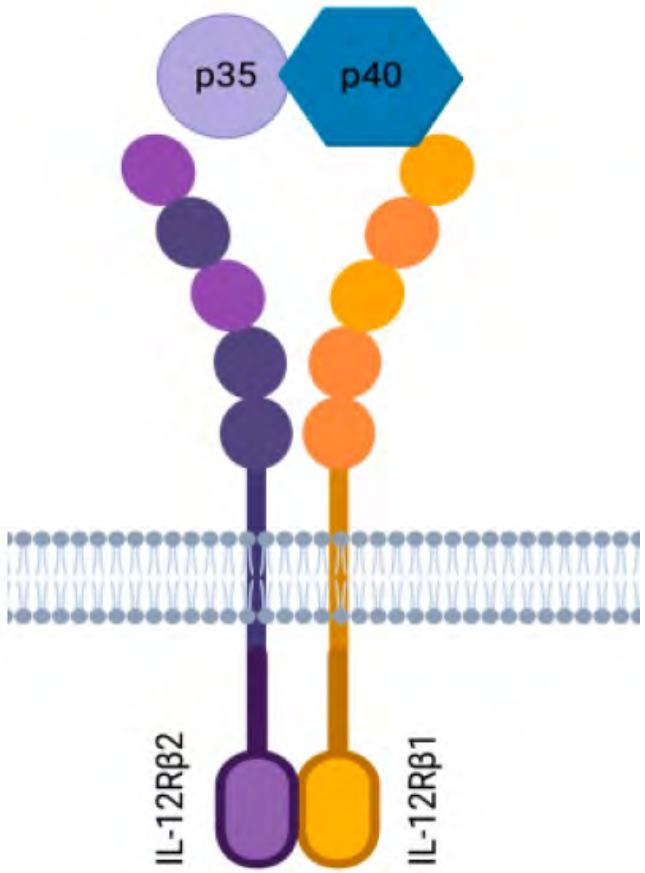
CPA: célula presentadora de antígeno; IL: interleucina; Th: T helper.

Vignali DA, et al. Nat Immunol. 2012 Jul 19;13(8):722-8.



Singh S, et al. mAbs. 2015;7:778–91. **Sofen H,** et al. J Allergy Clin Immunol. 2014;133:1032–40. **Bell GM**, et al. Nat Rev Rheumatol 2011;7:507–16. **4. Li Zhou L**, et al. mAbs. 2021;13(1):e1964420

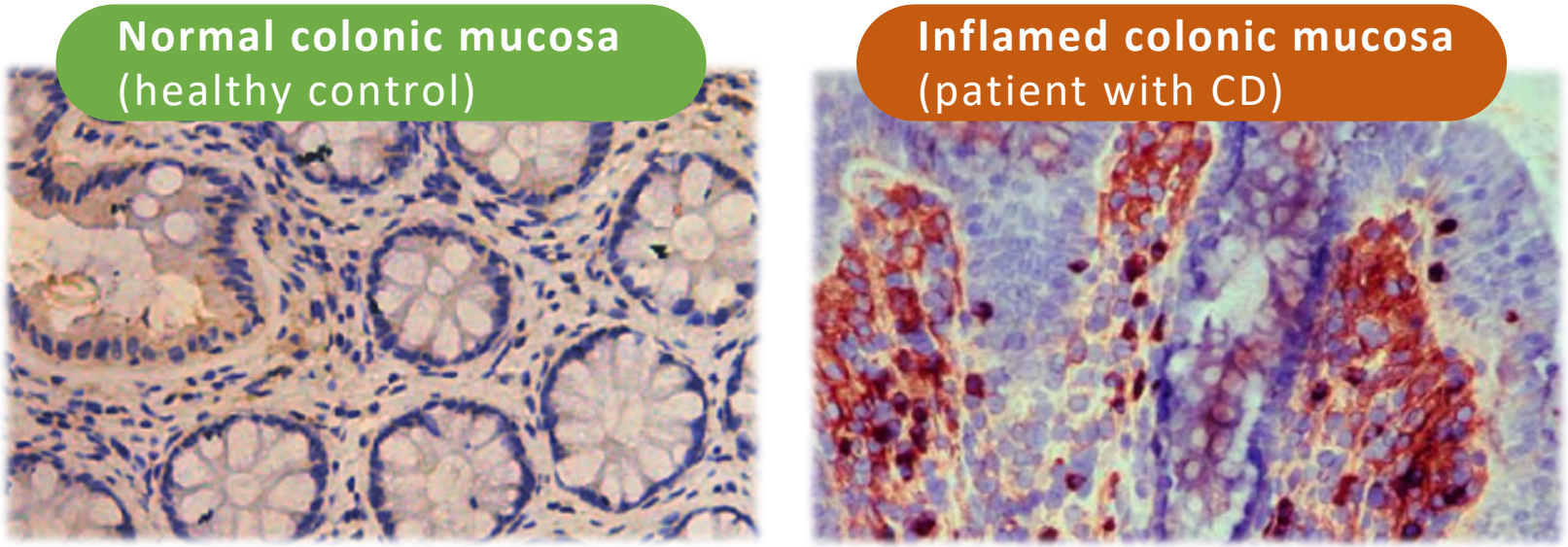
IL 12



- Via TH1: **IMPORTANCIA DE LA RESPUESTA TH1**
- Producción de ***INF Gamma***
- Protección frente a microorganismos intracelulares: **micobacterias, Salmonella**
- Acción antitumoral en modelos murinos

Variantes en IL-23, R IL-23 y genes via Th17 se asocian a riesgo de EII

- Niveles L-23 y citocinas inducidas por Th17 estan elevadas en la mucosa intestinal y Suero de paracientes con EC y CU

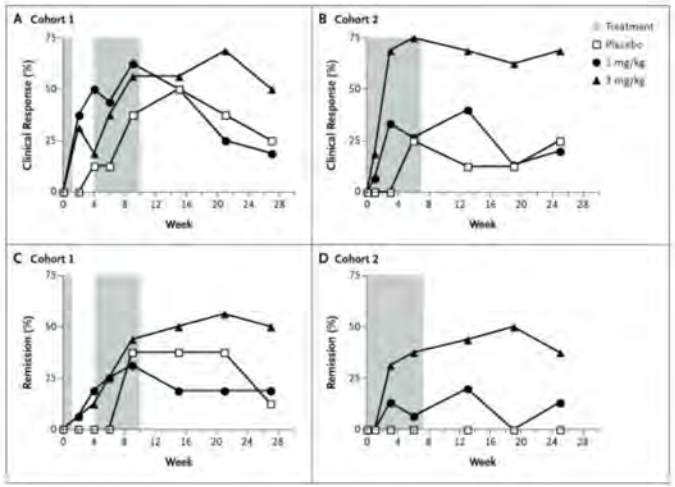


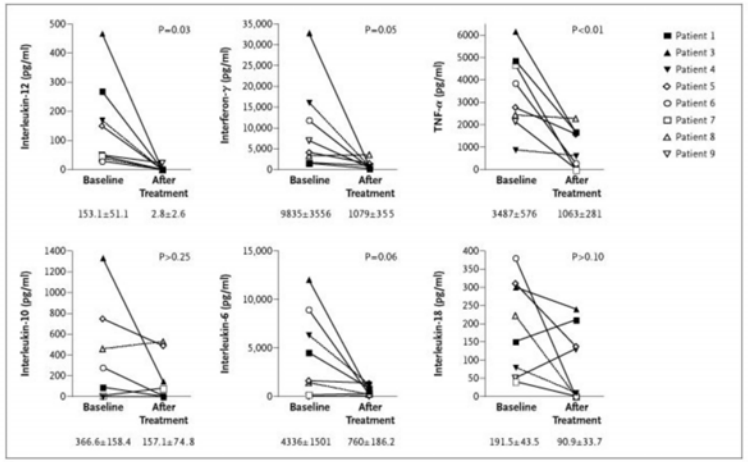
IL-23p19 expression analysed by immunohistochemistry[2]

1. Fujino S, et al. Gut 2003;52:65–70; 2. Liu Z, et al. J Leukoc Biol 2011;89:597–606; 3. El-Bassat H.Adv Dig Med2016;3:88–94; 4. Sivanesan D, et al. J Biol Chem 2016;291:8673–85.

Inhibición IL 12-23

- Anti IL -12

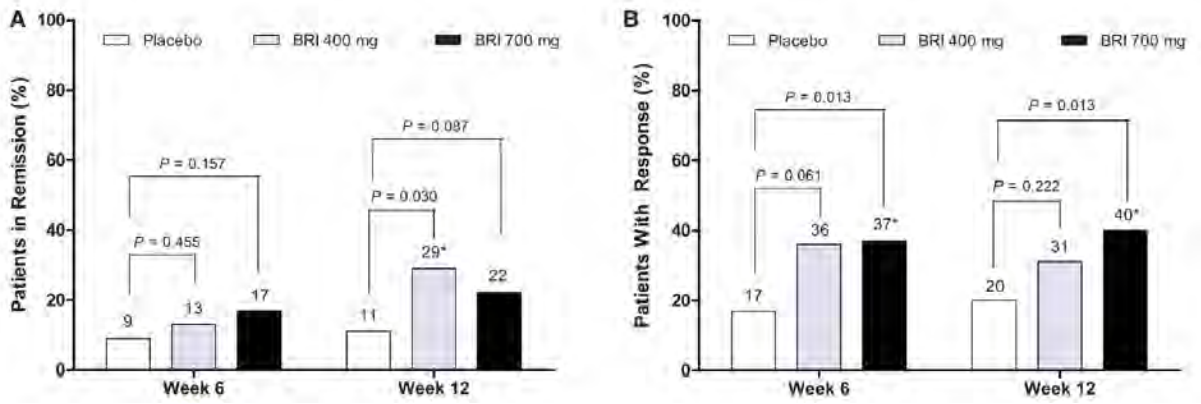




Mannon, N Engl J Med 2004; 351:2069-2079

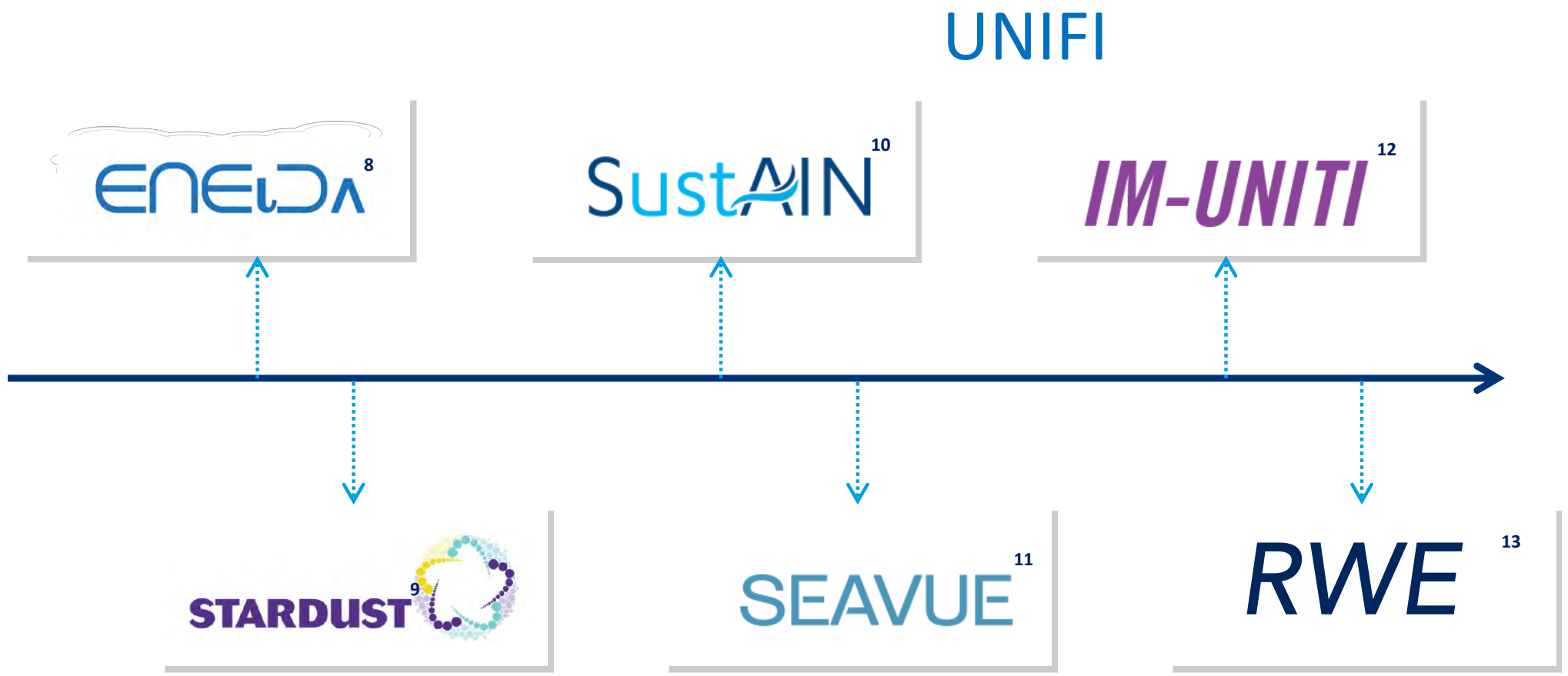
- AntiIL 12-23

Briakinumab

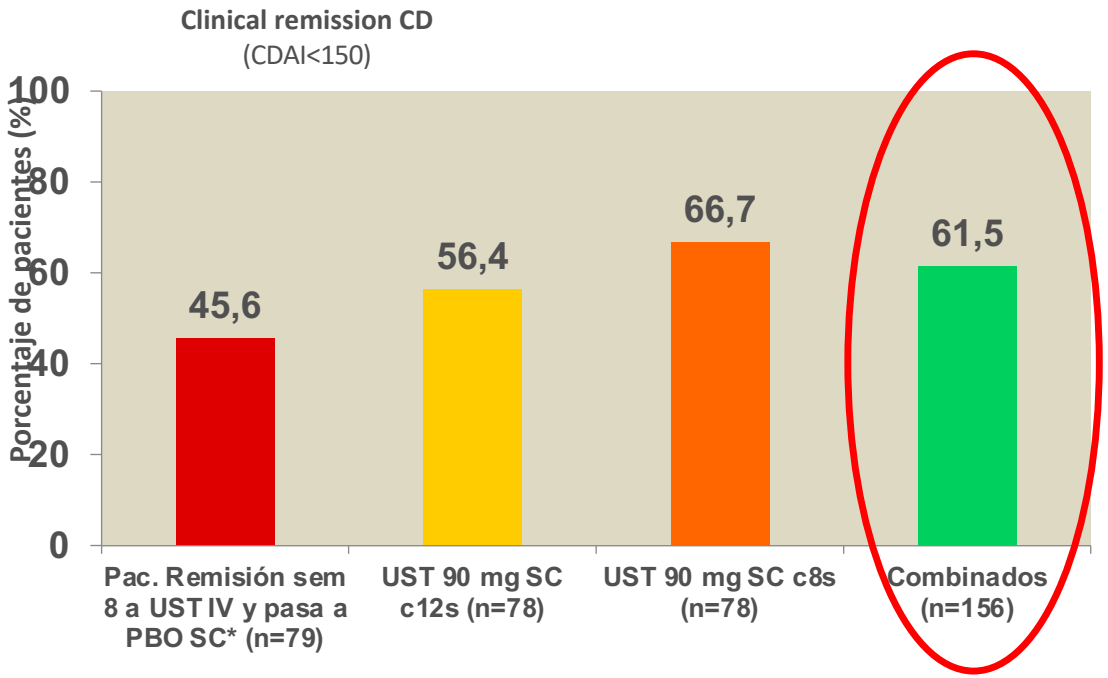


Panaccione IBD 2015; 21(6):1329-1340

Evidencia acumulada eficacia Ustekinumab Inh IL 12-23

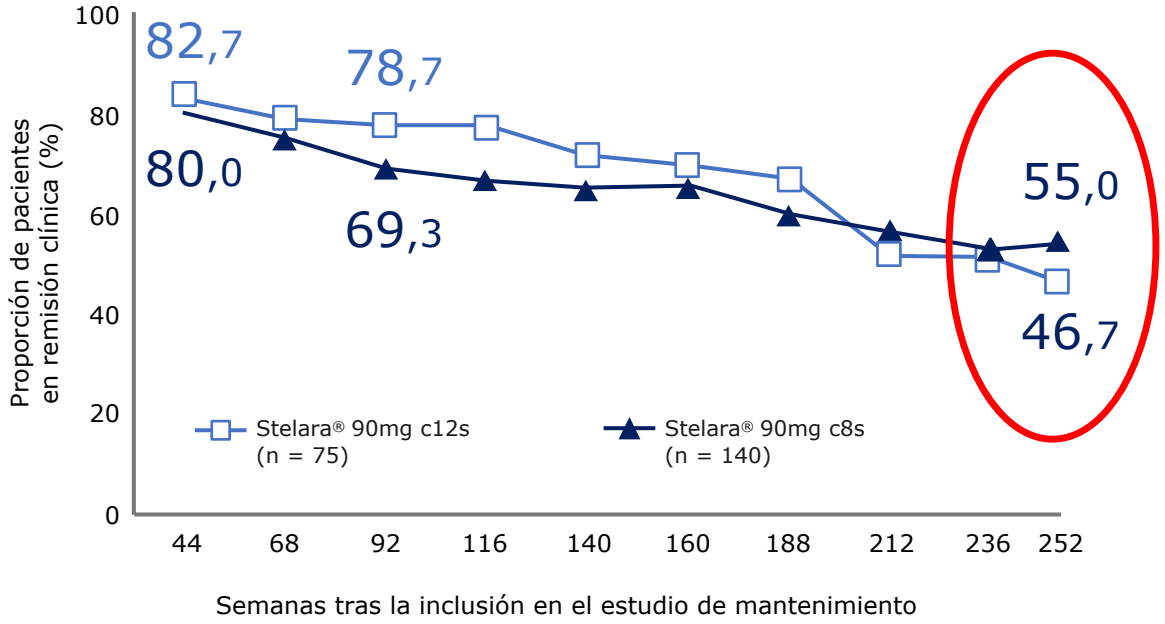


Estudio IM-UNITI



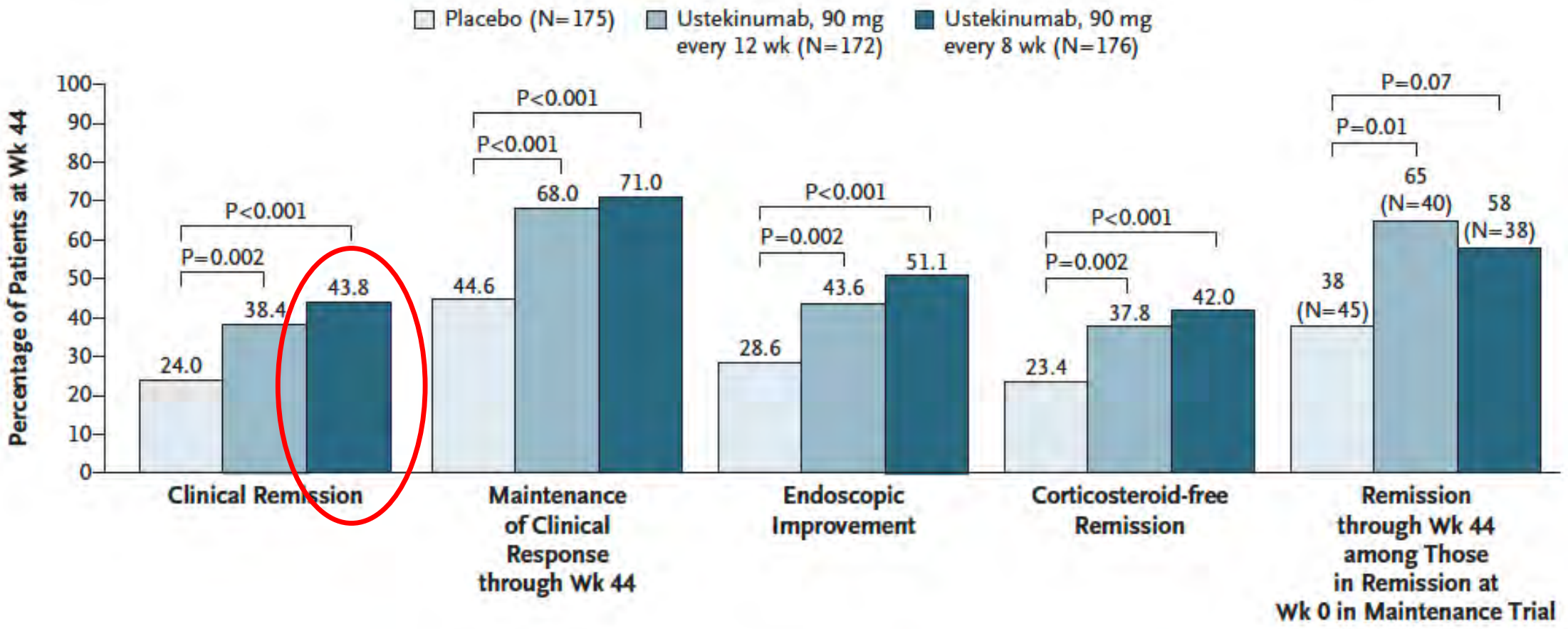
EC semana 44

IM-UNITI A 5 AÑOS



EC semana 252

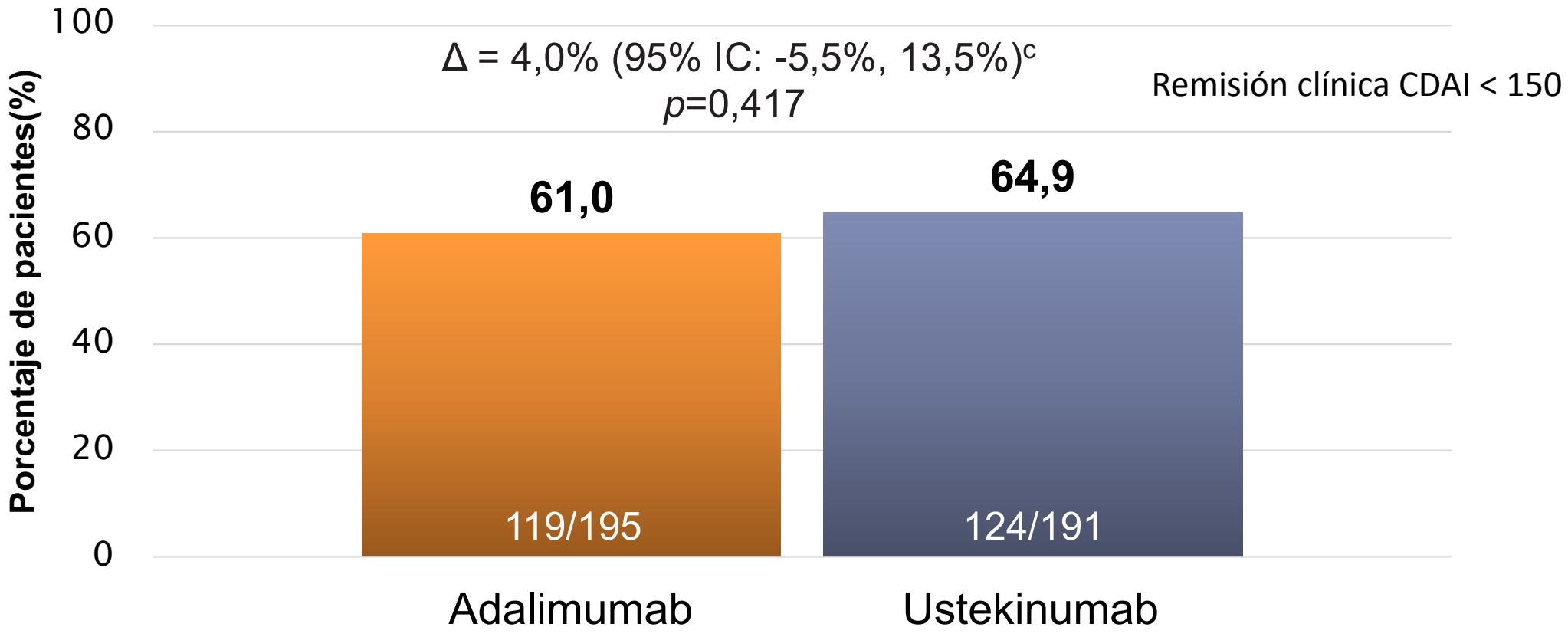
UNIFI, Ustekinumab en CU



Sands, N Engl J Med 2019; 381:1201-1214

HEAD TO HEAD EC: Estudio SEAVUE

Criterio de Valoración Primario[a,b]



Potencial Riesgo de Inhibición IL-12

Table 1. Cellular and clinical phenotypes of IL-12Rβ1- and IL-12p40-deficient patients

Clinical phenotype	Cellular phenotype		
	Complete IL-12Rβ1 deficiency *n*=54 (74%)	Complete IL-12p40 deficiency *n*=19 (26%)	Total *n*=73
BCG disease/BCG inoculation	26 out of 35 (74%)	16 out of 16 (100%)	42 out of 51 (82%)
Environmental mycobacteriosis	12 out of 54 (22%)	2 out of 19 (11%)	14 out of 73 (19%)
Non-typhoid salmonellosis	25 out of 54 (46%)	5 out of 19 (26%)	30 out of 73 (42%)
Tuberculosis	3 out of 54 (6%)	1 out of 19 (5%)	4 out of 73 (5%)
Other infections	*P. brasiliensis* (*n*=1)	*N. asteroides* (*n*=1)	
Asymptomatic siblings	5 out of 15 (33%)	1 out of 4 (25%)	6 out of 19 (32%)
Deaths	8 out of 54 (15%)	7 out of 19 (37%)	15 out of 73 (21%)

Fieschi, Eur J Inmunol 2003;33:1461-64

Seguridad Anti IL 12-23

Safety of ustekinumab in IBD: Final pooled long-term safety analysis through 5 years in CD and 4 years in UC

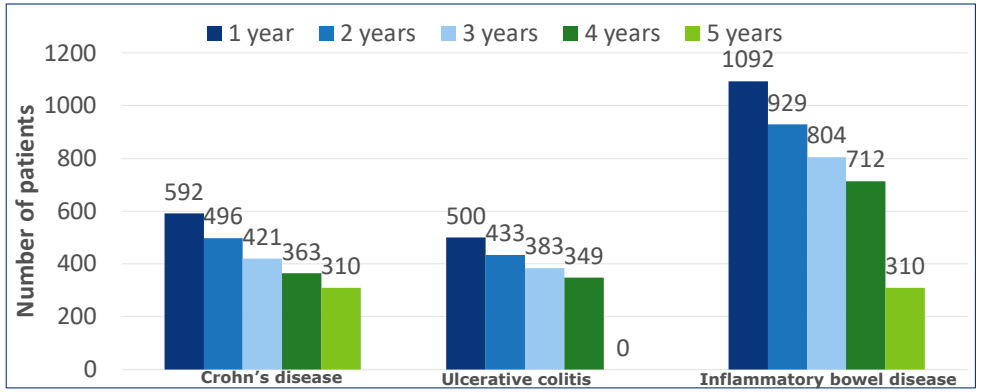


Table 1: Key safety events in phase 2/3 IBD clinical studies through up to 5 years in CD and 4 years in UC; number of events per 100 PYs of follow-up and 95% confidence intervals

	Pooled IBD	
	PBO[a] (n=1389)	UST[b] (n=2575)
Total PYs of follow-up	943	4826
Adverse events	482.41	347.47
95% CI	(468.49, 496.64)	(342.23, 352.77)
Serious adverse events	29.39	18.85
95% CI	(26.03, 33.06)	(17.65, 20.12)
Infections	108.64	88.87
95% CI	(102.09, 115.50)	(86.23, 91.57)
Serious infections	5.52	3.71
95% CI	(4.12, 7.23)	(3.19, 4.29)
MACE	0.32	0.25
95% CI	(0.07, 0.93)	(0.13, 0.43)
Discontinuation due to adverse events	11.56	5.51
95% CI	(9.50, 13.95)	(4.87, 6.22)
Malignancies (excluding NMSC)	0.32	0.41
95% CI	(0.07, 0.93)	(0.25, 0.64)

Gosh, OP-39 ECCO 2023

Anti p19 → Anti IL-23 (iv, sc)

	CD			UC	
Brazikumab	Phase 2/3	STOP		Phase 2	STOP
Mirikizumab (Omvoh®)	Phase 2 (ind) SERENITY	Phase 3 (LTE) VIVID-1 VIVID-2	Aprobado por EMA para CU (no por FDA)	Phase 3 (ind-man) LUCENT 1-2	Phase 3 (LTE) LUCENT 3
Guselkumab	Phase 2/3 GALAXI (iv-sc)	Phase 2/3 GRAVITY (sc)	Psoriasis y artritis psoriásica	Phase 2/3 (ind) QUASAR (iv-sc)	Phase 3 (ind) ASTRO (sc)
Risankizumab (Skyrizi®)	Phase 3 (ind) MOTIVATE-ADVANCE	Phase 3 (mant) FORTIFY		Phase 2/3 (ind) INSPIRE	Phase 3 (MANT) COMMAND

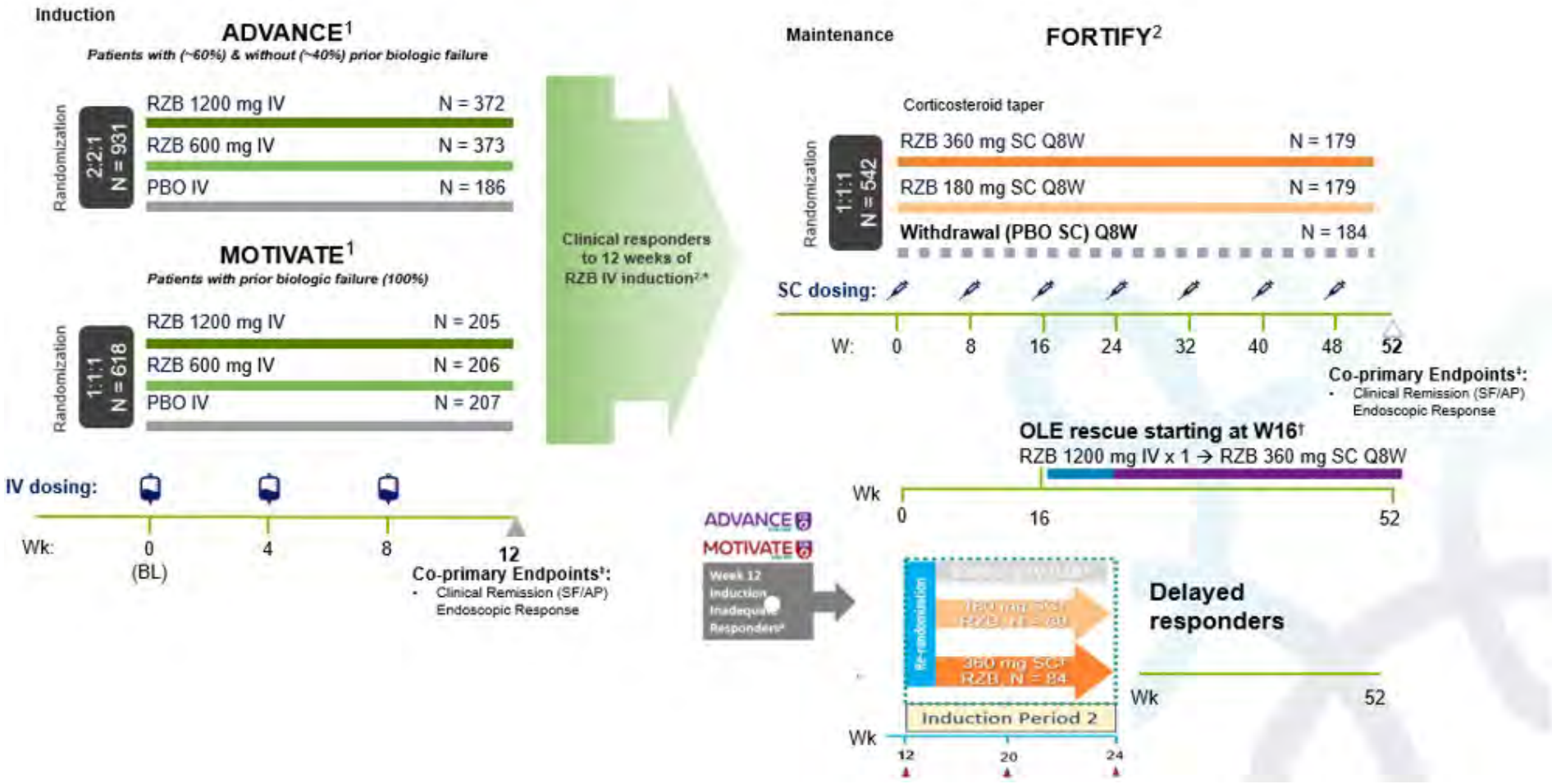
Aprobado por EMA y FDA EC, psoriasis y AP

Cortesía Dra Lobatón

Risankizumab

Criterios de inclusión
- EC moderada a grave (CDAI 220-450)
- Evidencia endoscópica de actividad (SES-CD)

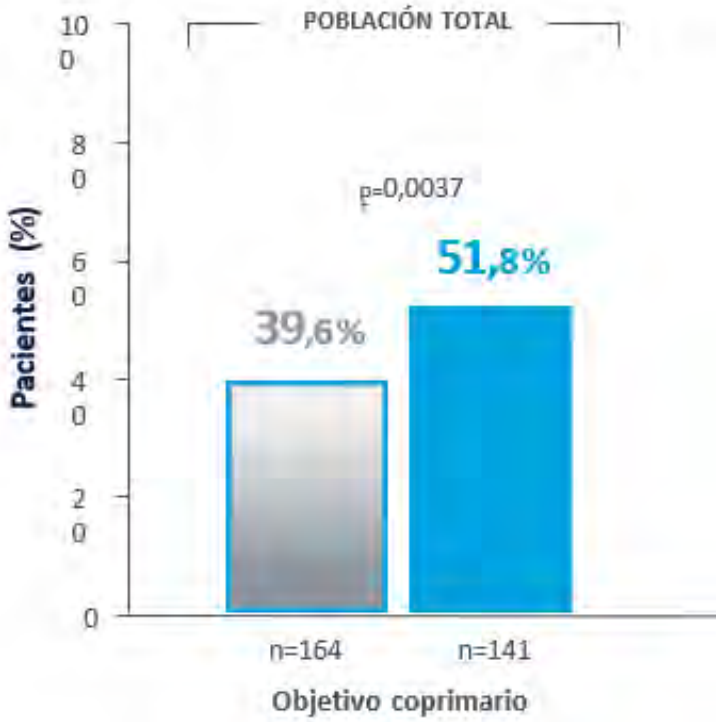
- Fallo previo a convencional y/o biológicos (MOTIVATE: todos fallo a biológicos)



D'Haens, Lancet. 2022;399:2015-2030. Ferrante M et al. Lancet. 2022;399:2031-2046

Risankizumab: mantenimiento semana 52

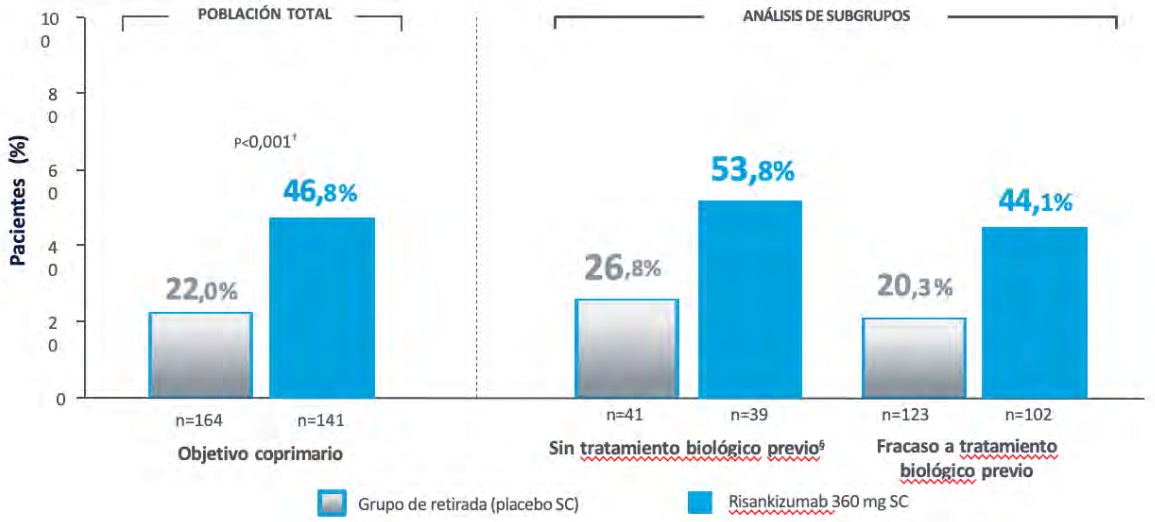
Remisión Clínica



REMISIÓN CLÍNICA SF/AP

Frecuencia media diaria de deposiciones (SF) ≤2,8 y no peor que el valor inicial y **media de la puntuación de dolor abdominal diaria (AP) ≤1** y no peor que el valor inicial.

Respuesta endoscópica



RESPUESTA ENDOSCÓPICA

Disminución del SES-CD >50% respecto a la situación inicial (o en los pacientes con una enfermedad ileal aislada y un SES-CD inicial de 4, una reducción de como mínimo 2 puntos respecto a la situación inicial), confirmado por un revisor central.

N=542 pacientes

Corticoides basales 30%

IMN basales 25%

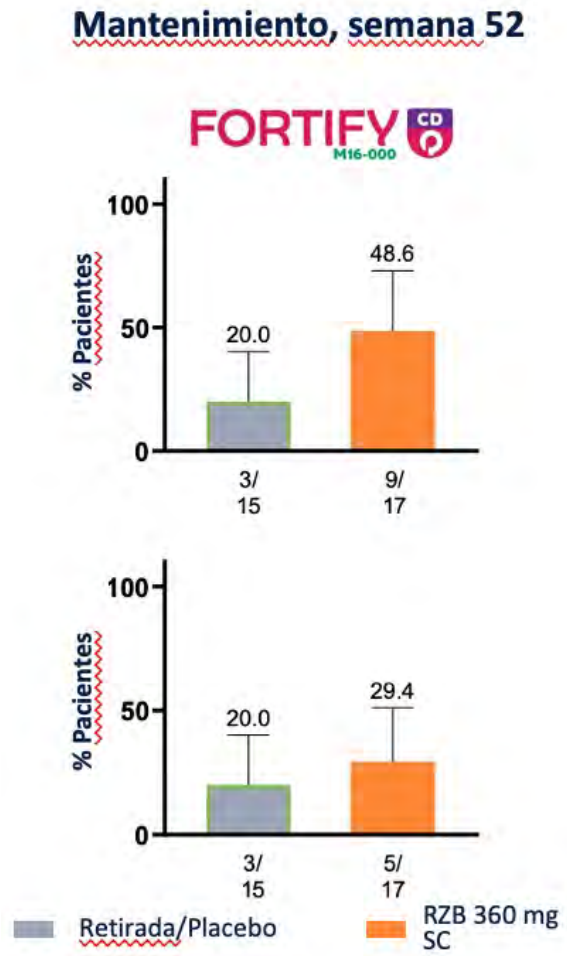
Bionaive 40%

Fallo 1 biológico 30%

Fallo > 1 30%

Ferrante M et al. *Lancet.* 2022;399:2031-2046

Risankizumab: mantenimiento semana 52
Post- hoc tras ustekinumab



N=542 pacientes
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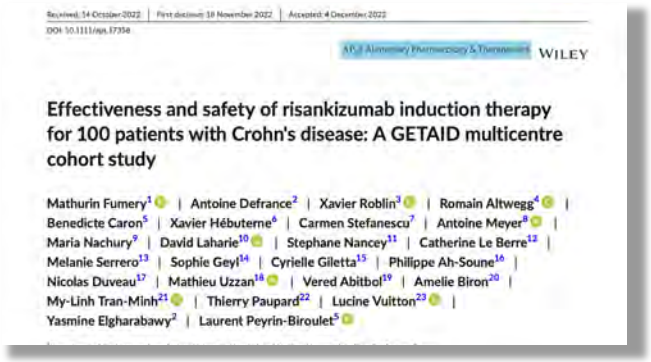
Ferrante M et al. *Lancet.* 2022;399:2031-2046

Risankizumab Real life GETAID

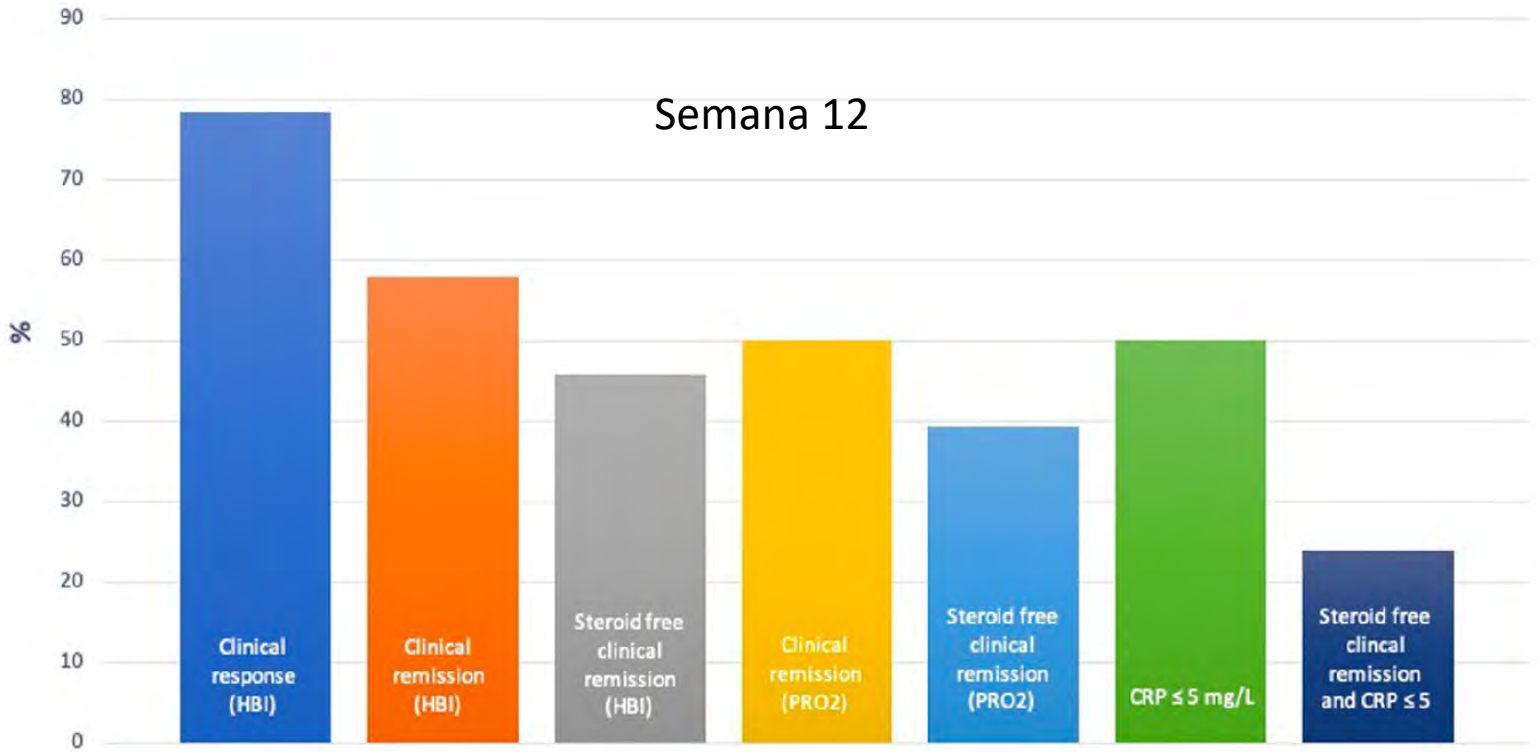


Effectiveness and safety of risankizumab induction therapy for 100 patients with Crohn's disease: A GETAID multicentre cohort study

Mathurin Fumery[1] | Antoine Defrance[2] | Xavier Roblin[3] | Romain Altwegg[4] | Benedicte Caron[5] | Xavier Hébuterne[6] | Carmen Stefanescu[7] | Antoine Meyer[8] | Maria Nachury[9] | David Laharie[10] | Stephane Nancey[11] | Catherine Le Berre[12] | Melanie Serrero[13] | Sophie Geyl[14] | Cyrielle Giletta[15] | Philippe Ah-Soune[16] | Nicolas Duveau[17] | Mathieu Uzzan[18] | Vered Abitbol[19] | Amelie Biron[20] | My-Linh Tran-Minh[21] | Thierry Paupard[22] | Lucine Vultton[23] | Yasmine Elgharabawy[2] | Laurent Peyrin-Biroulet[5]

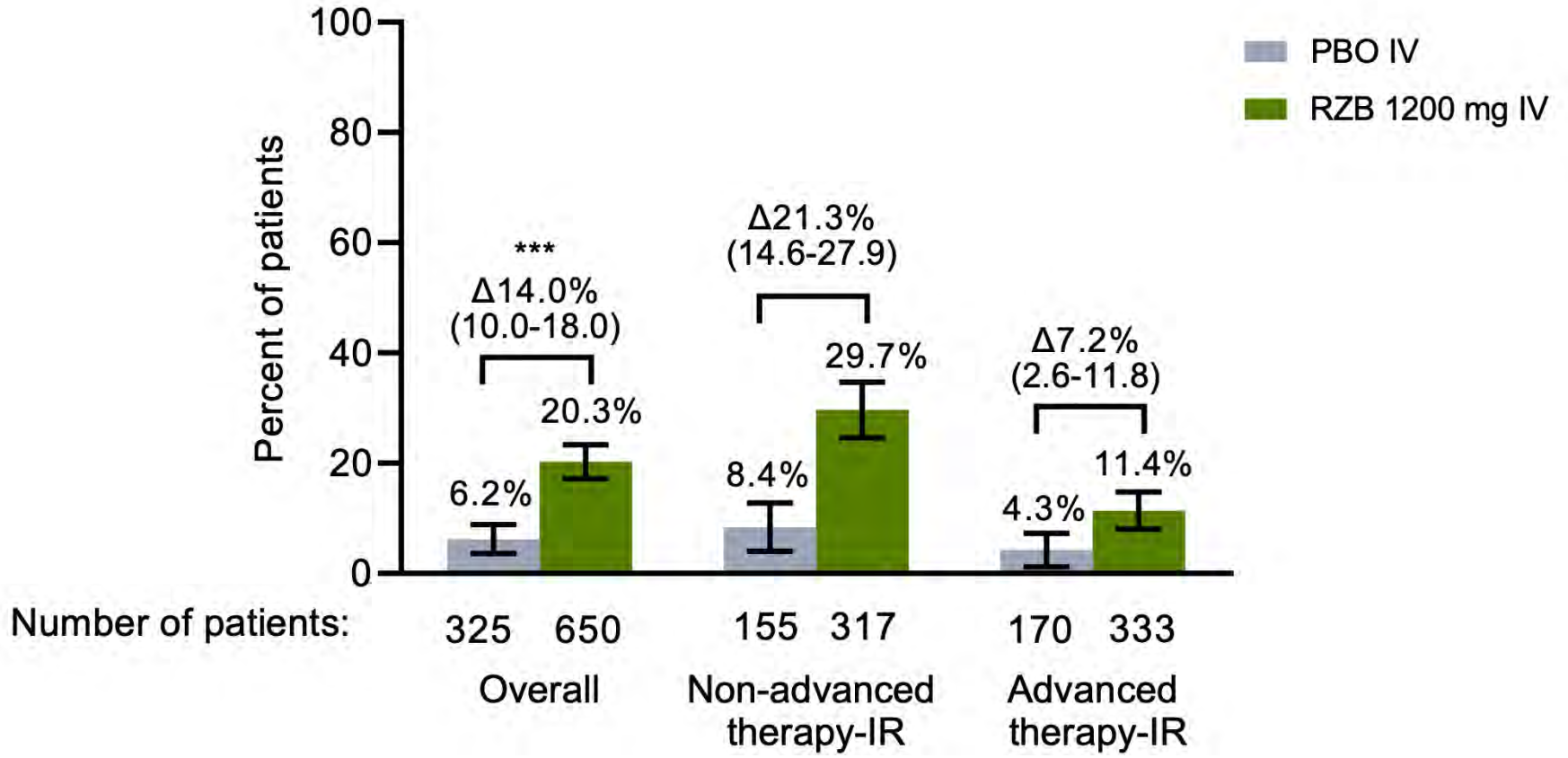
- ✓ 100 PACIENTES REFRACTARIOS
- ✓ 98/100 expuestos a USTE
- ✓ 94 expuestos a VEDO
- ✓ TODOS 3 ó más biológicos

OR: 2.80; 95% CI: 1.07–7.82; *p* = 0.041 **Remisión clínica si pérdida de respuesta a USTE y no fallo 1**



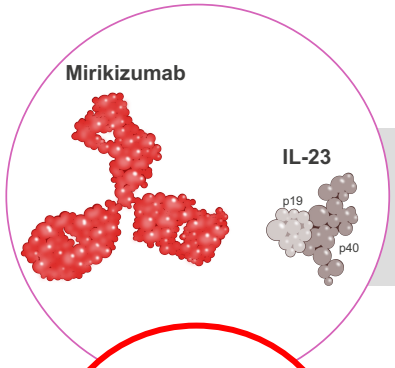
Risankizumab en CU: INSPIRE

Semana 12



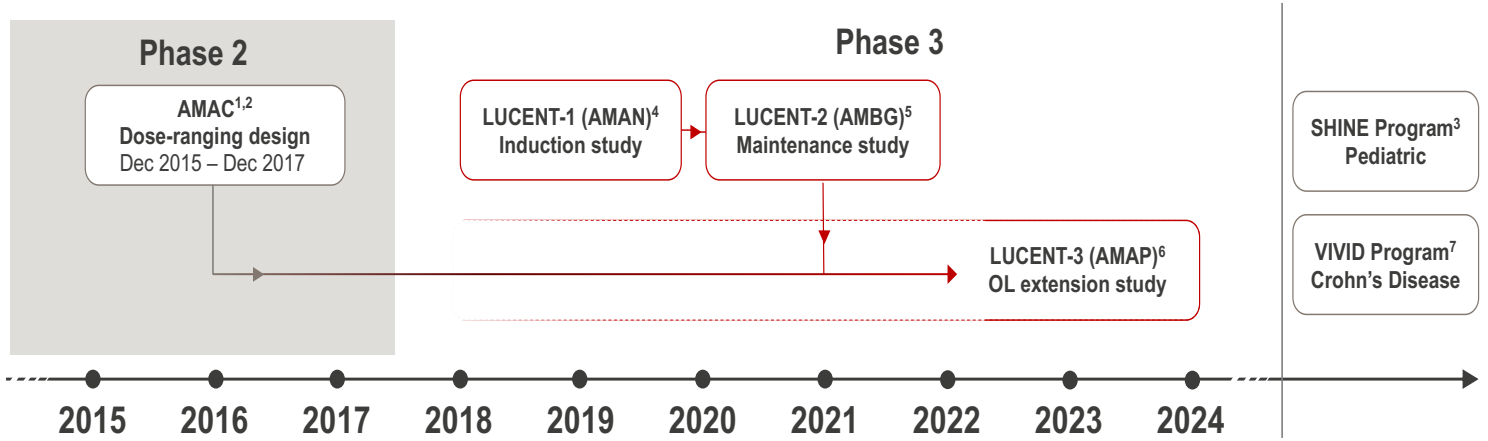
Louis et al., United European Gastroenterology Week (UEGW). October 2023.

Mirikizumab



Mirikizumab is an immunoglobulin G4 (IgG4) **monoclonal antibody (mAb)** that specifically **targets IL-23**.[1]

Ig G4

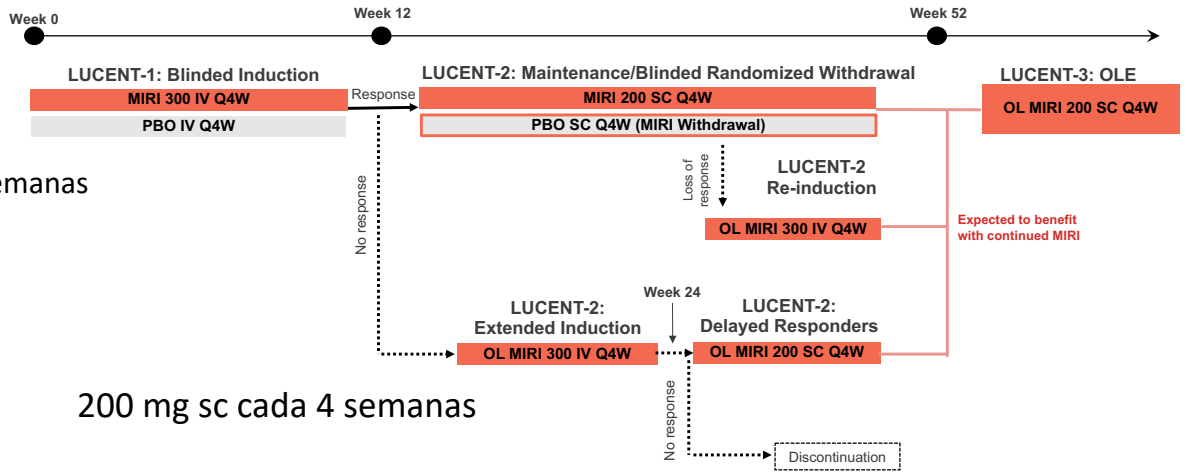


Inducción

300 mg iv/4 semanas

Mantenimiento

LUCENT Study Design



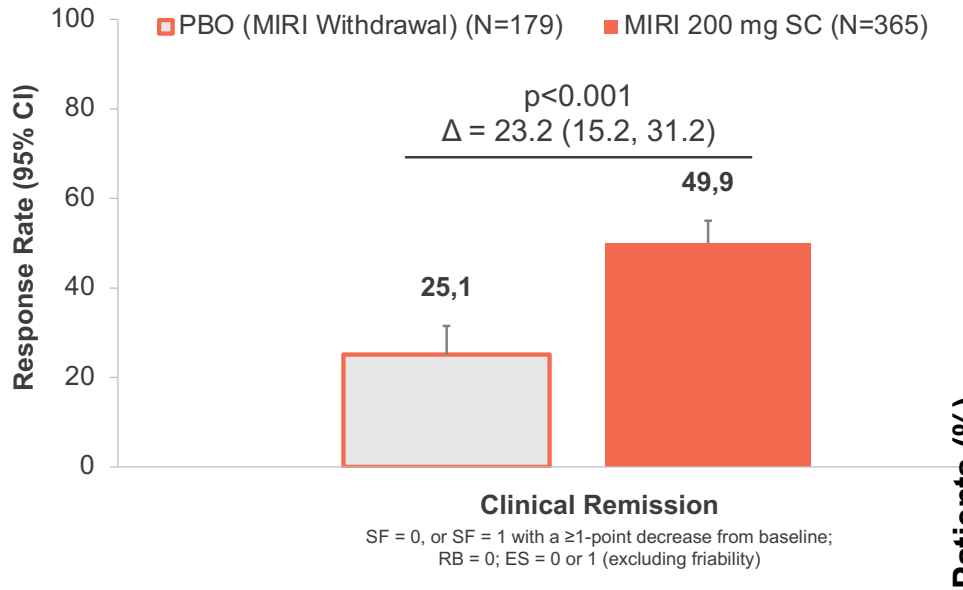
200 mg sc cada 4 semanas

40% Fallo a biológicos o TOFA
Excluyen expuestos a UST o anti IL-23 o fallo a >= 3 biológicos

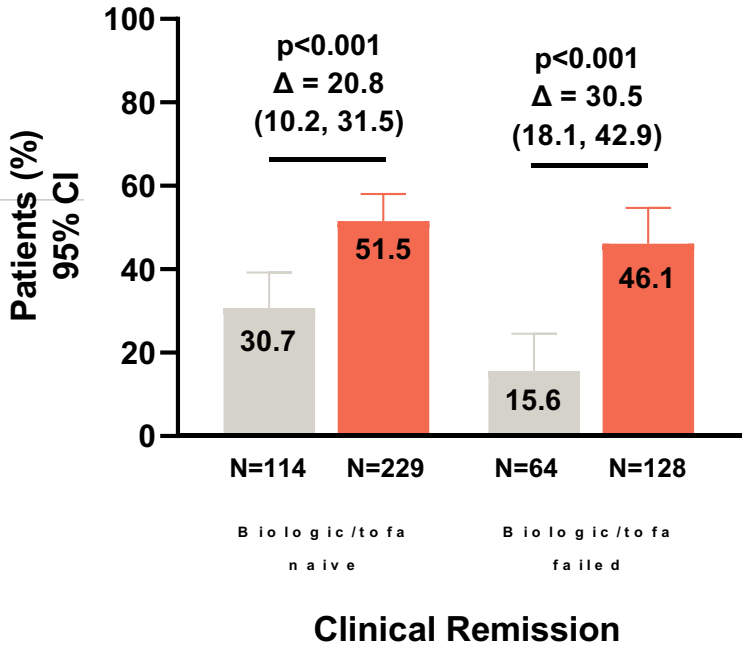
Note: Responders to induction MIRI at Week 12 of LUCENT-1, defined as achieving ≥2-point and ≥30% decrease in the MMS from baseline with RB = 0 or 1, or ≥1-point decrease from baseline, were randomized to receive maintenance MIRI or PBO in LUCENT-2. D'Haens G, et al. N Engl J Med. 2022;388(26):2444-2455).

Mirikizumab, semana 52 objetivo primario remisión clínica

N=544 PACIENTES



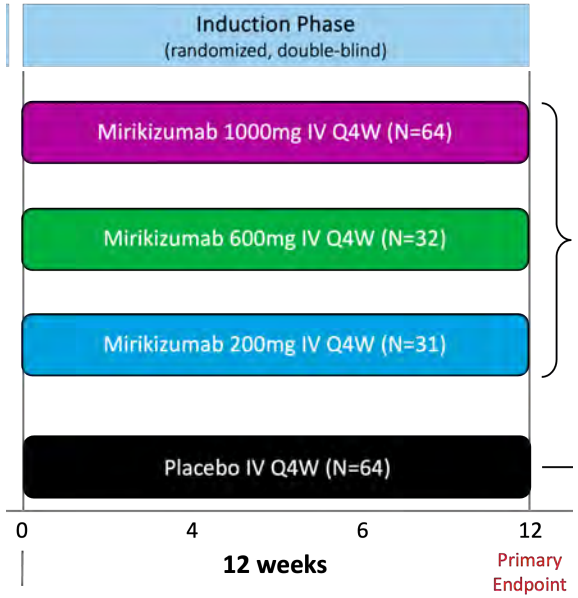
CI=Confidence Interval; ES=Endoscopic Subscore; MIRI=Mirikizumab; PBO=Placebo; RB=Rectal Bleeding; SC=Subcutaneous; SF=Stool Frequency.
Dubinsky MC, et al. Presented at: *DDW 2022*; 867e.



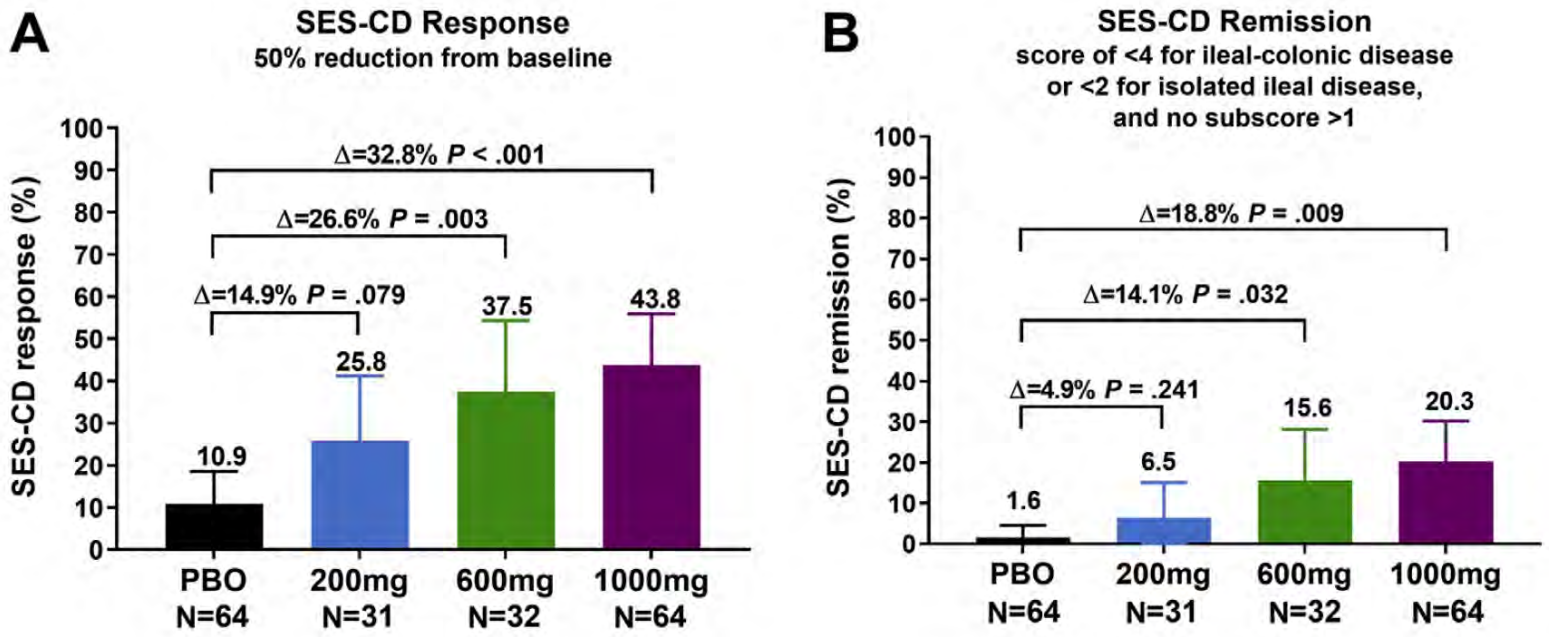
	PBO N=294	Miri 300 mg IV N=868
Baseline corticosteroid use, n (%)	113 (38.4)	351 (40.4)
Baseline immunomodulator use, n (%)	69 (23.5)	211 (24.3)
Prior biologic (or tofacitinib) failure, n (%)	118 (40.1)	361 (41.6)
Prior anti-TNF failure, n (%)	97 (33.0)	325 (37.4)
Prior vedolizumab failure, n (%)	59 (20.1)	159 (18.3)
Prior tofacitinib failure, n (%)	6 (2.0)	34 (3.9)
Number of failed biologics (or tofacitinib), n (%)*		
0	176 (59.9)	507 (58.4)
1	65 (22.1)	180 (20.7)
2	49 (16.7)	154 (17.7)
>2	4 (1.4)	27 (3.1)

*In the published abstract the ITT population values for number of failed biologics were reported. To ensure consistency with other endpoints, here we report those data in the modified ITT population which excludes patients impacted by the eCOA transcription error in Poland and Turkey.

Mirikizumab en EC: Serenity

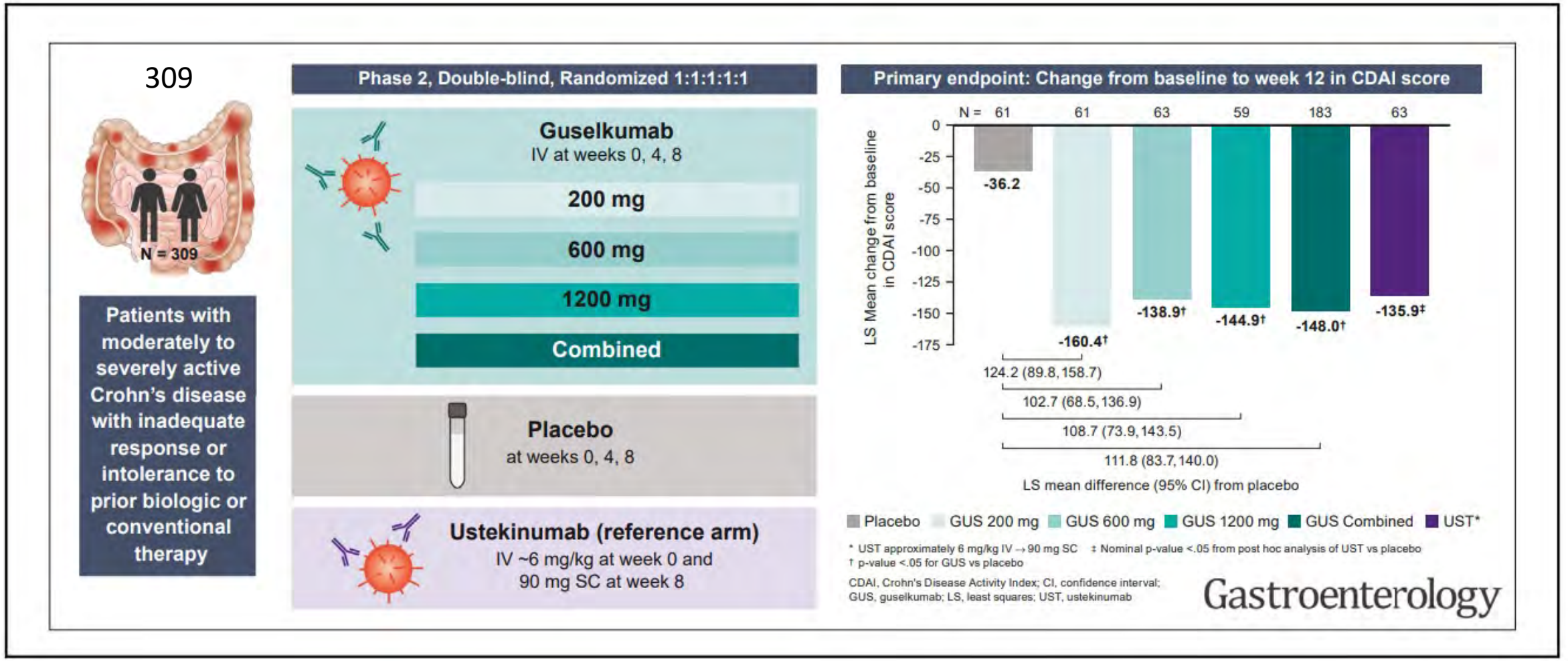


Objetivo primario Respuesta endoscópica semana 2



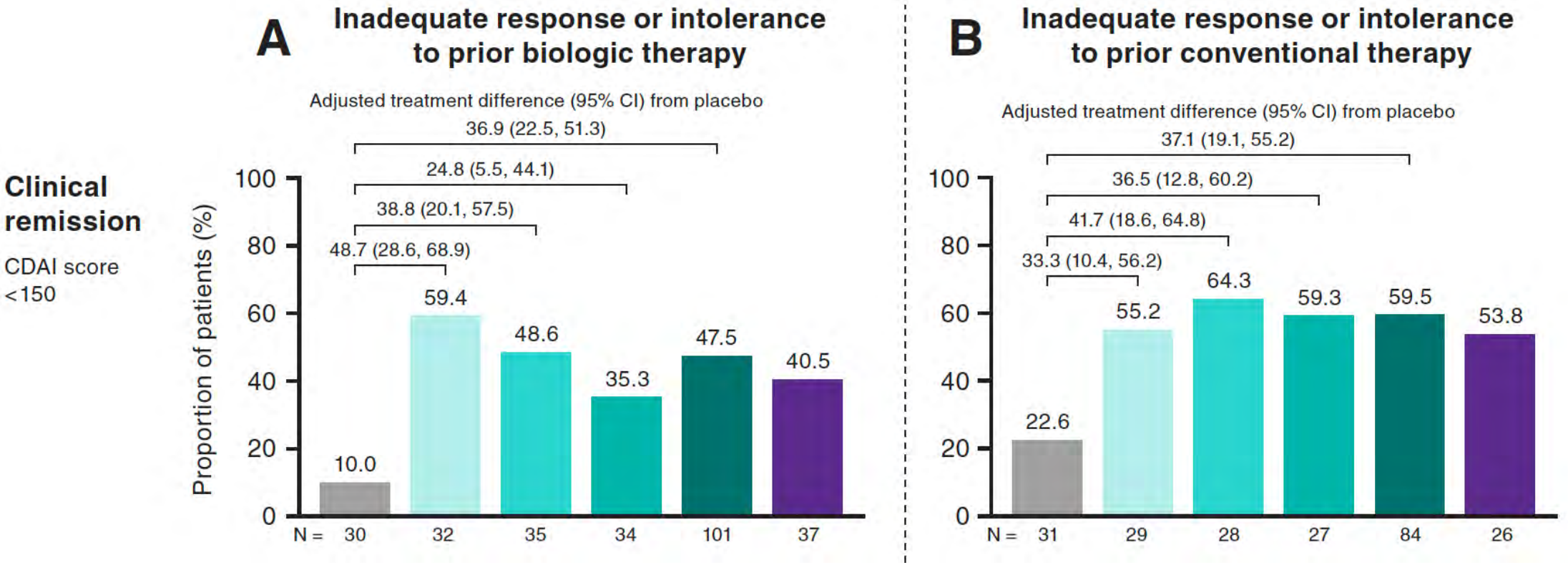
Sands et al, Gastroenterology 2022

Guselkumab: GALAXY EC



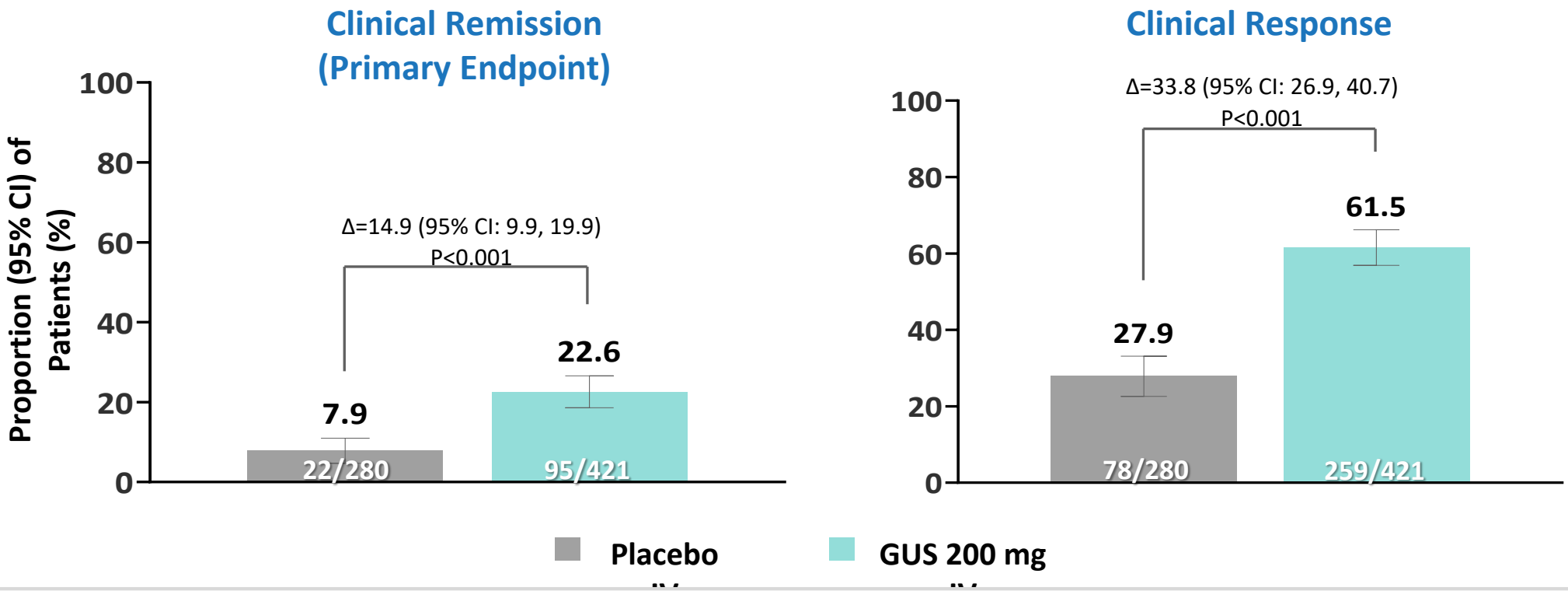
Sandborn, Gastroenterology. 2022 May;162(6):1650-1664.e8.

Guselkumab: GALAXY EC



Sandborn, Gastroenterology. 2022 May;162(6):1650-1664.e8

Guselkumab: QUASAR CU



Clinical remission: A Mayo stool frequency subscore of 0 or 1 and not increased from baseline, a Mayo rectal bleeding subscore of 0, and a Mayo endoscopy subscore of 0 or 1 with no friability present on the endoscopy

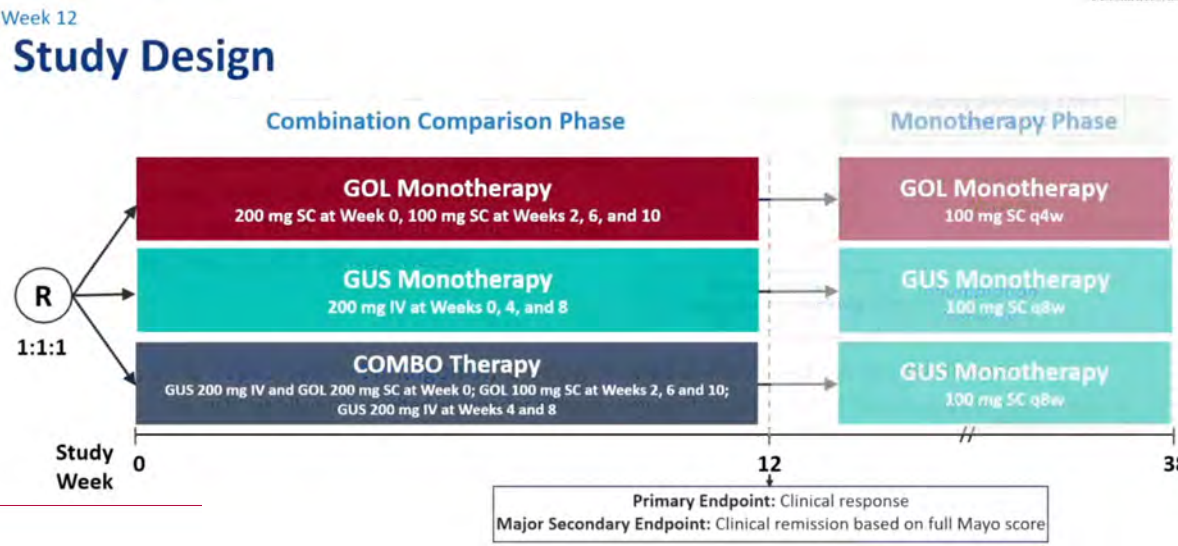
Clinical response: A decrease from baseline in the modified Mayo score by ≥30% and ≥2 points, with either a ≥1-point decrease from baseline in the rectal bleeding subscore or a rectal bleeding subscore of 0 or 1

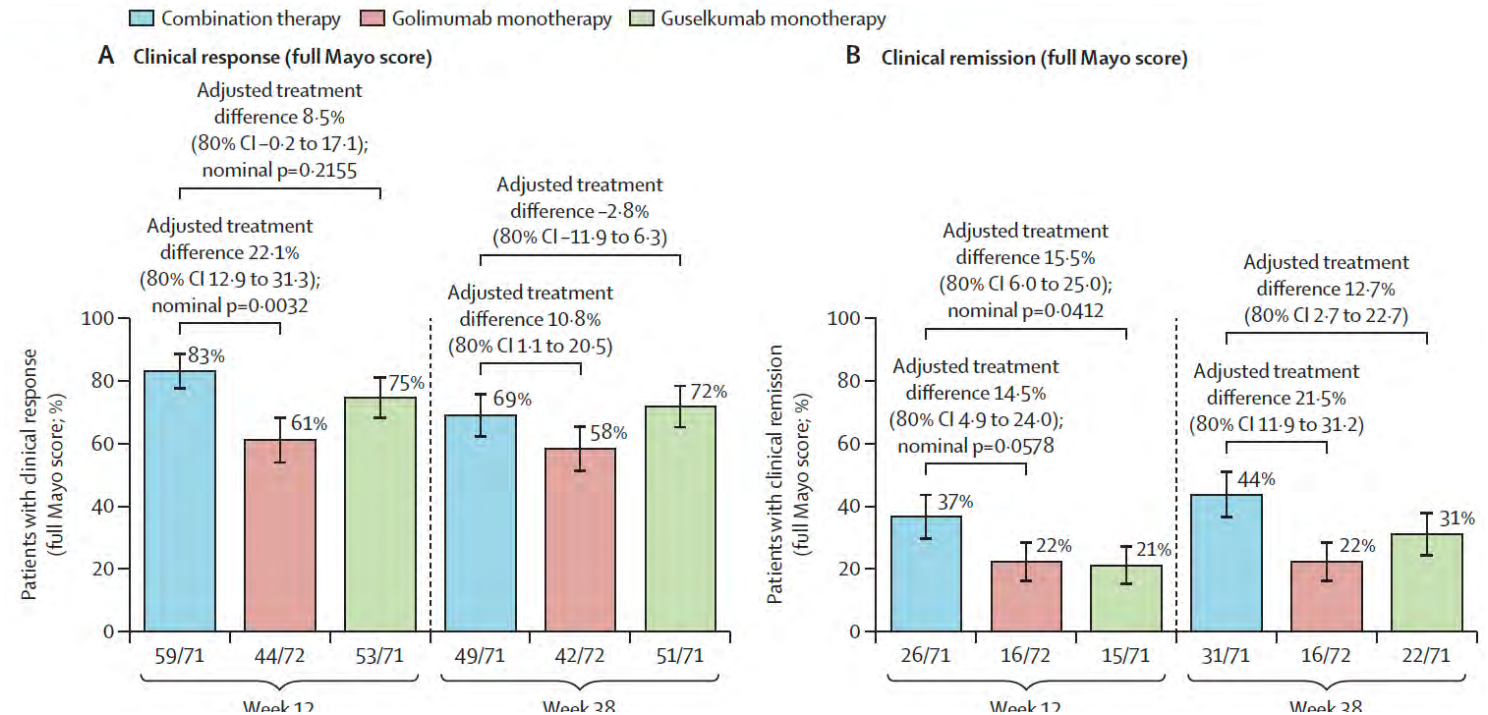
Peyrin-Biroulet, Gastroenterology. 2023 Sep 1:S0016-5085(23)04963-6.

Guselkumab

Guselkumab plus golimumab combination therapy versus guselkumab or golimumab monotherapy in patients with ulcerative colitis (VEGA): a randomised, double-blind, controlled, phase 2, proof-of-concept trial

*Brian G Feagan, Bruce E Sands, William J Sandborn, Matthew Germinaro, Marion Vetter, Jie Shao, Shihong Sheng, Jewel Johanns, Julián Panés, for the VEGA Study Group**

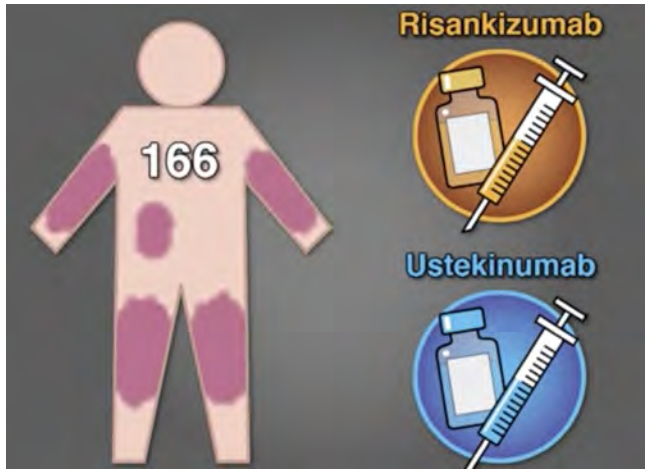


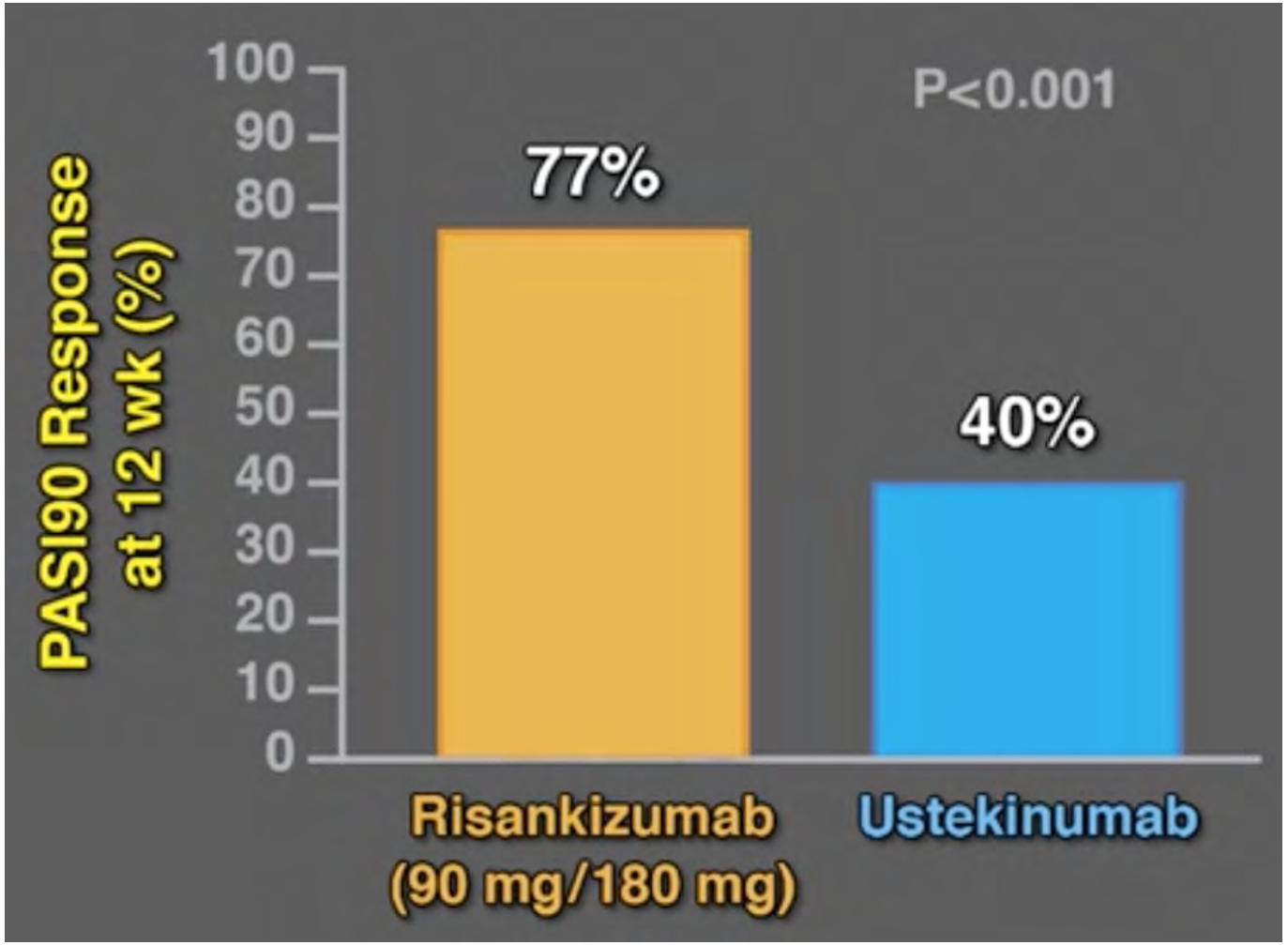


Feagan, Lancet Gastroenterol Hepatol 2023Apr;8(4):307-320.

Que vía elegir: Inhibición IL-12-23 vs IL-23?

Risankizumab vs Ustekinumab: Psoriasis en Placas





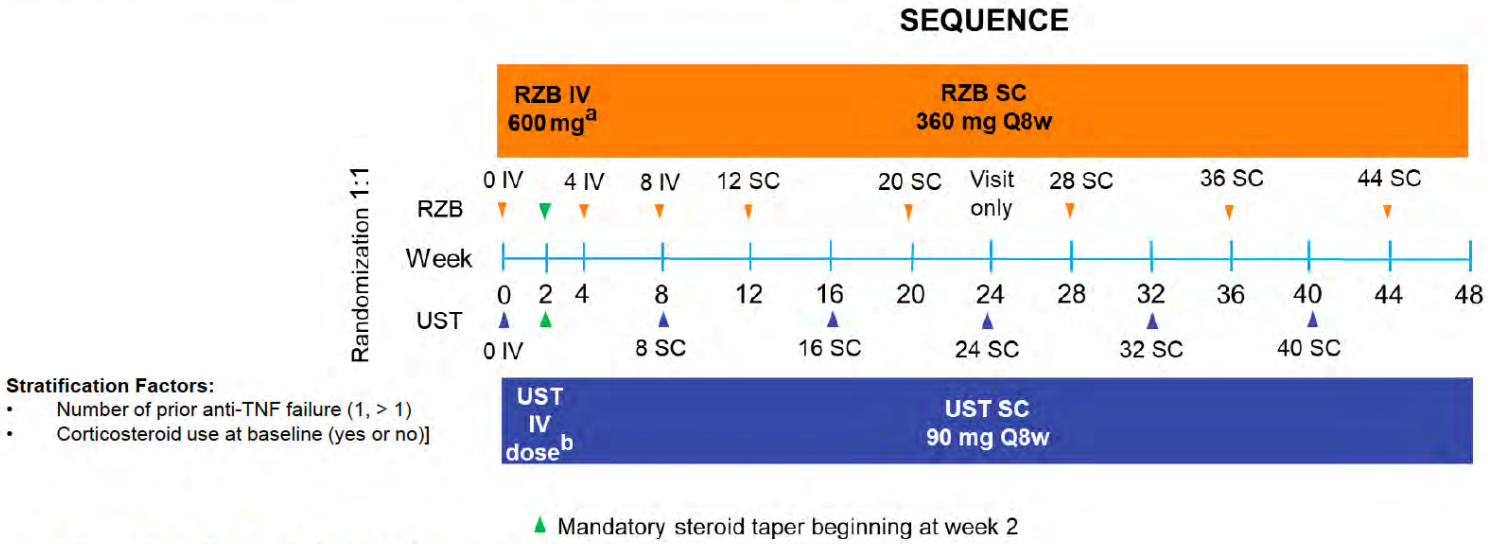
Papp, N Engl J Med. 2017 Apr 20;376(16):1551-1560

Risankizumab Versus Ustekinumab for Patients With Moderate to Severe Crohn's Disease: Results From the Phase 3b SEQUENCE Study

Laurent Peyrin-Biroulet,[1] J. Casey Chapman,[2,3,4] Jean-Frederic Colombel,[5] Flavio Caprioli,[6,7] Geert D'Haens,[8] Marc Ferrante,[9] Stefan Schreiber,[10] Raia Atreya,[11] Silvio Danese,[12] James O. Lindsay,[13] Peter Bossuyt,[14] Br Anschutz,[15] Kristina Kligys,[16] W Rachel Duan,[16]

The SEQUENCE study directly compared the efficacy and safety of RZB versus UST over a 48-week period in patients (pts) with moderate to severe CD who previously failed ≥ 1 anti-TNF therapies

Study Design and Key Eligibility Criteria



Stratification Factors:
- Number of prior anti-TNF failure (1, > 1)
- Corticosteroid use at baseline (yes or no)]

Key Eligibility Criteria

Moderate to severe CD
- CDAI 220-450
- Average daily SF ≥4 and/or average daily APS ≥2
- SES-CD, excluding the narrowing component, ≥6 (≥4 for isolated ileal disease), as scored by the site Investigator and confirmed by a central reader

Prior failure of ≥1 anti-TNF therapies
- Prior biologic therapy that could potentially influence the therapeutic impact on CD was exclusionary, including vedolizumab

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The SEQUENCE study directly compared the efficacy and safety of RZB versus UST over a 48-week period in patients (pts) with moderate to severe CD who previously failed ≥ 1 anti-TNF therapies

Study Endpoints

Primary endpoints

1. CDAI clinical remission at wk 24 (non-inferiority [10% margin] RZB to UST assessed in 50% of patients)
2. Endoscopic remission at wk 48 (superiority RZB to UST)

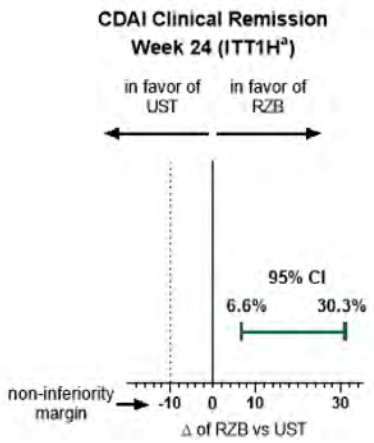
Ranked secondary endpoints (all superiority RZB to UST)

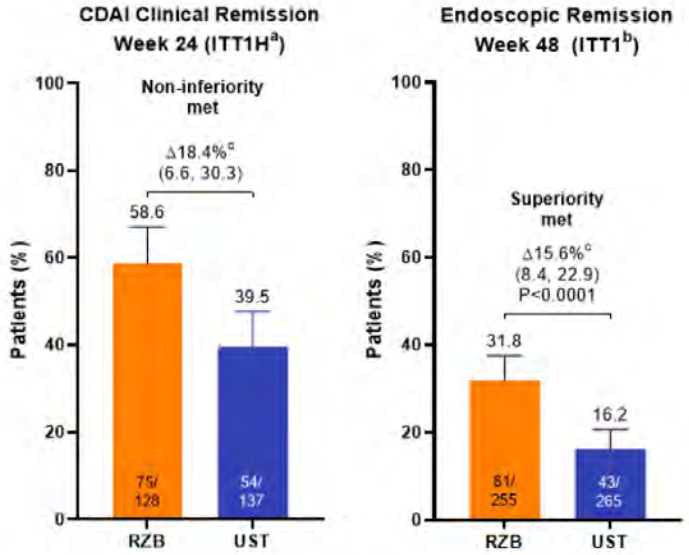
1. Clinical remission at wk 48
2. Endoscopic response at wk 48
3. Endoscopic response at wk 24
4. Steroid-free endoscopic remission at wk 48
5. Steroid-free clinical remission at wk 48

Overall Type I error rate was strongly controlled at 2-sided alpha level of 0.05 by the fixed-sequence multiplicity control method for this study.

The site's investigator and personnel were blinded to CDAI and centrally read endoscopy scores during the study. Central reader for SES-CD was blinded to study treatment.

Primary Endpoints: RZB demonstrated non-inferiority to UST for achieving clinical remission at week 24 and superiority to UST for achieving endoscopic remission at week 48





CDAI clinical remission: CDAI < 150
Endoscopic remission: SES-CD ≤ 4 and at least a 2-point reduction versus BL and no subscore > 1 in any individual variable, as scored by a central reviewer

Nominal $P < 0.01$ from a post hoc analysis testing for superiority

[a]ITT1H population: a subset of ITT1 population which includes the first ~50% of ITT1 patients
[b]ITT1 population includes patients who were randomized to UST or RZB (600 mg IV, 360 mg SC) and received at least one dose of study drug
[c]Differences adjusted by the stratification factors (number of times the subject failed prior anti-TNF therapy [≤ 1, > 1] and steroid use at baseline [yes, no])
% (n) represents the synthesized results from non-responder imputation incorporating multiple imputation to handle missing data
Non-inferiority for CDAI clinical remission at wk 24 was met if the lower bound of the 95% CI of adjusted risk difference was above -10%; if met, superiority for endoscopic remission at wk 48 was assessed

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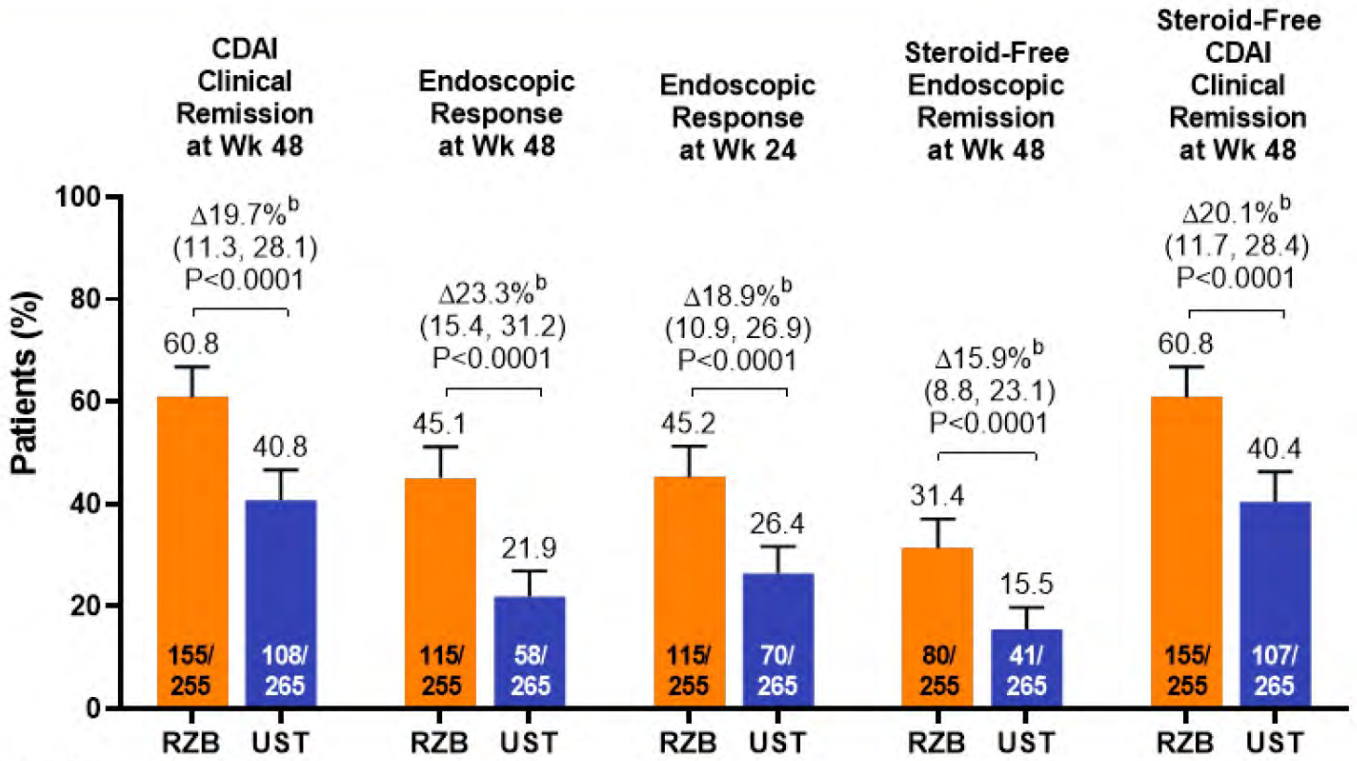
Ranked Secondary Endpoints (ITT1[a]): RZB demonstrated superiority to UST for all secondary endpoints



Superiority met for all endpoints

CDAI clinical remission: CDAI < 150
Endoscopic response: Decrease in SES-CD > 50% from BL (or for subjects with isolated ileal disease and a baseline SES-CD of 4, at least a 2-point reduction from baseline), as scored by central reviewer.
Endoscopic remission: SES-CD ≤4 and at least a 2-pt reduction versus BL and no subscore > 1 in any individual variable, as scored by a central reviewer
Steroid-free: Patient not receiving steroids at the corresponding visit

[a]ITT1 population - includes patients who were randomized to UST or RZB (600 mg IV, 360 mg SC) and received at least one dose of study drug
[b]Differences adjusted by the stratification factors (number of times the subject failed prior anti-TNF therapy [≤ 1, > 1] and steroid use at baseline [yes, no])
% (n) represents the synthesized results from non-responder imputation incorporating multiple imputation to handle missing data
Secondary endpoints tested sequentially in the order specified

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Seguridad anti IL 12-23 vs anti-IL23

Treatment Emergent Adverse Events (TEAEs) (SA1[a])

Treatment Emergent Adverse Events (TEAEs)	Risankizumab		Ustekinumab	
	N=262 n (%)	PYs=257.6 Events (E/100PYs)	N=265 n (%)	PYs=269.9 Events (E/100PYs)
Any TEAE	223 (85.1)	879 (341.2)	219 (82.6)	763 (282.7)
TEAEs related to study drug according to the investigator[b,c]	73 (27.9)	167 (64.8)	58 (21.9)	111 (41.1)
Severe TEAEs	42 (16.0)	60 (23.3)	51 (19.2)	82 (30.4)
Serious TEAEs	27 (10.3)	36 (14.0)	46 (17.4)	64 (23.7)
TEAEs leading to discontinuation of study drug	10 (3.8)	10 (3.9)	13 (4.9)	14 (5.2)
Deaths	0	0	0	0

E, events; PY, patient years
[a]SA1: all patients who were randomized and received at least one dose of study drug
[b]As assessed by investigator
[c]RZB related: 3 patients with SAEs related to RZB (anal fistula, anal abscess, campylobacter, cystitis, localized infection, genital fistula); 8 patients with SAEs related to UST (abdominal pain, anal fistula, Crohn's disease, ileal stenosis, vomiting)

Que via eligiremos en el futuro anti IL 12-23 ó antiIL 23??

- Precio: biosimilares….
- Experiencia
- Distinto perfil de seguridad…. No parece
- Distinta eficacia: estudio head to head en pacientes con fracaso a antiTNF superioridad RISANKIZUMAB
- Extrapolar a pacientes naive?
- ¿Son distintos entre sí los anti p-19?

CONCLUSIONES

- ✓ Inhibición IL12-23 ha demostrado efectividad en EC y CU en pacientes naive y expuestos a biológicos y perfil seguridad excelente
- ✓ La inhibición IL-12 en práctica clínica no parece incrementar R carcinogénesis y determinadas infecciones
- ✓ IL-23 está implicada en la patogenia de la EII
- ✓ Evidencia creciente efectividad inhibición IL-23 en EII, EC y CU
- ✓ Mayor efectividad IL-23 vs IL 12-23?, sí en EC RISAN VS USTE tras fracaso de antiTNF
- ✓ Similar perfil de seguridad
- ✓ Posiblemente anti-IL-23 efectivo en fallo IL 12-23, especialmente tras PRS

Muchas gracias por vuestra atención

GETECCU

3-5 octubre 2024