GETECCU Grupo Español de Trabajo en Enfermedad de Crohn y Colitis Ulcerosa
www.geteccu.org
SEGHNP Sociedad Española de Gastroenterología Hepatología y Nutrición Pediátrica
XIII CURSO GETECCU-SEGHNP sobre EII Pediátrica

Eficacia comparada de biológicos de administración endovenosa y subcutánea. Hacia los"biobetters"

Dra Elena Ricart. Hospital Clínic Barcelona

Infliximab y vedolizumab subcutáneos

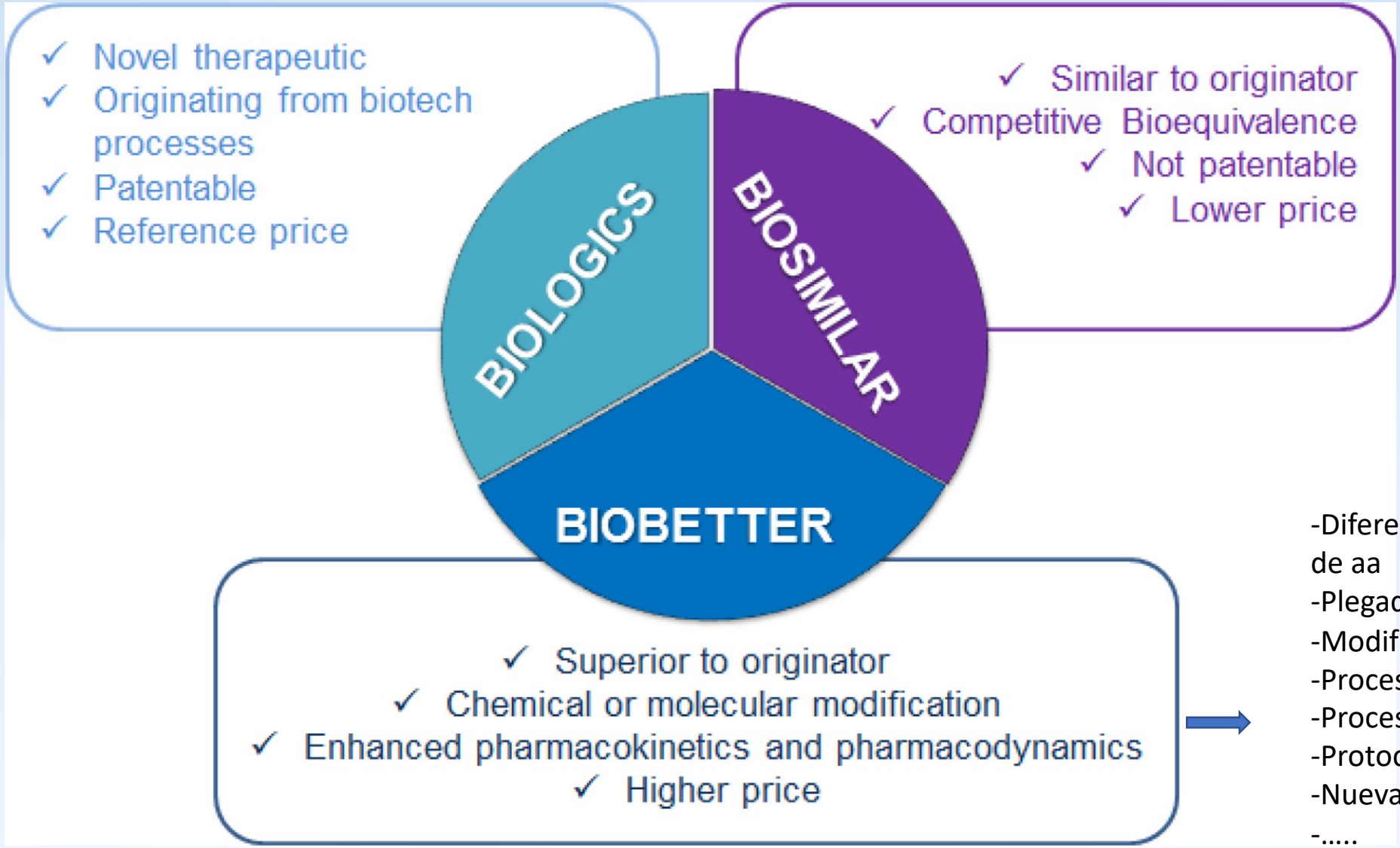
- ✓ Mayor autonomia
- ✓ Menor pérdida de productividad
- ✓ Menores requerimientos de infraestructura hospitalaria

Biobetter: Concepto

NIH: Biobetters are new drugs designed from existing peptide or protein-based therapeutics by improving their properties such as affinity and selectivity for the target epitope, stability against degradation, half-life and/or lower toxicity/immunogenicity preserving the therapeutic objective.

Delphi IMIDs experts: Biobetter is a modified version of a specific approved biologic that enhances clinical outcomes (e.g. improved efficacy) and/or drug pharmacology (e.g. pharmacokinetics and/or pharmacodynamics).

D'Amico F, Solitano V, Aletaha D, et al. Biobetters in patients with immune-mediated infammatory disorders: an international Delphi consensus. Autoimmun Rev. 2021;20(7):102849.



-Diferencias en la secuencia de aa
-Plegado de proteínas
-Modificación química
-Proceso de humanización
-Proceso de producción
-Protocolo de purificación
-Nueva vía de administración
-…..

Torres-Obreque KM. Drug Discovery Today 2022;27:65-81

Son vedolizumab e infliximab sc biobetters?

Table 1. Categories for biobetters and requirements.

True-Biobetter	- Target/class/indication is the same as a reference drug - Improved pharmacologic, pharmacokinetics, safety, and/or efficacy over reference drug - Approved by the respective government authorities as a new drug
Potential-Biobetter	- Has yet to be approved by the government authorities but has met the first two parameters
Non-Biobetter	- Failed to meet two of the three necessary parameters or has already been approved by the FDA as a reference drug or biosimilar

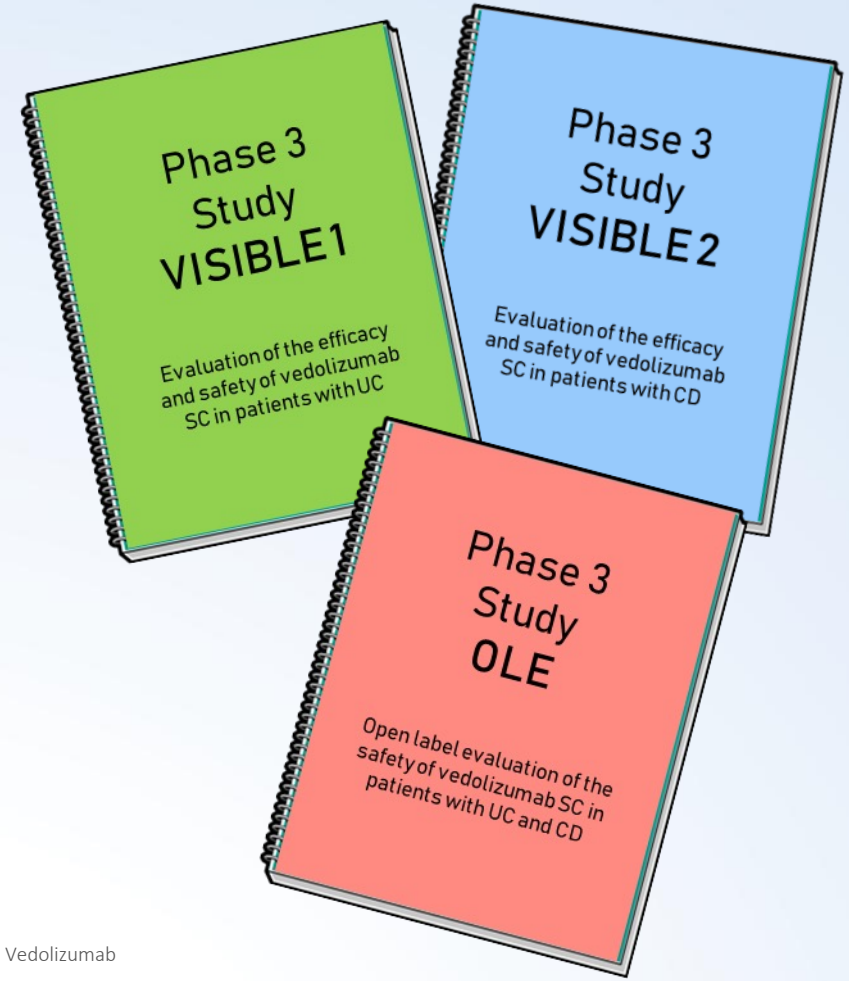
Rohan Purvin Zaveri, et al. Medical Research Archives 2022 vol 10 issue 3.

Vedolizumab

Desarrollo clínico vedolizumab sc

Programa VISIBLE (fase 3)

- **VISIBLE 1:**[1] tratamiento de inducción con VDZ IV y de mantenimiento con VDZ SC en pacientes con CU
- **VISIBLE 2:**[2] tratamiento de inducción con VDZ IV y de mantenimiento con VDZ SC en pacientes con EC
- **VISIBLE OLE:**[3] evaluación abierta de seguridad a largo plazo -



CD: *Crohn's Disease;* **CU: Colitis Ulcerosa; EC:** Enfermedad de Crohn; **IV:** Intravenoso; **OLE:** *open-label extension;* **SC:** Subcutáneo; **UC:** *Ulcerative Colitis;* **VDZ:** Vedolizumab

1. Sandborn *et al*. Efficacy and Safety of Vedolizumab Subcutaneous Formulation in a Randomized Trial of Patients With Ulcerative Colitis. Gastroenterology. 2020;158(3):562-572

2. Vermiere *et al*. Efficacy and safety of subcutaneous vedolizumab in patients with moderately to severely active Crohn's Disease: Results From the VISIBLE 2 Randomised Trial. J Crohns Colitis. 2022;16(1):27-38.

3. A Study of Long-term Effects of Vedolizumab Subcutaneous in Adults With Ulcerative Colitis and Crohn's Disease. Identificador NCT02620046. ClinicalTrials.Gov, NIH. Consultado en Marzo 2022 en: https://clinicaltrials.gov/ct2/show/NCT02620046

Estudio VISIBLE 1

Diseño del estudio

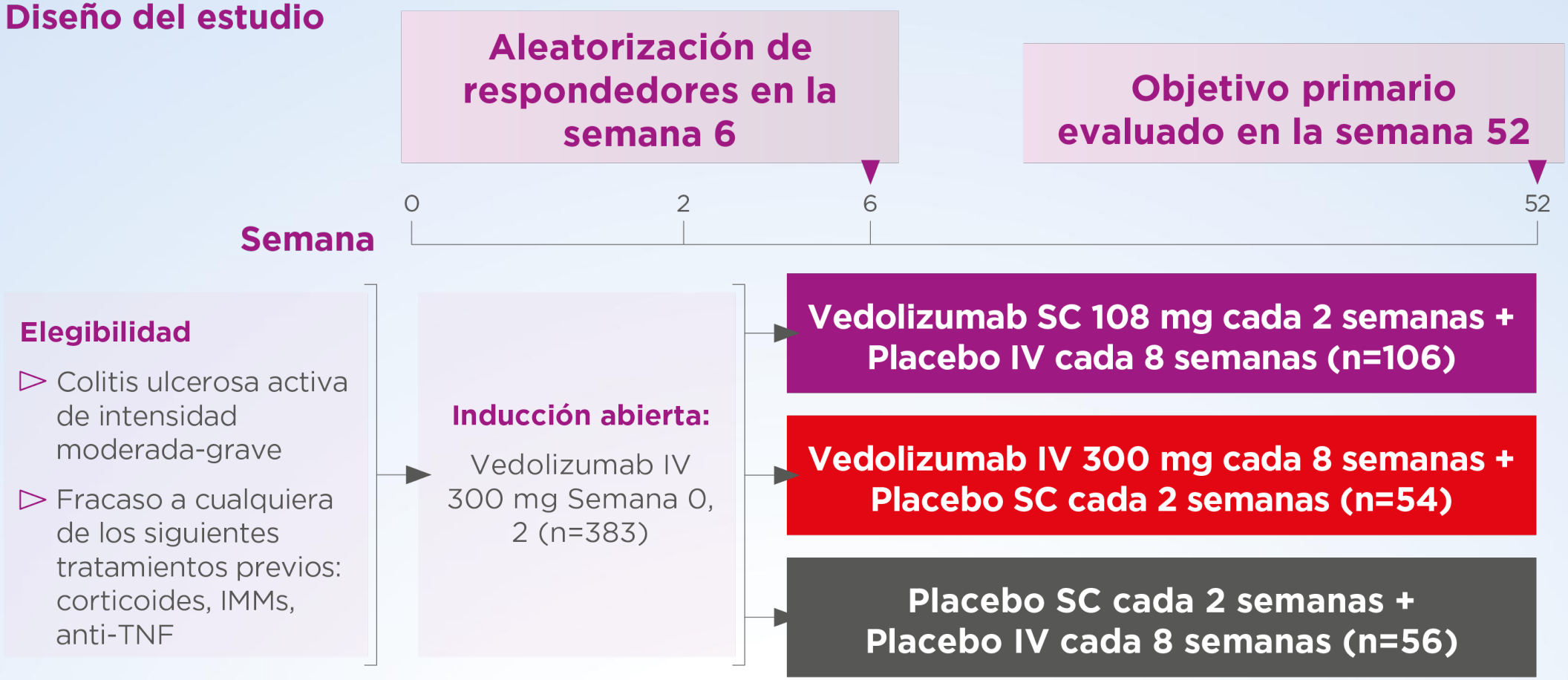


Figura extraída de *Sandborn et al. Efficacy and Safety of Vedolizumab Subcutaneous Formulation in a Randomized Trial of Patients With Ulcerative Colitis*[1]

IMM: Inmunomoduladores; **IV:** Intravenoso; **SC:** Subcutáneo; **TNF**: Factor de Necrosis Tumoral alfa

1. Sandborn *et al.* Efficacy and Safety of Vedolizumab Subcutaneous Formulation in a Randomized Trial of Patients With Ulcerative Colitis. Gastroenterology. 2020;158(3):562-572

Estudio VISIBLE 1

Eficacia

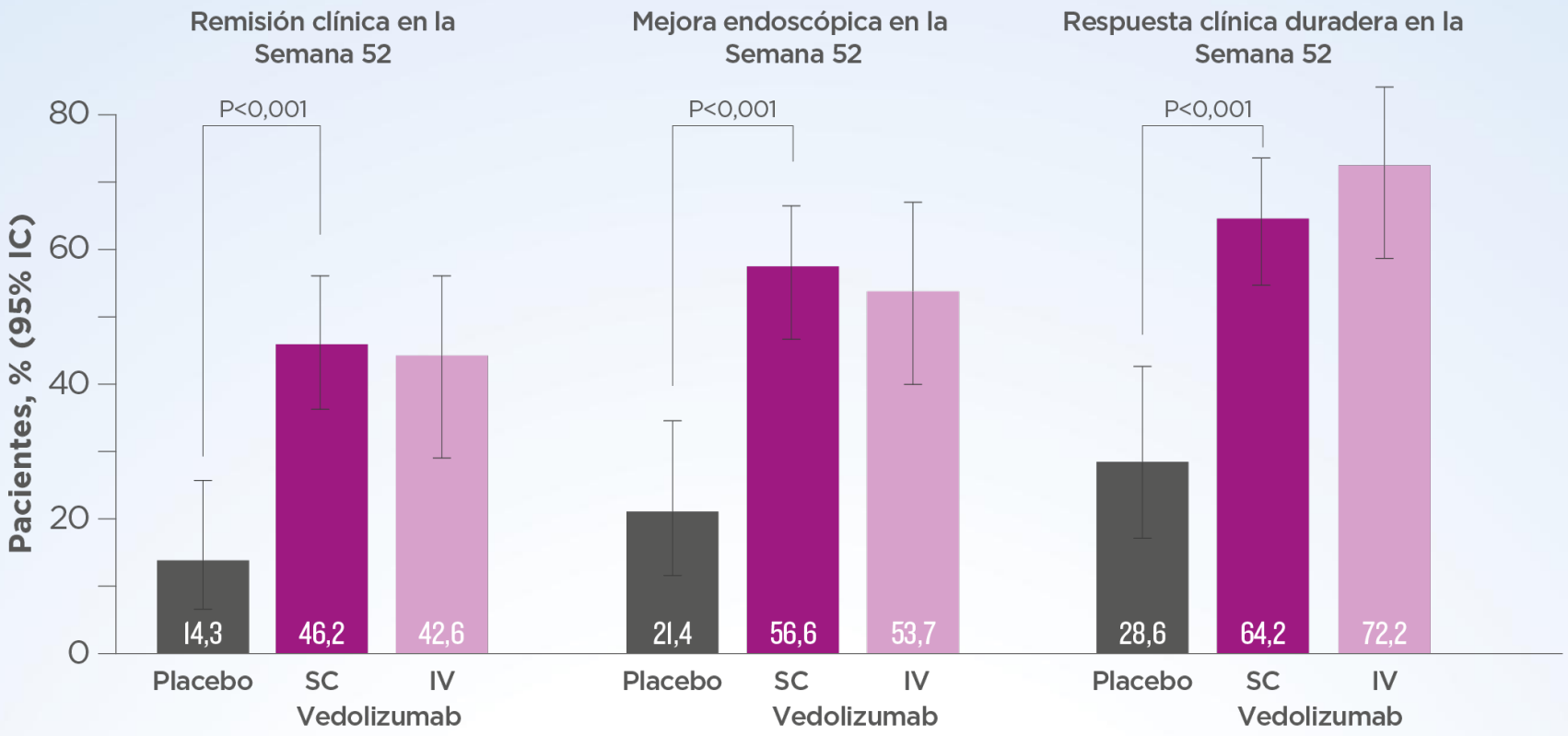


Figura extraída de *Sandborn et al. Efficacy and Safety of Vedolizumab Subcutaneous Formulation in a Randomized Trial of Patients With Ulcerative Colitis*[1]

CU: Colitis Ulcerosa; **IC:** Intervalo de Confianza; **IV:** Intravenoso; **SC:** Subcutáneo

1. Sandborn *et al.* Efficacy and Safety of Vedolizumab Subcutaneous Formulation in a Randomized Trial of Patients With Ulcerative Colitis. Gastroenterology. 2020;158(3):562-572

Estudio VISIBLE 2

VISIBLE 2:
ensayo clinico de fase 3 aleatorizado, doble ciego, controlado frente a placebo de vedolizumab subcutáneo (SC) en pacientes con la Enfermedad de Crohn (EC)

Periodo de Screening: Pacientes con EC activa de moderada a grave

Inducción abierta (n=644)

Vedolizumab intravenoso (IV)

(Semanas 0,2)

Respondedores semana 6 (n=412)

2:1

Tratamiento de mantenimiento aleatorizado, doble ciego cada dos semanas, desde la semana 6 (n=410)

Vedolizumab SC 108 mg cada dos semanas (n=275)

Placebo SC cada dos semanas (n=135)

Evaluación de los resultados clínicos

(Semana 52)

Figura extraída de Vermiere et al. Efficacy and safety of subcutaneous vedolizumab in patients with moderately to severely active Crohn's Disease: Results From the VISIBLE 2 Randomised Trial. J Crohns Colitis. 2022;16(1):27-38.

EC: Enfermedad de Crohn; **SC:** Subcutáneo; **IV:** Intravenoso

1. Vermiere *et al.* Efficacy and safety of subcutaneous vedolizumab in patients with moderately to severely active Crohn's Disease: Results From the VISIBLE 2 Randomised Trial. J Crohns Colitis. 2022;16(1):27-38.

Estudio VISIBLE 2

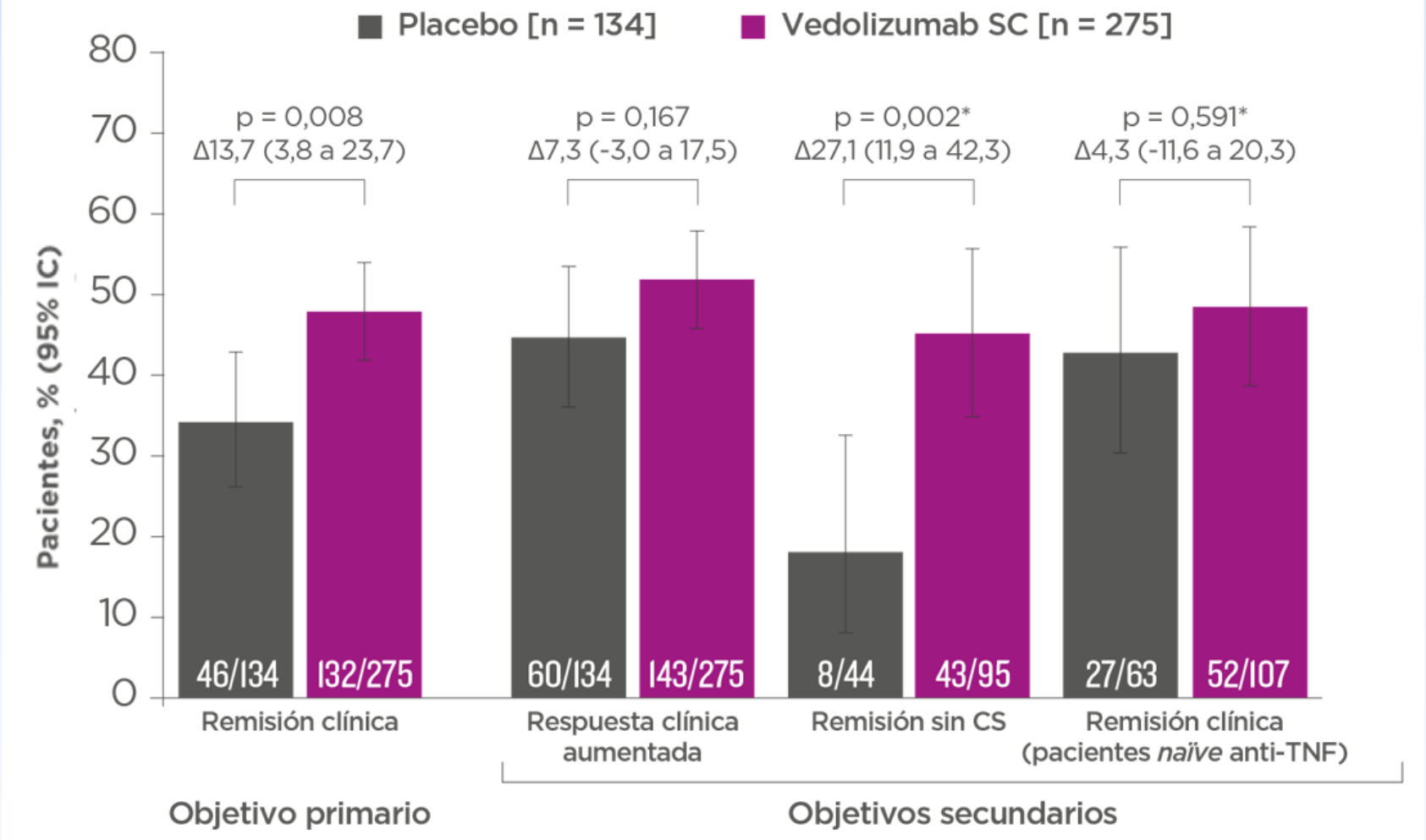
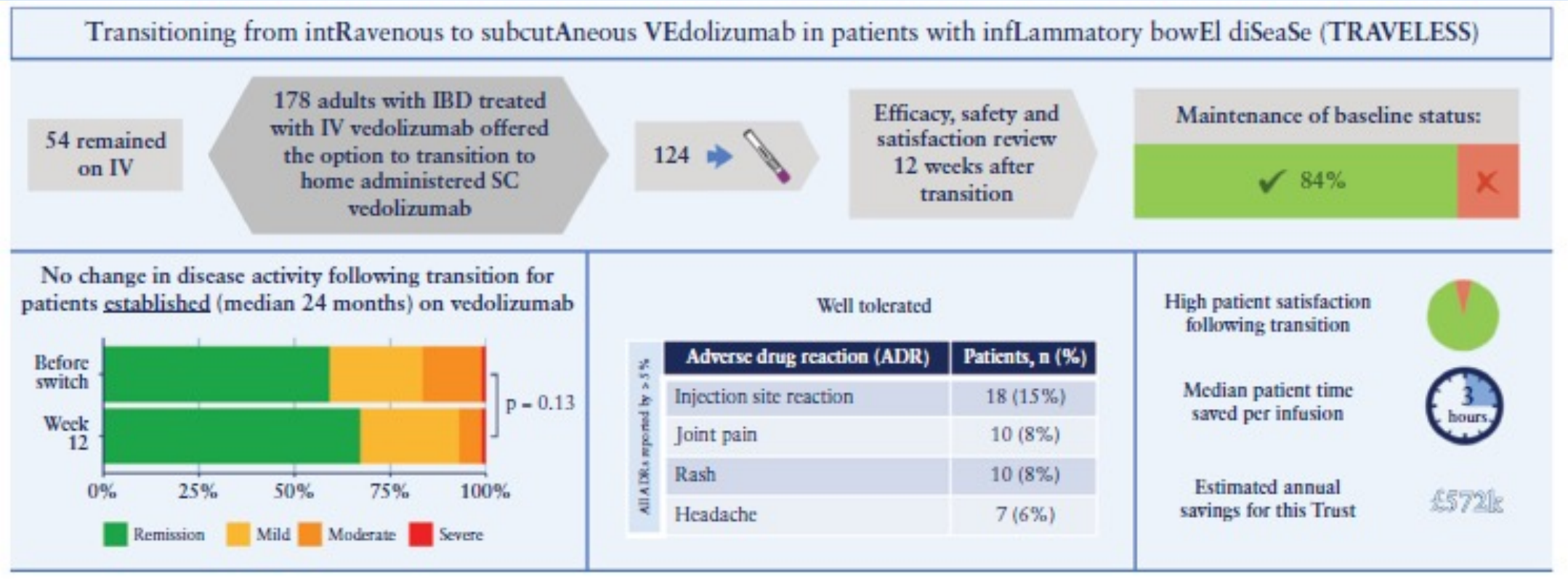


Figura extraída de Vermiere et al. Efficacy and safety of subcutaneous vedolizumab in patients with moderately to severely active Crohn's Disease: Results From the VISIBLE 2 Randomised Trial. J Crohns Colitis. 2022;16(1):27-38.

CS: Corticoides; **DE:** Desviación Estándar; **EC**: Enfermedad de Crohn; **IC:** Intervalo de Confianza; **SC**: Subcutáneo; **TNF**: factor de necrosis tumoral alfa

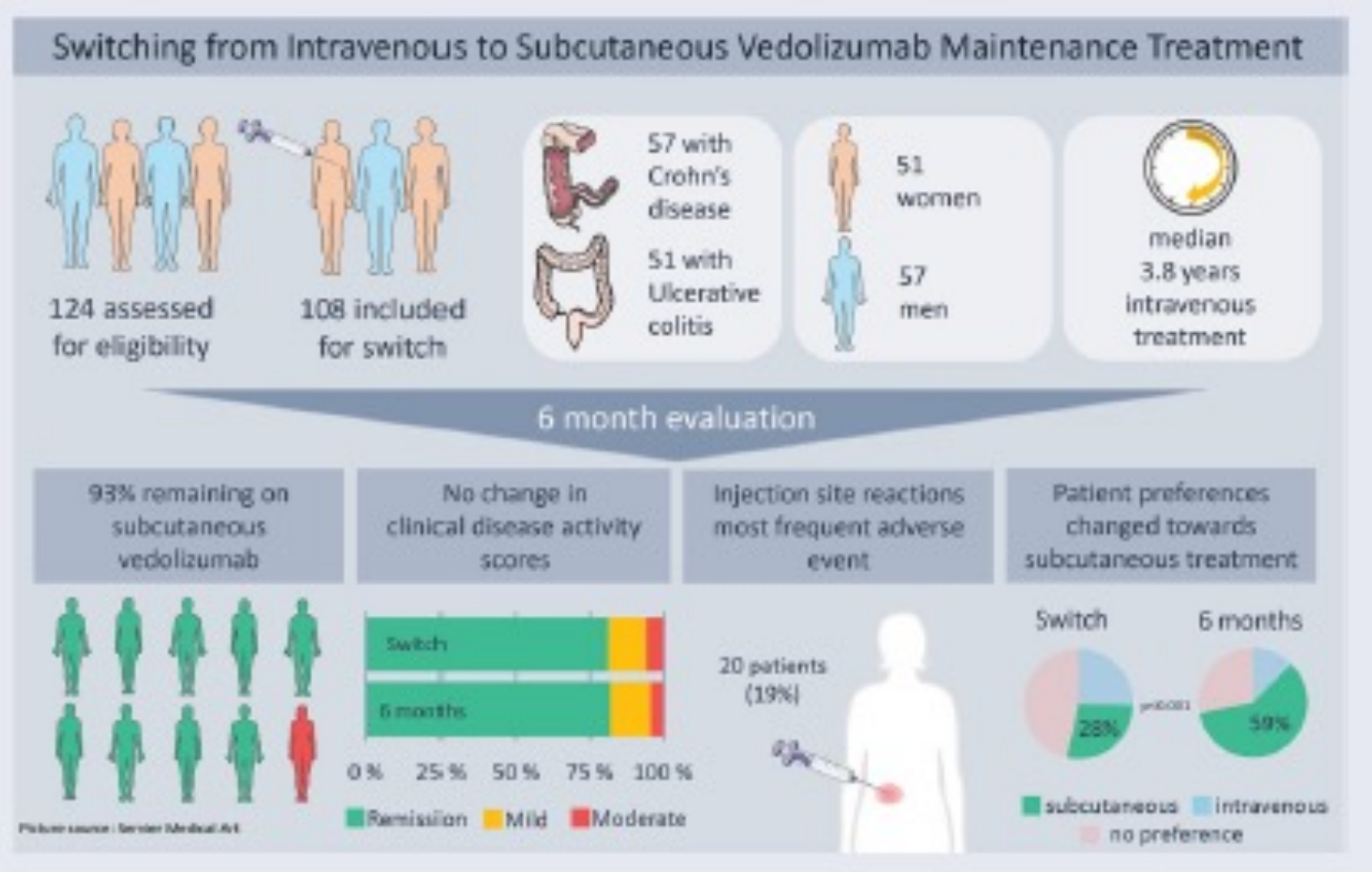
1. Vermiere *et al*. Efficacy and safety of subcutaneous vedolizumab in patients with moderately to severely active Crohn's Disease: Results From the VISIBLE 2 Randomised Trial. J Crohns Colitis. 2022;16(1):27-38.

Evidencia del cambio de VDZ ev a sc



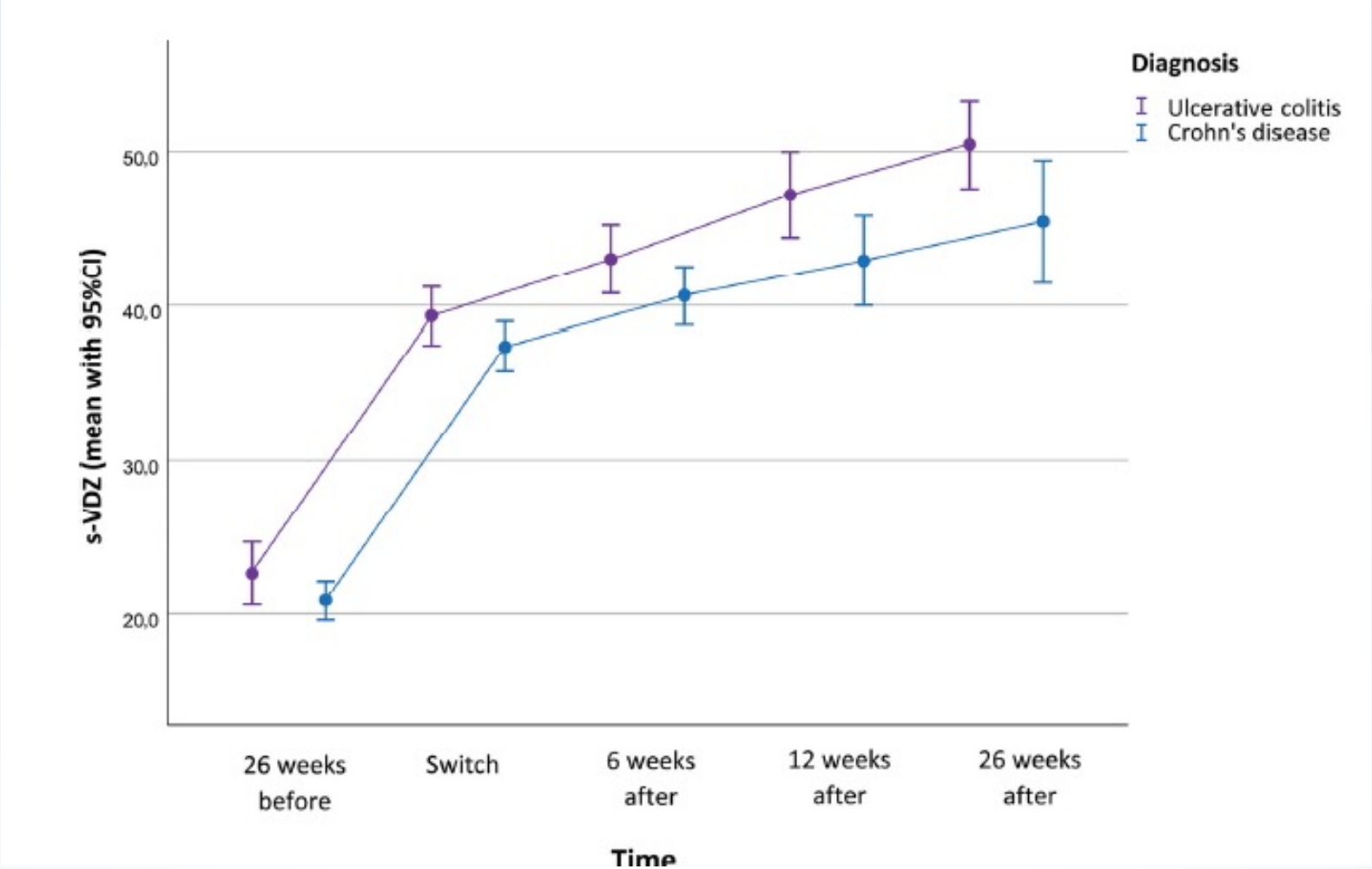
Ventress E. J Crohns Colitis 2022;16:911-921

Evidencia del cambio de VDZ ev a sc



Wiken TH. Scand J Gastroenterol 2023; 58: 863-873

Evidencia del cambio de VDZ ev a sc



Wiken TH. Scand J Gastroenterol 2023; 58: 863-873

Conclusiones

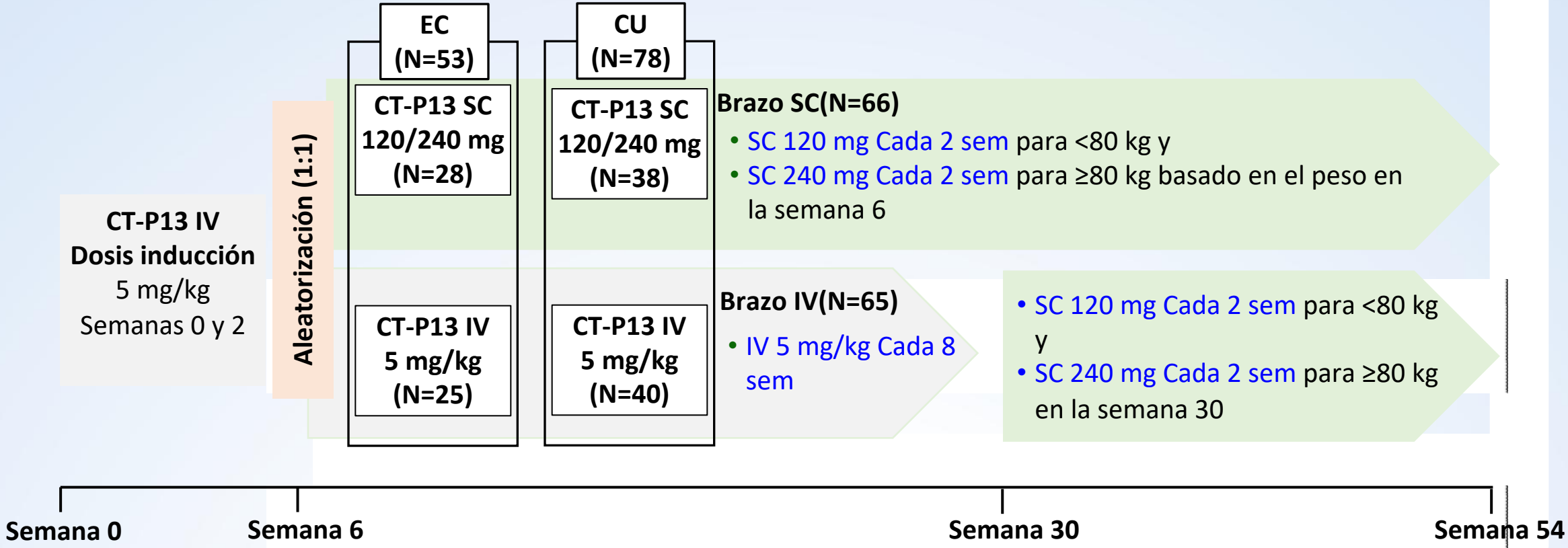
- El tratamiento con VDZ sc es eficaz y seguro, sin diferencias respecto al tratamiento ev tanto en EC como en CU
- Se observa un aumento de los niveles plasmáticos (significado incierto)
- Es seguro cambiar de la vía ev a la sc en práctica clínica
- Muy buena aceptación por parte de los pacientes

Infliximab

Gastroenterology 2021;160:2340–2353

Randomized Controlled Trial: Subcutaneous vs Intravenous Infliximab CT-P13 Maintenance in Inflammatory Bowel Disease

Stefan Schreiber,[1,*] **Shomron Ben-Horin**,[2,*] Jaroslaw Leszczyszyn,[3] Robert Dudkowiak,[3,4] Adi Lahat,[2] Beata Gawdis-Wojnarska,[5] Aldis Pukitis,[6] Marek Horynski,[7] Katalin Farkas,[8] Jaroslaw Kierkus,[9] Maciej Kowalski,[10] Sang Joon Lee,[11] Sung Hyun Kim,[12] Jee Hye Suh,[12] Mi Rim Kim,[12] Seul Gi Lee,[13] Byong Duk Ye,[14] and Walter Reinisch[15]



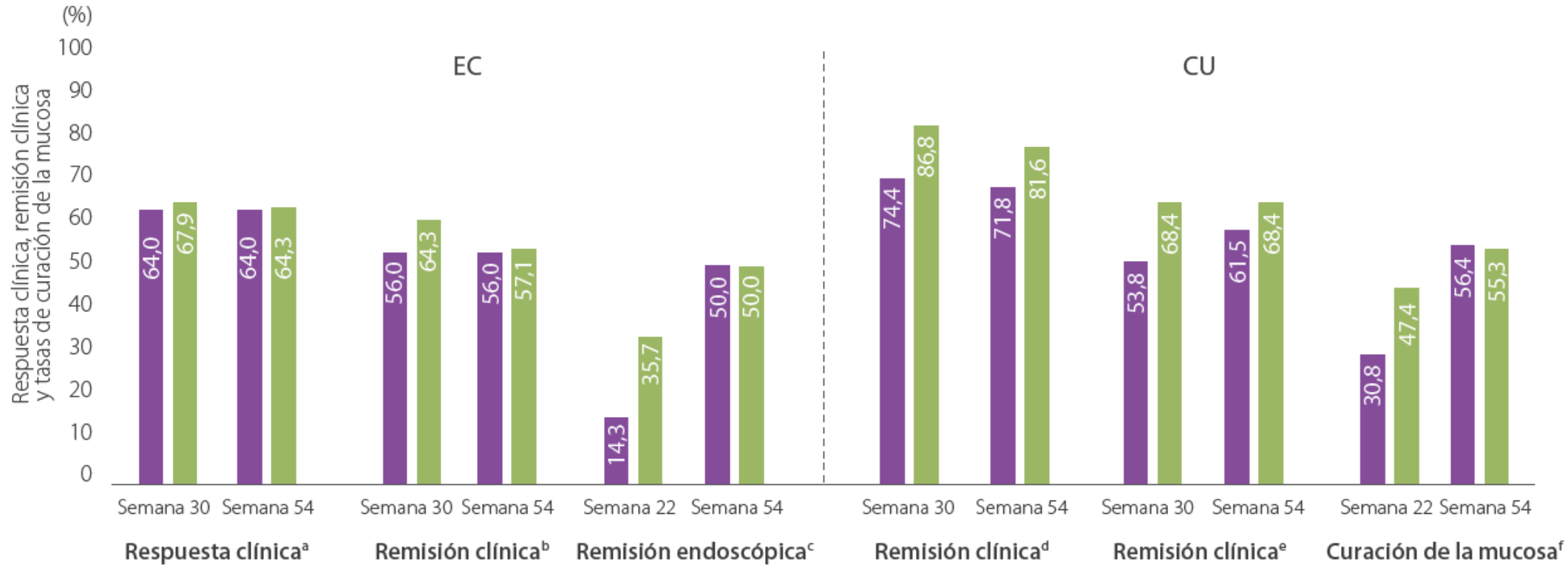
Schreiber et al. Gastroenterology 2021;160:2340-53

Eficacia

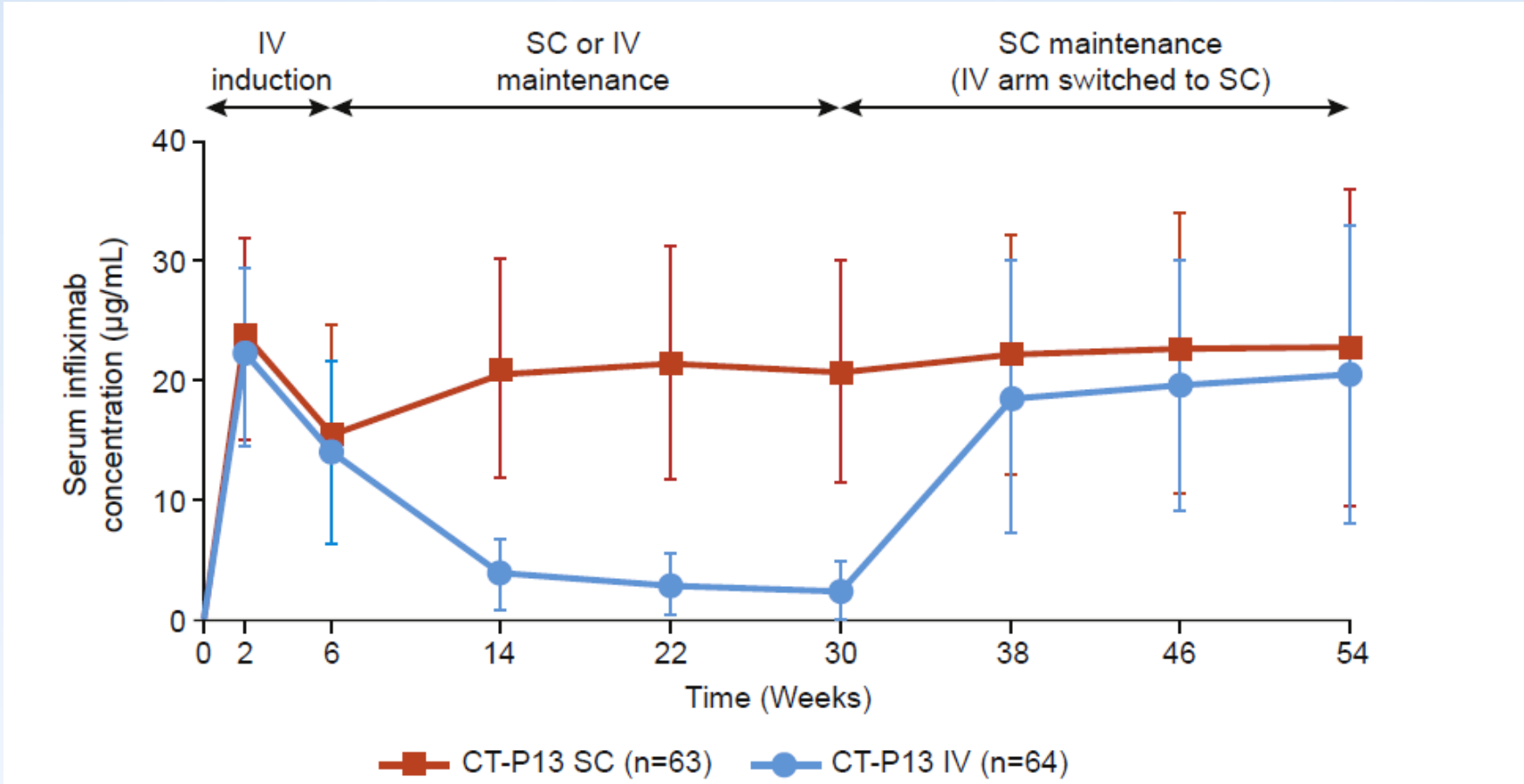
Respuesta clínica a largo plazo, remisión clínica y curación de la mucosa en EC y CU[1,4]

IV 5 mg/kg — SC 120/240 mg

EC: IV 5 mg/kg (n = 25), SC 120/240 mg (n = 28) CU: IV 5 mg/kg (n = 39), SC 120/240 mg (n = 38)



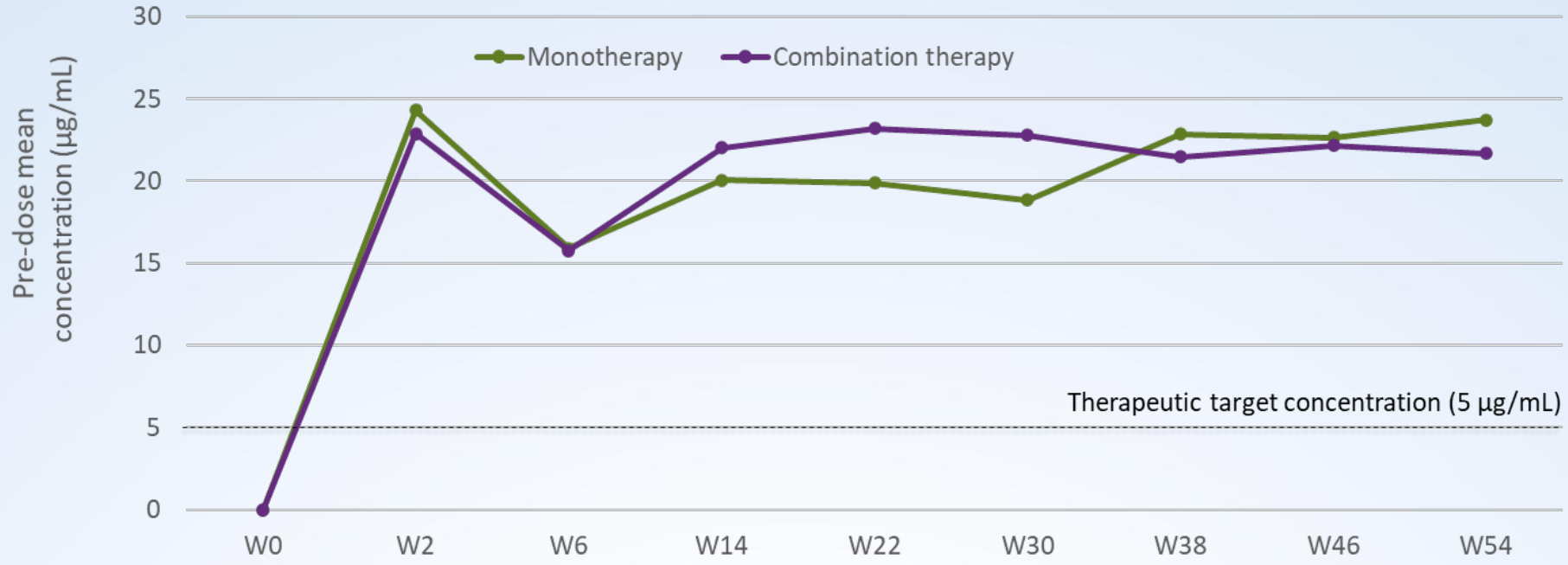
Farmacocinética



Semana	0	2	6	14	22	30	38	46	54
SC 120/240 mg	0	23.5	15.5	21.0	21.5	20.7	22.2	22.4	22.8
IV 5 mg/kg	0	21.9	14.1	3.8	2.9	2.4	18.6	19.6	20.6

Schreiber et al. Gastroenterology 2021;160:2340-53

Análisis post-hoc mono-combo: Biodisponibilidad

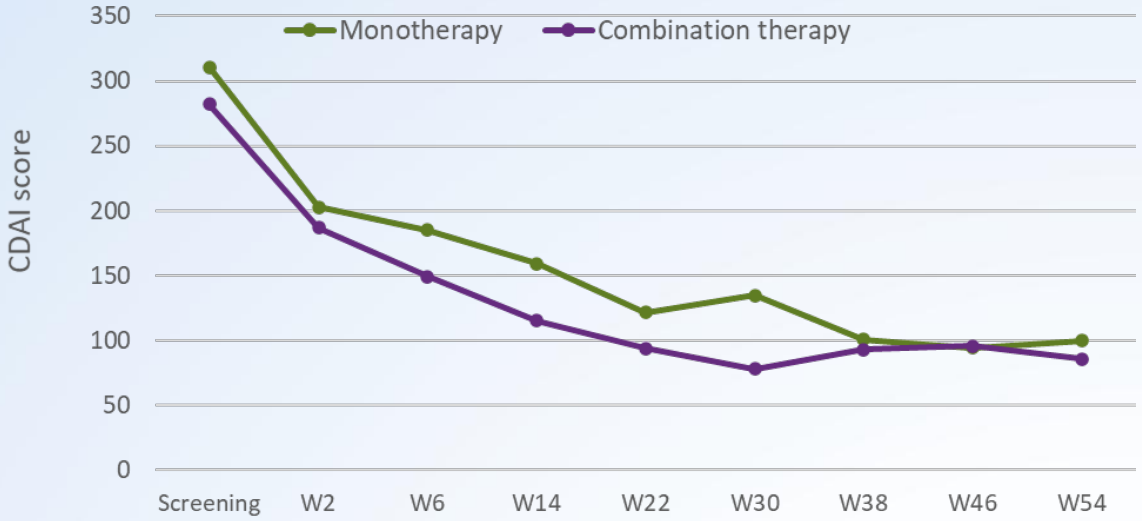


N=66 pacientes con IFX sc
N=37 en monoterapia
N=29 en comboterapia

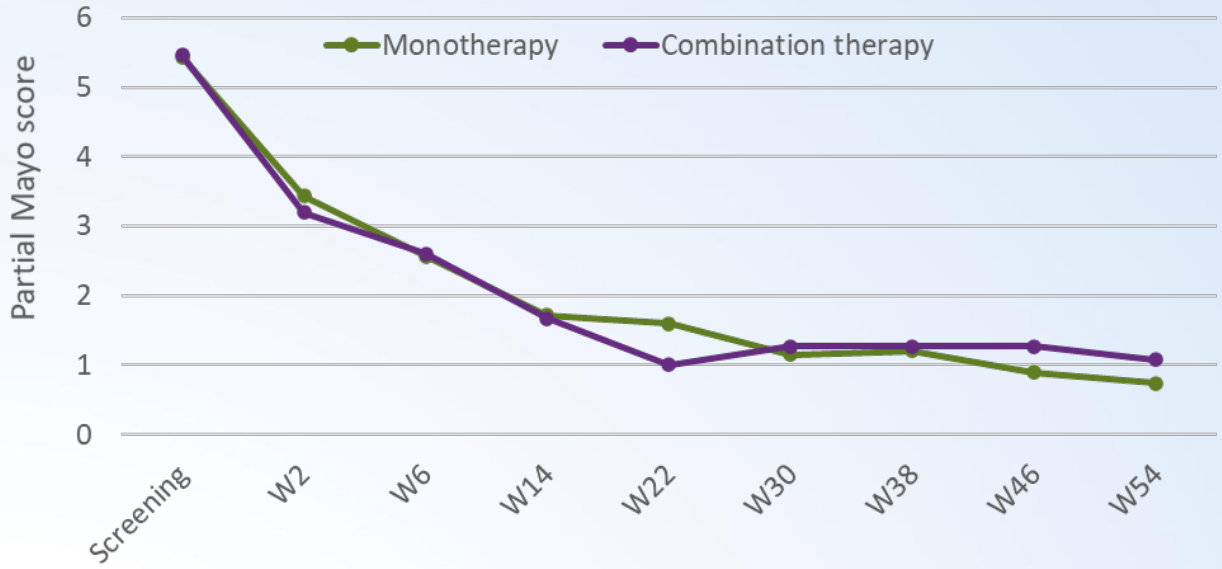
D'Haens G et al., Clinical Drug Investigation 2023

Análisis post-hoc mono-combo: Eficacia

Mean CDAI score over time



Mean partial Mayo score over time



D'Haens G et al., Clinical Drug Investigation 2023

Análisis post-hoc mono-combo: Inmunogenicidad

Immunogenicity [a]	Mono, n (%)	Combo, n (%)	P-value
ADA positive	19 (65.52)	12 (48.00)	0.2711
ADA negative	10 (34.48)	13 (52.00)	
NAb positive	2 (6.90)	4 (16.00)	0.3987
NAb negative [b]	27 (93.10)	21 (84.00)	

[a] Patients with available data at W54 were analysed
[b] ADA negative was regarded as NAb negative.

D'Haens G et al., Clinical Drug Investigation 2023

Cambio de IFX ev a sc en práctica clínica: nuestra experiencia

Estudio observacional, prospectivo y unicéntrico

Objetivo:

Evaluar la eficacia, seguridad, cambios farmacocinéticos y aceptación del cambio de IFX ev a sc en práctica clínica

Métodos:

Se incluyen pacientes en remisión clínica y biológica tratados con IFX ev con dosis estables >6 meses

El cambio a IFX sc se realiza a la dosis de 120mg cada 2 semanas

Demographics

		Patients at W-16	Patients at W-52
Number of patients		**75**	**41**
Age		46 (20–71)	46 (21 - 71)
Male gender		44 (58.7%)	25 (60.9%)
Body mass index		25.4 (17.7 – 54.8)	25.6 (17.7 – 37.9)
Diagnosis	**Crohn's disease**	**45**	**26**
	L1/L2/ L3/ L4	11 / 23 / 11 / 3	6 / 13 / 7 / 1
	B1/ B2/ B3	23/ 13 /13	11 / 10 / 9
	Perianal disease	20	10
	Ulcerative colitis	**30**	**15**
	E1/ E2 / E3	0 / 11 / 19	0 / 5 / 10
Disease duration		11.9 (0.4–49.7)	11.1 (0.4 – 49.7)
Previous intestinal resection		13 (17.3%)	8 (19.5%)
Previous biologic treatments	None	56	34
	Infliximab	7	2
	Adalimumab	11	5
	Golimumab	2	0
	Vedolizumab	1	0
	Ustekinumab	1	0
IFX duration at inclusion		5.9 (0.6 – 21.1)	5.7 (0.6 – 21.1)
IV IFX dose at inclusion	Standard → 5 mg/kg/8w	56	38
	Intensified → > 5 mg/kg/8w	19	6
Time since last IFX dose modification		4.5 (0.5 – 21.1)	4.8 (0.6 – 21.1)
Concomitant treatment	None	40	22
	Azathioprine	32	19
	Methotrexate	3	0

Median and ranges. Time variables are expressed as years

Clinical and biological disease activity

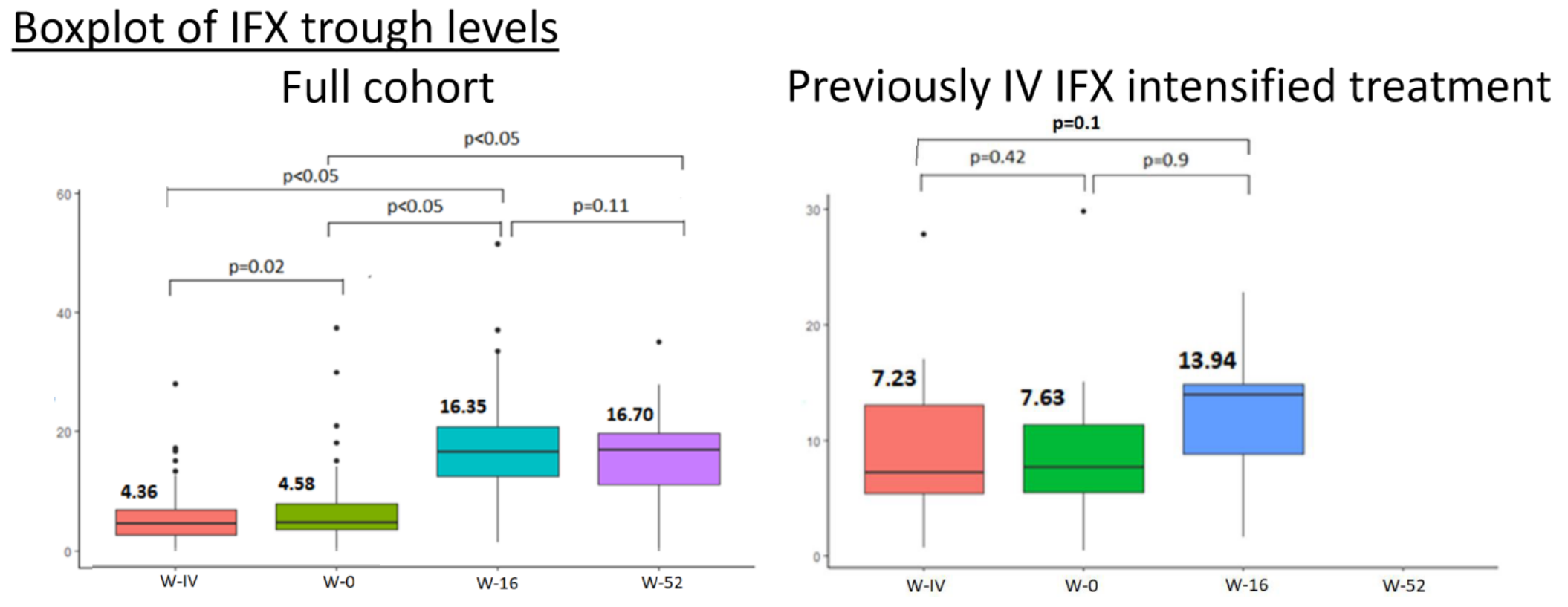
	W-IV	W-0	W-16	W-52	W-IV *versus* W-0	W-0 *versus* W-16	W-0 *versus* W-52	W-16 *versus* W-52
CDAI	28.7 (-19 - 336)	27.9 (-40 – 361)	24.7 (-22 – 303)	9.3 (-31 – 132)	P=0.92	P=0.39	0.26	0.66
Partial Mayo	0 – 2	0 – 3	0 - 1	0	P=1	P=0.41	P=0.15	1
IBDQ	191 (63 – 220)	187.5 (62 – 223)	190 (61 – 222)	183 (118 – 220)	P=0.80	P=0.07	P=0.76	P=0.35
C reactive protein (mg/dl)	0.4 (0.4 – 1.52)	0.4 (0.4 - 1.1)	0.4 (0.4 – 1.17)	0.4 (0.4 – 1.24)	P= 0.29	P=0.50	0.73	0.29
Calprotectin (µg/g)	NA	131 (30 - 1000)	62.5 (30 - 1000)	104 (30 - 1000)	NA	P=0.14	0.78	0.48

Median and range

Caballol et al., JCC 2023, 17, suppl 1

Persistencia:

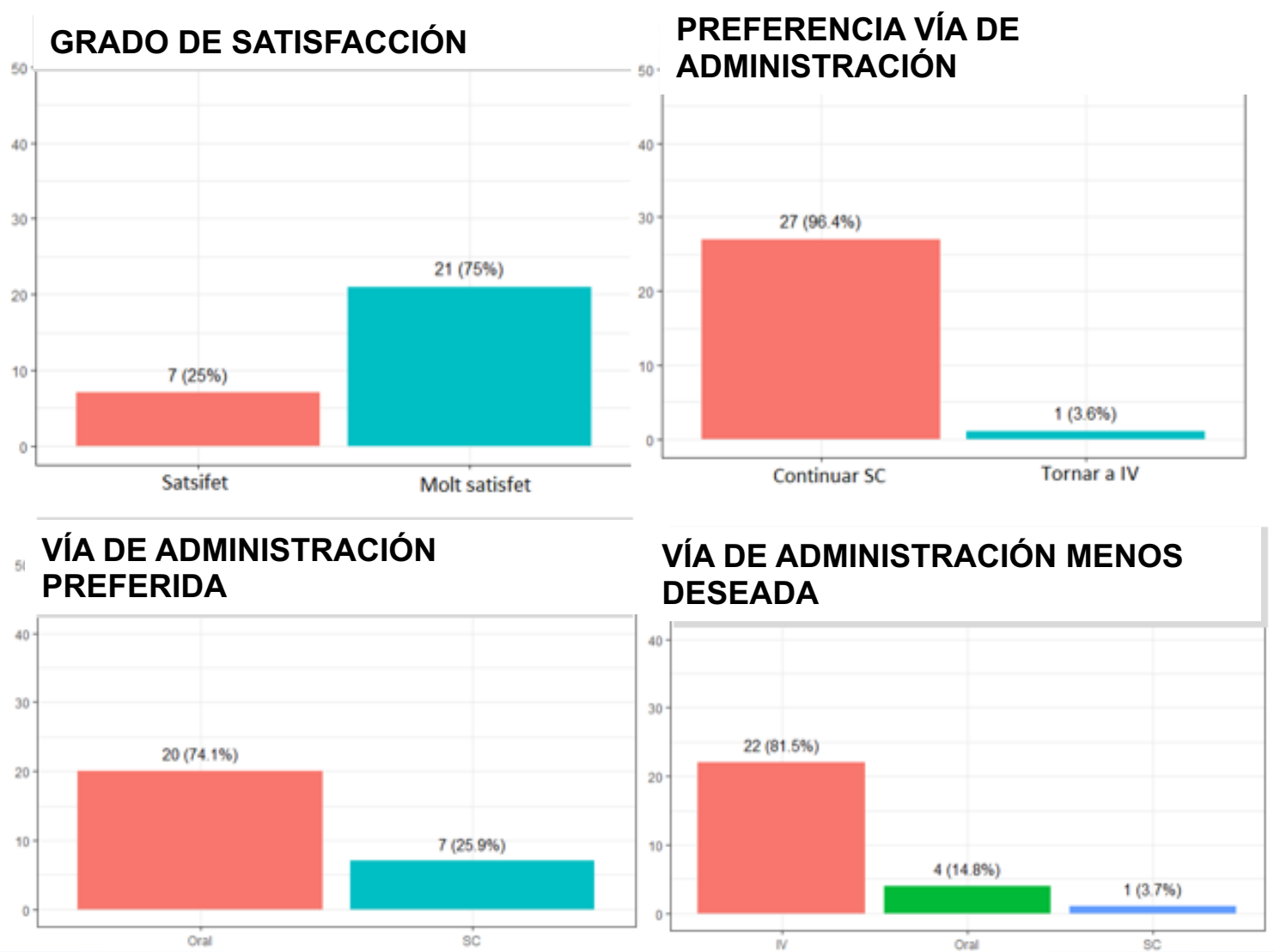
A la semana 16: 73/75 (97,3%)
A la semana 52: 36/41 (87,8%)



No se detectan ATIs contra IFX en ningún paciente tras el cambio

Caballol et al., JCC 2023, 17, suppl 1

Grado de satisfacción en semana 52



Caballol B. Póster CCD 2023

Factores predictores de recidiva tras el cambio

Serie francesa; N=133 pacientes; (74 intensificados)

Supplementary Table 2. Multivariable Analysis Assessing the Predictor Factors of Relapse in Patients With Inflammatory Bowel Disease After Switching From IV to Subcutaneous Infliximab

Parameter	*P* Value	Odds Ratio	95% Confidence Interval
Serum levels of infliximab at baseline >11 μg/mL	.234	2.789	0.515–15.108
Fecal calprotectin level >250 μg/g at baseline	.042[a]	5.426[a]	1.067–27.596[a]
IV maintenance regimen 10 mg/kg every 4 wk	.017[a]	12.423[a]	1.569–98.360[a]
IV maintenance regimen 10 mg/kg every 6 wk	.492	1.905	0.303–11.960
Other IV maintenance regimens	Reference		
Age at baseline >40 y	.066	4.205	0.908–19.478

IV, intravenous.
[a]Statistically significant associations.

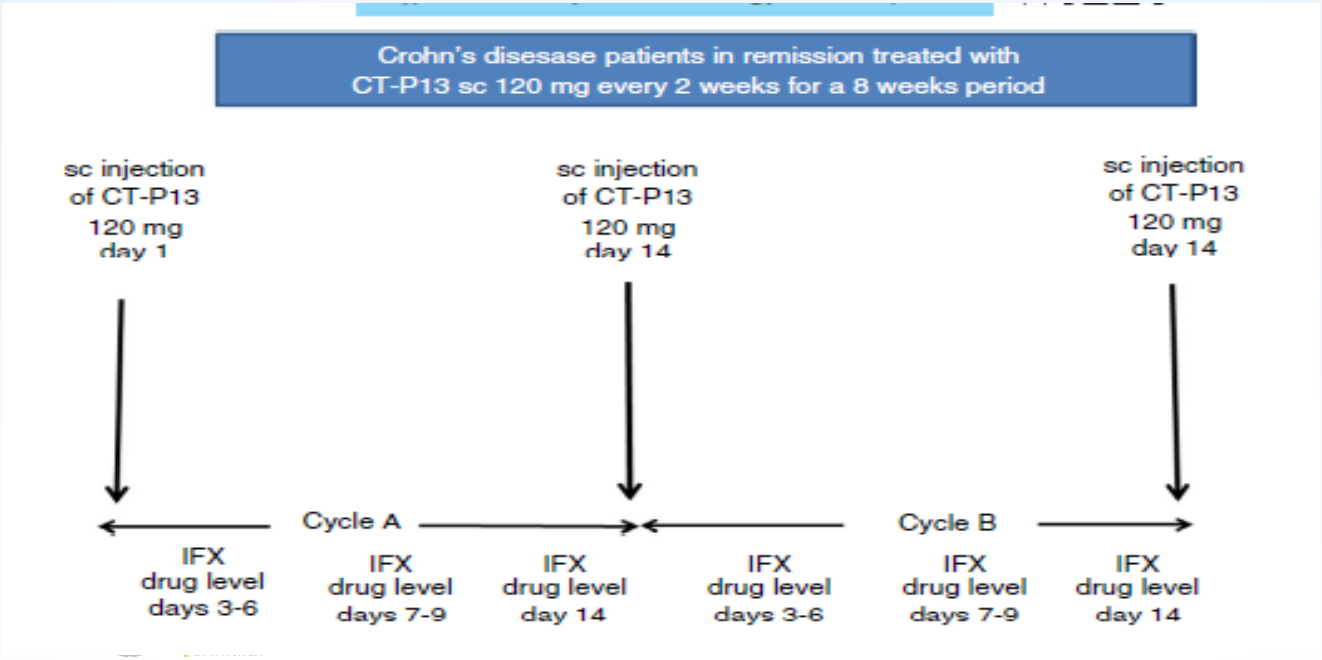
Buisson A et al. Clinical Gastroenterology and Hepatology 2022 (in press)

Received: 10 January 2022 | First decision: 7 February 2022 | Accepted: 14 February 2022
DOI: 10.1111/apt.16852
AP&T Alimentary Pharmacology & Therapeutics WILEY

Subcutaneous injection of infliximab CT-P13 results in stable drug levels within 14-day treatment cycle in Crohn's disease

Xavier Roblin[1,2] | Pauline Veyrard[1] | Laetitia Bastide[1] | Anne E. Berger[2,3] | Mathilde Barrau[1] | Anne-Sophie Paucelle[1] | Louis Waeckel[2,3] | Sany Kwiatek[4] | Bernard Flourie[2,5] | Stephane Nancey[2,5] | Stéphane Paul[2,3]

- Objectivo: Evaluar la variación intraindividual de los niveles de IFX evaluados en diferentes tiempos durante 2 ciclos consecutivos del tratamiento de mantenimiento con IFX sc en pacientes con EC
- Seis determinaciones a partir de semana 8 de la primera dosis sc, dos ciclos de tratamiento (3 determinaciones en cada ciclo)
- 20 pacientes, 120 determinaciones



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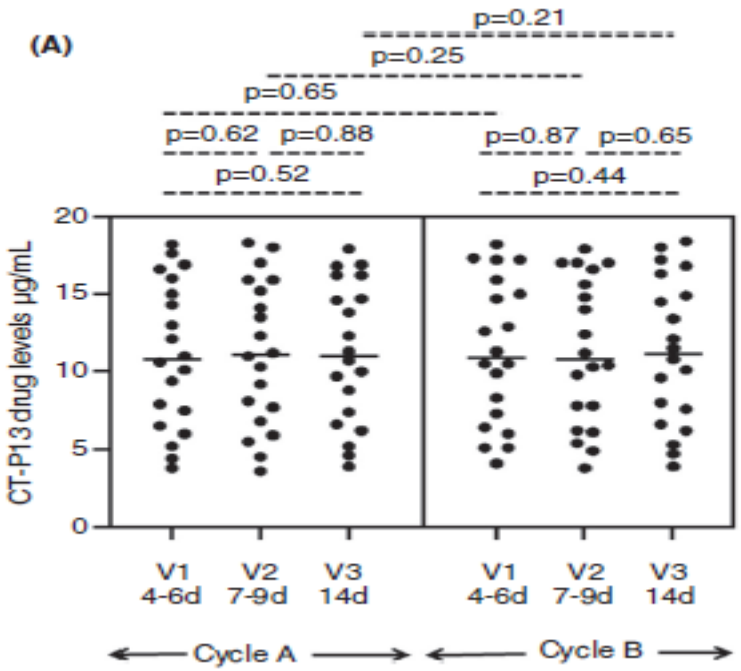
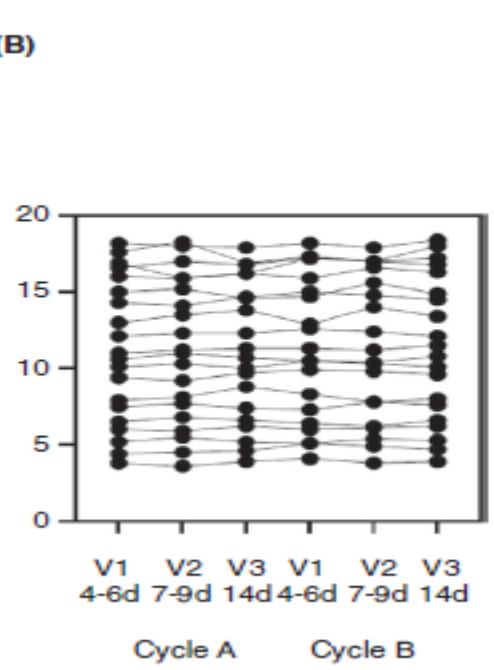


IFX levels according to study visits during the two cycles. Bars represent median values (*n = 20 patients).*



Individual variation in drug levels over time (*n = 20 patients)*

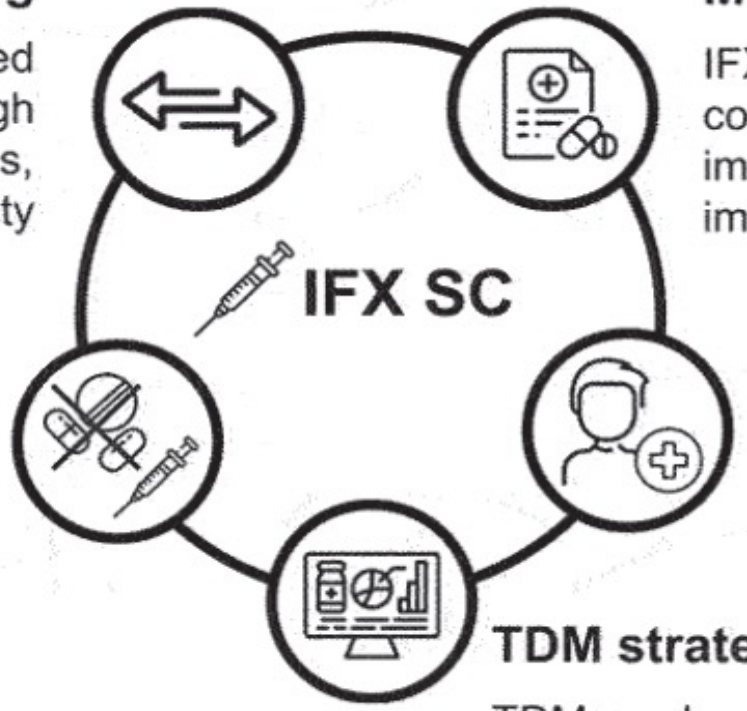
Conclusiones

SC switching

Data show that clinical benefits associated with switching may include: higher trough concentrations, improved efficacy outcomes, comparable safety, and lower immunogenicity

Monotherapy

IFX SC monotherapy may provide comparable clinical efficacy, PK, and immunogenicity to combination therapy with immunosuppressants



High disease activity or refractory disease

Patients with high disease activity (e.g. perianal fistulizing CD) and those refractory to IFX IV could benefit from IFX SC

Self-administration

Patient acceptance and satisfaction rates were higher with IFX SC than IFX IV

TDM strategy

TDM can be conducted at any time between IFX SC injections, improving convenience for patients

Smith PJ, et al. Expert Review of Clinical Immunology, 19:9, 1143-1156, DOI: 10.1080/1744666X.2023.2231148

Perfil de paciente especialmente idóneo:

- Paciente joven, estudiante, viajero o laboralmente activo con dificultad para acudir a hospital de día
- Problemas de movilidad
- Dificultad de accesos venosos
- Pérdida de respuesta farmacocinética

Para IFX además:

- Monoterapia
- Situaciones clínicas en las que se precise mayor exposición al fármaco
- Paciente intensificado?
- Mayor riego de inmunogenicidad ?(HLA DQA1*05)