GRUPO ESPAÑOL DE TRABAJO EN ENFERMEDAD DE CROHN Y COLITIS ULCEROSA
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SOCIEDAD ESPAÑOLA DE GASTROENTEROLOGÍA HEPATOLOGÍA Y NUTRICIÓN PEDIÁTRICA
SEGHNP

XIII CURSO GETECCU-SEGHNP
sobre EII Pediátrica

Actualización en el uso de biosimilares en EII pediátrica: del switch al multiswitch.

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Hospital Universitario Virgen del Rocío. Sevilla.

Conflictos de interés

He recibido apoyo para asistir a congresos y he realizado conferencias remuneradas para empresas dedicadas a desarrollar tratamientos para la EII: Ferrer, Abbvie, Takeda, Nestlé, Otsuka, Adacyte.

Sin conflictos de interés para desarrollar este tema.

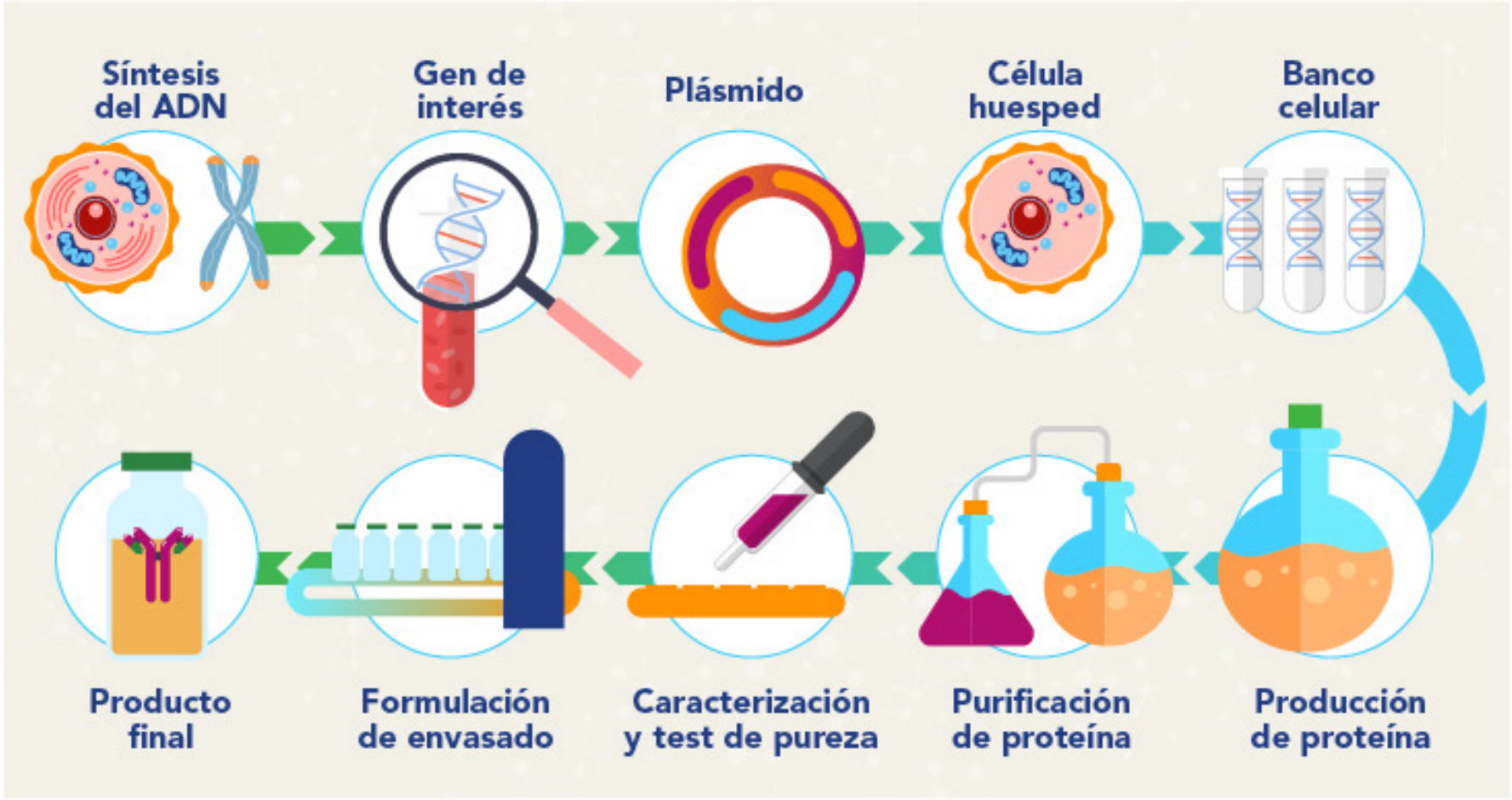
Agenda

1. Introducción y definiciones
2. Comentarios *económicos*
3. Marco regulatorio en España y Europa
4. Diferentes escenarios en el switch/multiswitch
5. Controversias

Introducción y definiciones

- **BIOLÓGICO:**
  - Medicamento que contiene *principios activos producidos por organismos o células vivas*, variables por naturaleza.
  - El medicamento biológico puede presentar un cierto grado de **variabilidad** (dentro del rango aceptable para garantizar una calidad, eficacia y seguridad homogéneas).
  - CARO

- **BIOSIMILAR:**
  - Según la EMA y la FDA, *medicamento biológico que se desarrolla para que sea **similar** a un medicamento biológico de referencia ya comercializado, cuya patente ha caducado.*



https://www.pfizerpro.es/medicamentos/biosimilares/sobre-biosimilares-caracteristicas

https://www.pfizerpro.es/medicamentos/biosimilares/sobre-biosimilares-caracteristicas

ECCO position statement: The use of biosimilar medicines in the treatment of inflammatory bowel disease (IBD)

Journal of Crohn's and Colitis (2013) 7, 586–589

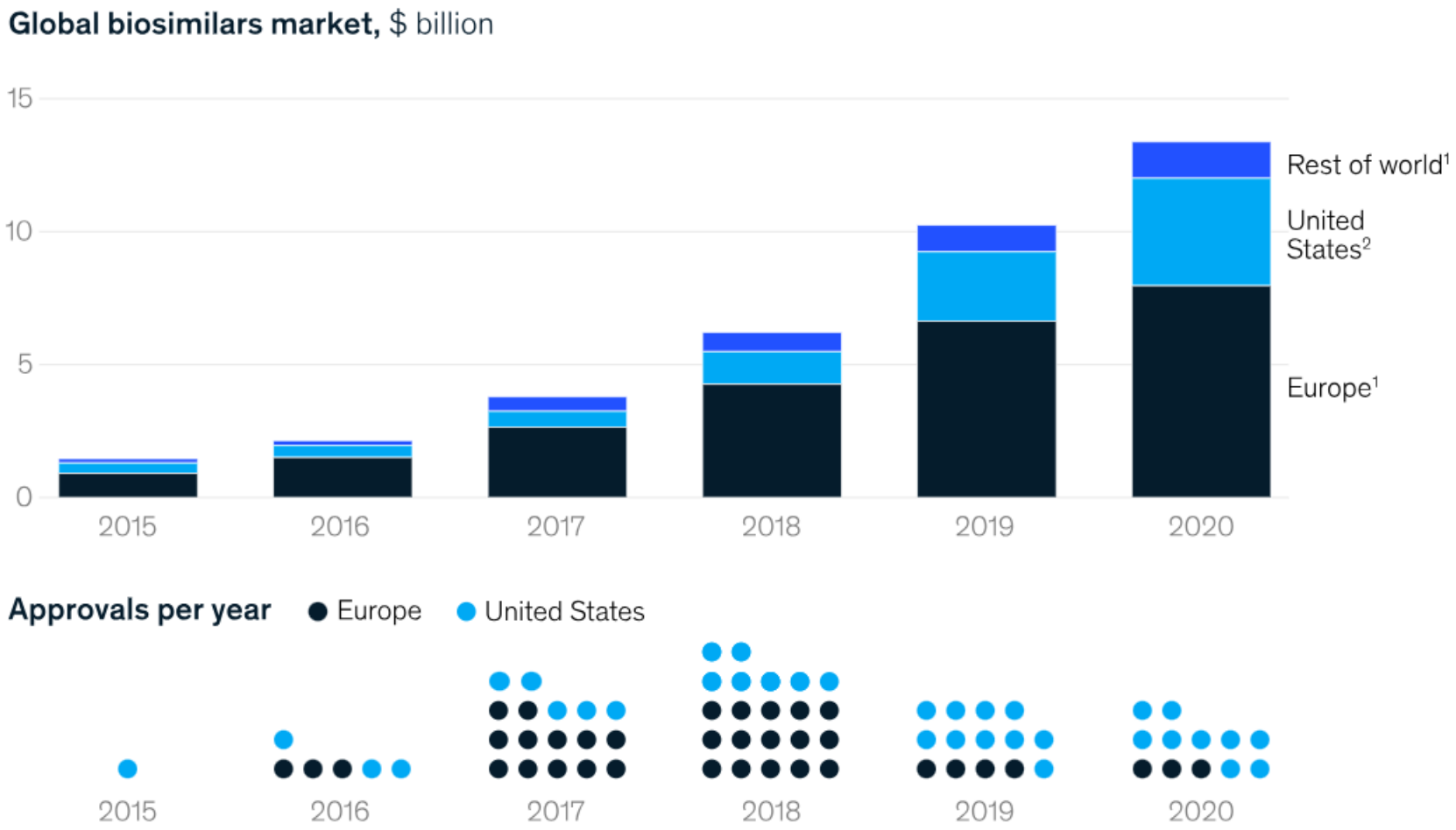
Use of Biosimilars in Paediatric Inflammatory Bowel Disease: A Position Statement of the ESPGHAN Paediatric IBD Porto Group

(*JPGN* 2015;61: 503–508)

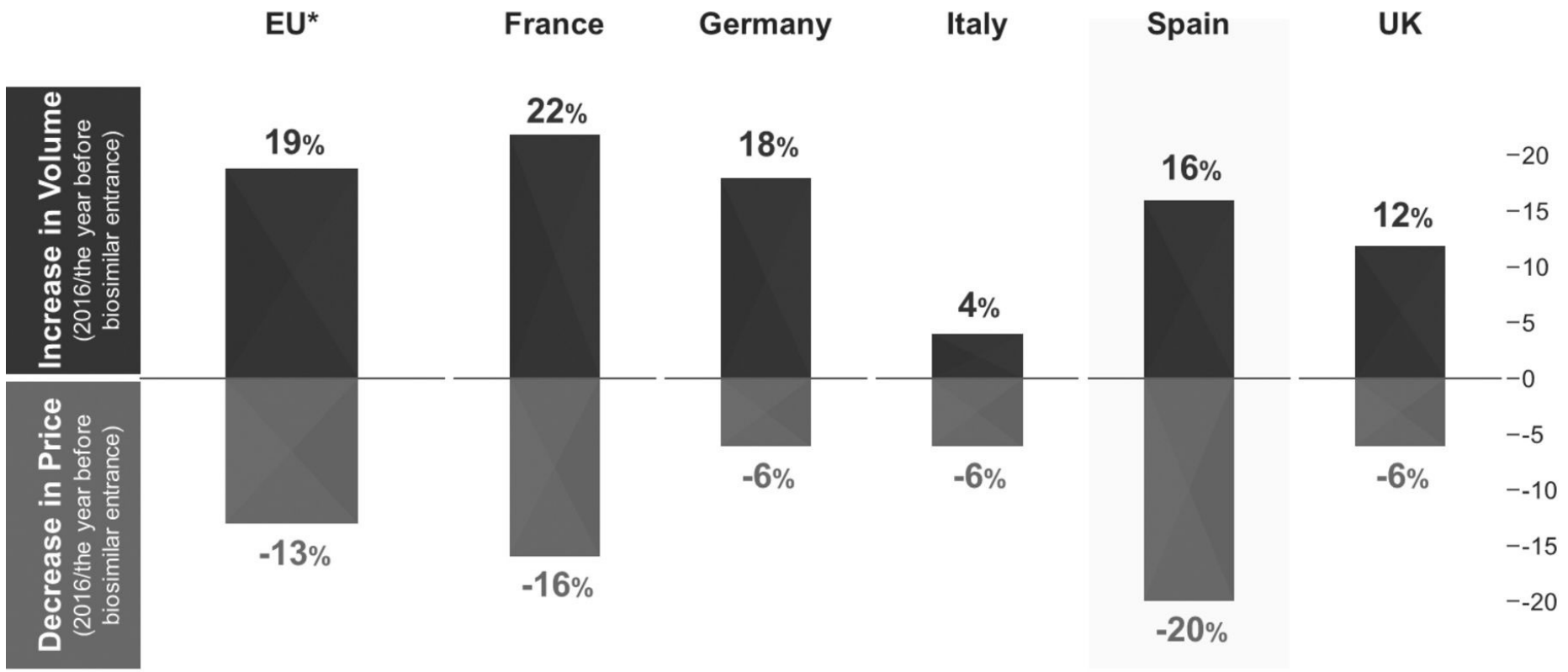
Joint position statement by "Sociedad Española de Patología Digestiva" (Spanish Society of Gastroenterology) and "Sociedad Española de Farmacología" (Spanish Society of Pharmacology) on biosimilar therapy for inflammatory bowel disease

Rev Esp Enferm Dig (Madrid)
Vol. 105. N.° 1, pp. 37-43, 2013

Biosimilars have recorded impressive growth in recent years.



[1]Based on data from IQVIA Analytics.
[2]Based on data from EvaluatePharma.
Source: EvaluatePharma, February 2021, Evaluate Ltd.; IQVIA Analytics Link, February 2021; US Food and Drug Administration; McKinsey analysis



*Included EU countries: Austria, Belgium, Bulgaria, Czech Republic, Denmark, Finland, France, Germany, Greece, Hungary, Ireland, Italy, Netherlands, Norway, Poland, Portugal, Romania, Slovakia, Slovenia, Spain, Sweden, Switzerland, UK

Smolen JS et al. RMD Open 2019;5:e000900.

Perspectiva histórica Biosimilares

2013

Pérdida patente IFX

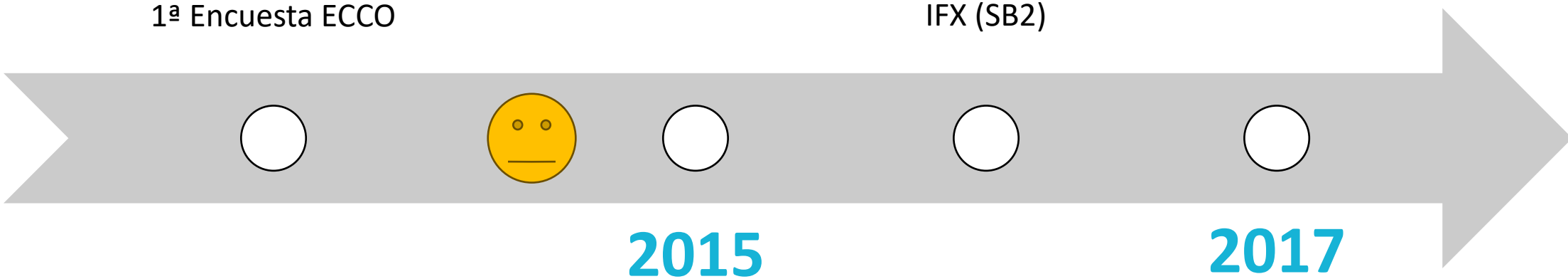
1º Biosimilar IFX (CT-P13)

1ª Encuesta ECCO

2016

2ª Encuesta ECCO

2º Biosimilar IFX (SB2)



2015

¿Perspectiva del Paciente?

2017

NOR-SWITCH

PROSIT-BIO

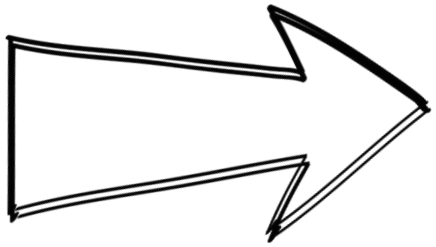
1ª Encuesta ECCO: Danese S, et al. J Crohns Colitis. 2014;8:1548–1550.
Perspectiva del Paciente: Peyrin-Biroulet L, et al. J Crohns Colitis. 2017;11:128–133.
2ª Encuesta ECCO: Danese S, et al. J Crohns Colitis. 2016;10:1362–1365.

Perspectiva histórica Biosimilares

2018

3º Biosimilar IFX (GP111)

1º Biosimilar ADA (ABP501)



2024

Pérdida patente GOLI

Pérdida patente VEDO

Reference product	Biosimilar product[a]	Location and approval date	
		EU	US
Infliximab	Infliximab-dyyb (Inflectra)	October 2013	April 2016
	Infliximab (Remsima)	October 2013	
	Infliximab (Flixabi)	May 2016	
	Infliximab-abda (Renflexis)		May 2017
	Infliximab-qbtx (Ixifi)		December 2017
	Infliximab (Zessly)	May 2018	
	Infliximab-axxq (Avsola)		December 2019
Adalimumab	Adalimumab-atto (Amgevita in EU/ Amjevita in US)	March 2017	September 2016
	Adalimumab (Imraldi)	August 2017	
	Adalimumab-adbm (Cyltezo)		August 2017
	Adalimumab (Hyrimoz)	July 2018	October 2018
	Adalimumab-fkjp (Hulio)	September 2018	July 2020
	Adalimumab (Idacio)	April 2019	
	Adalimumab-bwwd (Hadlima)		July 2019
	Adalimumab-afzb (Abrilada)		November 2019
	Adalimumab (Amsparity)	February 2020	

EU = European Union; US = United States

[a]The Food and Drug Administration (FDA) has mandated biosimilars containing a suffix composed of four lowercase letters; however, the European Medicines Agency (EMA) does not require suffixes but use identification tools that already exist within their pharmacovigilance system

Digestive Diseases and Sciences (2021) 66:2513–2532

Intercambiabilidad, sustitución y switch

- La **intercambiabilidad terapéutica** es la *posibilidad de cambiar un fármaco por otro que se espera que tenga el mismo efecto clínico*. Esto incluye *intercambiar un biológico original por su biosimilar o viceversa*, o *un biosimilar por otro*, y puede realizarse mediante **switch** o **sustitución**.
- El switch lo realiza el médico prescriptor, mientras que la sustitución la realiza directamente el farmacéutico.

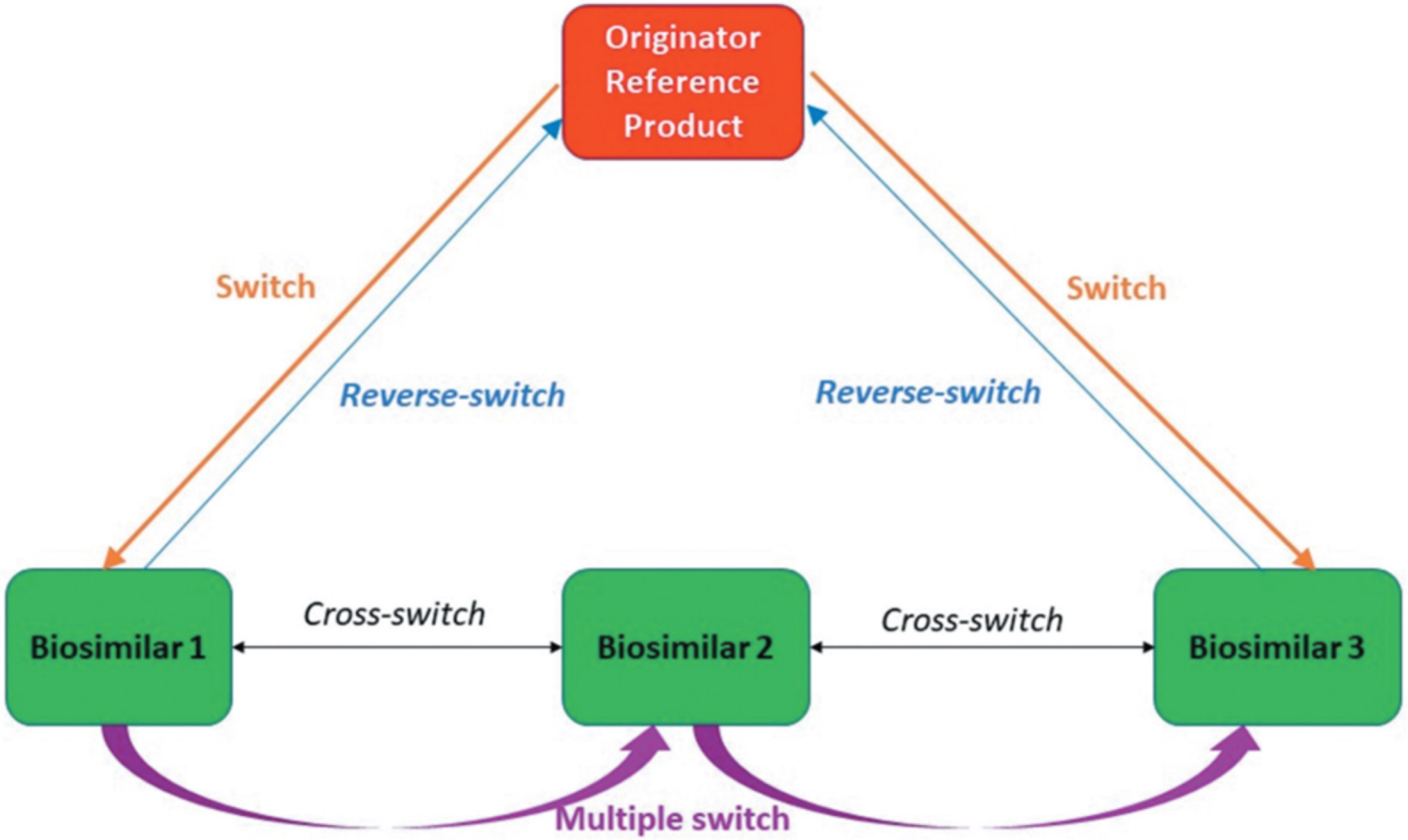


Figure 1. Switching of biologic agents and biosimilars.

Solitano V, et al. Expert Review of Clinical Immunology 2020; 16: 1019-1028

Marco Regulatorio

- La evaluación de **la EMA no incluía recomendaciones** sobre intercambiabilidad.
- La postura conjunta de la EMA y la CE es que **la intercambiabilidad es competencia de los estados miembros.**
- En España:
  - En la prescripción vía receta, la Orden Ministerial SCO/2874/2007 Y el RD Ley 1/2015 establecen que los medicamentos biológicos son medicamentos no sustituibles por el farmacéutico de oficina de farmacia.
  - **Se permite el switch** pero **impide la sustitución automática** cuando no hay un consenso previo con el prescriptor. En los hospitales este consenso se establece en las *Comisiones de Farmacia y Terapéutica.*

EUROPEAN MEDICINES AGENCY
SCIENCE MEDICINES HEALTH

HMA
Heads of Medicines Agencies

19 September 2022
EMA/627319/2022

Joint EMA-HMA statement on interchangeability:

Biosimilars approved in the EU are interchangeable

Interchangeability refers to the possibility of exchanging one medicine for another medicine that is expected to have the same clinical effect.

HMA and EMA consider that once a biosimilar is approved in the EU it is interchangeable, which means the biosimilar can be used instead of its reference product (or vice versa) or one biosimilar can be replaced with another biosimilar of the same reference product.

Decisions regarding substitution (the practice of dispensing one medicine instead of another medicine without consulting the prescriber), are not within the remit of the EMA and are managed by individual member states.

Pais	Cambio o switch	Sustitución
España	**Si**	**No. Existe regulación.**
Portugal	Si, en pacientes näive o pacientes con BR > 6 m	No. No existe regulación.
Alemania	Si, con excepciones	No
Reino Unido	Si	No sin autorización del presciptor.
Francia	Si, en pacientes näive	Si, pacientes näive.
Italia	Si	No
Dinamarca	Si	No
Suecia	No recomendado, pero posible	No
EEUU	Si, si la FDA declara el BR intercambiable	Distintas normas regionales
Australia	Si	No
Japón	No	No sin autorización del presciptor.

2017 Posicionamiento nacional sobre la intercambiabilidad de biosimilares en la UE y en otros países

L'evoluzione dell'intercambiabilità in Europa

Legal regulations against automatic substitution

Guidelines prohibiting automatic substitution

No substitution and no law/guidance

Law/regulations/guidance for restricted automatic substitution

No law/guidance but automatic substitution

2017

2022

https://www.pharmadoc.it/intercambiabilita-a-livello-di-farmacia-dei-biosimilari-nei-paesi-europei-in-italia-solo-se-cambia-la-legge-che-la-vieta-espressamente/

Intercambio de BR a Biosimilar IFX

- **CT-P13**, el más estudiado.
- Extrapolación de estudios PLANETAS y PLANETRA.
- **NOR-SWITCH** (2017)
  - Ensayo randomizado doble ciego, de no inferioridad.
  - 482 pacientes >18 años, con enfermedades inflamatorias inmunomediadas (155 EC y 91 CU).
  - Switch a CT-P13 (tras 6 m con IFX) vs continuar con IFX
  - Seguimiento a 52 semanas

PLANETAS: Park W, et al. Ann Rheum Dis. 2013;72:1605–1612.
PLANETRAS: Yoo Dh, et al. Ann Rheum Dis. 2013;72:1613–1620.
NOR-SWITCH: Jørgensen KK et al. Lancet. 2017;389:2304–2316.

	Infliximab originator n=202	CT-P13 n=206	Risk difference (95% CI)
Diagnosis			
Crohn's disease	14 (21·2%)	23 (36·5%)	−14·3% (−29·3 to 0·7)
Ulcerative colitis	3 (9·1%)	5 (11·9%)	−2·6% (−15·2 to 10·0)
Spondyloarthritis	17 (39·5%)	14 (33·3%)	6·3% (−14·5 to 27·2)
Rheumatoid arthritis	11 (36·7%)	9 (30·0%)	4·5% (−20·3 to 29·3)
Psoriatic arthritis	7 (53·8%)	8 (61·5%)	−8·7% (−45·4 to 28·1)
Psoriasis	1 (5·9%)	2 (12·5%)	−6·7% (−26·7 to 13·2)
Overall	**53 (26·2%)**	**61 (29·6%)**	**−4·4% (−12·7 to 3·9)**

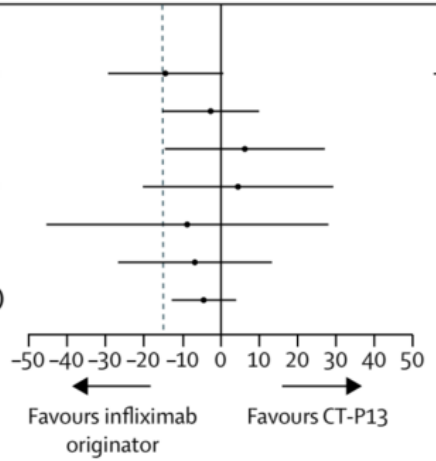
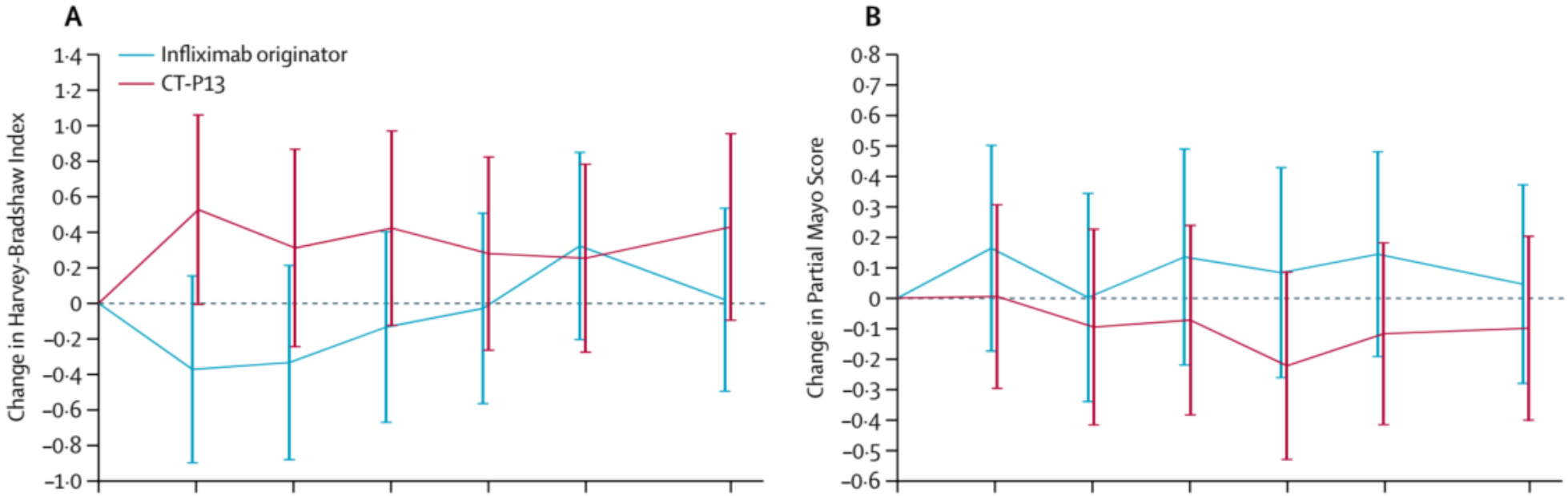


Figure 2: **Forest plot of risk difference according to disease**
Figure shows data for the per-protocol set. Risk difference is adjusted for treatment duration of infliximab originator at baseline.



NOR-SWITCH: Jørgensen KK et al. Lancet. 2017;389:2304–2316.

Intercambio de BR a Biosimilar IFX

- **Extensión NOR-SWITCH** (2019)
  - Switch a CT-P13 vs mantenimiento con CT-P13 desde semana 52
  - N=380, 207 EII. Seguimiento 78 semanas.

Diagnosis	Maintenance (*n* = 190)	Switch (*n* = 173)	Risk difference (95% CI)
Crohn's disease	13/63 (20.6%)	8/61 (13.1%)	7.9% (–5.2 to 21)
Ulcerative colitis	6/39 (15.4%)	1/35 (2.9%)	12.4% (–0.1 to 25)
Spondyloarthritis	3/38 (7.9%)	2/28 (7.1%)	0.6% (–12.2 to 13.5)
Rheumatoid arthritis	9/26 (34.6%)	6/27 (22.2%)	10.5% (–13.6 to 34.6)
Psoriatic arthritis	1/8 (12.5%)	3/9 (33.3%)	–20.8% (–59.1 to 17.6)
Psoriasis	0/16 (0%)	0/13 (0%)	0% (–20.6,24.7)
Overall	**32/190 (16.8%)**	**20/173 (11.6%)**	**5.9% (–1.1 to 12.9)**

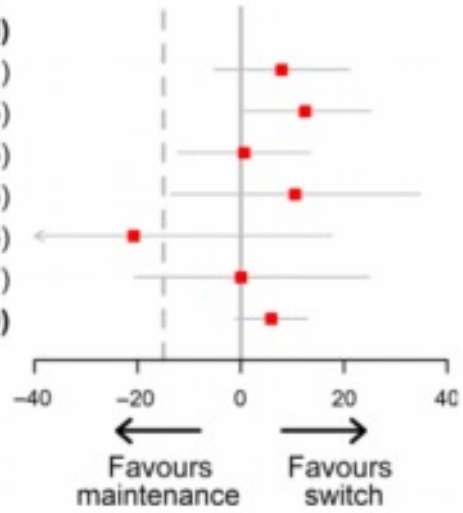
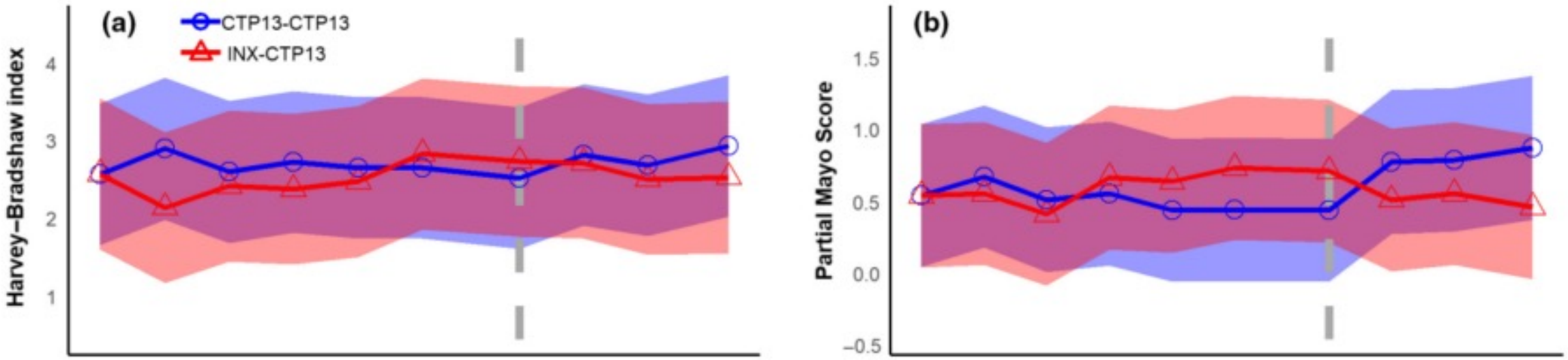


Fig. 2 *Forest plot of risk difference according to disease. The figure shows data for the per-protocol set. Risk difference is adjusted for treatment duration of infliximab originator at extension study baseline (week 52).*

NOR-SWITCH Ext: Goll GL, et al. J Intern Med. 2019; 285:653-669.

Intercambio de BR a Biosimilar IFX

- **Extensión NOR-SWITCH** (2019)
  - Switch a CT-P13 vs mantenimiento con CT-P13 desde semana 52
  - N=380, 207 EII. Seguimiento 78 semanas.



Sin diferencias en cuanto a eficacia, seguridad e inmunogenicidad.

NOR-SWITCH Ext: Goll GL, et al. J Intern Med. 2019; 285:653-669.

Intercambio de BR a Biosimilar IFX Real Word Data

- **PROSIT-BIO, 2017.**
  - Pacientes adultos. EC(n=313); CU (n=234).
  - IFX vs Switch CT-P13 (tras una media de 18 ± 14 infusiones).
  - Seguimiento 4.3 ± 2.8 meses.
  - *Primary endpoint*: seguridad.
  - *Secodary endpoints*: eficacia, inmunogenicidad, factores predictores.
  - **No comparación entre grupos, pero resultados en la línea de los existentes para IFX.**

- **Extensión PROSIT-BIO, 2019.**
  - + pacientes, + seguimiento. Endpoints similares.
  - Resultados similares al previo.

PROSIT-BIO: Fiorino G, et al. Inflamm Bowel Dis 2017;23:233–243
Extensión PROSIT-BIO: Armuzzi A, et al. Inflamm Bowel Dis. 2019;25:568-579.

Intercambio de BR a Biosimilar IFX Real Word Data

- Ye BD, et al. Lancet 2019.
  - Ensayo doble ciego, fase 3220 pacientes adultos con Crohn.
  - 4 grupos:
    1. Inicia CT-P13 y mantiene CT-P13
    2. Inicia CT-P13 y switch a IFX
    3. Inicia IFX y mantiene IFX
    4. Inicia IFX y switch a CT-P13
  - **No diferencias en semana 6, semana 14 ni semana 30 en CDAI-70, CDAI-100, respuesta clínica, remisión libre de esteroides, calpro, efectos adversos o inmunogenicidad.**

Ye BD, et al. Lancet 2019; 393: 1699–707.

Intercambio de BR a Biosimilar IFX Real Word Data

- Gonczi L, et al. Long-term efficacy, safety, and immunogenicity of biosimilar infliximab after one year in a prospective nationwide cohort. *Inflamm Bowel Dis. 2017;23:1908–1915.*
- Bergqvist V, et al. Switching from originator infliximab to the biosimilar CT-P13 in 313 patients with inflammatory bowel disease. *Therap Adv Gastroenterol. 2018;11: ecollection.*
- Meyer A, et al. Effectiveness and safety of reference infliximab and biosimilar in Crohn disease: a French equivalence study. *Ann Int Med. 2019;170:99–107.*
- Meyer A, et al. The effectiveness and safety of infliximab compared with biosimilar CT-P13, in 3112 patients with ulcerative colitis. *Aliment Pharmacol Ther. 2019;50:269–277.*
- Massimi D, et al. Switching from Infliximab Originator to SB2 Biosimilar in Inflammatory Bowel Diseases: A Multicentric Prospective Real-Life Study. Therap *Adv Gastroenterol 2021; 14: 1756284821023384*
- …

Multi-Intercambio IFX (De CT-P13 a SB2 / De CT-P13 a GP1111)

First Author (year)	Country	Study design	Indication	N° Pts	Comparison	Main results	Author conclusion
Infliximab							
Lovero et al. (2021)	Italy	Cohort study (R)	IBD	36	CT-P13 to SB2 vs. multiple switch	Clinical remission rate, LOR, and AEs: no differences	Switching from CT-P13 to SB2 seems to be safe and effective either in pts with single and multiple switches
Macaluso et al. (2021)	Italy	Cohort study (P)	IBD	276	CT-P13 to SB2 vs. multiple switch vs. IFX originator to SB2	SAEs, n (%)*: CT-P13 to SB2: 11. (25.6) Multiple switches: 4 (16.7)	Safety and effectiveness of IFX SB2 similar to those of IFX originator; switching from originator or CT-P13 (and multiple switches) not dangerous
Hanzel et al. (2021)	The Netherlands	Cohort study (P)	IBD	176	CT-P13 to SB2 vs. multiple switch vs. IFX originator to CT-P13	Clinical remission n (%): CT-P13 to SB2: 55 (69); multiple switch: 58 (84); IFX originator to CT-P13: 25 (93). Discontinuation (HR 95% CI): CT-P13 to SB2: 0.42 (0.16–1.12); multiple switch: 0.39 (0.14–1.11). ADA (%): CT-P13 to SB2: 8.8% (7/80); multiple switch: 5.8% (4/69); IFX originator to CT-P13: none	No significant differences in clinical, CRP, or fecal calprotectin remission at 12 months; lower rates in pts switching from CT-P13 to SB2; multiple switching and switching between biosimilars of IFX seemed effective and safe
Mazza et al. (2022)	Italy	Cohort study (R)	IBD	118	Multiple switch vs. IFX originator to CT-P13	Clinical remission (adjusted OR, 95% CI): 1.3 (0.3–6.2). Total AE n (%): multiple switch 5 (9.6); IFX originator to CT-P13 8 (12.4); discontinuation (adjusted HR, 95% CI) 1.3 (0.3–6.2)	No significant differences in terms of safety and efficacy when comparing double switch with a single switch; data consistent with the safety profile of IFX

Cohen HP, et al. BioDrugs (2022) 36:625–637
Allocati E, et al. Front. Pharmacol. 2022; 13:917814.

Multi-Intercambio IFX (De CT-P13 a SB2 / De CT-P13 a GP1111)

Luber et al. (2021)	United Kingdom	Cohort study (P)	IBD	186	CT-P13 to SB2 vs. multiple switch	Disease activity n (%) 1 year: CT-P13 to SB2: 6 (9.5); multiple switch: 1 (1.3). ADA 1 year: none in both arms	Biosimilar switching does not have negative influence in terms of infliximab trough levels and disease activity
Harris et al. (2019)	United Kingdom	Cohort study (P)	IBD	133	CT-P13 to SB2 vs. historic control (no switch)	Disease activity (mean ± SD) week 16–18: Crohn's disease: 3.15 ± 3.17; Ulcerative colitis: 0.91 ± 1.64	No significant difference in drug levels between historical CT-P13 pts and SB2 pts
Trystram et al. (2021)	France	Cohort study (P)	IBD	204	CT-P13 to SB2 vs. multiple switch	Discontinuation rate n (%): CT-P13 to SB2: 5 (11.6); multiple switch: 7 (6.2). LOR n (%): 17 (10.8) both groups. Clinical remission n (%): CT-P13 to SB2 36/40 (90); multiple switch: 104/113 (92). AEs n (%): CT-P13 to SB2: 13 (31.6); multiple switch: 50 (41.4)	Switching from the originator to CT-P13 and then to SB2 did not impair the effectiveness, immunogenicity or safety of anti-TNF therapy after 54 weeks of follow-up
Bouhnik et al. (2020)	France	Single-arm (R)	IBD	109	IFX (biosimilar or originator) to SB2	LOR n: 19. Discontinuation due to AEs n: 9. Discontinuation due to unspecified reasons n: 16	Switch references or biosimilar IFX to SB2 without loss disease control and no need for dose escalation
Mott et al. (2021)	United Kingdom	Single-arm (P)	IBD	289	CT-P13 to GP1111	LOR n (%): 17 (6)	Proportion of pts who discontinued due to LOR consistent with historical norm; switching between biosimilar IFX is safe and effective
Siakavellas et al. (2021)	United Kingdom	Single-arm (P)	IBD	246	CT-P13 to GP1111	ADA n (%): 5 (2). Discontinuation rate n (%): 10 (3.7). LOR n (%): 5 (2)	Single and multiple biosimilar IFX switching is safe with no negative effects in clinical outcomes at 6 months

Cohen HP, et al. BioDrugs (2022) 36:625–637
Allocati E, et al. Front. Pharmacol. 2022; 13:917814.

Intercambio de BR a Biosimilar ADA

- ABP 501 y SB5, los primeros (2017).
- Extrapolación de estudios en AR y psoriasis en placas.
- **VOLTAIRE-CD** (2021)
  - EC fase III, randomizado, doble ciego. 147 Adultos 18-80 años.
  - BI 695501 (no comercializado en España) (n=72) vs ADA (+switch a las 24 s) (n=75).
  - *Primary endpoint*: eficacia (proporción de pacientes con respuesta clínica) en semana 4.
  - *Secondary endpoint*: seguridad.
  - **Eficacia y seguridad similar entre pacientes tratados con BI 695501 y los tratados con ADA.**

Cohen S, et al. Ann Rheum Dis. 2017;76(10):1679–1687.
Papp K, et al. J Am Acad Dermatol. 2017;76 (6):1093–1102.
Weinblatt ME, et al. Arthritis Rheumatol. 2018;70:40–48.
Weinblatt ME, et al. Arthritis Rheumatol. 2018;70:832–840
VOLTAIRE CD – Hanauer S, et al. Lancet Gastroenterol Hepatol. 2021; 6:816-825.

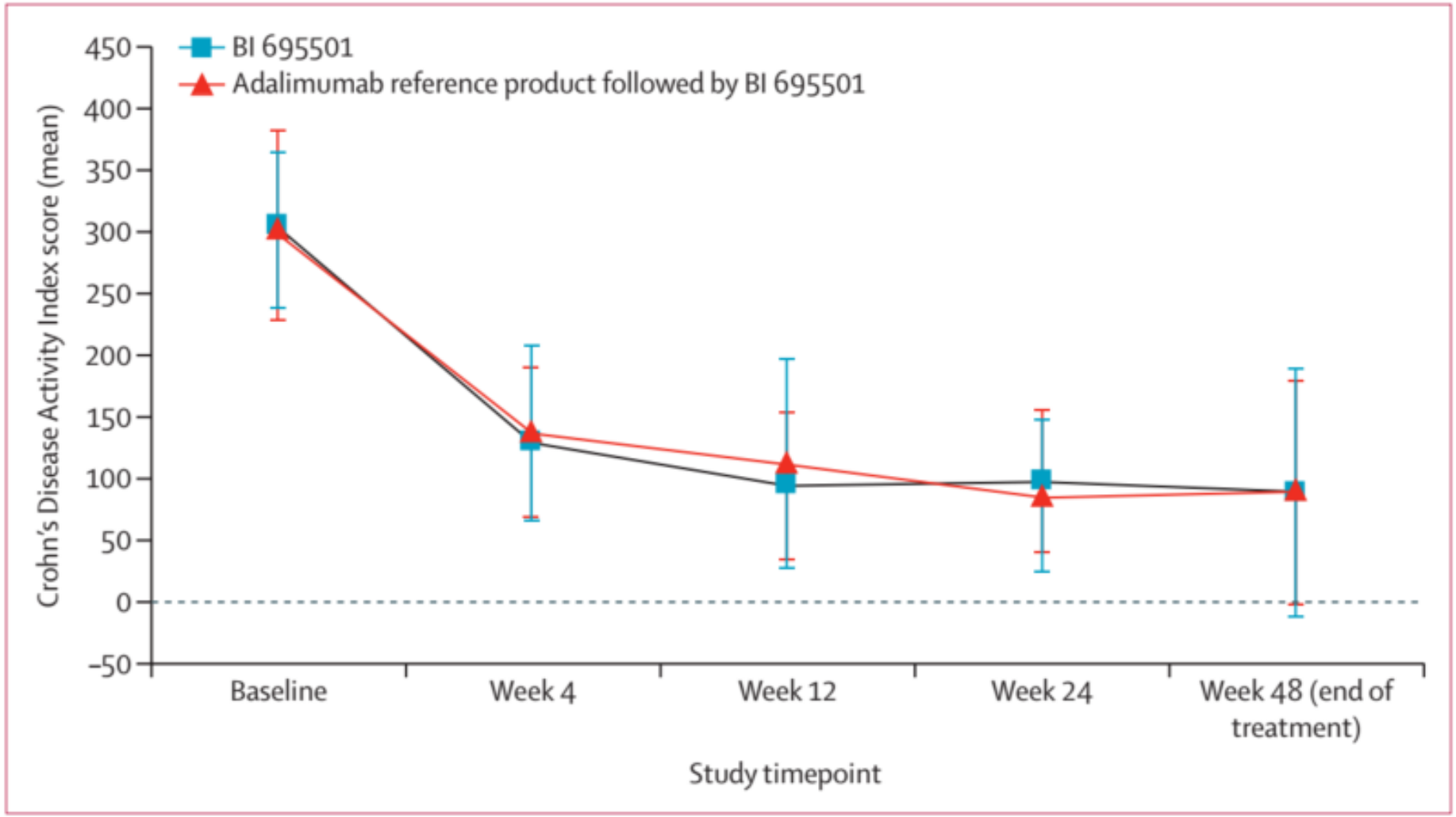


***Figure 2*: Changes over time in mean Crohn's Disease Activity Index scores (modified full analysis set)**
Error bars show SD.

VOLTAIRE CD – Hanauer S, et al. Lancet Gastroenterol Hepatol. 2021; 6:816-825.

	Weeks 0–24		Weeks 24–56	
	BI 695501 (n=72)	Adalimumab reference product (n=75)	BI 695501 (n=72)	Adalimumab reference product followed by BI 695501 (n=75)
Any adverse event	45 (63%)	42 (56%)	31 (43%)	34 (45%)
Drug-related adverse event	15 (21%)	17 (23%)	10 (14%)	11 (15%)
Upper respiratory tract infection	0	3 (4%)	0	0
Injection-site erythema	0	3 (4%)	0	0
Pruritis	0	2 (3%)	0	1 (1%)
Weight increase	3 (4%)	1 (1%)	2 (3%)	0
Hypercholesterolaemia	2 (3%)	0	1 (1%)	0
Alopecia	2 (3%)	0	0	0
Arthralgia	2 (3%)	0	0	0
Increased γ-glutamyltransferase	1 (1%)	0	2 (3%)	0

VOLTAIRE CD – Hanauer S, et al. Lancet Gastroenterol Hepatol. 2021; 6:816-825.

Intercambio de BR a Biosimilar ADA Real Word Data

Switching between reference adalimumab and biosimilars in chronic immune-mediated inflammatory diseases: A systematic literature review

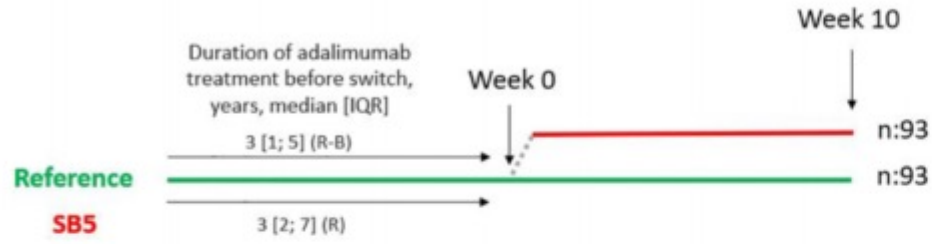
Br J Clin Pharmacol. 2022;88:1529–1550.

- 21 estudios (8 biosimilares de ADA ≠) que incluyeron AR, Ps, EII y otros.
- En general, y en particular en la EII, no se encontraron diferencias entre los diferentes biosimilares de ADA (ABP 501 y SB5) y ADA en los estudios analizados en cuanto a **eficacia**, **seguridad** o **inmunogenicidad**.

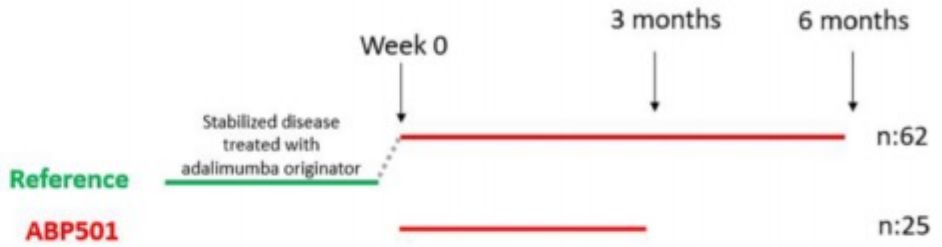
Garcia-Veloso N, et al. Br J Clin Pharmacol 2022; 88:1529-1550.

Study population: Inflammatory bowel disease

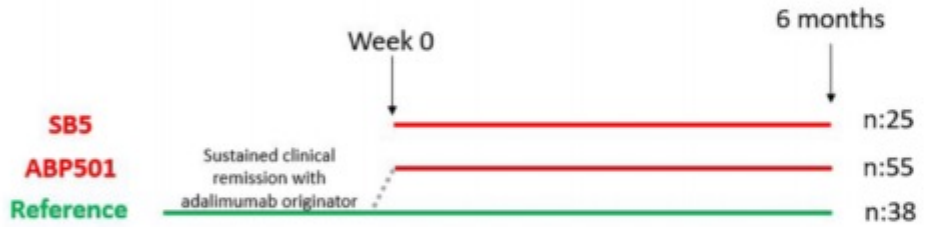
(A) Lukas, 2020 Retrospectivo



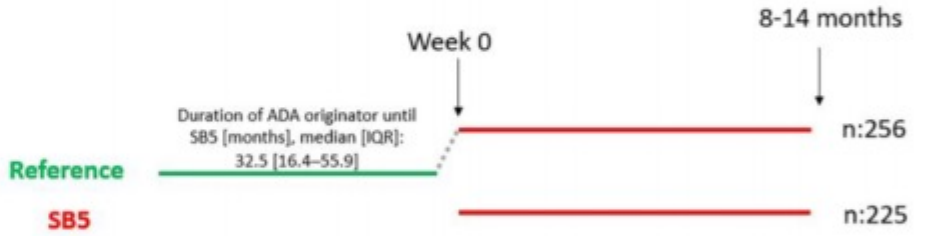
(B) Ribaldone, 2020 Observacional Prospectivo



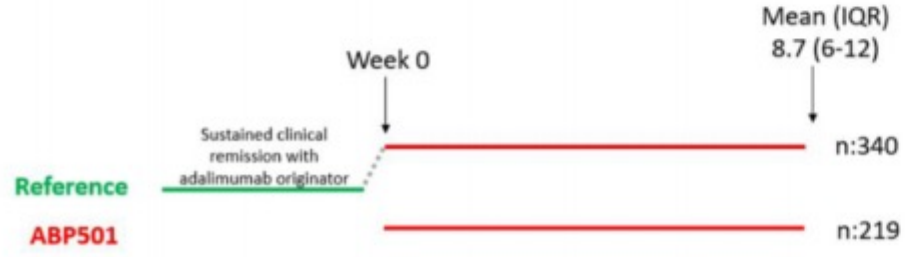
(C) Cingolani, 2021 Cohortes Prospectivo



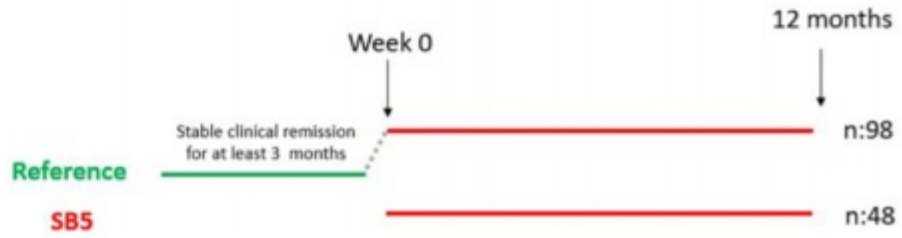
D) Derikx, 2021 Cohortes Prospectivo



(E) Macaluso, 2021 Cohortes Prospectivo



(F) Tapete, 2021 Cohortes Prospectivo



Garcia-Veloso N, et al. Br J Clin Pharmacol 2022; 88:1529-1550.

Multi-Intercambio ADA

Adalimumab

Ribaldone et al. (2021)	Italy	Single-arm (P)	CID	68	ABP501 to SB5	Success rate (clinical remission) n (%): 50 (82) discontinuation n (%): 7 (11.5). AE n (%): 7 (11.5)	Switching between biosimilars is safe and effective; switch not recommended if positive CRP is found at the time of switching
Lontai et al. (2022)	Hungary	Cohort study (P)	IBD	246	ADM bio 1 to ADM bio 2 vs. ADM originator to ADM bio	Clinical remission % (week 20–24): bio1 to bio2: 77.6; originator to bio: 85	No differences in pts who switched from originator to biosimilar or between biosimilars

Cohen HP, et al. BioDrugs (2022) 36:625–637
Lontai L, et al. Digestive and Liver Disease 54 (2022) 1639–1645

Biosimilares en Pediatría

Biosimilars in Pediatric Inflammatory Bowel Diseases: A Systematic Review and Real Life-Based Evidence

Front. Pharmacol. 13:846151.
doi: 10.3389/fphar.2022.846151

*Valeria Dipasquale[1], Giuseppe Cicala[2], Edoardo Spina[2] and Claudio Romano[1]**

- 9 estudios con CT-P13. No otros biosimilares de IFX o ADA.
- En total, 394 pacientes (316 EC, 61 CU y 17 EIInc)
- **Eficacia:**
  - Sólo se evalúa el switch de IFX a biosimilar de IFX.
  - 5/9 estudios, 152 niños (116 EC, 33 CU y 3 EIInc)
  - **No diferencias en cuanto a eficacia.**

Dipasquale V, et al. Front Pharmacol 2020; 13: 8461451.

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*Valeria Dipasquale[1], Giuseppe Cicala[2], Edoardo Spina[2] and Claudio Romano[1]**

- **Cambios en biomarcadores**:
  - 7/9 estudios. Después del switch y durante el seguimiento, **sin diferencias.**
- **Cambios en los niveles y en la inmunogenicidad:**
  - 5/9 estudios. **Sin diferencias.**
- **Seguridad:** Idem
- **Costes:**

Dipasquale V, et al. Front Pharmacol 2020; 13: 8461451.

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TABLE 4 | Cost saving in comparison to treatment with originator.

References	Drugs	Estimated saving	Time period
Richmond L et al. (Richmond et al., 2018)	Remsima© vs. Remicade©	38% average per phial £47,800 (€57,000) for the total number of infusions	12 weeks
Chanchlani N et al. (Chanchlani et al., 2018)	Remsima© or Inflectra© vs. Remicade©	£875,000 (€998,526) for the total number of infusions	1 year
Gervais L et al. (Gervais et al., 2018)	Remsima© vs. Remicade©	£66,000 (€75,900) £1,500 per patient per year	1 year

Dipasquale V, et al. Front Pharmacol 2020; 13: 8461451.

Table 4 Studies Investigating the Use of CT-P13 in Pediatric IBD

Year of Publication	Design	Patients on Anti-TNF-α	Main Findings	Other Endpoints Included
2016	Prospective	N=39 (elected to switch)	88–57% clinical remission rate at the last follow-up assessment for CD and UC patients, respectively	Inflammatory biomarkers, adverse reactions
2017[40]	Prospective	N=36	86% clinical response rate and 67% remission rate at the end of induction	Inflammatory biomarkers, adverse reactions
2018[41]	Prospective	N=40	67% remission rate at the end of induction	Inflammatory biomarkers, adverse reactions
2018[42]	Prospective	N=257 (N=82 on biosimilar)	No significant difference in remission rates between reference and biosimilar at the end of induction	Adverse reactions, costs
2018[43]	Prospective	N=74 (N=38 elected to switch)	No significant difference in remission rates between reference and biosimilar	Inflammatory biomarkers, trough levels, adverse reactions
2018[44]	Prospective	N=33 (elected to switch)	No significant difference in remission rates within 12 months after the switch	Inflammatory biomarkers, trough levels, adverse reactions, costs
2019[45]	Prospective	N=42 (elected to switch)	No significant difference in remission rates in comparison to baseline or at the last infusion before the switch	Inflammatory biomarkers, trough levels, adverse reactions
2020[46]	Retrospective	N=51 (N=28 on biosimilar)	No significant difference in clinical response rates between reference and biosimilar IFX at the end of induction	Inflammatory biomarker (fecal calprotectin), trough levels, adverse reactions
2021[47]	Prospective	N=56 (N=15 elected to switch)	Reduced PCDAI score at month 6 compared with baseline	Adverse reactions

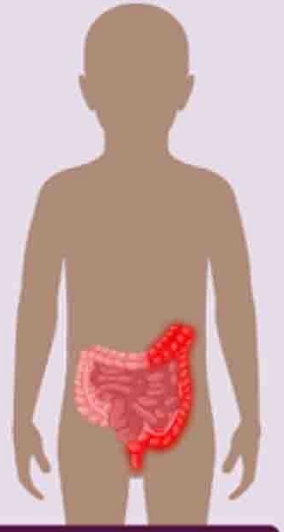
Abbreviations: IBD, inflammatory bowel disease; TNF-α, tumor necrosis factor-α.

Dipasquale V, et al. Front Pharmacol 2020; 13: 8461451.

Treatment Outcomes in Patients Receiving Infliximab Biosimilar SB2 Therapy

Biosimilars of infliximab (IFX), a tumor necrosis factor inhibitor, can be used to effectively treat paediatric inflammatory bowel disease (IBD)

However, more data on their practical, long-term use are needed



Analysing outcomes of treatment with IFX biosimilar SB2 therapy in:

	IFX-naïve patients	Patients switched from reference IFX
Crohn's disease (CD)	51	51
Ulcerative colitis (UC)	9	15

Results of a 12-month follow-up

Naïve → SB2

- Patient disease scores in both groups and C-reactive protein (CRP) levels in patients with CD decreased
- Height z-scores in patients with CD increased
- Clinical remission rates improved

Reference IFX → SB2

- Patient disease scores and CRP levels remained stable
- Height z-scores in patients with CD and UC increased
- No temporary loss of disease control

SB2 therapy provides effective disease control for switched and naïve paediatric patients with IBD

PERFUSE: Non-interventional cohort study of patients receiving infliximab biosimilar SB2; results in paediatric patients
Martinez-Vinson *et al.* (2022)

JPGN JOURNAL OF PEDIATRIC GASTROENTEROLOGY AND NUTRITION

Martinez-Vinson C, et al. J Pediatr Gastroenterol Nutr. 2023; 76: 451–459.

Real-life experience of infliximab biosimilar in pediatric-onset inflammatory bowel disease: data from the Sicilian Network for Inflammatory Bowel Disease

European Journal of Gastroenterology & Hepatology 2022, 34:1007–1014

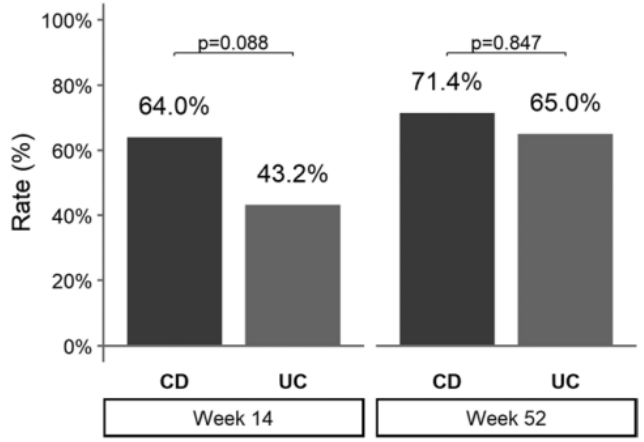
Objective To provide data on the use of infliximab biosimilars (IFX-BioS) in children with inflammatory bowel disease (IBD).

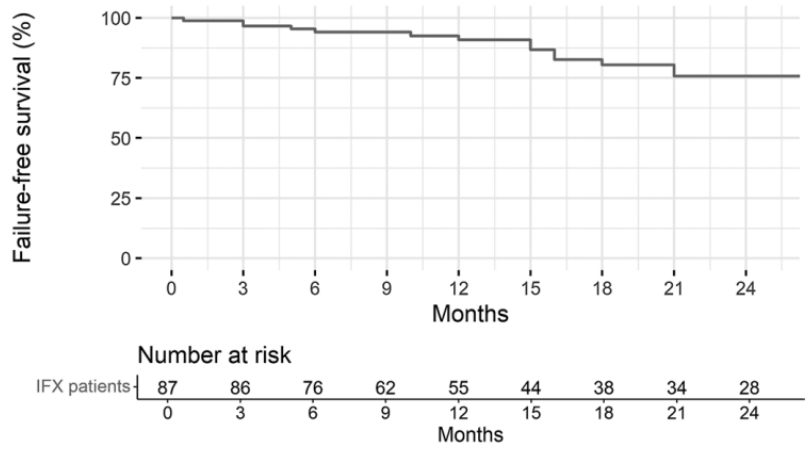
Methods A multicenter, observational, retrospective study was performed among the cohort of the Sicilian Network for IBD. All consecutive IBD children who had at least completed the induction with IFX-BioS from its introduction in Sicily to January 2021 were enrolled. Clinical remission at weeks 14 and 52, treatment persistence, and adverse events were the study outcomes.

Results Eighty-seven patients [Crohn's disease (CD): 57.5% and ulcerative colitis (UC): 42.5%] were included: 75 (86.2%) were antitumor necrosis factor-α (anti-TNF-α) agent naïve, while three (3.45%) were switched from the originator to IFX-BioS. Twenty (23%) patients were multiply switched from the biosimilar CT-P13 to SB2 or GP1111 or vice versa. The median follow-up time was 15 months. Clinical remission was achieved by 55.2 and 65.5% of patients at weeks 14 and 52, respectively, with no differences between CD and UC. Dose escalation was needed in 8.0 and 35.7% of patients during induction and maintenance, respectively. Nine adverse events occurred (incidence rate: 6.13/100 person-year). Treatment persistence was 90.8% at 1 year and 75.7% at 2 years (patients on IFX-BioS at 2 years, $n = 28$). The risk of treatment discontinuation was higher in patients with extraintestinal manifestations ($P = 0.018$) and in those who were nonnaïve to anti-TNF-α ($P = 0.027$).

Conclusion This is the largest cohort of pediatric IBD patients treated with IFX-BioS. Real-life data show that IFX-BioS is efficacious in IBD children, with high percentages of treatment persistence and a low incidence of nonserious adverse events.

Eur J Gastroenterol Hepatol 34: 1007–1014





Dipasquale V, et al. Eur J of Gastroenterol Hepatol 2022; 34:1007–1014.

Biosimilares en Pediatría

Crecimiento y biosimilares

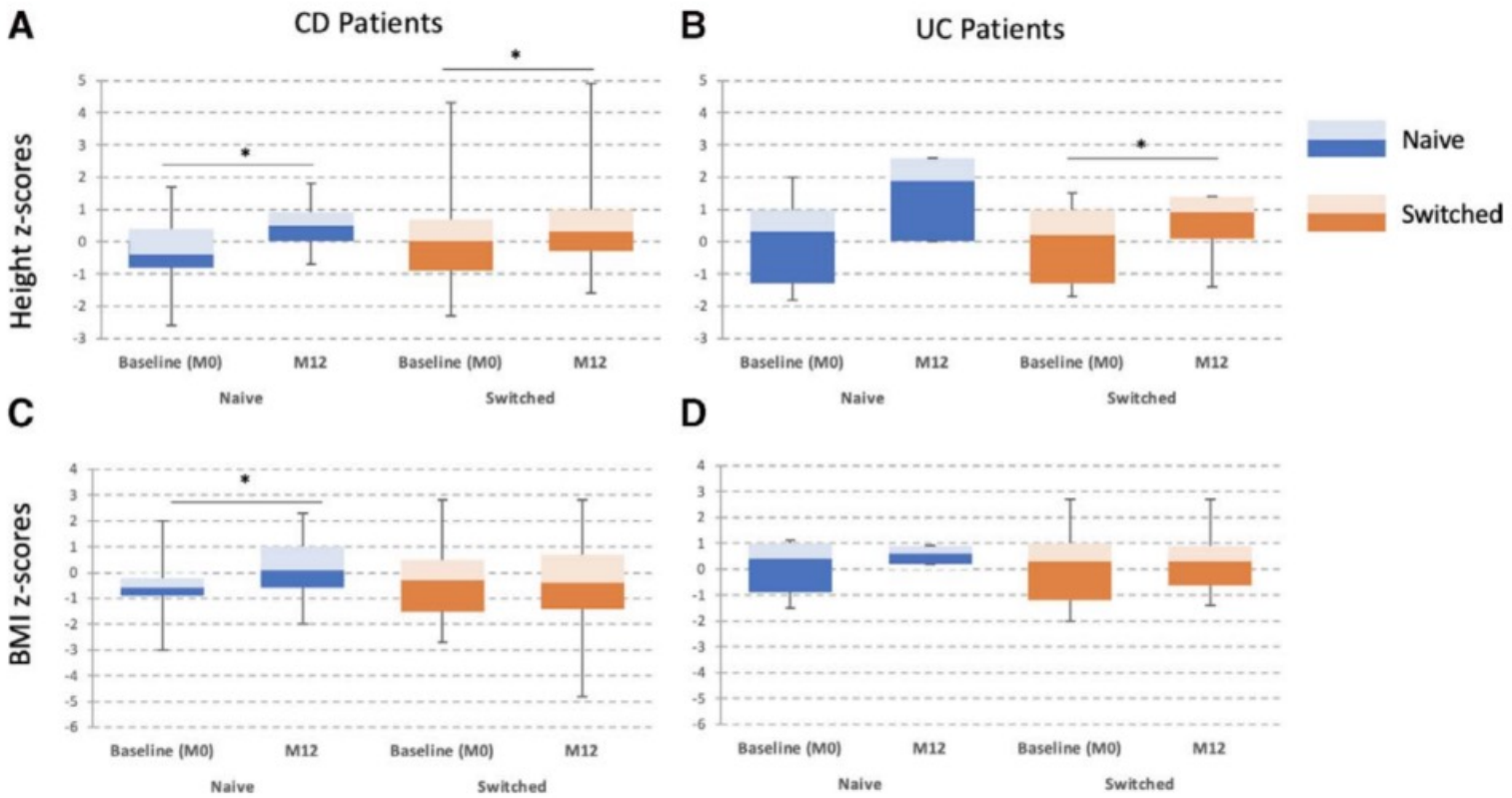


FIGURE 2. Patient growth metrics: growth was measured using the height *z* score and ponderal growth was measured using BMI. (A and B) Distributions of height *z* scores for naïve (blue) and switched (orange) CD and UC patients at baseline and at 12 months. (C and D) Distributions of BMI for naïve (blue) and switched (orange) CD and UC patients at baseline and at 12 months. Significant differences ($P < 0.05$) between baseline and M12 are indicated with a star. BMI = body mass index; CD = Crohn disease; UC = ulcerative colitis.

Martinez-Vinson C, et al. J Pediatr Gastroenterol Nutr. 2023; 76: 451–459.

Crecimiento y biosimilares

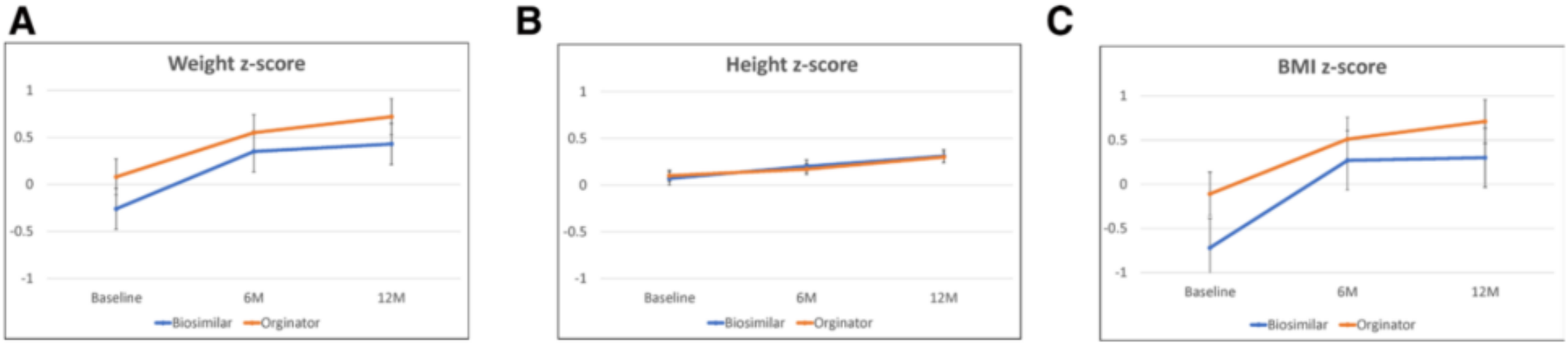


FIGURE 2. (A) Weight, (B) height, and (C) BMI *z* scores baseline to 12 months. BMI = body mass index.

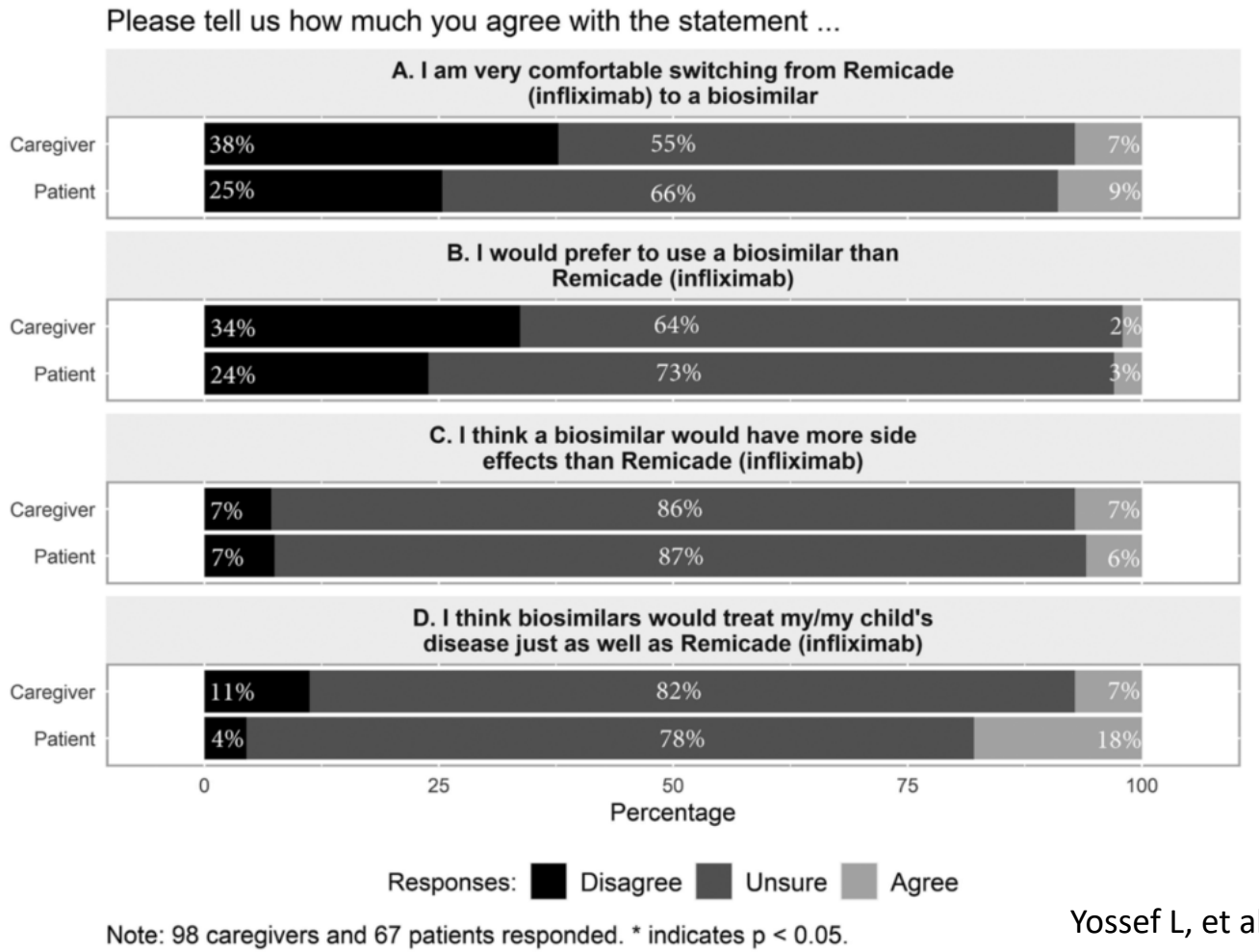
- Estudio retrospectivo
- 113 pacientes con IFX vs 39 con biosimilar CT-P13.
- Datos de eficacia, crecimiento, biomarcadores.

McClinchie MG, et al. JPGN 2023;77: 499–504

Patient and Caregivers' Perspectives on Biosimilar Use in Pediatric Inflammatory Bowel Disease

*Lina Yossef, *Molly Wright, †Jason Benedict, *Grant A. Morris, ‡Megan McNicol, *§Brendan Boyle, *§‖Jennifer L. Dotson, *§Hilary K. Michel, and *§Ross M. Maltz

(*JPGN* 2022;75: 59–63)



Pacientes con EII entre 11-21 años y cuidadores.

67 pacientes / 98 cuidadores

TABLE 1. Patient and caregiver demographics

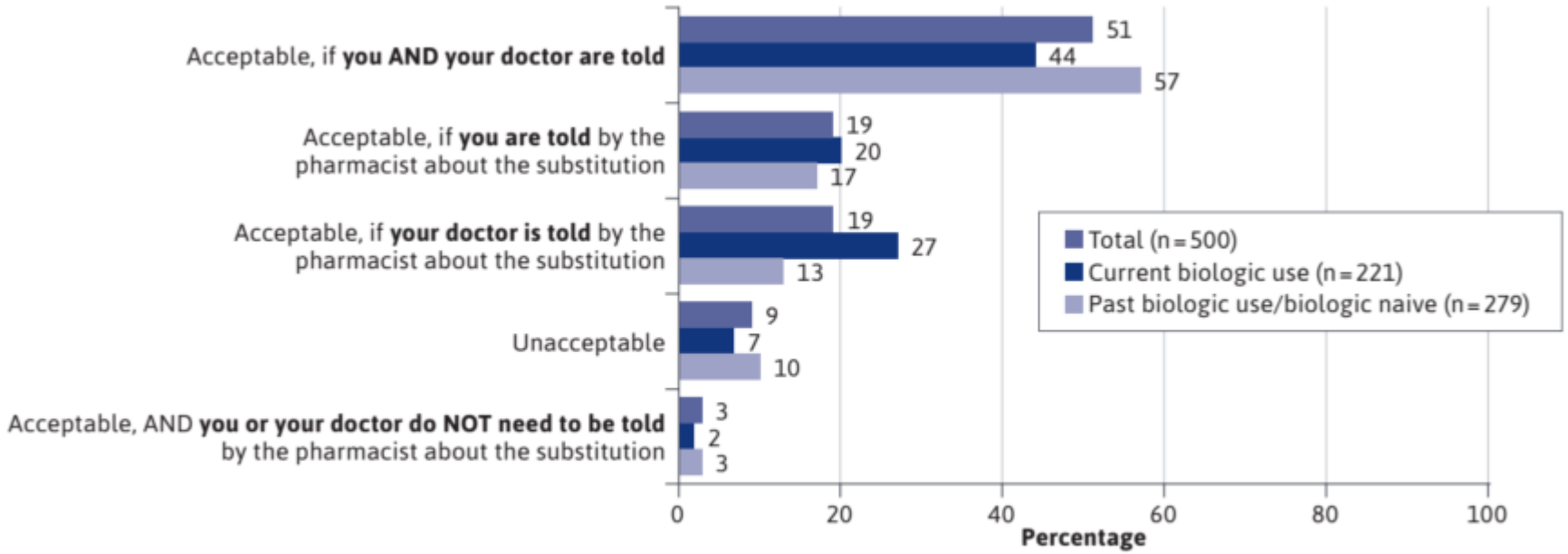
	Patient report N = 98	Caregiver report N = 67
Have you heard of a biosimilar medication?		
No	79%	64%
Yes	21%	36%

Patients may have more than one type of insurance. Ohio Children with Medical Handicaps is healthcare coverage through Children with Special Health Care Needs. It is authorized by Title V of the Social Security Act. TNF = tumor necrosis factor.

Caregivers that had heard of biosimilars before the study were more likely to have a negative perception of them.

Yossef L, et al. JPGN 2022;75: 59–63

FIGURE 2 Patient Attitudes About Interchangeable Biologics



Patients were asked, "Consistent with state law, an interchangeable biologic product is one that can be substituted for the original biologic by your pharmacist (without the intervention of the prescriber). Currently, no biosimilars of anti-TNFα medicines are interchangeable, but in the future they could be. Do you think this idea is:" (see figure for responses). Results are presented by condition and current biologic use vs past biologic use/biologic naive. Since this survey was conducted, 2 interchangeable biologics have been approved by the US Food and Drug Administration.

Giborfsky A, et al. J Manag Care Spec Pharm. 2023;29(4):343-349

Controversias

- Los estudios que avalan el intercambio de anti-TNF prácticamente se han hecho exclusivamente con **IFX y sus biosimilares**.
- **En pediatría**, dichos estudios se han realizado **con CT-P13**.
- No hay datos de seguridad/eficacia suficientes en la EII (de adultos o de niños) en otros intercambios, ni en otros anti-TNF.
- Los estudios de intercambio se han realizado en *pacientes "estables".*
- Los estudios en adultos tienen un periodo de **seguimiento corto**. Muchos de estos estudios son estudios de **baja calidad**.
- El intercambio no tiene en cuenta la **perspectiva del paciente** (o de sus padres).

Conclusiones

- En general, los biosimilares parecen **seguros y eficaces** para su empleo en EII.
- El **intercambio** de un antiTNF por alguno de sus biosimilares parece una **práctica segura y eficaz**, bien sea switch propuesto por un facultativo, bien sea sustitución por un farmacéutico.
- No obstante, **la evidencia en pediatría es escasa y de baja calidad.**
- La utilización de biosimilares puede ayudar a la **sostenibilidad del SNS**, además de permitir la incorporación de nuevas opciones terapéuticas en la EII.