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- Professor of Rheumatology, University of Oslo, Norway
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GaBI Educational Workshops

24 September 2019, Ankara HiltonSA, Turkey

2nd Turkish Interactive Workshop on
REGULATORY ASSESSMENT OF BIOSIMILARS

An update on biosimilars and switching experience – the clinical perspective

Professor Tore Kristian Kvien, MD, PhD

24 September 2019

GaBi
GENERICS AND BIOSIMILARS INITIATIVE
Building trust in cost-effective treatments

PPCI
Pro Pharma Communications International

An update on biosimilars and switching experience – the clinical perspective

Tore K Kvien

Dept of Rheumatology
Diakonhjemmet Hospital
Oslo, Norway

Tore K Kvien – disclosures

	Honorarium		Institutional support NOR-DMARD	
	Presentation	Advice	Previous	Current
AbbVie	X	X	X	
BMS	X	X	X	X
MSD	X	X	X	
Pfizer/Wyeth	X	X	X	
Roche	X	X	X	
UCB	X	X	X	
Hospira/Pfizer	X	X		
Epirus		X		
Orion	X	X		
Merck Serono		X		
Mundipharma	X			
Celltrion	X	X		
Sandoz	X			
Samsung	X			
Biogen	X	X		
Amgen	X			

What is a biosimilar?

- A biosimilar is a legitimate copy of a biopharmaceutical, which no longer is protected by patent, that has:
  - Undergone rigorous analytical and clinical assessment, in comparison to its reference product, *and*
  - Been approved by a regulatory agency according to a specific pathway for biosimilar evaluation

Intended copies/Me-too biologicals

… While these products apparently meet local regulatory requirements, they should not be considered biosimilars, but rather, 'intended copies'. Physicians must be aware of the distinction between these and 'true' biosimilars that meet EMA/FDA standards, as well as the differences between biosimilars and other 'biological copies'.

■ **'Intended copies' of innovator biologics currently in use for treatment of rheumatoid arthritis (not subjected to current European Medicines Agency/ Food and Drug Administration Standards for bio similarity at the time of approval)[1]**

Reference product	Manufacturer	'Intended copy'	Marketed locations
Rituximab	Dr Reddy's laboratories (India)	Reditux	Bolivia, Chile, India and Peru
Rituximab	Probiomed (Mexico)	Kikuzubm	Bolivia, Chile, Mexico and Peru
Etanercept	Shanghai CP Guojian Pharmaceutical Co (China)	Etanar	Colombia
Etanercept		Yisaipu	China

1. Dörner T et al. The role of biosimilars in the treatment of rheumatic diseases. Ann Rheum Dis 2013;72:322-8

Why Biosimilars?

- Similar to the originator product
  - Not better
  - Not worse

  - But less expensive!

Could improve accessibility to good therapies for more people with RMDs

EXTENDED REPORT

Inequities in access to biologic and synthetic DMARDs across 46 European countries

Polina Putrik,[1] Sofia Ramiro,[2] Tore K Kvien,[3] Tuulikki Sokka,[4] Milena Pavlova,[5] Till Uhlig,[6] Annelies Boonen,[7] Working Group 'Equity in access to treatment of rheumatoid arthritis in Europe'

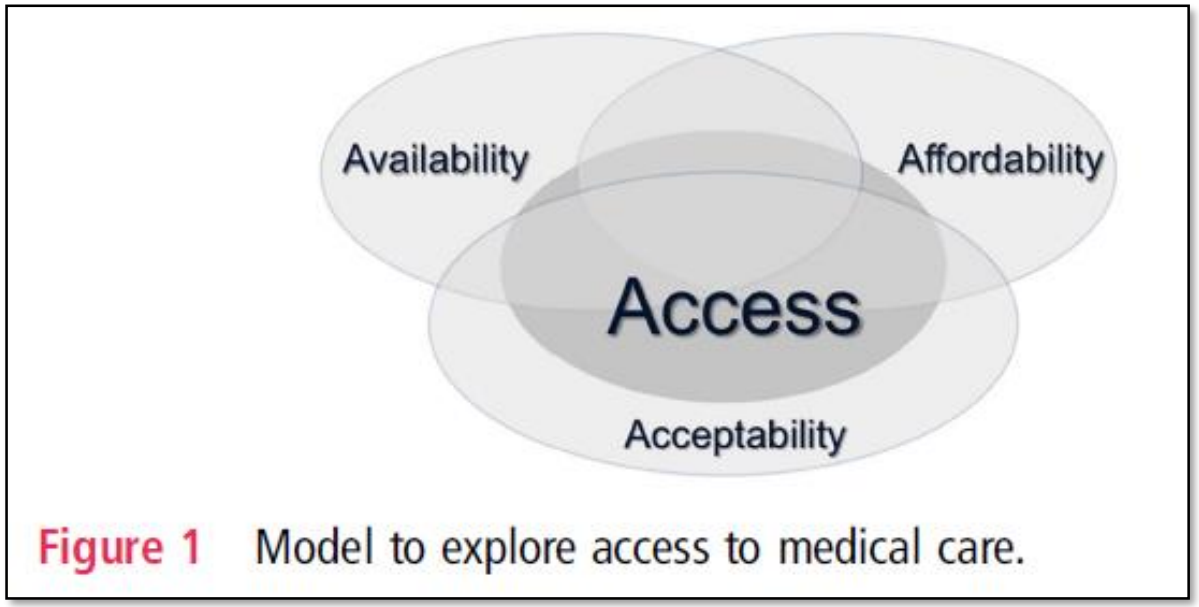


Figure 1 Model to explore access to medical care.

Putrik P, et al. Ann Rheum Dis 2014;73:198-206.

Inequities in Access to Biologic and Synthetic DMARDs Across 46 European Countries

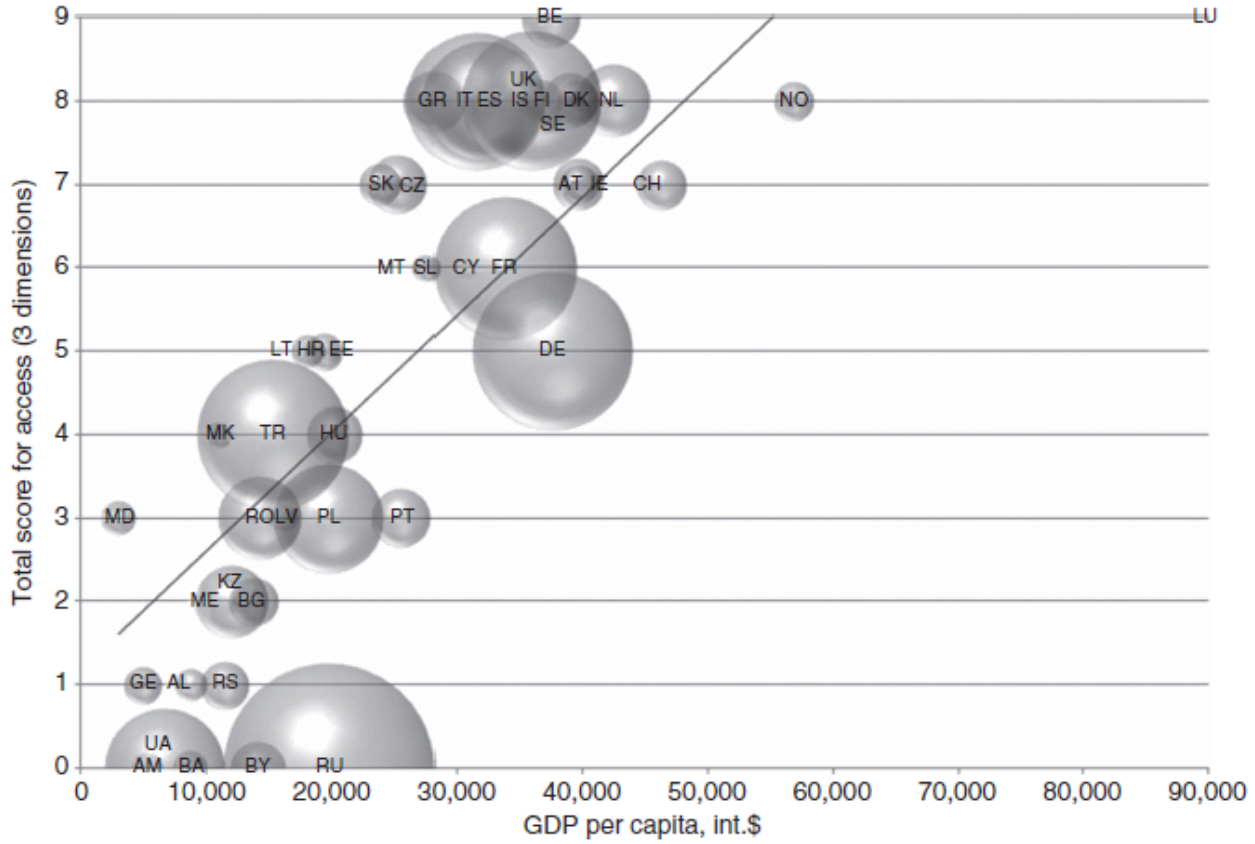


Figure 3 Access to biologic disease modifying antirheumatic drugs and gross domestic product per capita, international dollars (n=44). Size of the bubbles is proportional to the population size of the country. AL, Albania; AM, Armenia; AT, Austria; BA, Bosnia and Herzegovina; BE, Belgium; BG, Bulgaria; BY, Belarus; CH, Switzerland; CY, Cyprus; CZ, Czech Republic; DE, Germany; DK, Denmark; EE, Estonia; ES, Spain; FI, Finland; FR, France; GE, Georgia; GR, Greece; HR, Croatia; HU, Hungary; IE, Ireland; IS, Iceland; IT, Italy; KZ, Kazakhstan; LT, Lithuania; LU, Luxemburg; LV, Latvia; MD, Moldova; ME, Montenegro; MK, Macedonia; MT, Malta; NL, Netherlands; NO, Norway; PL, Poland; PT, Portugal; RO, Romania; RS, Serbia; RU, Russia; SE, Sweden; SK, Slovakia; SL, Slovenia; TR, Turkey; UA, Ukraine; UK, United Kingdom.

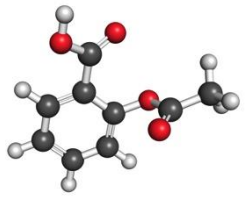
Putrik P, et al. Ann Rheum Dis 2014;73:198-206.

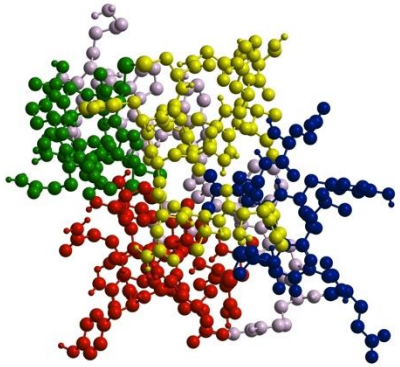
Generics and Biosimilars

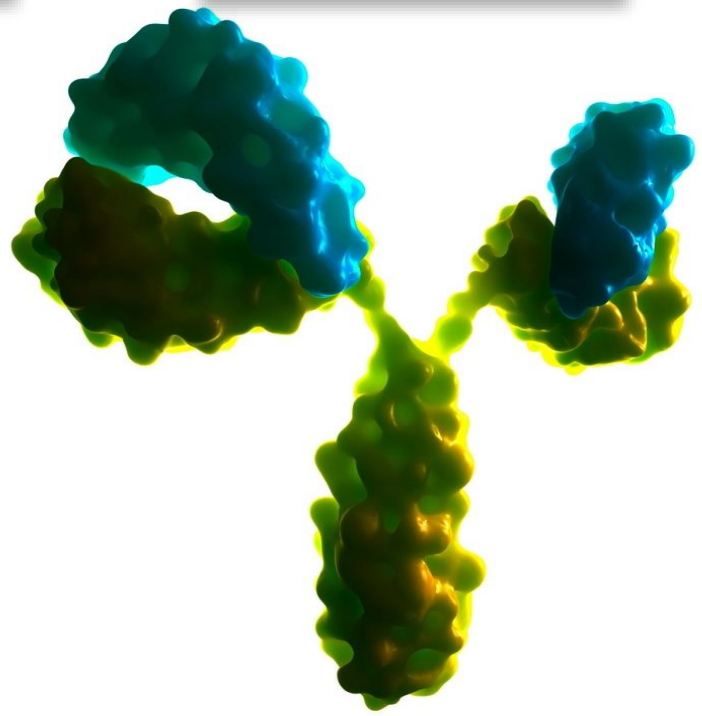
Generic

1st generation biosimilar

2nd generation biosimilar







Aspirin (chemical)
180 daltons

Insulin
5,700 daltons

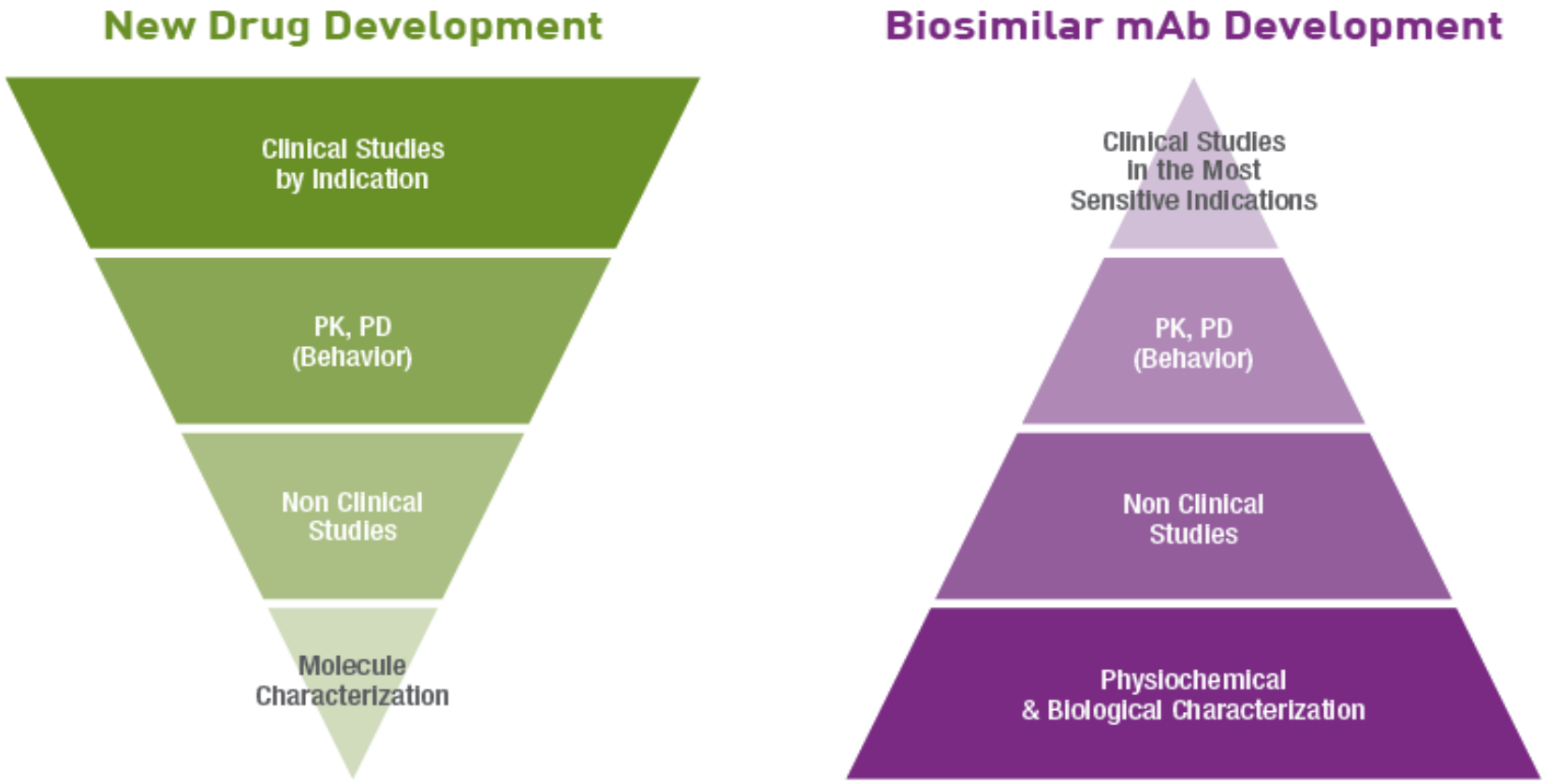
mAb
~150,000 daltons

Two Main Questions

- Prescription of biosimilar when to start new therapy or to change therapy for medical reasons?
  - Not controversial (?)

Comparison of Regulatory Requirements

- The aim of a biosimilar development program is to establish ***"biosimilarity"*** based upon totality of evidence.



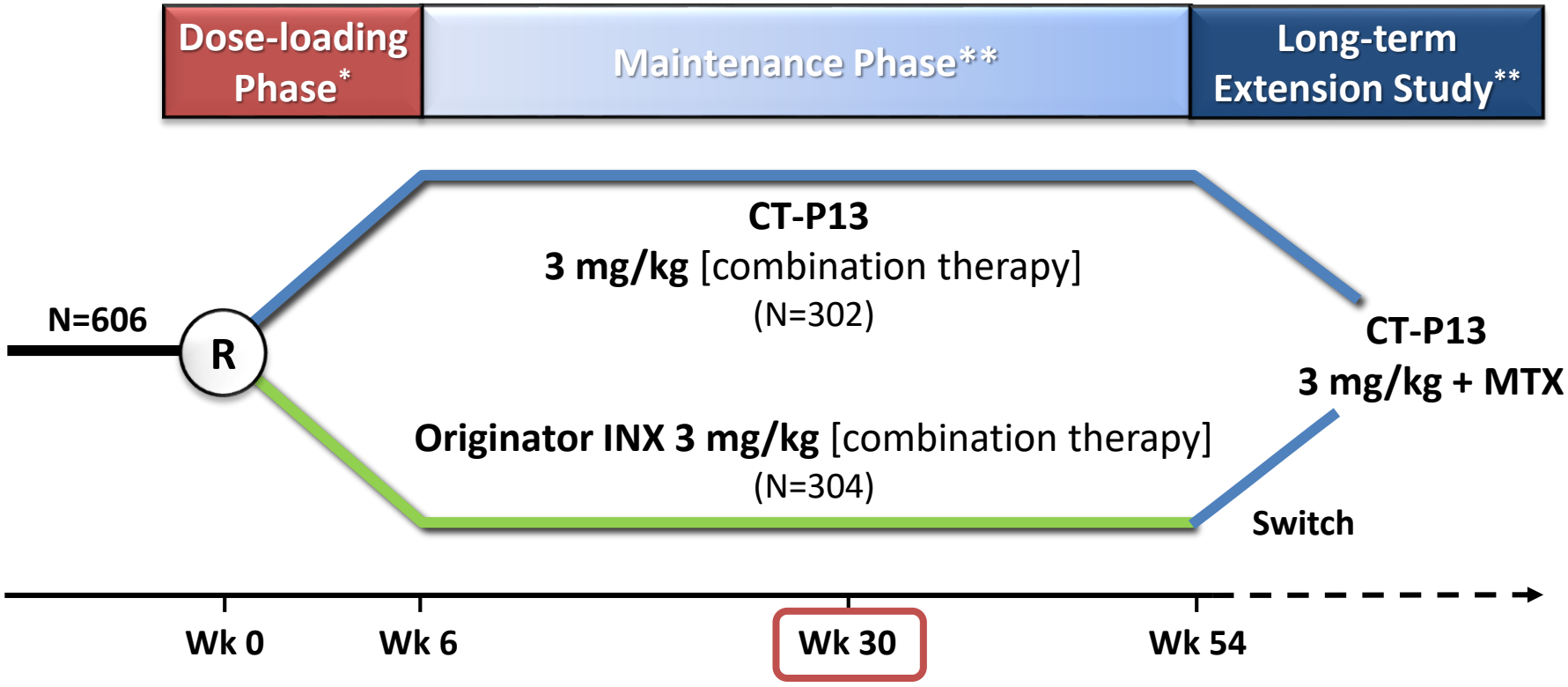
1. Guideline on similar biological medicinal products. European Medicines Agency 23rd October 2014.
2. http://www.ema.europa.eu/docs/en_GB/document_library/Scientific_guideline/2014/10/WC500176768.pdf (Accessed October 2016).

PLANETRA

- Standard design and inclusion criteria for phase 3 trial in pts being IA responders to MTX
- Primary endpoint ACR20 week 30
- Equivalence of efficacy if the 95% CI for treatment difference was within + 15%

Phase 3 Therapeutic Equivalence Trial in RA: Study Schematic

Randomised double-blind study in patients with RA

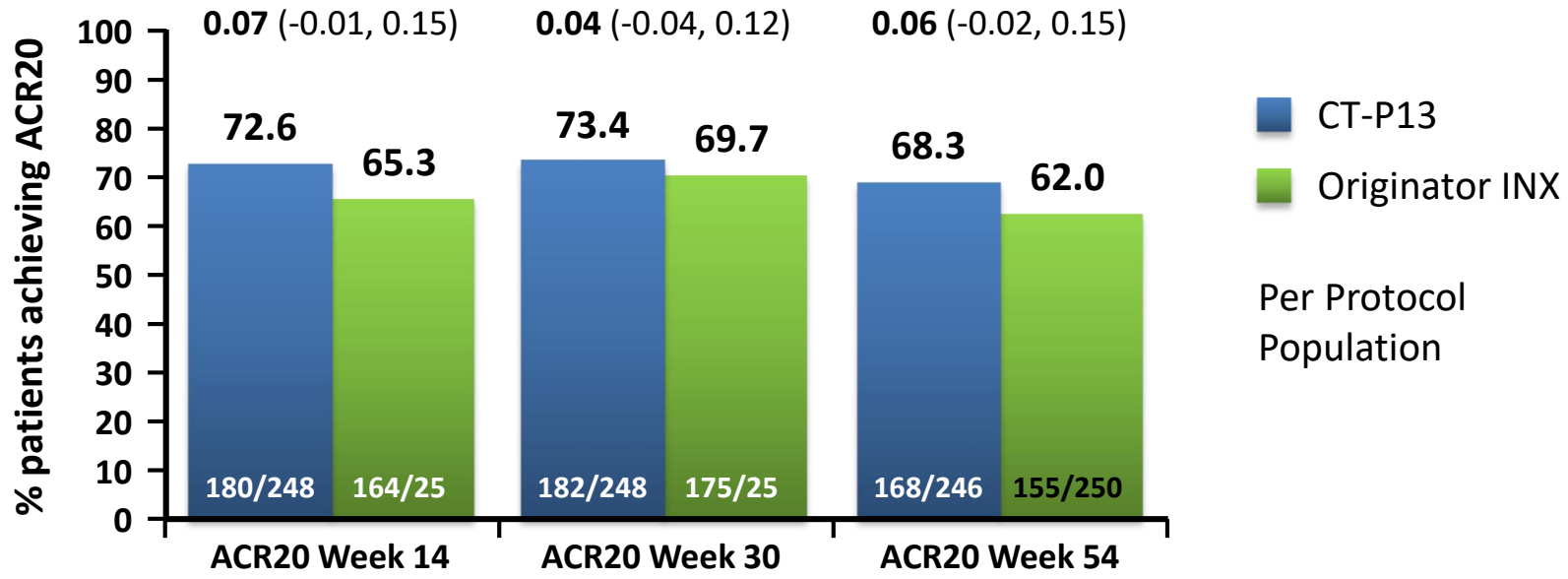


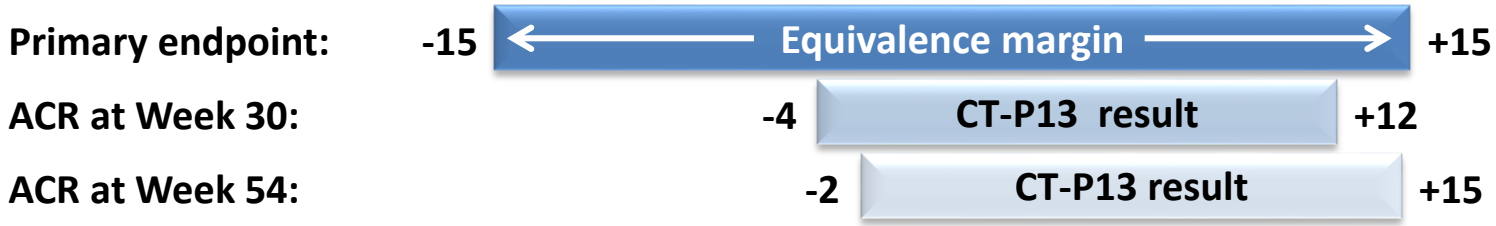
*Doses at weeks 0, 2 and 6 by 2-hr IV infusion.
**Doses every 8 weeks up to 54 weeks by 2-hr IV infusion.

EMA/CHMP/589422/2013; CT-P13 Assessment Report

CT-P13 Study in RA: ACR20 Response

ACR response at Weeks 14, 30 and 54
Estimate of treatment difference (95% CI)





Source: EMA Inflectra EPAR, June 2013

ARD Online First, published on September 22, 2015 as 10.1136/annrheumdis-2015-207588

OPEN ACCESS

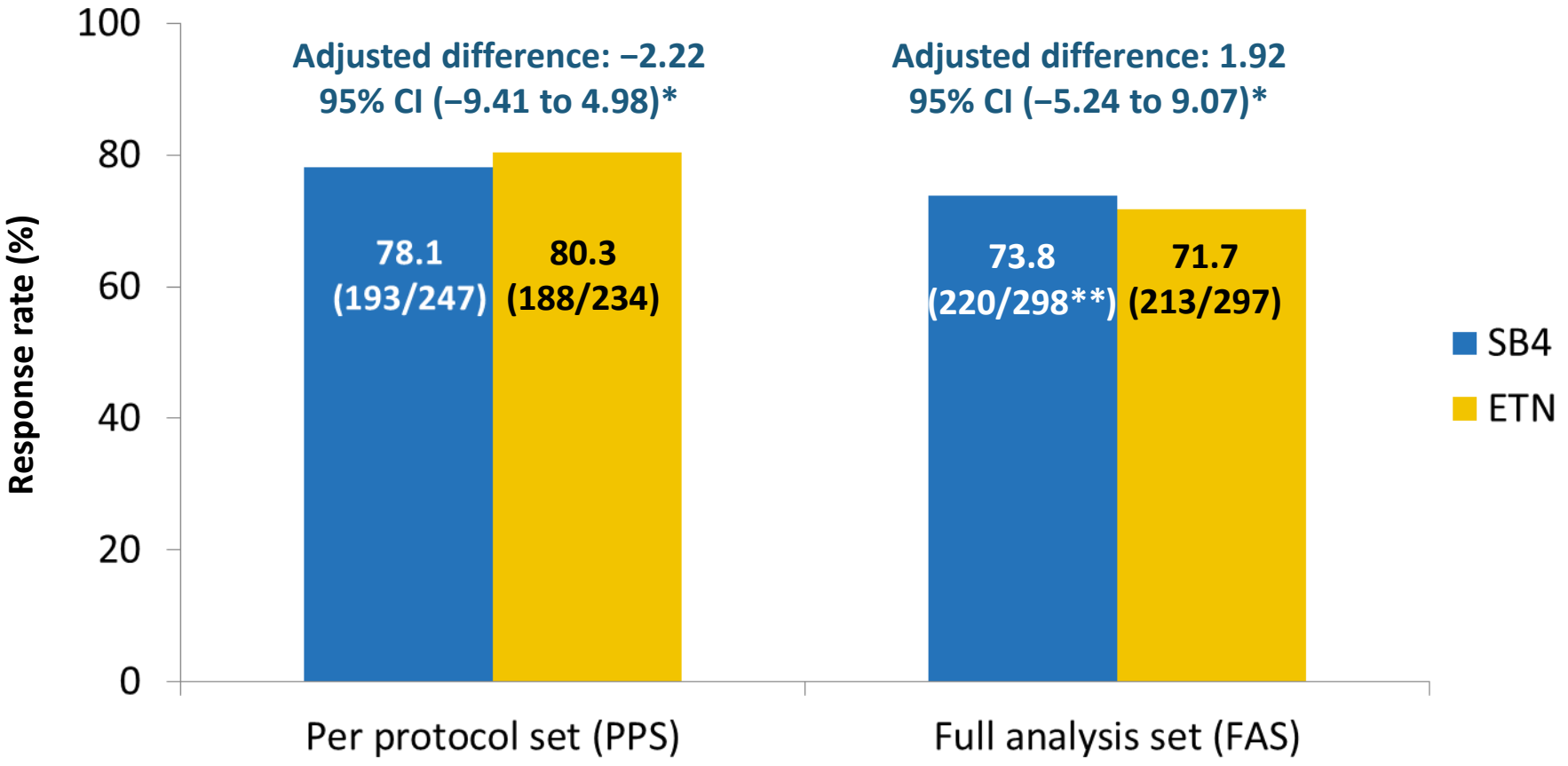
EXTENDED REPORT

A phase III randomised, double-blind, parallel-group study comparing SB4 with etanercept reference product in patients with active rheumatoid arthritis despite methotrexate therapy

Paul Emery,[1] Jiří Vencovský,[2] Anna Sylwestrzak,[3] Piotr Leszczyński,[4] Wieslawa Porawska,[5] Asta Baranauskaite,[6] Vira Tseluyko,[7] Vyacheslav M Zhdan,[8] Barbara Stasiuk,[9] Roma Milasiene,[10] Aaron Alejandro Barrera Rodriguez,[11] Soo Yeon Cheong,[12] Jeehoon Ghil[12]

To cite: Emery P, Vencovský J, Sylwestrzak A, *et al. Ann Rheum Dis* 2017;**76**:51–57.

ACR20 Response Rate at Week 24 Equivalent between SB4 and ETN



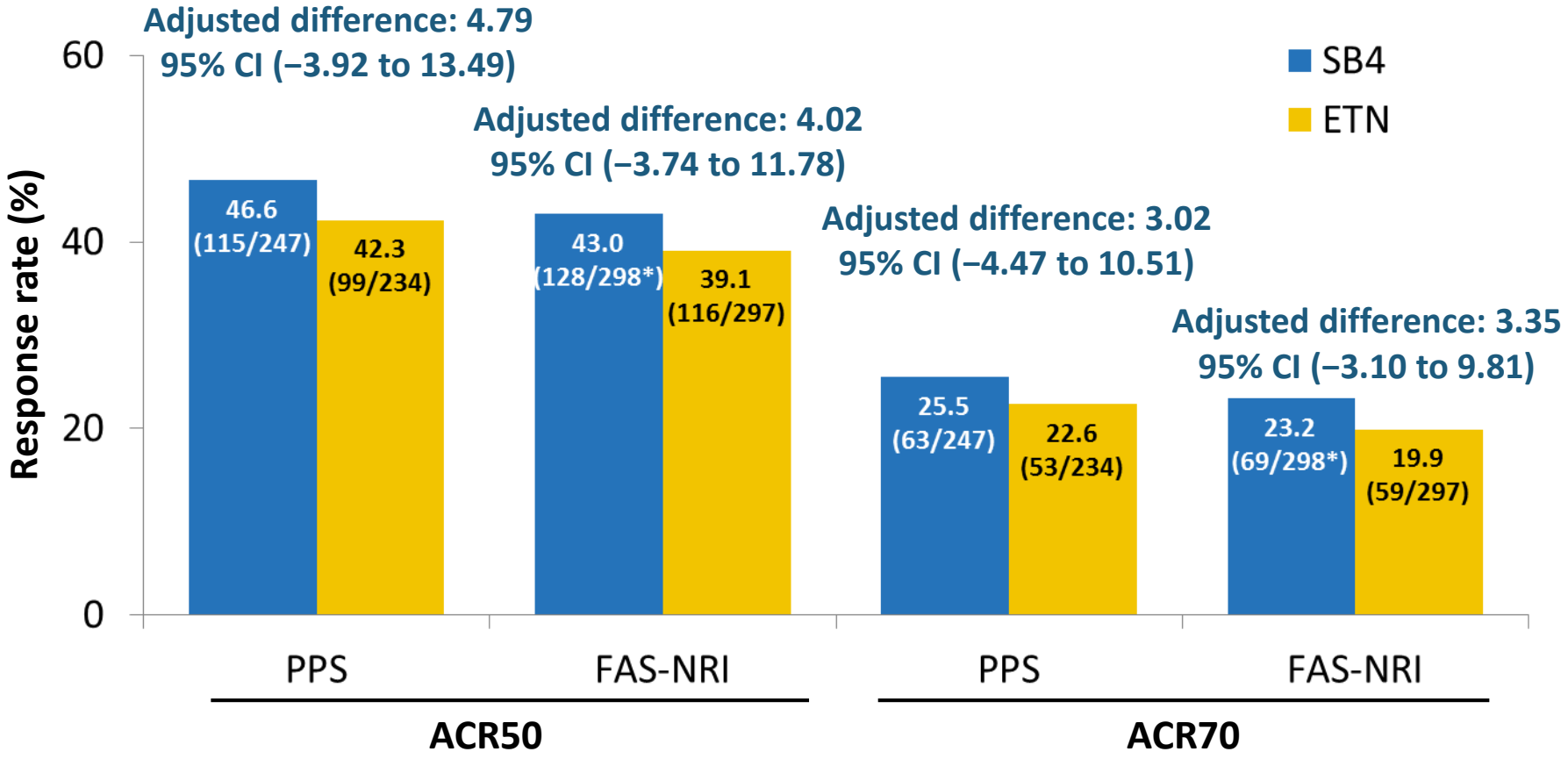
* Predefined equivalence margin -15% to 15%

**One patient from the SB4 group was excluded from the FAS due to missing efficacy data at baseline.

ACR20, American College of Rheumatology 20% response;
ETN, etanercept.

Emery P, et al. Ann Rheum Dis. Jul 6. pii: annrheumdis-2015-207588.

ACR50, ACR70 Response Rates at Week 24 Comparable between SB4 and ETN

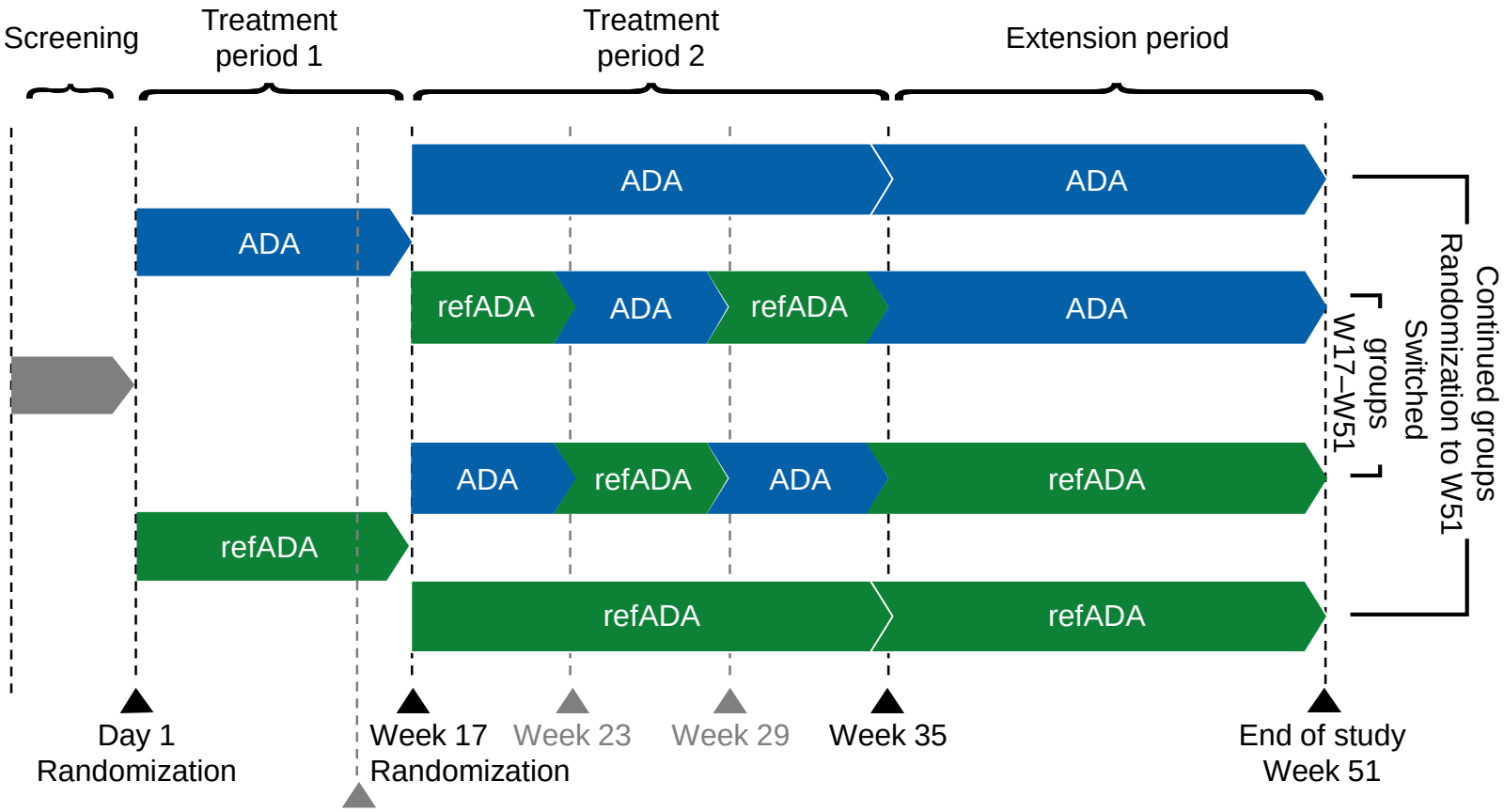


*One patient from the SB4 group was excluded from the FAS due to missing efficacy data at baseline.

ACR50/70, American College of Rheumatology 50%/70% response; ETN, etanercept; FAS: full analysis set; NRI: non-responder imputation; PPS, per-protocol set.

Emery P, et al. Ann Rheum Dis. Jul 6. pii: annrheumdis-2015-207588.

Multicenter, randomized, double-blind, comparator-controlled Phase III confirmatory study with four study periods



ADA, proposed biosimilar adalimumab; refADA, reference adalimumab

Table 1 Summary of primary and key secondary efficacy results

Logistic regression analysis on PASI 75 response at week 16 (primary end point)					
	Patients	Patients with PASI 75 response at week 16	Adjusted response rate, % ± SE	Adjusted response rate difference, % ± SE	95% CI (equivalence margin of ± 18%)
Analysis on per protocol set					
GP2017	197	132	66·8 ± 3·33	1·8 ± 4·75	−7·46 to 11·15
Ref-ADMB	196	127	65·0 ± 3·38		
Supportive analysis on full analysis set					
GP2017	231	134	58·1 ± 3·23	2·2 ± 4·56	−6·79 to 11·10
Ref-ADMB	234	131	55·9 ± 3·23		
Mixed-effects model for repeated measures analysis on percentage change from baseline in PASI up to week 16 (key secondary end point)					
	Patients	Patients with evaluable data	Least squares means, % ± SE	Least squares means difference, % ± SE	95% CI (equivalence margin of ± 15%)
Analysis on per protocol set					
GP2017	197	191	−60·7 ± 1·54	0·8 ± 2·03	−3·15 to 4·84
Ref-ADMB	196	192	−61·5 ± 1·55		
Supportive analysis on full analysis set					
GP2017	231	196	−60·1 ± 1·61	−0·7 ± 2·12	−4·85 to 3·47
Ref-ADMB	234	200	−59·4 ± 1·61		

PASI, Psoriasis Area and Severity Index; SE, standard error; CI, confidence interval; GP2017, Sandoz proposed biosimilar adalimumab; ref-ADMB, reference adalimumab.

Extrapolation of indications

- The stringency of the regulatory pathway for acceptance (“the comparability exercise”) also leads to acceptance of the concept of **extrapolation.**

- Some scepticism originally – but now generally accepted after 5 years experience and several studies with real life data also in IBD.

Types of Treatments for RA: Nomenclature

Disease Modifying Antirheumatic Drugs (DMARDs)			
Synthetic DMARDs (sDMARDs)		**Biological DMARDs (bDMARDs)**	
Conventional synthetic (csDMARDs	**Targeted synthetic (tsDMARDs)**	**Biological originator (boDMARDs)**	**Biosimilar (bsDMARDs)**
MTX, SSZ, LEF	*Tofacitinib* *Baricitinib*		

Smolen JS, et al. Ann Rheum Dis 2014 Jan;73(1):3-5.

Two main questions

- Prescription of biosimilar when to start new therapy or to change therapy for medical reasons?
  - Not controversial (?)

- **Can patients on stable treatment with an originator drug be switched to a cheaper biosimilar of this drug?**
  - **More controversial (concerning efficacy, safety and immunogenicity)**

Evidence to support switching from reference product to biosimilar for non-medical reasons

- Extension of phase 3 RCTs
- Switching within RCTs
- Real life data
- Randomizing patients on stable long-term treatment

Clinical and epidemiological research

OPEN ACCESS

EXTENDED REPORT

Efficacy and safety of switching from reference infliximab to CT-P13 compared with maintenance of CT-P13 in ankylosing spondylitis: 102-week data from the PLANETAS extension study

Won Park,[1] Dae Hyun Yoo,[2] Pedro Miranda,[3] Marek Brzosko,[4] Piotr Wiland,[5] Sergio Gutierrez-Ureña,[6] Helena Mikazane,[7] Yeon-Ah Lee,[8] Svitlana Smiyan,[9] Mie-Jin Lim,[1] Vladimir Kadinov,[10] Carlos Abud-Mendoza,[11] HoUng Kim,[12] Sang Joon Lee,[12] YunJu Bae,[12] SuYeon Kim,[12] Jürgen Braun[13]

Clinical and epidemiological research

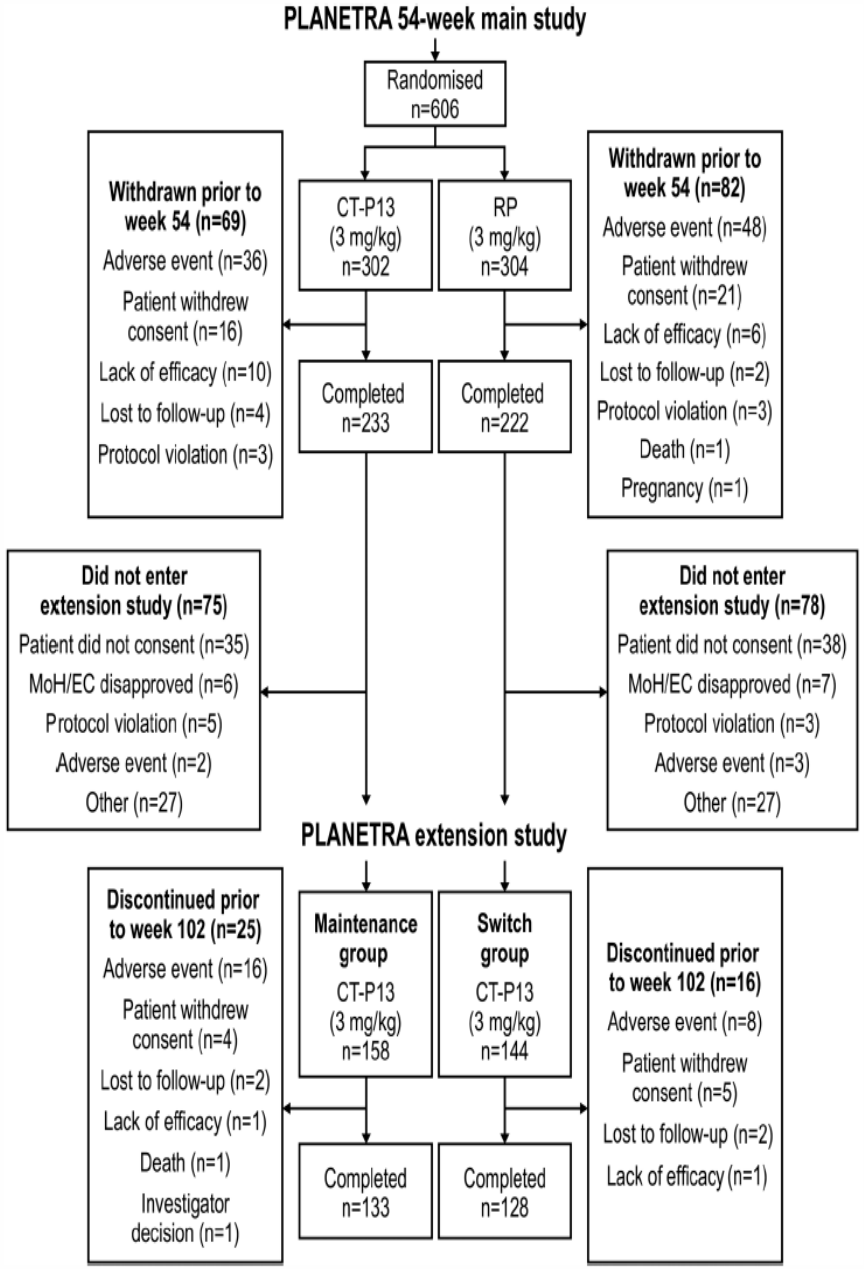
OPEN ACCESS

EXTENDED REPORT

Efficacy and safety of CT-P13 (biosimilar infliximab) in patients with rheumatoid arthritis: comparison between switching from reference infliximab to CT-P13 and continuing CT-P13 in the PLANETRA extension study

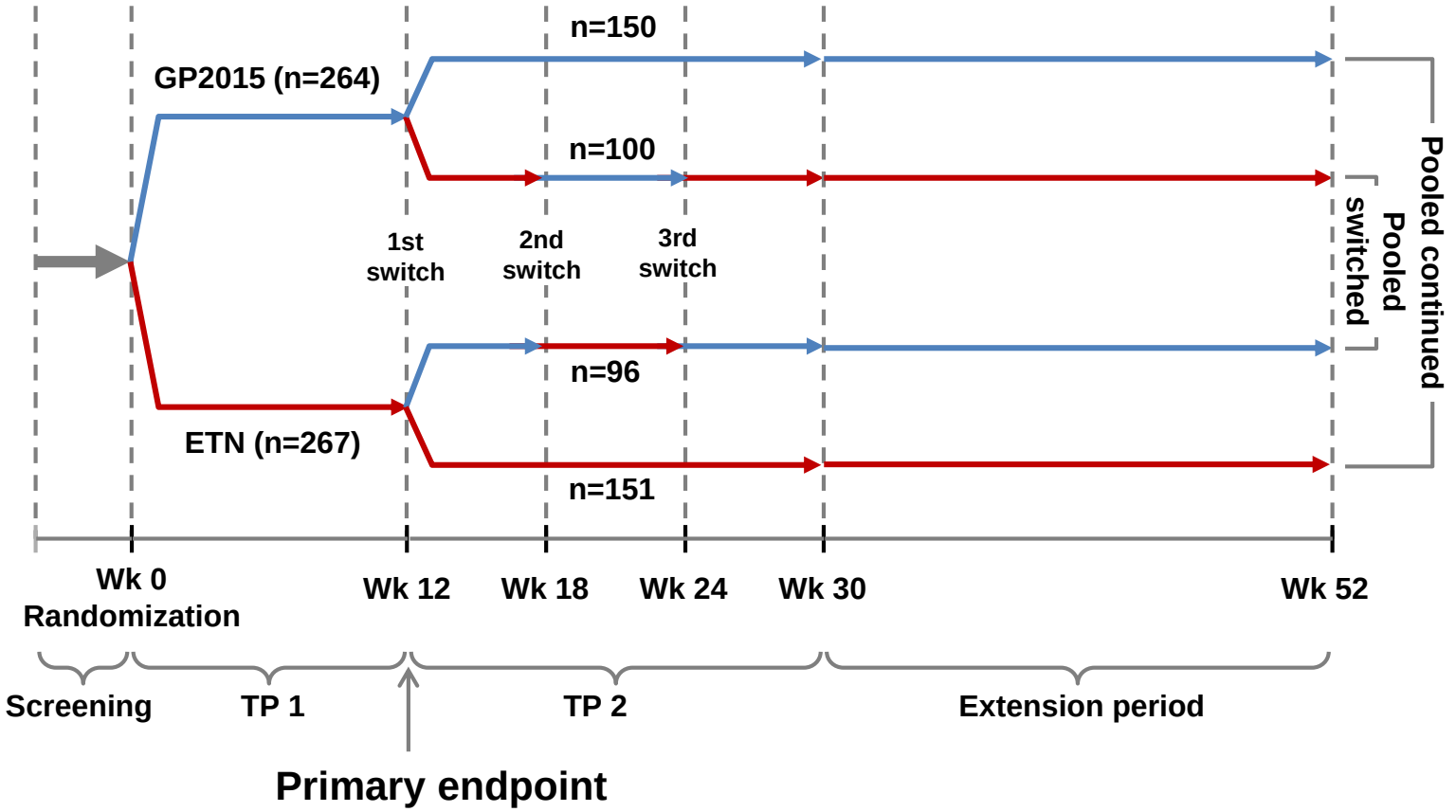
Dae Hyun Yoo,[1] Nenad Prodanovic,[2] Janusz Jaworski,[3] Pedro Miranda,[4] Edgar Ramiterre,[5] Allan Lanzon,[6] Asta Baranauskaite,[7] Piotr Wiland,[8] Carlos Abud-Mendoza,[9] Boycho Oparanov,[10] Svitlana Smiyan,[11] HoUng Kim,[12] Sang Joon Lee,[12] SuYeon Kim,[12] Won Park[13]

Park W, et al. Ann Rheum Dis. 2017;76:346–354;
Yoo DH, et al. Ann Rheum Dis. 2017;76:355–363.



Yoo DH, et al. Ann Rheum Dis. 2017;76:355–363.

Study design – EGALITY study

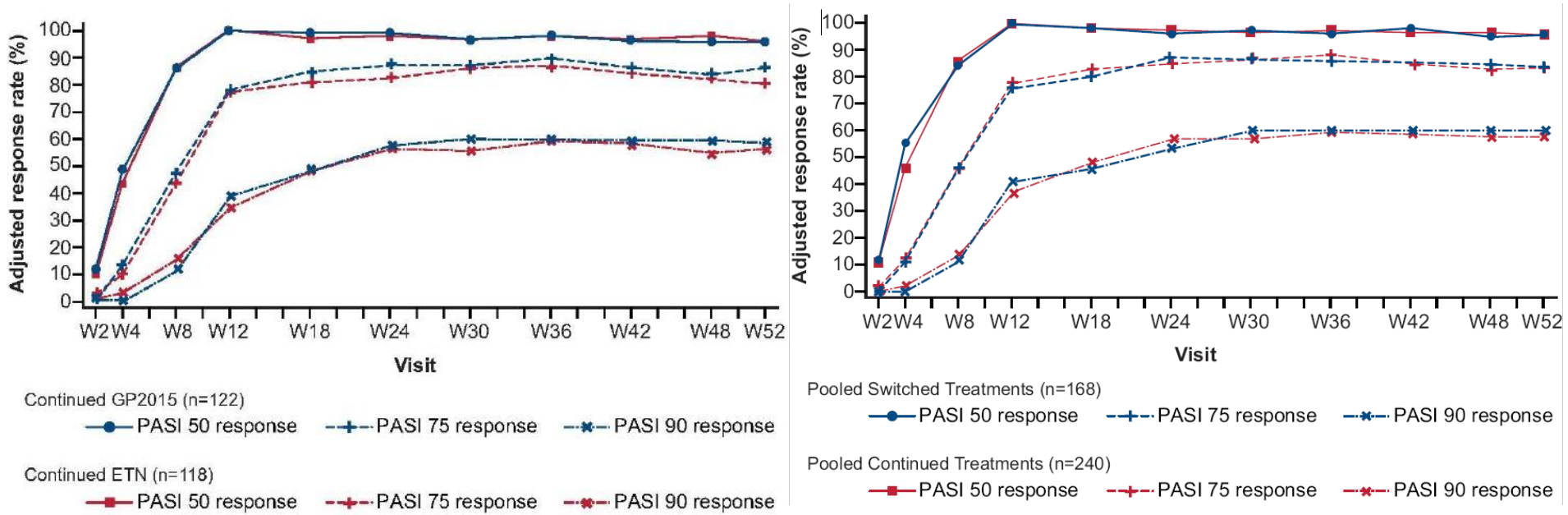


ETN, reference etanercept; TP, treatment period; Wk, week

Griffiths CE et al. Br J Dermatol. 2016 Oct 27. doi: 10.1111/bjd.15152. [Epub ahead of print]

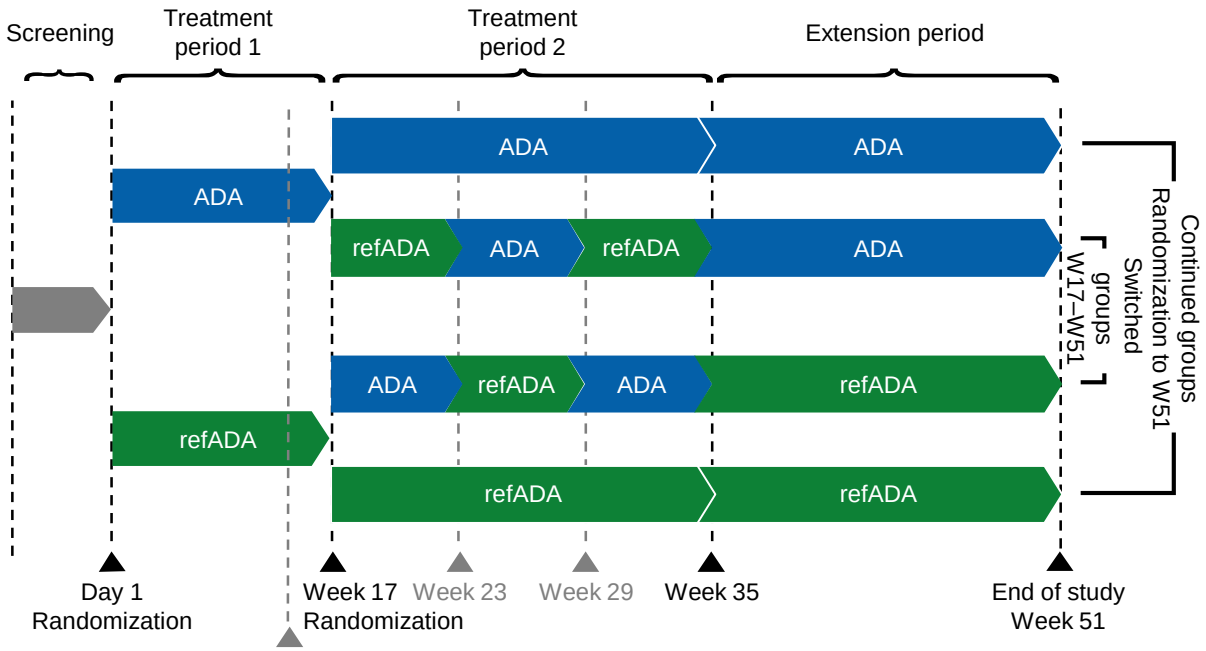
Biosimilar Switch Study

GP2015 in PsO [a]



[a] Griffiths, C.E.M., Thaçi, D., Gerdes, S., Arenberger, P., Pulka, G., Kingo, K., Weglowska, J., the EGALITY study group, Hattebuhr, N., Poetzl, J., Woehling, H., Wuerth, G. and Afonso, M. (2017), The EGALITY study: a confirmatory, randomized, double-blind study comparing the efficacy, safety and immunogenicity of GP2015, a proposed etanercept biosimilar, vs. the originator product in patients with moderate-to-severe chronic plaque-type psoriasis. Br J Dermatol, 176: 928–938. doi:10.1111/bjd.15152

Multicenter, randomized, double-blind, comparator-controlled Phase III confirmatory study with four study periods

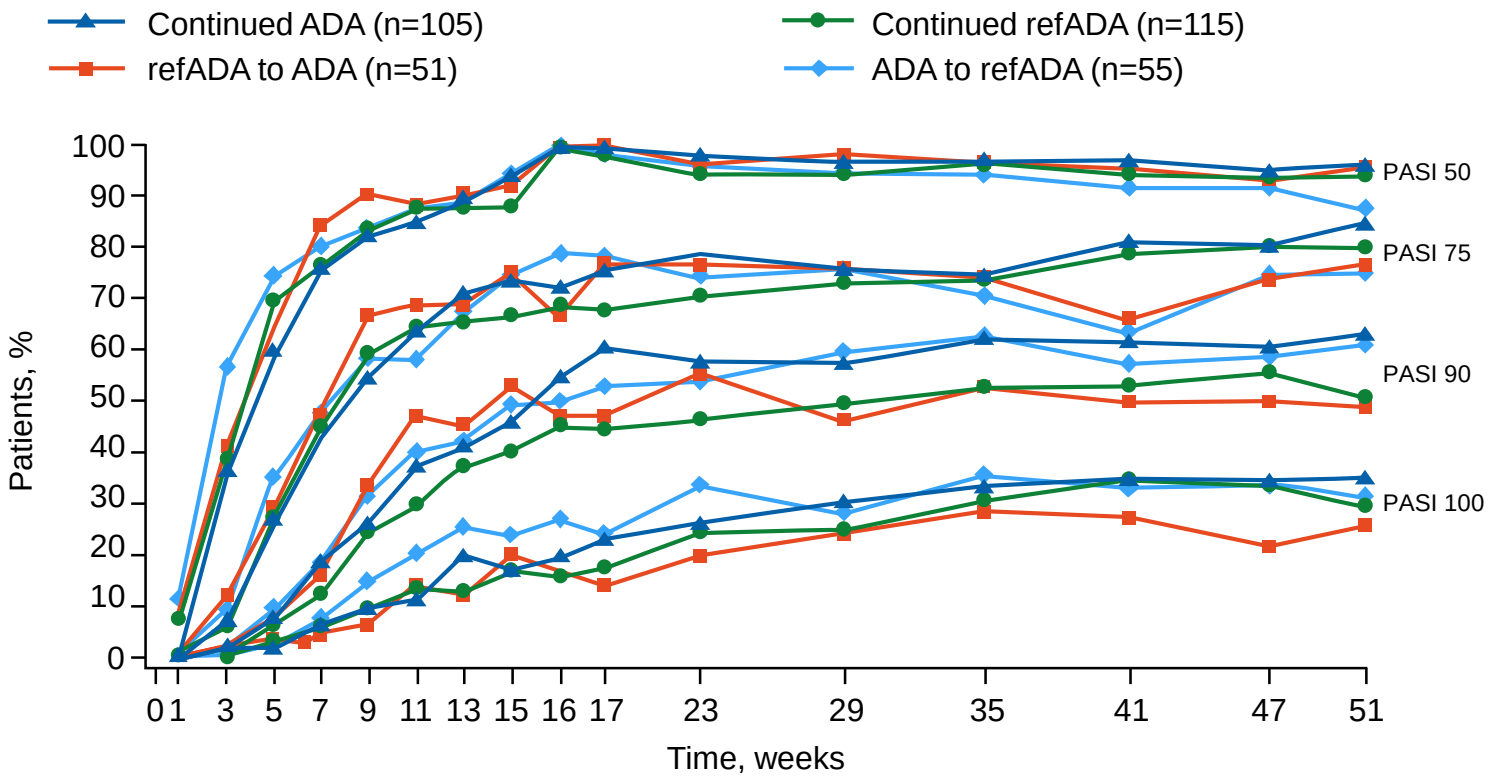


ADA, proposed biosimilar adalimumab; refADA, reference adalimumab

Efficacy was similar and sustained in patients continuously treated with ADA or refADA, or switched between ADA and refADA

Week 51

PASI response rates over time



ADA, proposed biosimilar adalimumab; PASI, Psoriasis Area and Severity Index; refADA, reference adalimumab

Non-Medical Switches

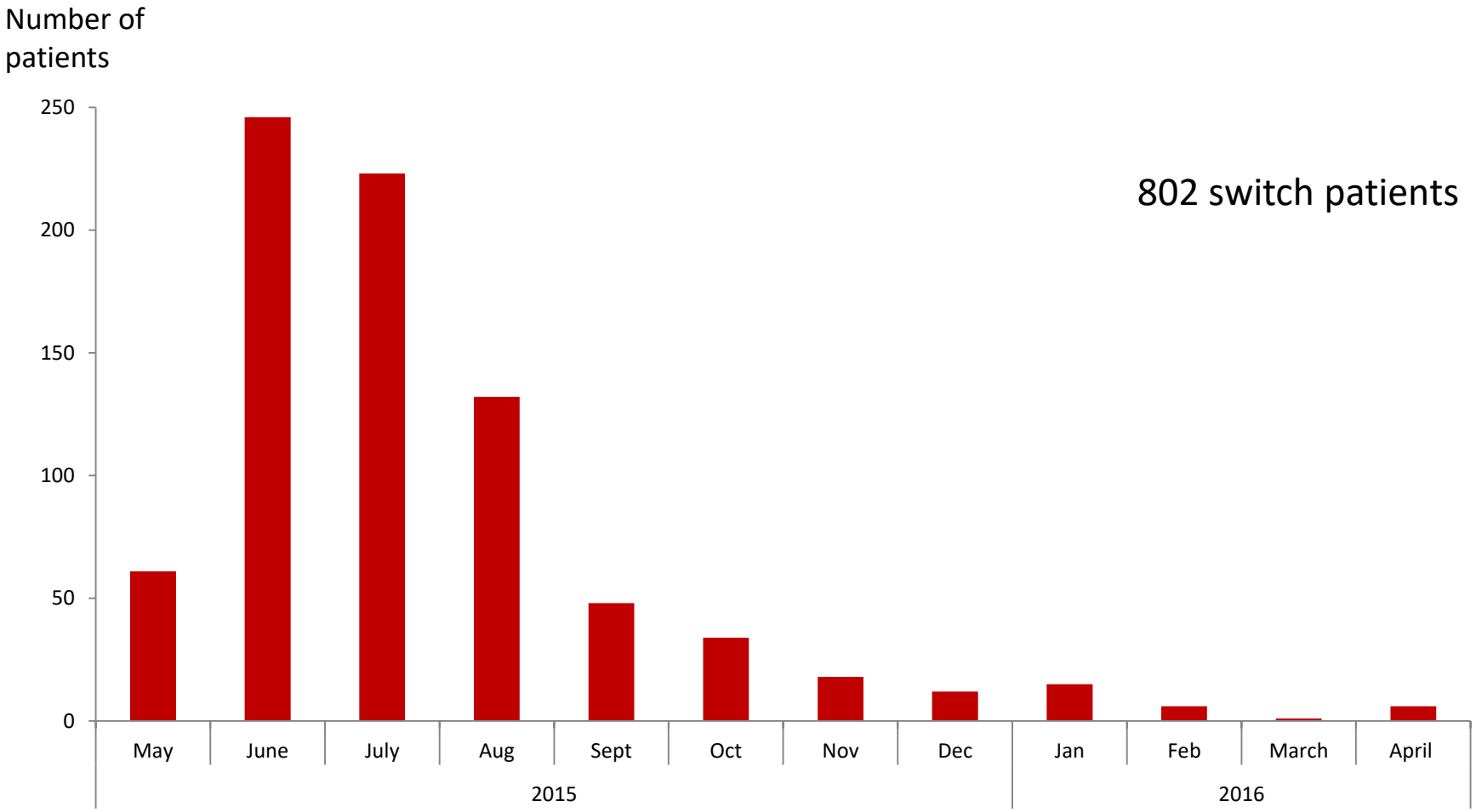
- Switch from originator bDMARD to biosimilar for non medical reasons
- Non-medical switch, DK:

  May 2015: originator infliximab → biosimilar CT-P13

  April 2016: originator etanercept → biosimilar SB4

- All Danish patients with inflammatory diseases (rheumatology, dermatology, gastroenterology)

Date of infliximab switch, DANBIO



CONCISE REPORT

A nationwide non-medical switch from originator infliximab to biosimilar CT-P13 in 802 patients with inflammatory arthritis: 1-year clinical outcomes from the DANBIO registry

Bente Glintborg,[1,2] Inge Juul Sørensen,[3,4] Anne Gitte Loft,[5] Hanne Lindegaard,[6] Asta Linauskas,[7] Oliver Hendricks,[8] Inger Marie Jensen Hansen,[9] Dorte Vendelbo Jensen,[2,3] Natalia Manilo,[10] Jakob Espesen,[11] Mette Klarlund,[12] Jolanta Grydehøj,[13] Sabine Sparre Dieperink,[3] Salome Kristensen,[14] Jimmi Sloth Olsen,[15] Henrik Nordin,[16] Stavros Chrysidis,[17] Dorte Dalsgaard Pedersen,[18] Michael Veedfald Sørensen,[19] Lis Smedegaard Andersen,[20] Kathrine Lederballe Grøn,[3] Niels Steen Krogh,[21] Lars Pedersen,[22] Merete Lund Hetland, [1,4]On behalf of all departments of rheumatology in Denmark

To cite: Glintborg B, Sørensen IJ, Loft AG, *et al*. *Ann Rheum Dis* Published Online First: [*please include* Day Month Year]. doi:10.1136/annrheumdis-2016-210742

Disease activity and flares

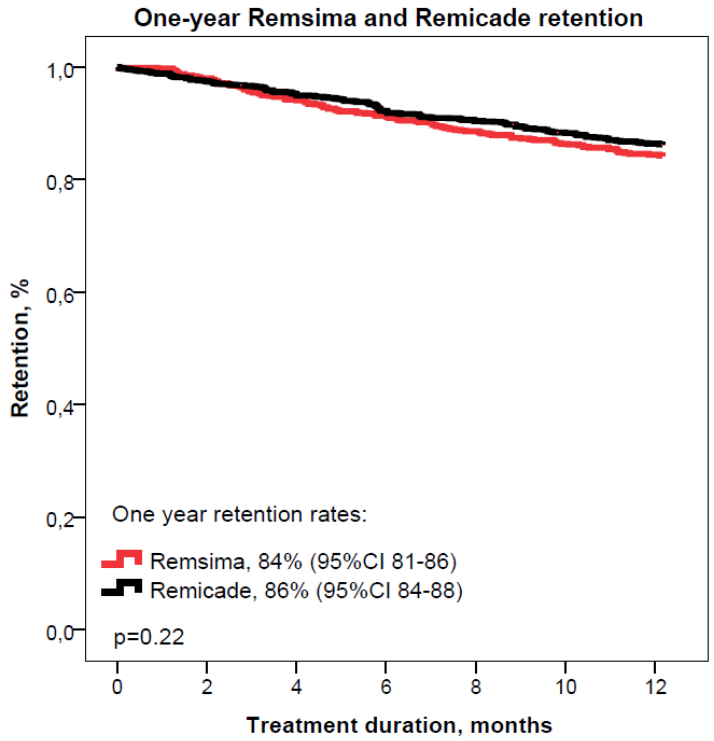
	Disease activity			Changes over time		P*
	3 months pre-switch	Switch	3 months post-switch	Δpre-switch	Δpost-switch	
RA, n=403						
Patients with available data, n	319	310	309	276	265	-
DAS28	2.2	2.2	2.2	0.1	0.0	0.8
HAQ (0-3)	0.6	0.6	0.6	0.0	0.1	0.3
CRP, mg/l (<10mg/L)	4	4.5	5	0	0	0.4
Patient's global score, mm	26	25	26	0.0	0.0	0.5
PsA, n=120						
Patients with available data, n	94	92	94	78	81	-
DAS28	2.5	2.3	2.4	0.0	0.1	0.10
HAQ (0-3)	0.5	0.6	0.5	0.0	0.0	0.5
CRP, mg/l (<10mg/L)	4	4	3	0	0	0.046
Patient's global score, mm	32	34	35	-3	0	0.01
AxSpA, n=279						
Patients with available data, n	202	199	204	160	169	-
BASDAI, mm	23	24	25	0	0	0.3
CRP, mg/l	3	4	4	0	0	0.2
Patient's global score, mm	26	31	27	1	-1	0.7
ASDAS	1.8	2.0	2.0	0.0	0.0	0.8
Flare rates pre-switch vs. post-switch						
RA and PsA (ΔDAS28≥0.6), %				22	22	
RA and PsA (ΔDAS28≥1.2), %				10	10	
AxSpA (ΔASDAS>1.1), %				3	4	

Numbers are medians unless otherwise stated

Glintborg B, Sørensen IJ, Loft AG, et al.
Ann Rheum Dis, Online First May 8th 2017
doi:10.1136/annrheumdis-2016-210742

Retention of Treatment

1 year treatment retention was compared to that of a historic cohort of all patients in DANBIO receiving treatment with Remicade by January 1st 2014



Glintborg B, Sørensen IJ, Loft AG, et al.
Ann Rheum Dis, Online First May 8th 2017
doi:10.1136/annrheumdis-2016-210742

EXTENDED REPORT

To switch or not to switch: results of a nationwide guideline of mandatory switching from originator to biosimilar etanercept. One-year treatment outcomes in 2061 patients with inflammatory arthritis from the DANBIO registry

Bente Glintborg,[1,2] Anne Gitte Loft,[3,4] Emina Omerovic,[5] Oliver Hendricks,[6] Asta Linauskas,[7] Jakob Espesen,[8] Kamilla Danebod,[2] Dorte Vendelbo Jensen,[2] Henrik Nordin,[9] Emil Barner Dalgaard,[10] Stavros Chrysidis,[11] Salome Kristensen,[12] Johnny Lillelund Raun,[13] Hanne Lindegaard,[14] Natalia Manilo,[15] Susanne Højmark Jakobsen,[16] Inger Marie Jensen Hansen,[16] Dorte Dalsgaard Pedersen,[17] Inge Juul Sørensen,[18,19] Lis Smedegaard Andersen,[20] Jolanta Grydehøj,[21] Frank Mehnert,[22] Niels Steen Krogh,[23] Merete Lund Hetland[18,19]

To cite: Glintborg B, Loft AG, Omerovic E, *et al*. *Ann Rheum Dis* Epub ahead of print: [*please include* Day Month Year]. doi:10.1136/annrheumdis-2018-213474

Table 2 Disease activity 3 months prior to vs 3 months after the switch from ETA to SB4 stratified by indication

	Disease activity			Changes over time	
	3 months preswitch	Switch	3 months postswitch	ΔPreswitch	ΔPostswitch
RA, n=933					
Patients with available data, n (%)*	639 (68)	745 (80)	568 (61)	485 (52)	436 (47)
DAS28	1.9 (1.3 to 2.8)	2.1 (1.6 to 3.0)	2.1 (1.7 to 3.1)	0.0 (0.0 to 0.0)	0.0 (–0.4 to 0.5)
HAQ (0–3)	0.8 (0.3 to 1.3)	0.8 (0.3 to 1.3)	0.8 (0.3 to 1.3)	0 (–1 to 1)	0 (–1 to 1)
CRP, mg/L	3 (1 to 7)	3 (1 to 6)	3 (1 to 6)	0 (–2 to 1)	0 (–1 to 1)
PGS, mm	30 (14 to 57)	29 (13 to 55)	32 (12 to 62)	0 (–11 to 8)	1 (–8 to 11)
PsA, n=351					
Patients with available data, n (%)*	223 (64)	253 (72)	197 (56)	158 (45)	152 (43)
DAS28	1.8 (1.1 to 2.4)	2.0 (1.6 to 2.8)	2.1 (1.5 to 2.8)	0.0 (0.0 to 0.0)	0.1 (–0.4 to 0.5)
HAQ (0–3)	0.5 (0.1 to 1.0)	0.5 (0.0 to 1.0)	0.5 (0.1 to 1.0)	0.0 (–0.1 to 0.1)	0.0 (–0.1 to 0.1)
CRP, mg/L	2 (1 to 4)	2 (1 to 4)	2 (1 to 4)	0 (–2 to 1)	0 (–1 to 1)
PGS, mm	33 (13 to 58)	30 (12 to 54)	31 (12 to 58)	0 (–9 to 6)	0 (–7 to 10)
AxSpA, n=337					
Patients with available data, n (%)*	187 (55)	217 (64)	243 (72)	117 (35)	168 (50)
BASDAI, mm	33 (15 to 52)	27 (12 to 47)	31 (18 to 52)	0 (–8 to 6)	1 (–3 to 10)
CRP, mg/L	3 (1 to 6)	3 (1 to 5)	3 (1 to 5)	0 (–2 to 1)	0 (–1 to 1)
PGS, mm	32 (15 to 59)	30 (12 to 53)	34 (17 to 60)	–1 (–13 to 6)	3 (–5 to 14)
ASDAS	1.9 (1.3 to 2.8)	1.9 (1.2 to 2.6)	1.9 (1.3 to 2.7)	–0.1 (–0.4 to 0.3)	0.1 (–0.2 to 0.6)
3 months' flare rates preswitch vs postswitch†					
RA (ΔDAS28 ≥0.6), %				22	24
PsA (ΔDAS28 ≥0.6), %				21	23
RA (ΔDAS28 ≥1.2), %				8	13
PsA (ΔDAS28 ≥1.2), %				8	11
AxSpA (ΔASDAS >1.1), %				4	5

Table 5 ETA-SB4-ETA back-switchers (n=120). Characteristics at the start of SB4, reasons for SB4 withdrawal and changes in disease activity among withdrawals due to LOE

	RA	PsA	AxSpA
Patient number, n	80	20	20
Characteristics at the start of SB4			
Female, n (%)	58 (73)	11 (55)	7 (35)
Age, years	59 (52 to 70)	45 (36 to 56)	43 (38 to 56)
Concomitant MTX, n (%)	39 (49)	7 (35)	1 (5)
Patients with available data, n*	64	17	18
In remission, %	61	82	19
PGS, mm*	27 (12 to 54)	25 (13 to 63)	23 (13 to 44)
DAS28	2.2 (1.6 to 3.2)	1.8 (1.4 to 2.2)	–
CRP, mg/L	3 (1 to 8)	1 (1 to 5)	3 (1 to 6)
Swollen joint count	0 (0 to 1)	0 (0 to 0)	–
ASDAS	–	–	1.7 (1.4 to 2.4)
PASS yes, %	81	82	88
Reason for SB4 withdrawal, n (%)			
AE	34 (42)	7 (35)	6 (30)
LOE	38 (48)	11 (55)	13 (65)
Other/several/not stated	8 (10)	2 (10)	1 (5)
Characteristics at the restart of ETA in patients who stopped due to LOE and back-switched, n=62			
Patient number, n	38	11	13
Swollen joint count	2 (0 to 5)	0 (0 to 2)	–
CRP, mg/L	3 (2 to 11)	3 (2 to 7)	4 (1 to 6)
PGS, mm	64 (50 to 76)	78 (18 to 90)	42 (35 to 63)
Delta values† in patients who stopped due to LOE and back-switched			
Patients with available data, n†	31	8	11
Delta-swollen joint count	1 (0 to 4)	0 (0 to 0)	–
Delta-CRP, mg/L	0 (-1 to 5)	1 (0 to 2)	0 (0 to 4)
Delta-PGS, mm	30 (12 to 52)	15 (7 to 77)	25 (19 to 35)

The Nor-Switch Study

A randomized, double-blind, parallel-group study to evaluate the safety and efficacy of switching from innovator infliximab to biosimilar infliximab compared with maintained treatment with innovator infliximab in patients with rheumatoid arthritis, spondyloarthritis, psoriatic arthritis, ulcerative colitis, Crohn's disease and chronic plaque psoriasis

EudraCT Number: 2014-002056-40

NOR SWITCH

Acknowledgements

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Statistician: Inge C Olsen
Project group: Jørgen Jahnsen, Cato Mørk, Nils Bolstad, Espen A Haavardsholm, Knut EA Lundin, Ingrid P Berset, Bjørg TS Fevang, Jon Florholmen, Synøve Kalstad, Nils J Mørk, Kristin Ryggen, Kåre S Tveit, Sigrun K Sæther.
Patient representatives: Bjørn Gulbrandsen, Jon Hagfors, Kenneth Waksvik

Investigators, nurses and participating patients at each study site

Data monitoring: Martha Colban, Nina Flatner, Trond Smedsrud, Bjørn Solvang, Inger Hilde Zahl, Cecilie Moe, Trude Langeng and the Norwegian Clinical Research Infrastructure Network (NorCRIN)

NOR SWITCH

Study objectives

Primary:

- To assess if CT-P13 is non-inferior to innovator infliximab (INX) with regard to disease worsening in patients who have been on stable INX treatment for at least 6 months

Secondary:

- To assess the safety and immunogenicity of CT-P13 compared to INX in patients who have been on stable INX treatment for at least 6 months
- To compare the efficacy of CT-P13 to INX in patients who have been on stable INX treatment for at least 6 months applying generic and disease-specific outcome measures

NOR SWITCH

Main Inclusion Criteria

- A clinical diagnosis of either rheumatoid arthritis, spondyloarthritis, psoriatic arthritis, ulcerative colitis, Crohn's disease or chronic plaque psoriasis
- Male or non-pregnant, non-nursing female
- >18 years of age at screening
- Stable treatment with innovator infliximab (Remicade®) during the last 6 months
- Subject capable of understanding and signing an informed consent form
- Provision of written informed consent

NOR SWITCH

Switching from originator infliximab to biosimilar CT-P13 compared with maintained treatment with originator infliximab (NOR-SWITCH): a 52-week, randomised, double-blind, non-inferiority trial

Kristin K Jørgensen, Inge C Olsen*, Guro L Goll*, Merete Lorentzen*, Nils Bolstad, Espen A Haavardsholm, Knut E A Lundin, Cato Mørk†, Jørgen Jahnsen†, Tore K Kvien†, on behalf of the NOR-SWITCH study group*

Published Online
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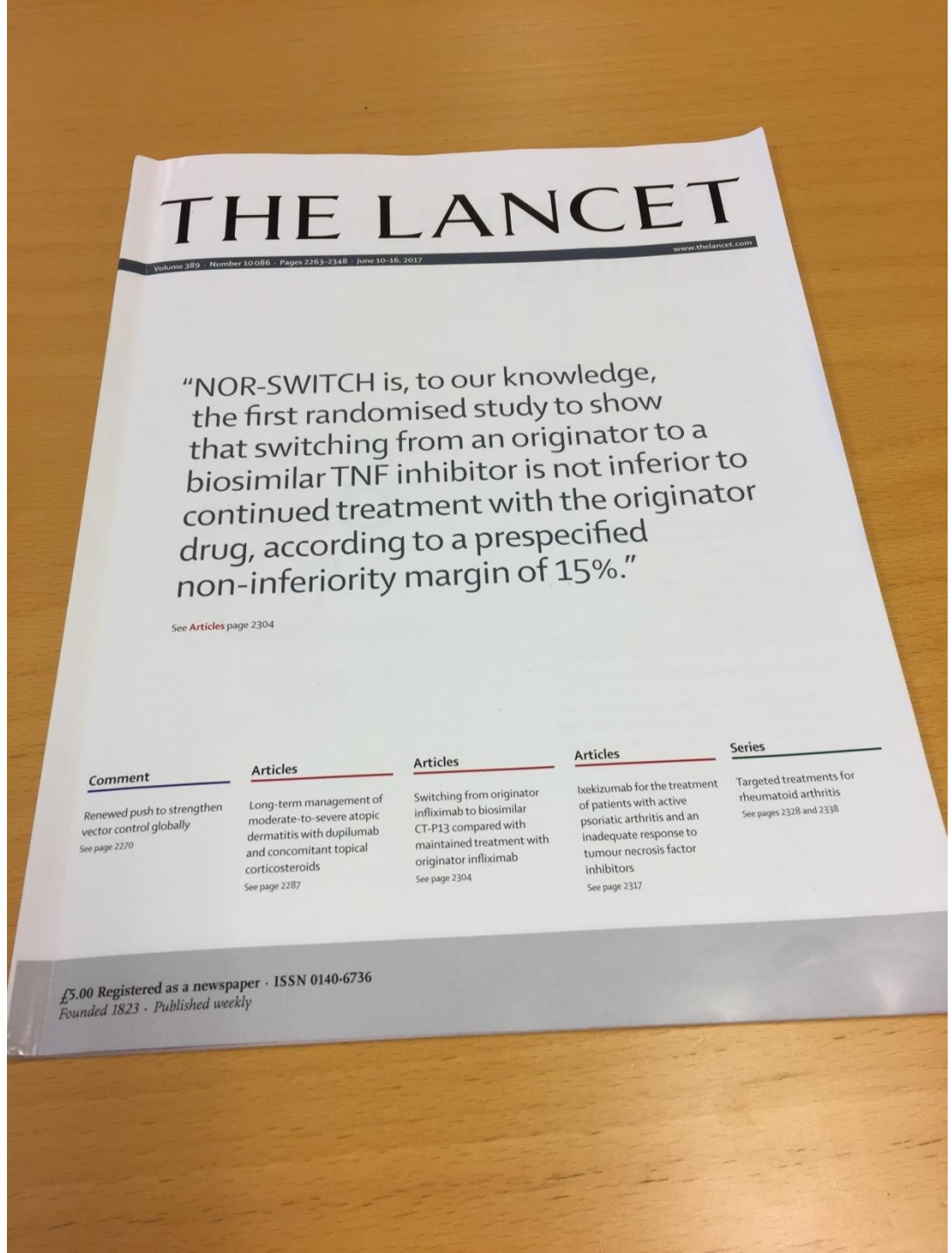
THE LANCET
Volume 389 · Number 10086 · Pages 2263-2348 · June 10-16, 2017
www.thelancet.com
"NOR-SWITCH is, to our knowledge, the first randomised study to show that switching from an originator to a biosimilar TNF inhibitor is not inferior to continued treatment with the originator drug, according to a prespecified non-inferiority margin of 15%."
See Articles page 2304
Comment
Renewed push to strengthen vector control globally
See page 2270
Articles
Long-term management of moderate-to-severe atopic dermatitis with dupilumab and concomitant topical corticosteroids
See page 2287
Articles
Switching from originator infliximab to biosimilar CT-P13 compared with maintained treatment with originator infliximab
See page 2304
Articles
Ixekizumab for the treatment of patients with active psoriatic arthritis and an inadequate response to tumour necrosis factor inhibitors
See page 2317
Series
Targeted treatments for rheumatoid arthritis
See pages 2328 and 2338
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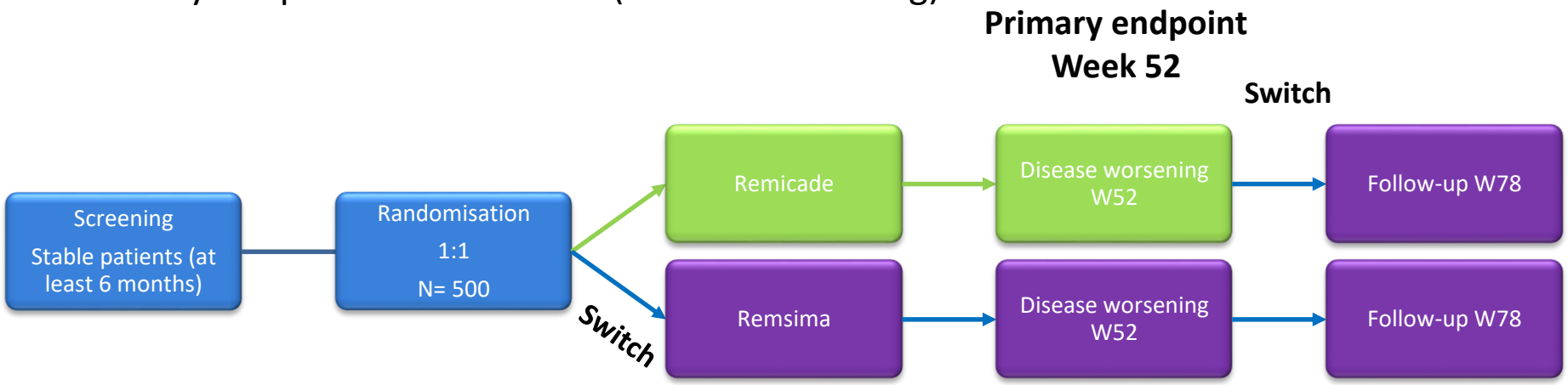
NOR-SWITCH Study Design

- Exploring switching for non-medical reasons
- Primary endpoint: Effectiveness (disease worsening)



A randomized, double-blind, parallel-group study to evaluate the safety and efficacy of switching from innovator infliximab to biosimilar infliximab compared with continued treatment with innovator infliximab in patients with rheumatoid arthritis, spondylarthritis, psoriatic arthritis, ulcerative colitis, Crohn's disease and chronic plaque psoriasis

Assumption : 30% worsening in 52 weeks
Non-inferiority margin:15%

Open Label Follow-up

NOR SWITCH

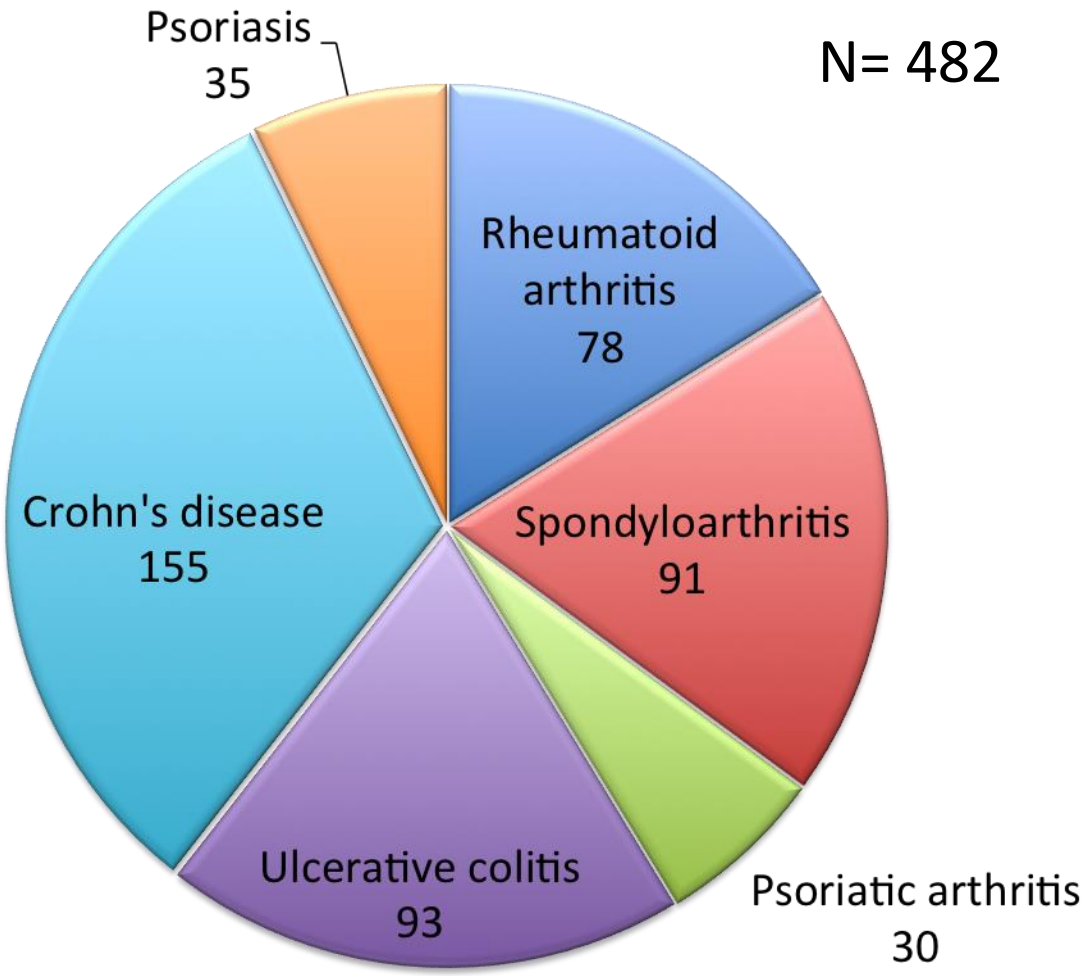
Table 1: The numbers in the cells represent the total number of patients needed in total. All calculations are based on a power of 80% and alpha 2.5%

Non-inferiority Margin	*10% disease worsening at 52 w*	*20% disease worsening at 52 w*	*30% disease worsening at 52 w*
10%	248	504	660
15 %	126	224	294
20 %	72	126	166

Table 2: The numbers in the cells represent the total number of patients needed in total. All calculations are based on a power of 90% and alpha 2.5%.

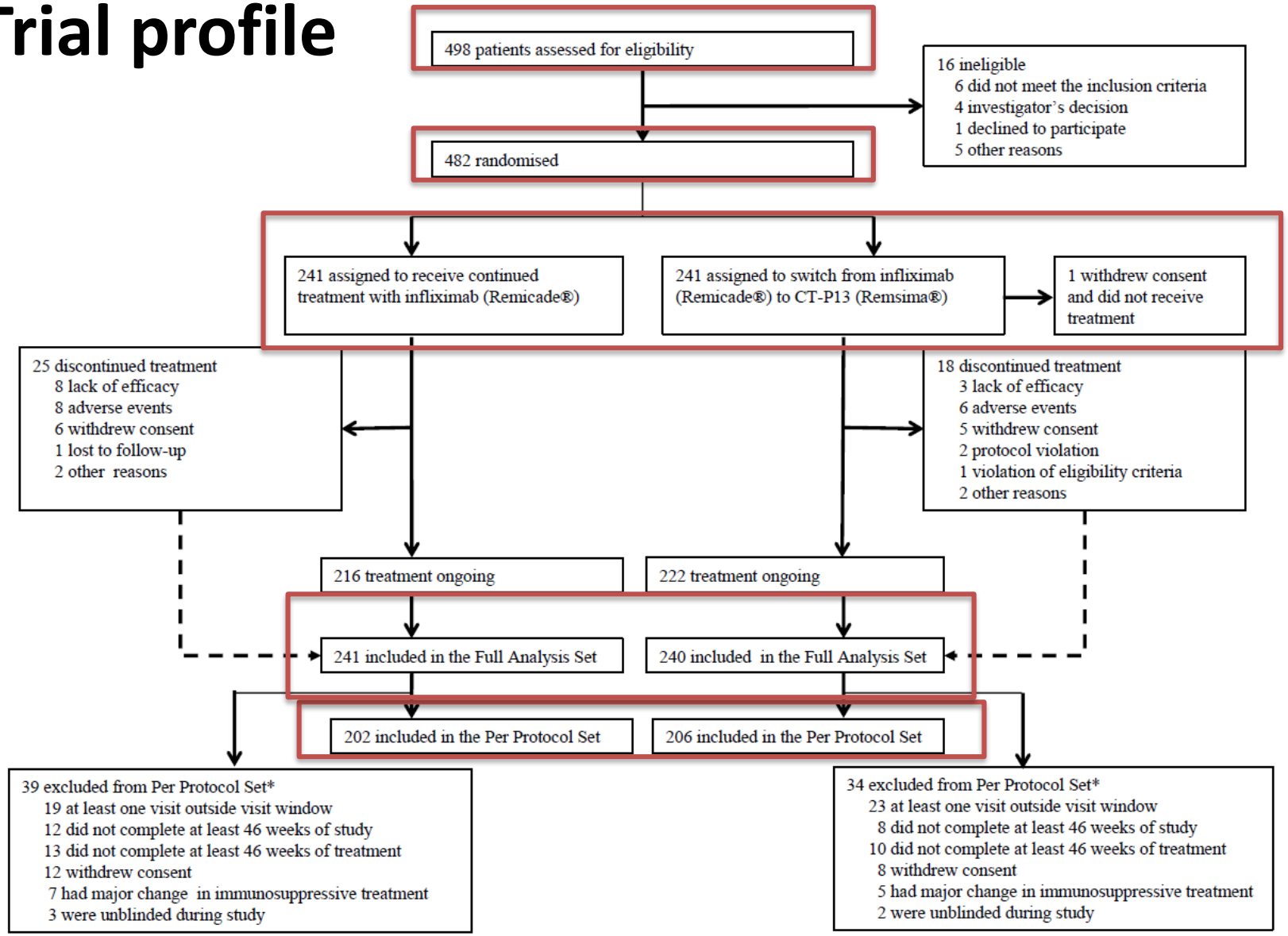
Non-inferiority Margin	*10% disease worsening at 52 w*	*20% disease worsening at 52 w*	*30% disease worsening at 52w*
10%	380	674	884
15 %	170	300	394
20 %	96	170	222

Diagnosis distribution



NOR SWITCH

Trial profile



Kvien T. NOR-SWITCH Principal Investigator. Unpublished data.

Primary endpoint

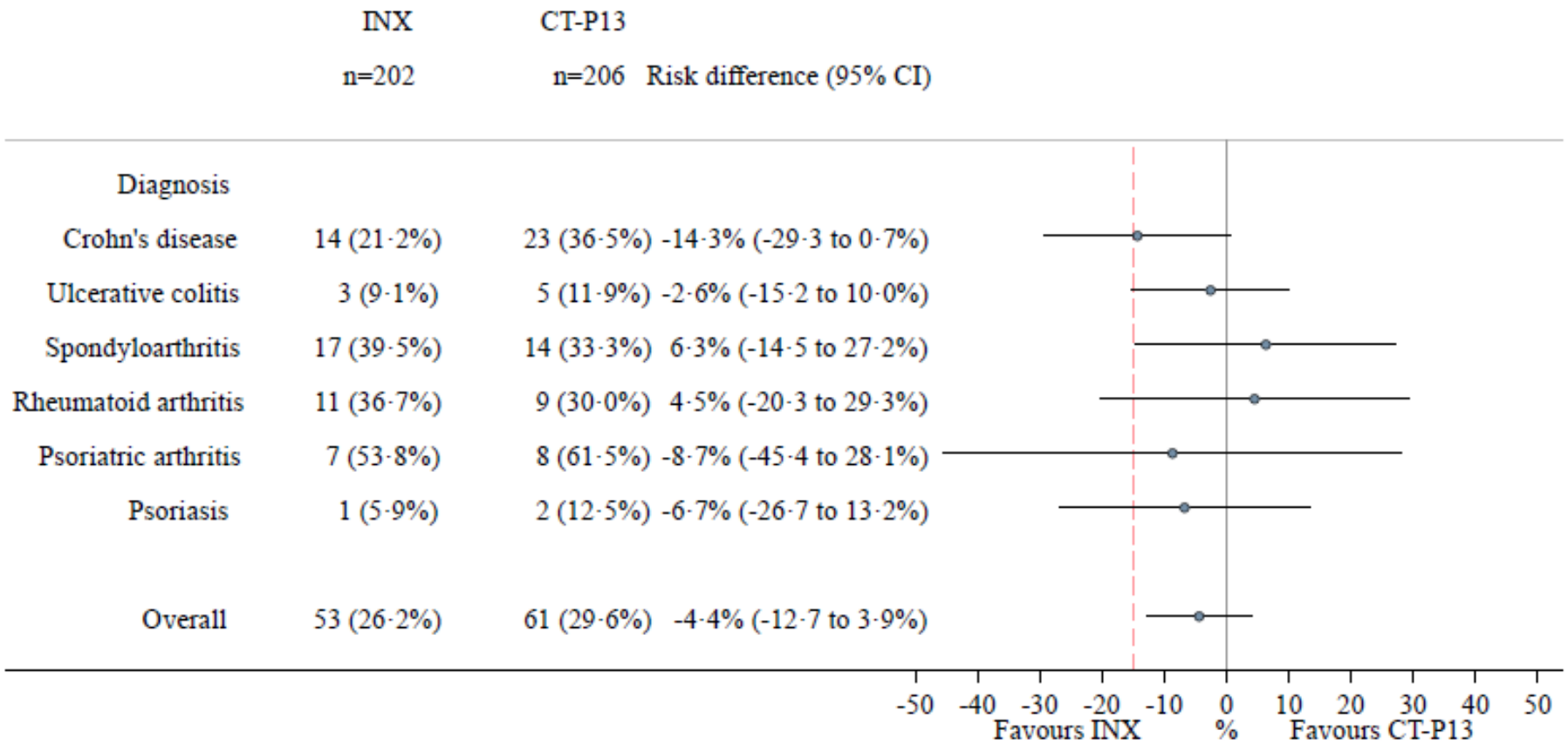
	INX (n= 202)	CT-P13 (n=206)	Rate difference (95% CI)
Disease worsening*	53 (26.2%)	61 (29.6%)	-4.4 (-12.7 – 3.9)

* UC: increase in p-Mayo score of ≥ 3 points and a p-Mayo score of ≥ 5 points,
CD: increase in HBI of ≥ 4 points and a HBI score of ≥7 points
RA/PsA: increase in DAS28 of ≥ 1.2 from randomization and a DAS score of ≥ 3.2
AS/SpA: increase in ASDAS of ≥1.1 and ASDAS of ≥ 2.1
Psoriasis: increase in PASI of ≥ 3 points from randomization and a minimum PASI score of ≥ 5

If a patient does not fulfill the formal definition, but experiences a clinically significant worsening according to both the investigator and patient and which leads to a major change in treatment this should be considered as a disease worsening but recorded separately in the CRF

NOR SWITCH

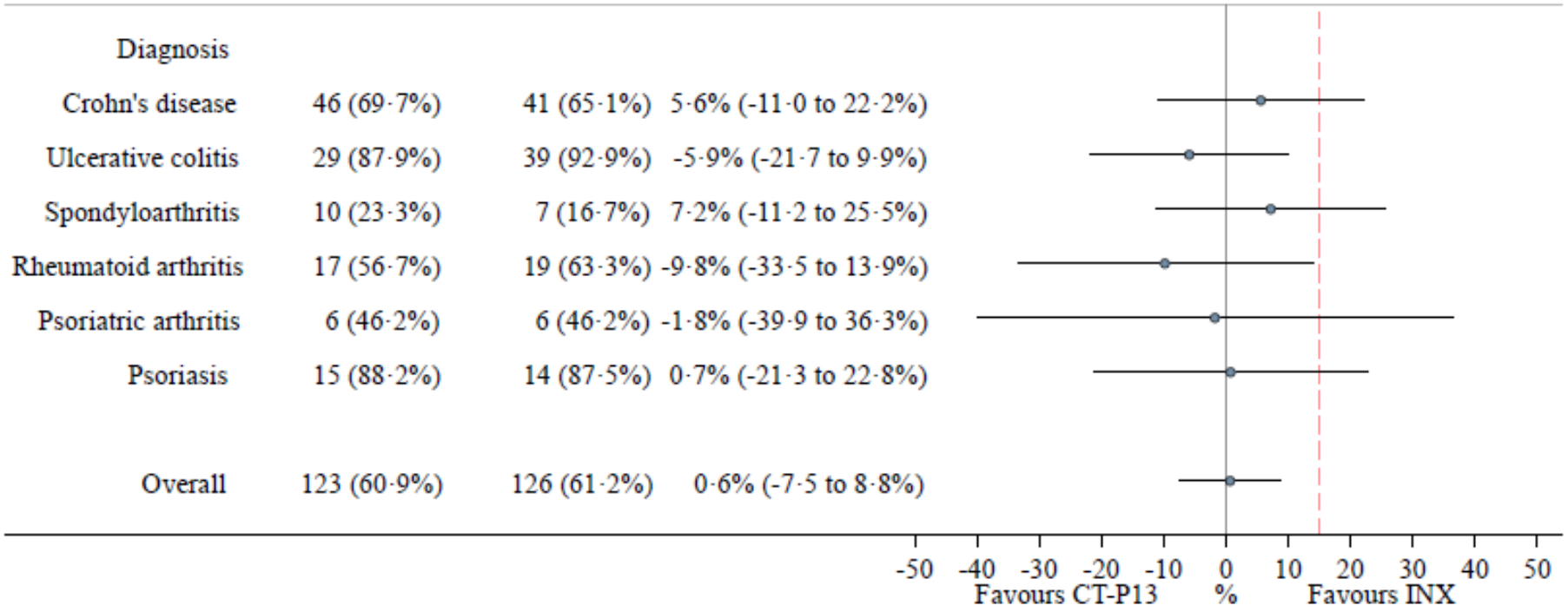
Disease Worsening



NOR SWITCH

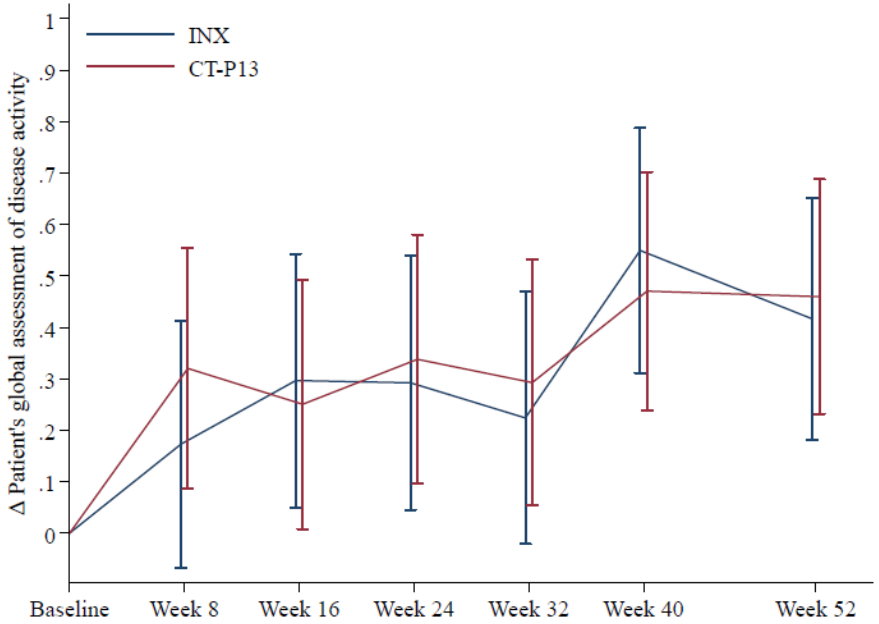
Remission

	INX n=202	CT-P13 n=206	Rate difference (95% CI)
Diagnosis			
Crohn's disease	46 (69·7%)	41 (65·1%)	5·6% (-11·0 to 22·2%)
Ulcerative colitis	29 (87·9%)	39 (92·9%)	-5·9% (-21·7 to 9·9%)
Spondyloarthritis	10 (23·3%)	7 (16·7%)	7·2% (-11·2 to 25·5%)
Rheumatoid arthritis	17 (56·7%)	19 (63·3%)	-9·8% (-33·5 to 13·9%)
Psoriatric arthritis	6 (46·2%)	6 (46·2%)	-1·8% (-39·9 to 36·3%)
Psoriasis	15 (88·2%)	14 (87·5%)	0·7% (-21·3 to 22·8%)
Overall	123 (60·9%)	126 (61·2%)	0·6% (-7·5 to 8·8%)

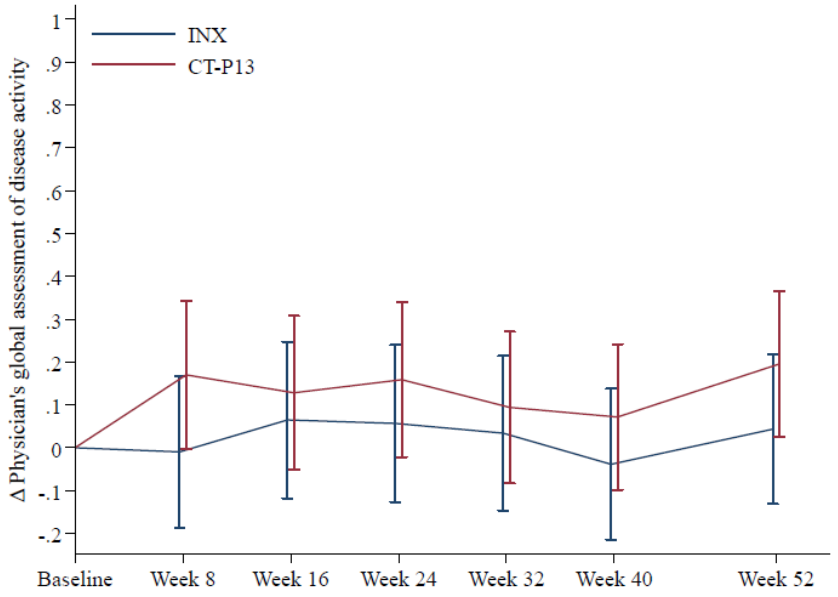


NOR SWITCH

Global Assessment of Disease Activity



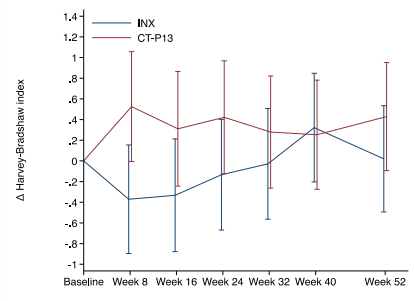
Patient



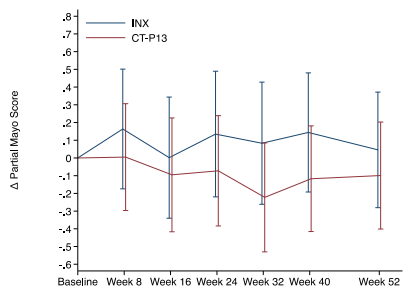
Physician

NOR SWITCH

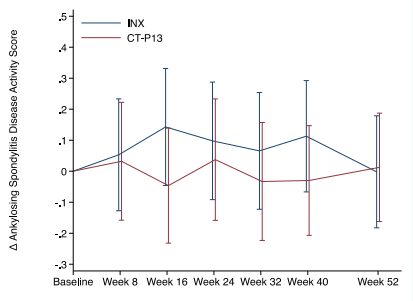
Disease Activity



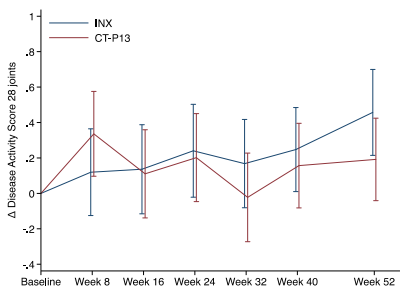
HBI



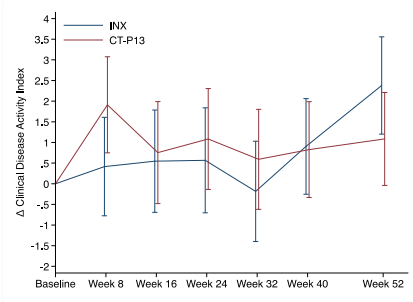
p-Mayo score



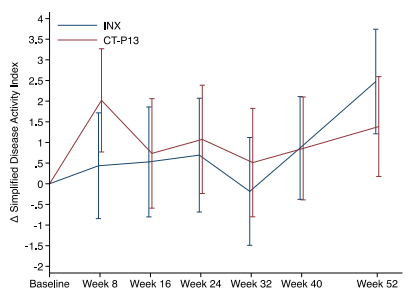
ASDAS



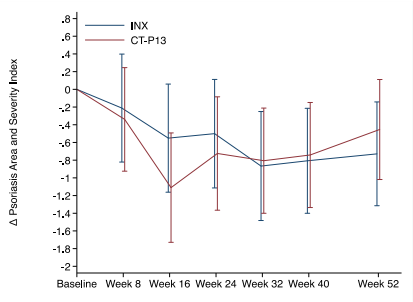
DAS28



CDAI



SDAI

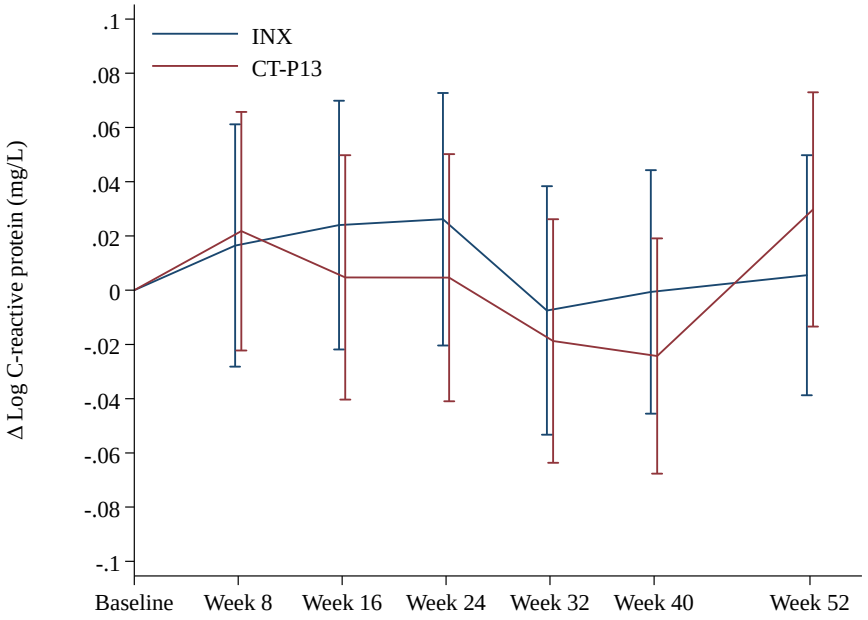


PASI

NOR SWITCH

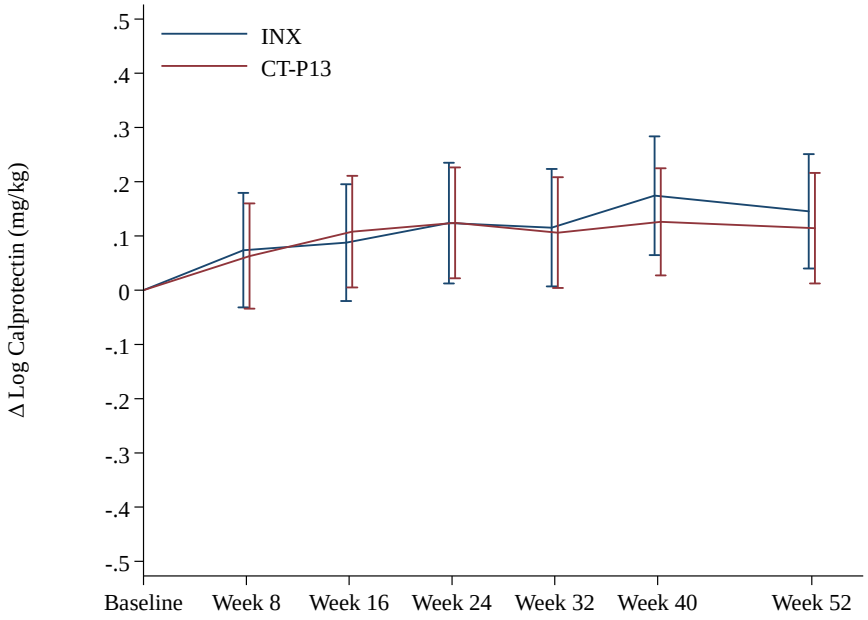
CRP and Calprotectin

Over all



CRP

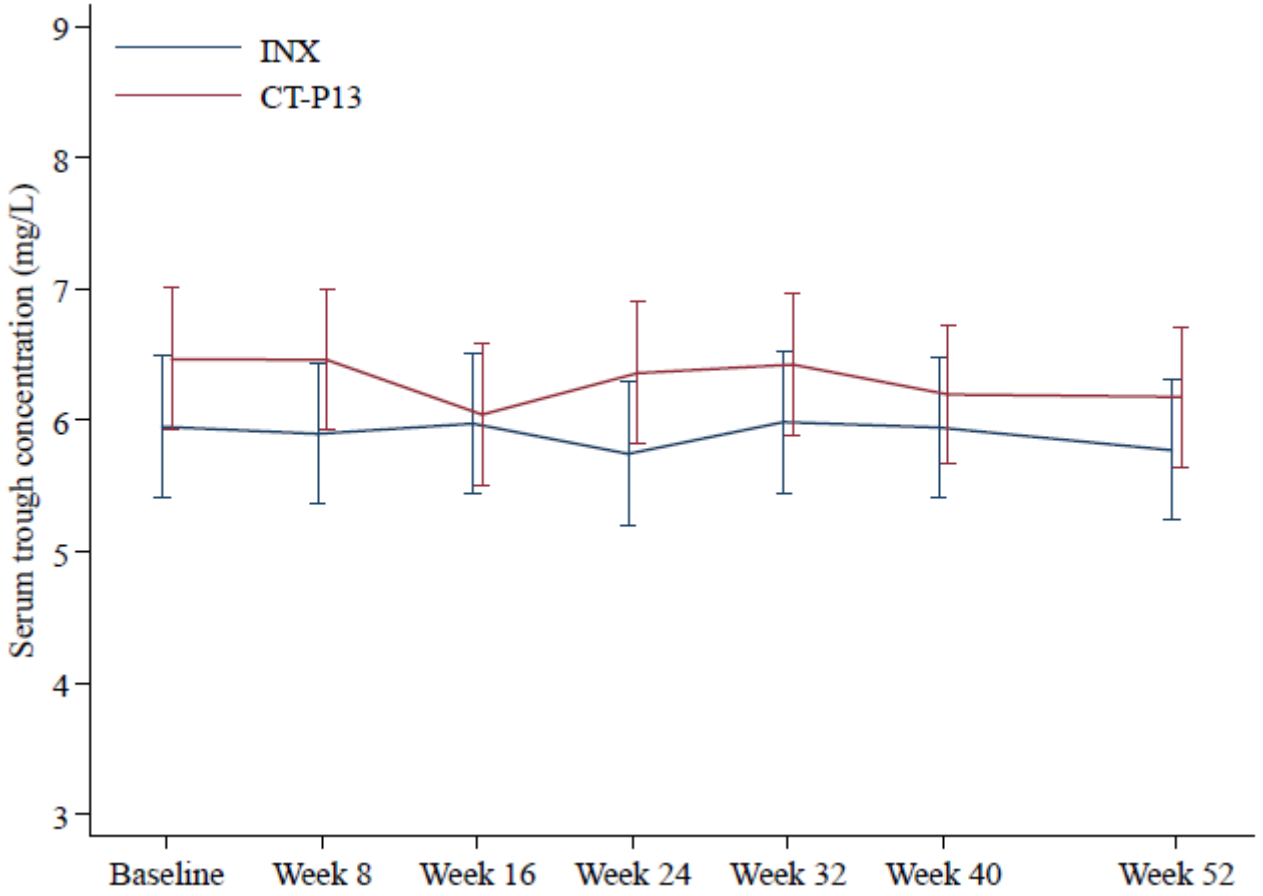
IBD



Calprotectin

NOR SWITCH

Drug Trough Levels



Over all

NOR SWITCH

Anti-drug Antibodies (ADAb)

	INX (n= 241)	CT-P13 (n=240)
ADAb observed at any time point	26 (10.8%)	30 (12.5%)
Incidence of ADAb	17 (7.1%)	19 (7.9%)

NOR SWITCH

Adverse events – safety population

Overview *	INX (n=241)	CT-P13 (n=240)
SUSAR	0	0
Serious adverse events (SAE)	[32] 24 (10·0%)	[27] 21 (8·8%)
Adverse events (AE)	[422] 168 (69·7%)	[401] 164 (68·3%)
Adverse event leading to study drug discontinuation	[18] 9 (3·7%)	[9] 8 (3·3%)

*[number of events] n (%)

NOR SWITCH

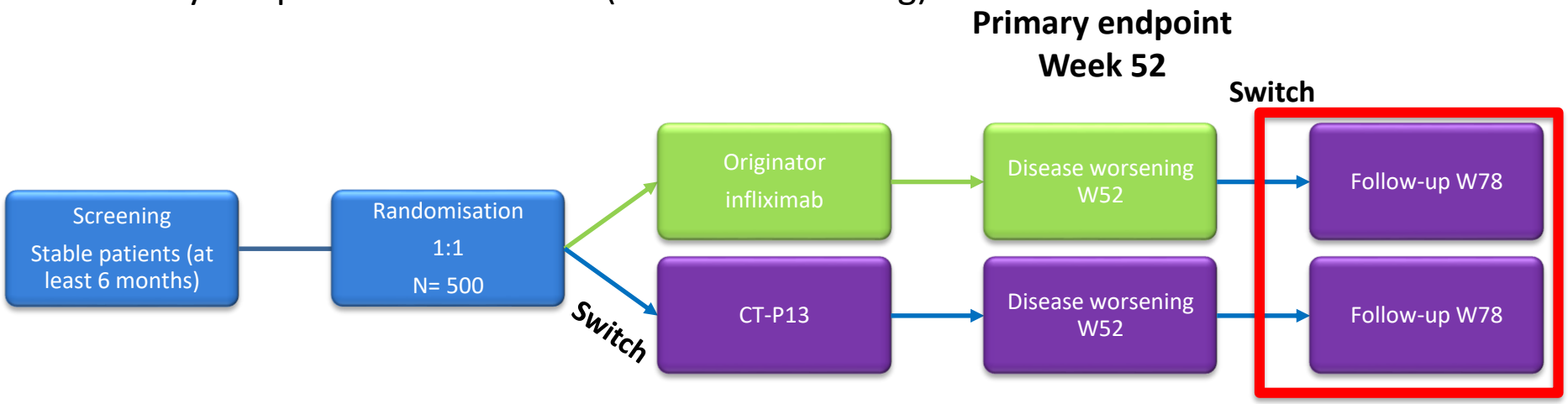
Interpretation

- The NOR-SWITCH trial demonstrated that switch from INX to CT-P13 was not inferior to continued treatment with INX
- The results support switching from INX to CT-P13 for non-medical reasons

NOR SWITCH

NOR-SWITCH Study Design

- Exploring switching for non-medical reasons
- Primary endpoint: Effectiveness (disease worsening)

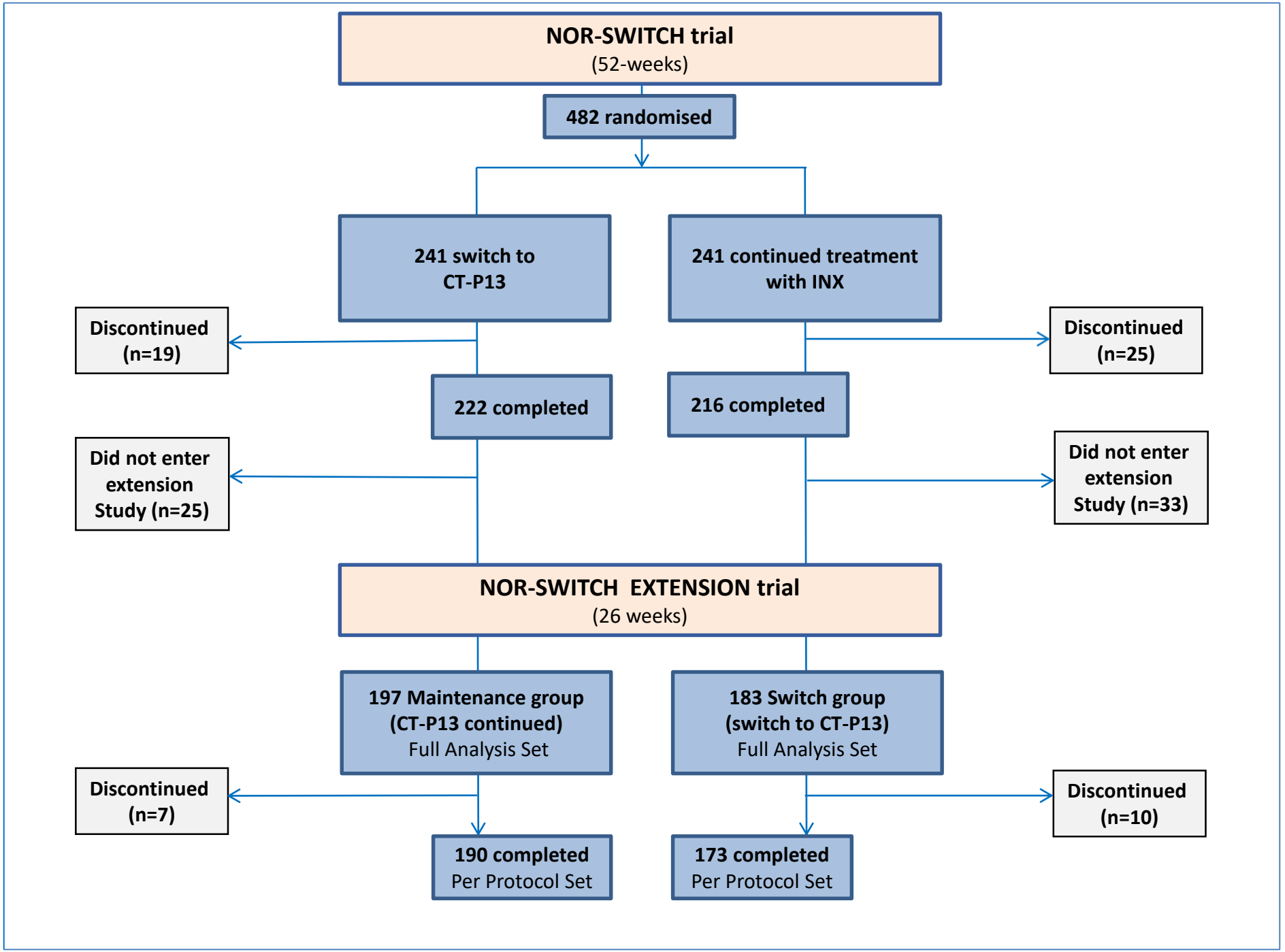


A randomized, double-blind, parallel-group study to evaluate the safety and efficacy of switching from innovator infliximab to biosimilar infliximab compared with continued treatment with innovator infliximab in patients with rheumatoid arthritis, spondylarthritis, psoriatic arthritis, ulcerative colitis, Crohn's disease and chronic plaque psoriasis

Assumption : 30% worsening in 52 weeks
Non-inferiority margin:15%

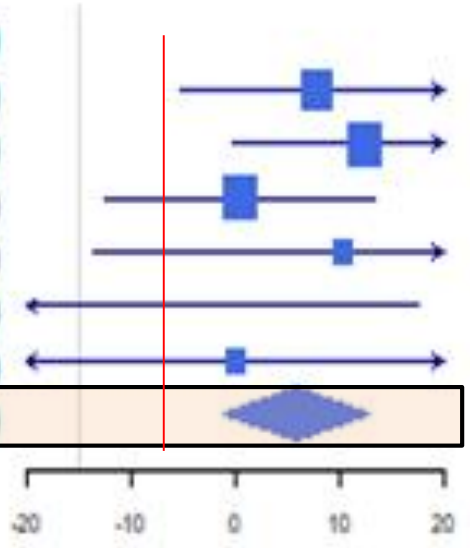
Open Label Follow-up

NOR SWITCH


NOR-SWITCH trial
(52-weeks)
482 randomised
241 switch to CT-P13
241 continued treatment with INX
Discontinued (n=19)
Discontinued (n=25)
222 completed
216 completed
Did not enter extension Study (n=25)
Did not enter extension Study (n=33)
NOR-SWITCH EXTENSION trial
(26 weeks)
197 Maintenance group (CT-P13 continued)
Full Analysis Set
183 Switch group (switch to CT-P13)
Full Analysis Set
Discontinued (n=7)
Discontinued (n=10)
190 completed
Per Protocol Set
173 completed
Per Protocol Set

Nor-Switch extension: disease worsening

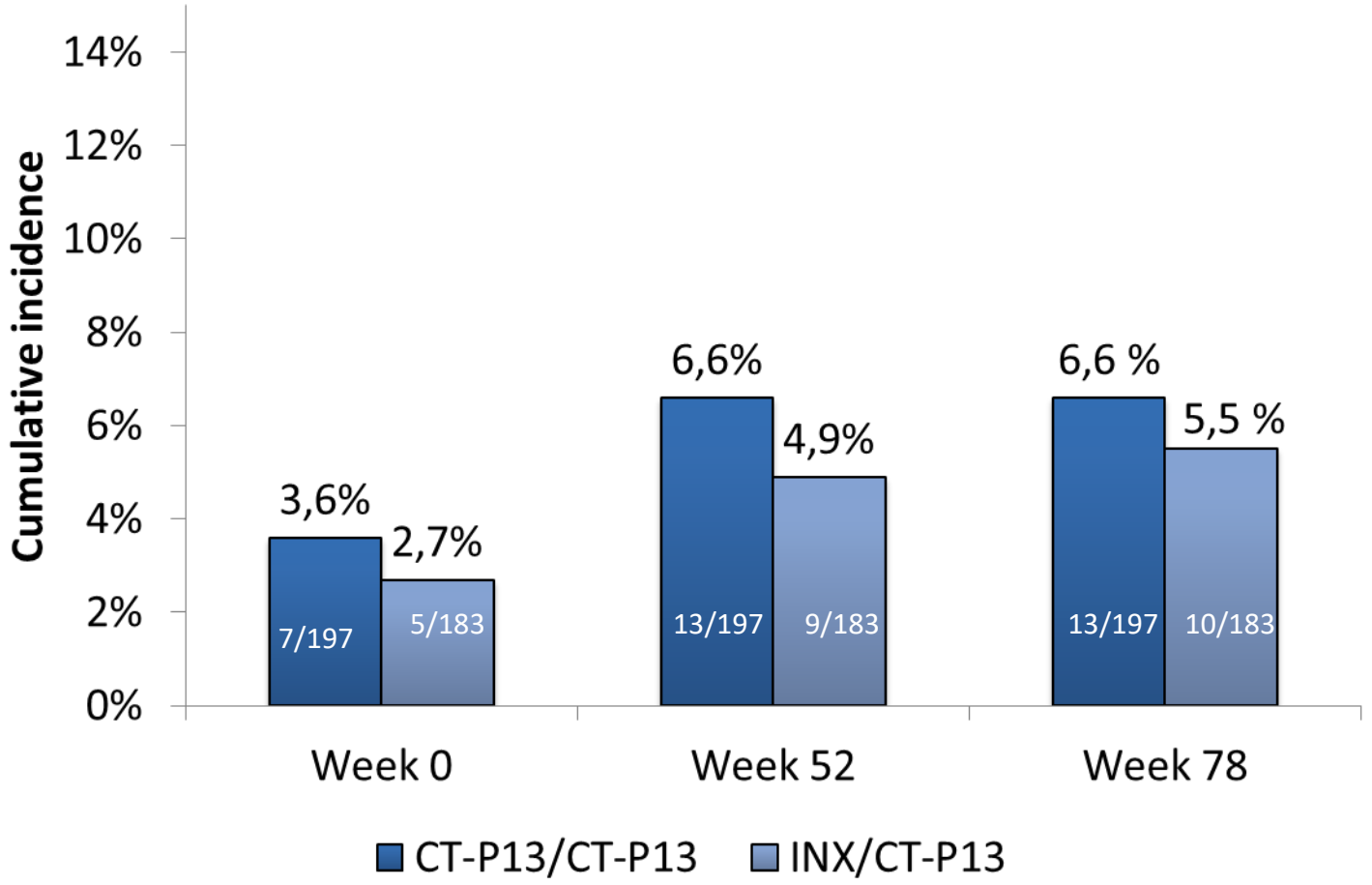
Diagnosis	Maintenance	Switch	Risk difference (95% CI)
Crohn's disease	13/63 (20.6%)	8/61 (13.1%)	7.9% (-5.2 to 21)
Ulcerative colitis	6/39 (15.4%)	1/35 (2.9%)	12.4% (-0.1 to 25)
Spondyloarthritis	3/38 (7.9%)	2/28 (7.1%)	0.6% (-12.2 to 13.5)
Rheumatoid arthritis	9/26 (34.6%)	6/27 (22.2%)	10.5% (-13.6 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)



Maintenance group: CT-P13 throughout study period
Switch group: INX main study period, switched to CT-P13

NOR SWITCH

Anti-drug Antibodies



*neutralising antibodies, measured only in patients with drug trough level ≤ 5 mg/L

NOR SWITCH

Interpretation

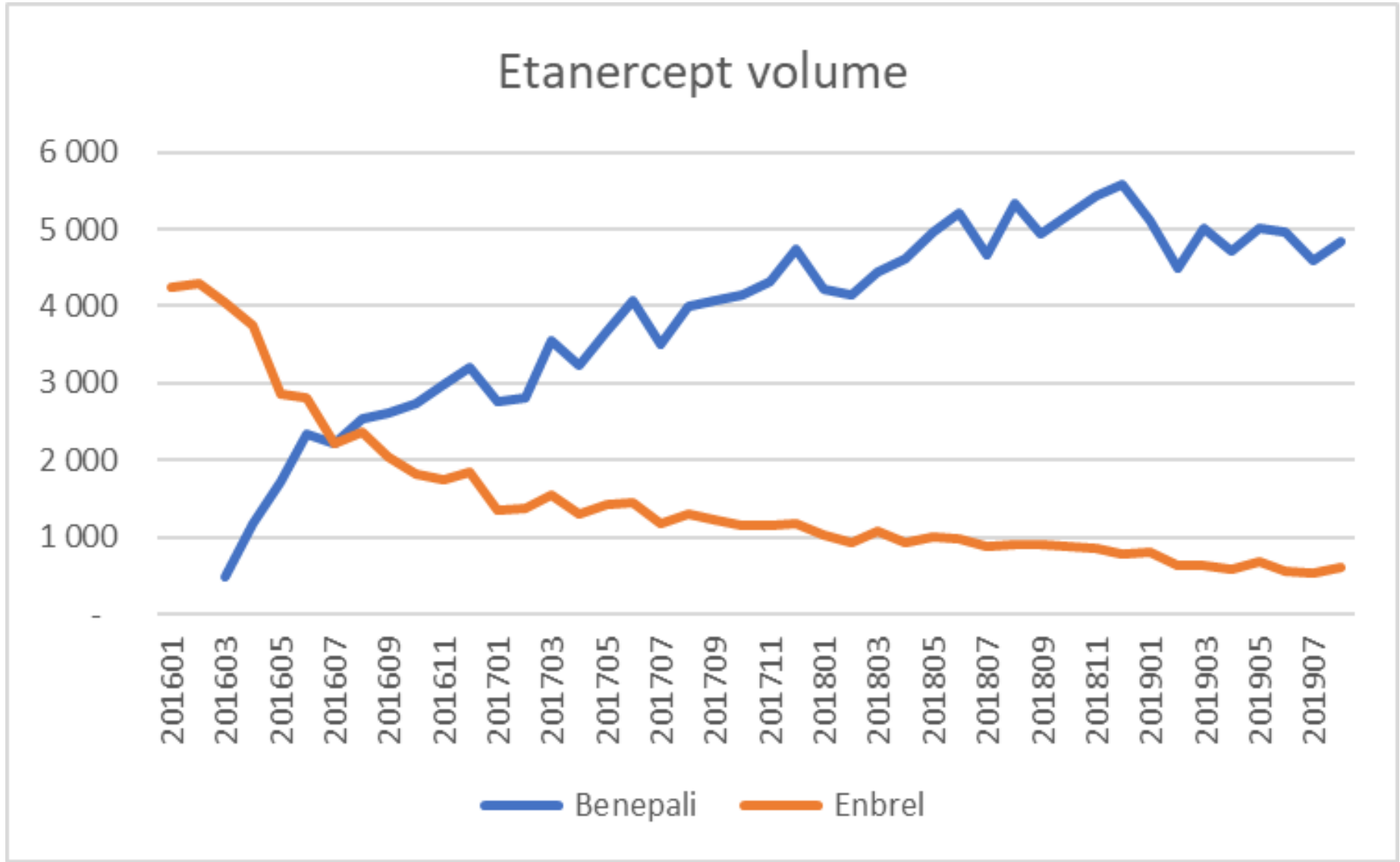
- The NOR-SWITCH extension trial confirms results from main trial:
  - a switch from INX to CT-P13 did not lead to an increased rate of disease worsening, adverse events or immunogenicity concerns in overall study population

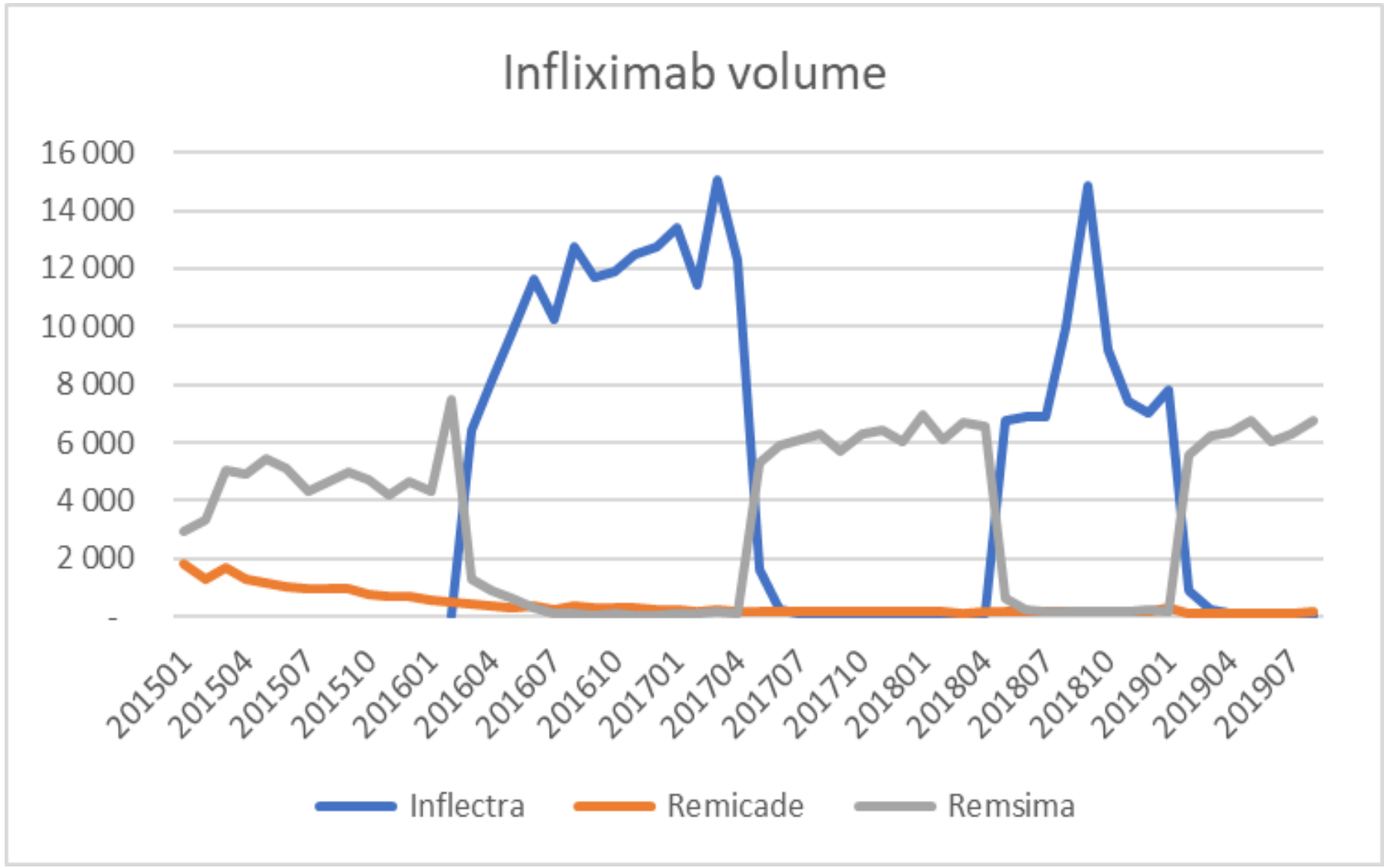
NOR SWITCH

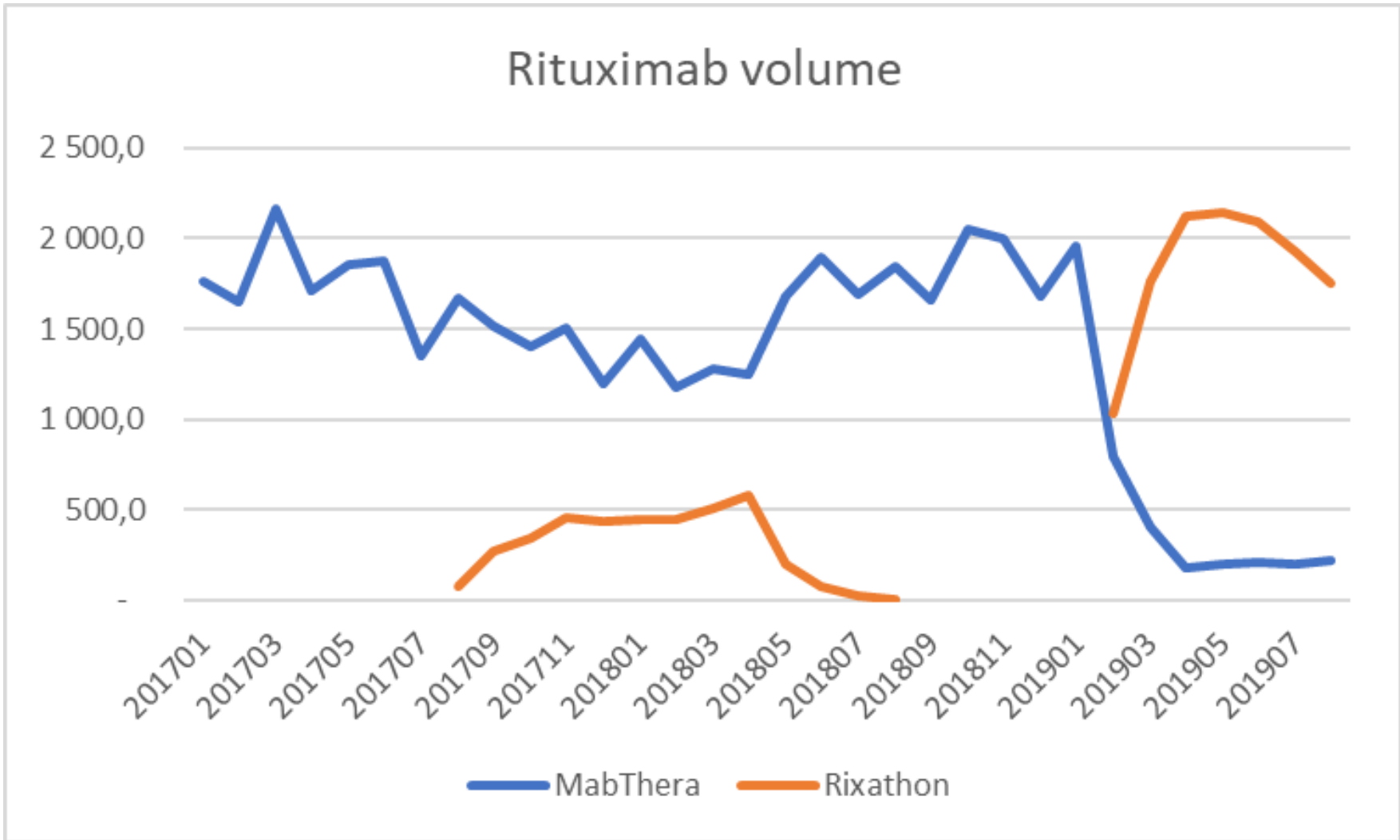
Conclusions

- Most data support that switching/transitioning from originator bDMARD to bsDMARD is safe
- Cost-saving is the major (only?) motivation combined with better access to good therapies for more people
- Nocebo-effect may be an issue and more data are needed on how information may improve acceptability and drug retention

Biosimilar uptake in Norway


Etanercept volume
6 000
5 000
4 000
3 000
2 000
1 000
-
201601
201603
201605
201607
201609
201611
201701
201703
201705
201707
201709
201711
201801
201803
201805
201807
201809
201811
201901
201903
201905
201907
Benepali
Enbrel


Infliximab volume
16 000
14 000
12 000
10 000
8 000
6 000
4 000
2 000
-
201501
201504
201507
201510
201601
201604
201607
201610
201701
201704
201707
201710
201801
201804
201807
201810
201901
201904
201907
Inflectra
Remicade
Remsima


Rituximab volume
2 500,0
2 000,0
1 500,0
1 000,0
500,0
-
201701
201703
201705
201707
201709
201711
201801
201803
201805
201807
201809
201811
201901
201903
201905
201907
MabThera
Rixathon

The future and research agenda

- Switching from biosimilar back to originator?
- Multiple switches between biosimilars
- Interchangeability versus automatic substitution
- Nocebo effect and communication strategies

Consensus-based recommendations for the use of biosimilars to treat rheumatological diseases

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Table 1 Overarching principles (A–E) and consensus recommendations (1–8) for biosimilars

		Agreement* (%)	Level of evidence†	Grade of recommendation‡
Overarching principles				
A.	Treatment of rheumatic diseases is based on a shared decision-making process between patients and their rheumatologists.	100	5	D
B.	The contextual aspects of the healthcare system should be taken into consideration when treatment decisions are made.	100	5	D
C.	A biosimilar, as approved by authorities in a highly regulated area, is neither better nor worse in efficacy and not inferior in safety to its bio-originator.	88	5	D
D.	Patients and healthcare providers should be informed about the nature of biosimilars, their approval process, and their safety and efficacy.	96	5	D
E.	Harmonised methods should be established to obtain reliable pharmacovigilance data, including traceability, about both biosimilars and bio-originators.	100	5	D
Consensus recommendations				
1.	The availability of biosimilars must significantly lower the cost of treating an individual patient and increase access to optimal therapy for all patients with rheumatic diseases.	100	5	D
2.	Approved biosimilars can be used to treat appropriate patients in the same way as their bio-originators.	100	1b	A
3.	As no clinically significant differences in immunogenicity between biosimilars and their bio-originators have been detected, antidrug antibodies to biosimilars need not be measured in clinical practice.	100	2b	B
4.	Relevant preclinical and phase I data on a biosimilar should be available when phase III data are published.	100	5	D
5.	Since the biosimilar is equivalent to the bio-originator in its physicochemical, functional and pharmacokinetic properties, confirmation of efficacy and safety in a single indication is sufficient for extrapolation to other diseases for which the bio-originator has been approved.	100	5	D
6.	Currently available evidence indicates that a single switch from a bio-originator to one of its biosimilars is safe and effective; there is no scientific rationale to expect that switching among biosimilars of the same bio-originator would result in a different clinical outcome but patient perspectives must be considered.	96	1b	A
7.	Multiple switching between biosimilars and their bio-originators or other biosimilars should be assessed in registries.	100	5	D
8.	No switch to or among biosimilars should be initiated without the prior awareness of the patient and the treating healthcare provider.	91	5	D

*Agreement indicates percentage of experts who approved the recommendation during the final voting round of the consensus meeting.
†1a: systematic review of randomised clinical trials (RCTs); 1b: individual RCT; 2a: systematic review of cohort studies; 2b: individual cohort study (including low-quality RCT; eg, <80% follow-up); 3a: systematic review of case–control studies; 3b: individual case–control study; 4: case-series (and poor quality cohort and case–control studies); 5: expert opinion without explicit critical appraisal, or based on physiology, bench research or 'first principles'.
‡A: based on consistent level 1 evidence; B: based on consistent level 2 or 3 evidence or extrapolations from level 1 evidence; C: based on level 4 evidence or extrapolations from level 2 or 3 evidence; D: based on level 5 evidence or on troublingly inconsistent or inconclusive studies of any level.