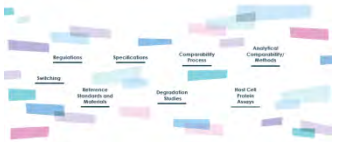


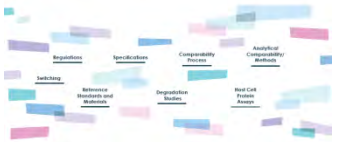
Professor Tore Kristian Kvien, MD, PhD, Norway

- Professor of Medicine and Rheumatology, Head of Department of Rheumatology, Diakonhjemmet Hospital, Norway

GaBI Scientific Meetings

Second Colombian Scientific Meeting on Quality Assessment of **BIOSIMILARS/SIMILAR BIOTHERAPEUTIC PRODUCTS**

15 August 2017, Hiilton Bogotá, Colombia



Switching from originator product to biosimilars in rheumatology, dermatology and gastroenterology: clinical evidence

Professor Tore Kristian Kvien, MD, PhD

15 August 2017

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

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Instituto Nacional de Vigilancia de Medicamentos y Alimentos

PPCI
Pro Pharma Communications International

Switching from originator product to biosimilars in rheumatology, dermatology and gastroenterology: clinical evidence

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			

Editor-in-Chief Annals of the Rheumatic Diseases

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'

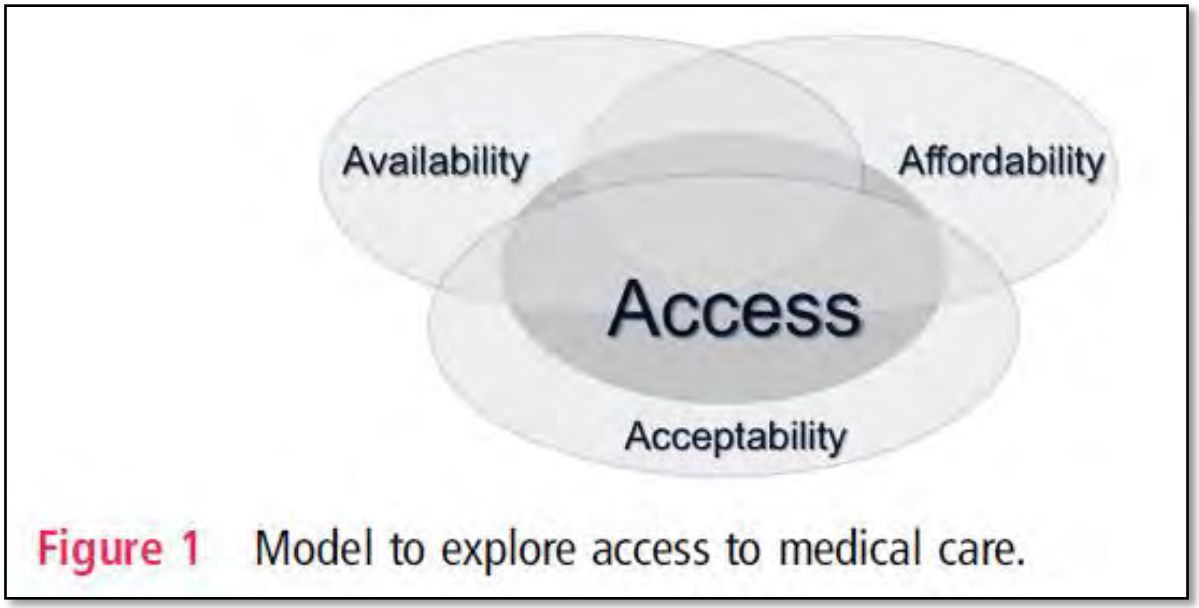


Figure 1 Model to explore access to medical care.

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

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

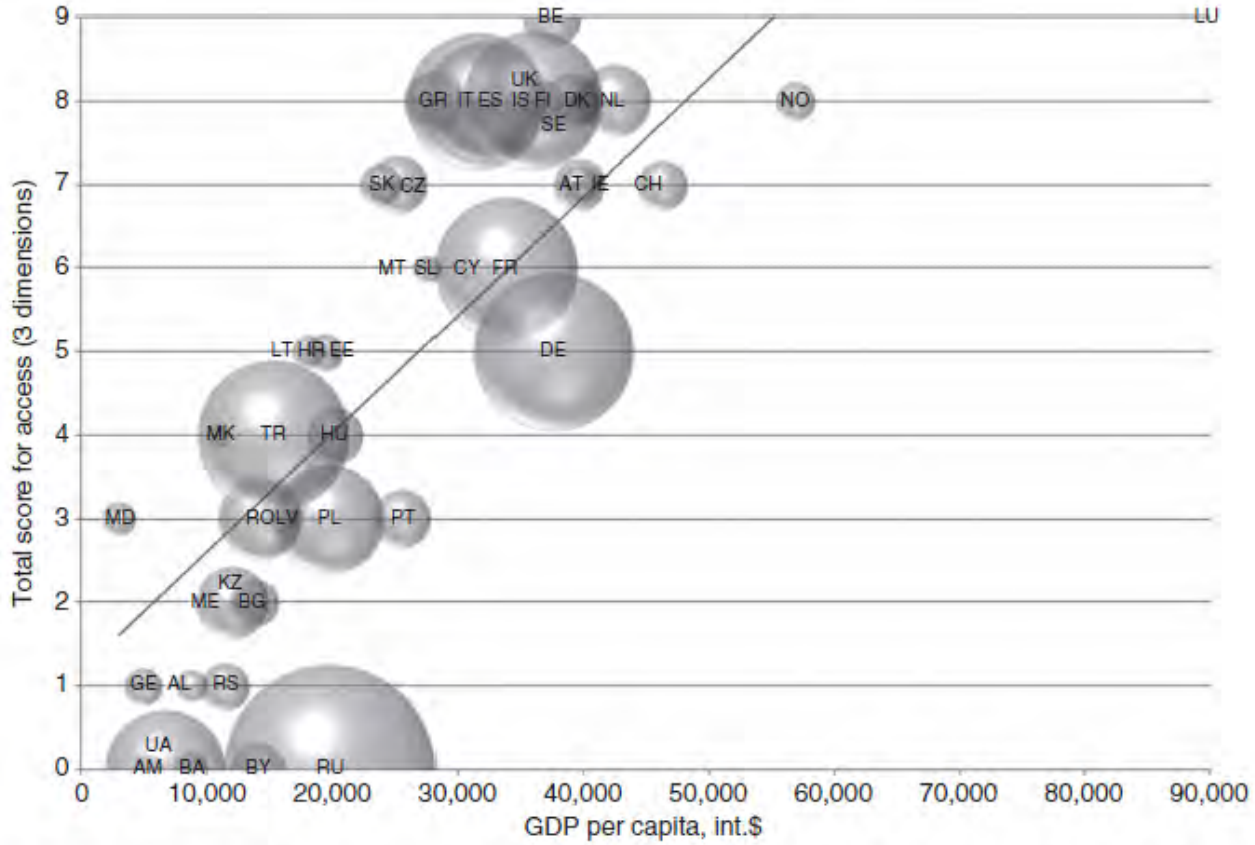


Figure 3 Access to biologic disease modifying antirheumatic drugs and gross domestic product per capita, international dollars (n=44). Size of the bubbles is proportional to the population size of the country. AL, Albania; AM, Armenia; AT, Austria; BA, Bosnia and Herzegovina; BE, Belgium; BG, Bulgaria; 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.

EXTENDED REPORT

Polina P et al Ann Rheum Dis 2014;73:2010-21

Variations in criteria regulating treatment with reimbursed biologic DMARDs across European countries. Are differences related to country's wealth?

Polina Putrik,[1] Sofia Ramiro,[2,3] Tore K Kvien,[4] Tuulikki Sokka,[5] Till Uhlig,[6] Annelies Boonen,[7] on behalf of Equity in Clinical Eligibility Criteria for RA treatment Working Group

Table 1 Clinical criteria for eligibility and maintenance of treatment with bDMARDs in 36 European countries with at least one biologic reimbursed

Country	Major source of eligibility criteria	Who can prescribe bDMARDs to patients with RA	Requirement to start the first biologic			Time point for the first assessment of response (weeks)	Criteria to stop at 6 months*	Criteria to switch at 6 months*	Composite score for restrictiveness of clinical criteria (0–5)
			Minimum disease duration	Level of disease activity	Number of sDMARDs to be failed, type of DMARD and length				
Albania (no written source provided, criteria reported are those used in practice according to contact person)	REIM	Rheumatology	No requirement	DAS28>4.5	2 sDMARDs: MTX (20 mg/week) and SSZ (2.5 g/day)	NA	No criteria	No criteria	2
Austria[24–26]	REIM=GUID	Rheumatology	No requirement	Moderate to high disease activity	1 sDMARD: MTX in adequate dose and adequate duration	12	No criteria	Moderate disease activity	4

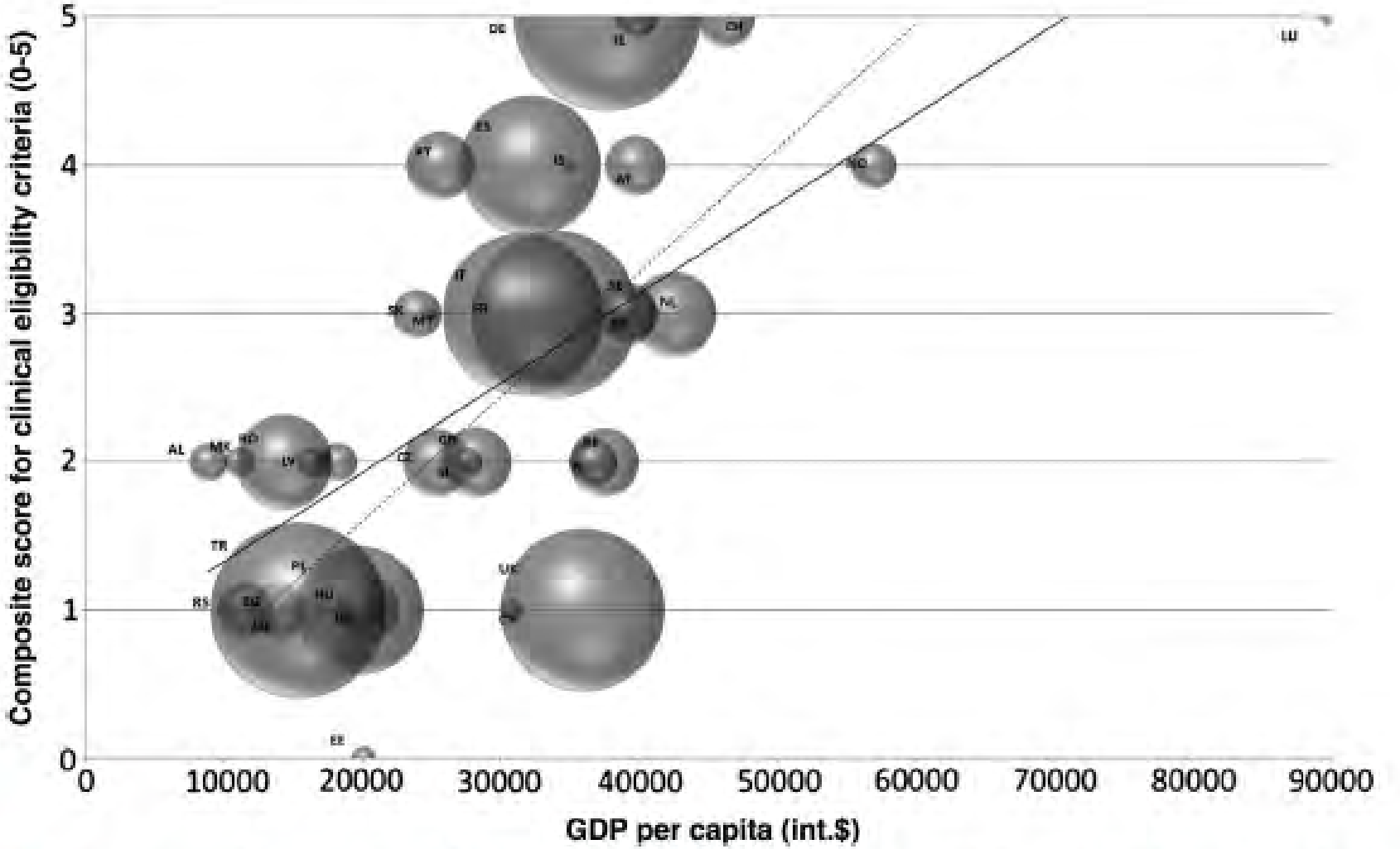


Figure 2 Composite score for restrictiveness of clinical criteria (0–5) and GDP per capita (int$), n=36. Size of the bubble is proportional to the population size of each country. Dashed trend line is added to show the linear trend if without data from Luxemburg, which can be considered an outlier GDP, gross domestic product.

AL, Albania; AT, Austria; BE, Belgium; BG, Bulgaria; HR, Croatia; CY, Cyprus; CZ, Czech Republic; EE, Estonia; FI, Finland; FR, France; DE, Germany; DK, Denmark; GR, Greece; HU, Hungary; IS, Iceland; IE, Ireland; IT, Italy; LV, Latvia; LT, Lithuania; LU, Luxemburg; MK, Macedonia; MT, Malta; ME, Montenegro; NL, the Netherlands; NO, Norway; PL, Poland; PT, Portugal; RO, Romania; RS, Serbia; SK, Slovakia; SL, Slovenia; ES, Spain; SE, Sweden; CH, Switzerland; TR, Turkey; UK, United Kingdom.

Polina P et al Ann Rheum Dis 2014;73:2010-21

Two Main Questions

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

Clinical and epidemiological research

OPEN ACCESS

EXTENDED REPORT

A randomised, double-blind, parallel-group study to demonstrate equivalence in efficacy and safety of CT-P13 compared with innovator infliximab when coadministered with methotrexate in patients with active rheumatoid arthritis: the PLANETRA study

Dae Hyun Yoo,[1] Pawel Hrycaj,[2] Pedro Miranda,[3] Edgar Ramiterre,[4] Mariusz Piotrowski,[5] Sergii Shevchuk,[6] Volodymyr Kovalenko,[7] Nenad Prodanovic,[8] Mauricio Abello-Banfi,[9] Sergio Gutierrez-Ureña,[10] Luis Morales-Olazabal,[11] Michael Tee,[12] Renato Jimenez,[13] Omid Zamani,[14] Sang Joon Lee,[15] HoUng Kim,[16] Won Park,[17] Ulf Müller-Ladner[18]

Clinical and epidemiological research

OPEN ACCESS

EXTENDED REPORT

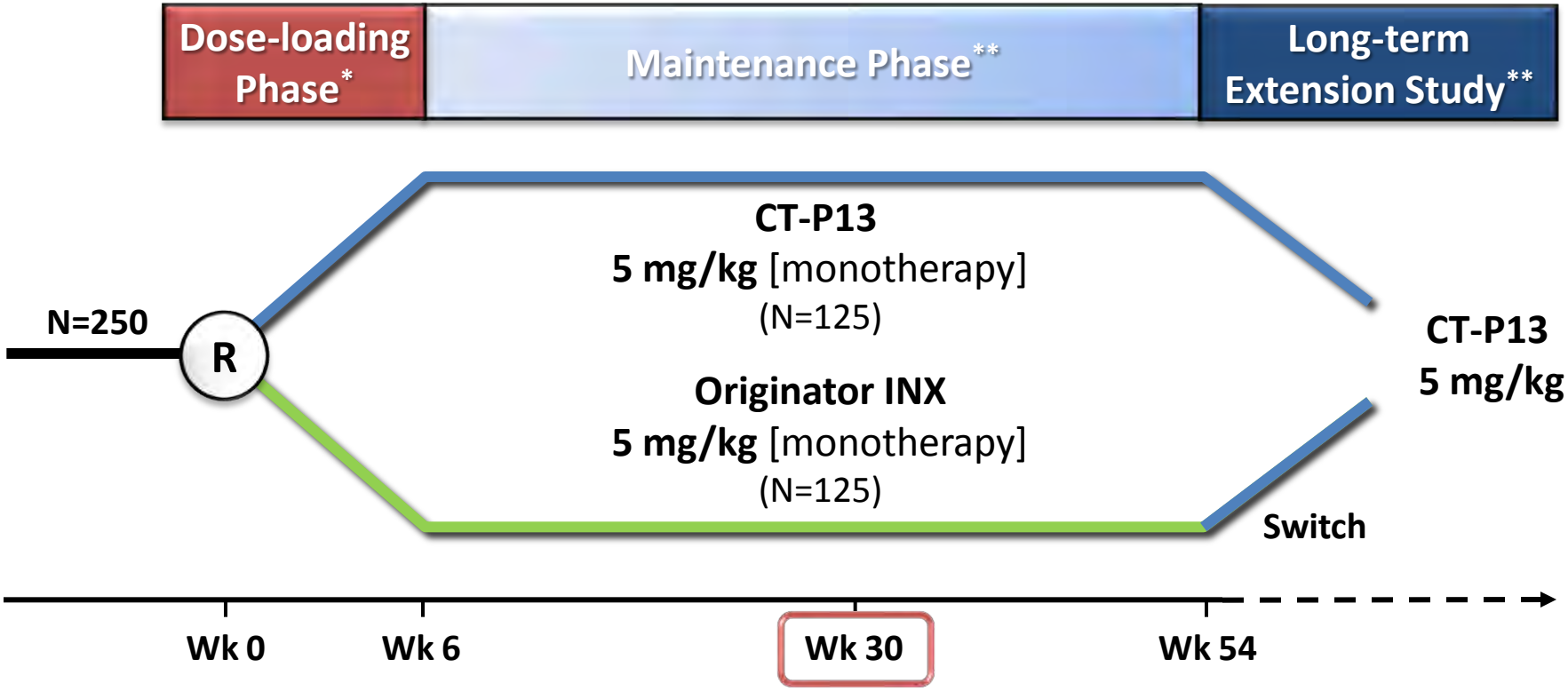
A randomised, double-blind, multicentre, parallel-group, prospective study comparing the pharmacokinetics, safety, and efficacy of CT-P13 and innovator infliximab in patients with ankylosing spondylitis: the PLANETAS study

Won Park,[1] Pawel Hrycaj,[2] Slawomir Jeka,[3] Volodymyr Kovalenko,[4] Grygorii Lysenko,[5] Pedro Miranda,[6] Helena Mikazane,[7] Sergio Gutierrez-Ureña,[8] MieJin Lim,[1] Yeon-Ah Lee,[9] Sang Joon Lee,[10] HoUng Kim,[11] Dae Hyun Yoo,[12] Jürgen Braun[13]

Yoo DH, et al. *Ann Rheum Dis* 2013;72:1613-1620.
Park W, et al. *Ann Rheum Dis* 2013;72:1605-1612.

CT-P13 Phase 1 Pharmacokinetic Equivalence Trial in AS: Study Schematic

Randomised double-blind study in patients with AS



*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 PK Study in AS: PK Analysis

The PK profiles of CT-P13 and the originator INX are equivalent in terms of AUC_T and $C_{max, ss}$

Dose 5 (Week 22)

Parameter	Treatment	N	Geometric Mean	Ratio (%) of Geometric Means	90% CI of Ratio (%)
AUC_τ (µg*h/mL)	**CT-P13** (5 mg/kg) **Originator INX** (5 mg/kg)	**111** **110**	**32,765.51** **31,475.68**	**104.10**	(93.93–115.36)
$C_{max,ss}$ (µg/mL)	**CT-P13** (5 mg/kg) **Originator INX** (5 mg/kg)	**112** **110**	**146.94** **144.81**	**101.47**	(94.57–108.86)

Pre-defined bioequivalence acceptance range:
80% – 125%

Source: EMA Inflectra EPAR, June 2013.

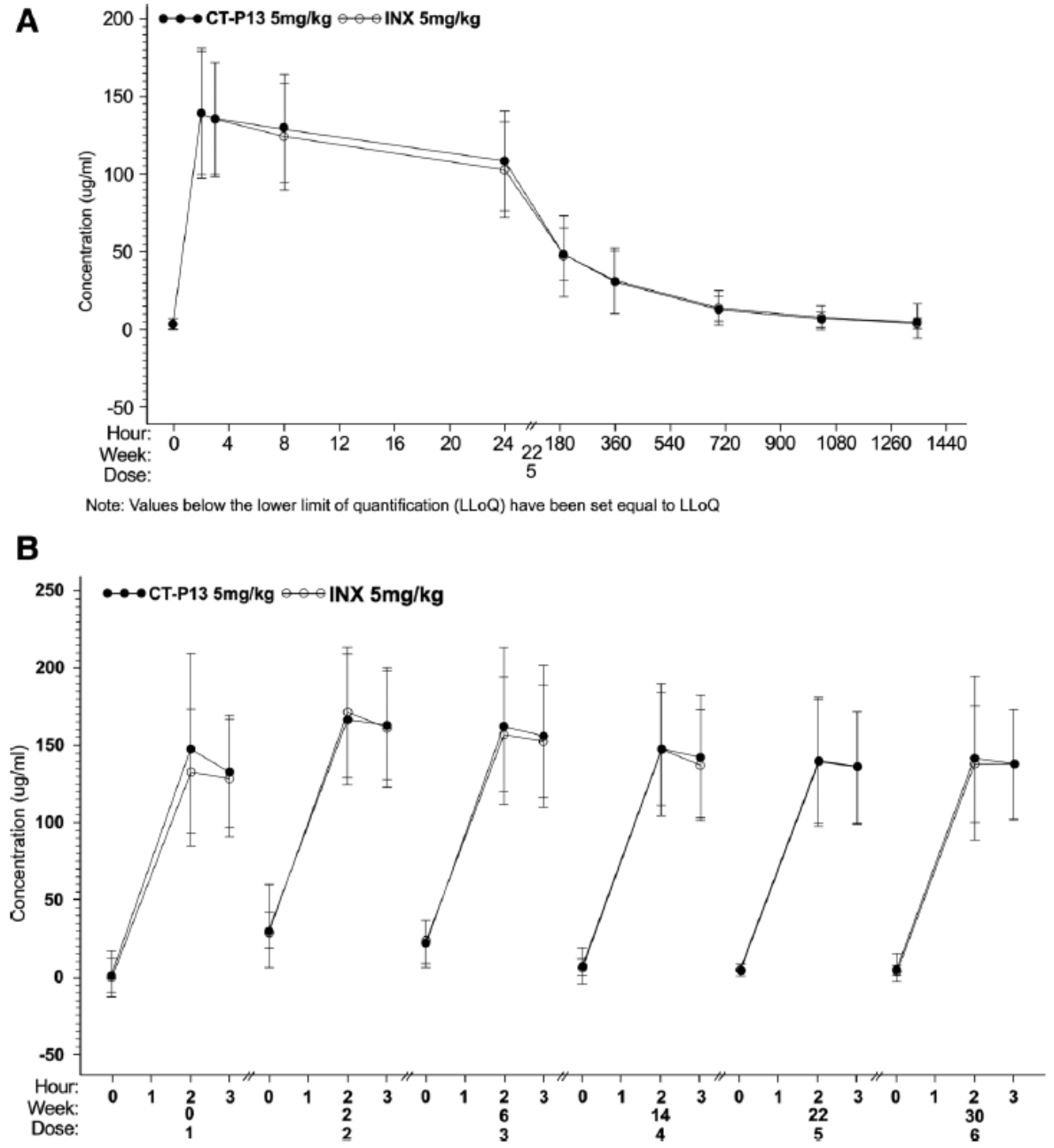


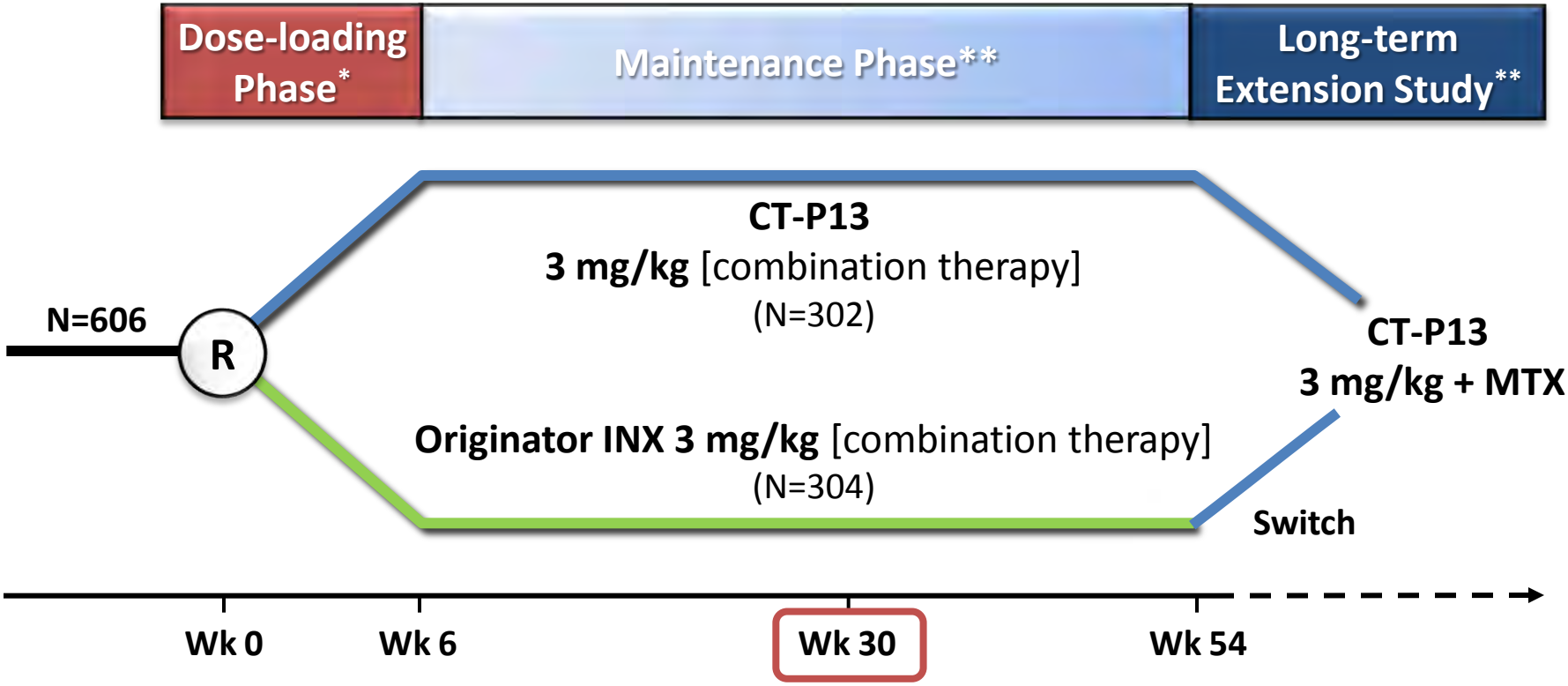
Figure 2 Mean (±SD) serum concentrations of innovator infliximab (INX) and CT-P13 versus time by treatment. Serum concentration of drug was measured using a flow-through immunoassay platform (GyrolabxP). Mean serum drug concentration profiles of CT-P13 and INX were plotted by treatment on scheduled sample times. (A) Mean serum drug concentration following administration of Dose 5 (10 scheduled sample times between weeks 22 and 30) of CT-P13 (5 mg/kg) or INX (5 mg/kg). (B) Mean serum drug concentration of CTP13 and INX following administration of Doses 1–6. Blood samples were obtained 15 min prior to infusion, at the end of the infusion and 1 h postinfusion.

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

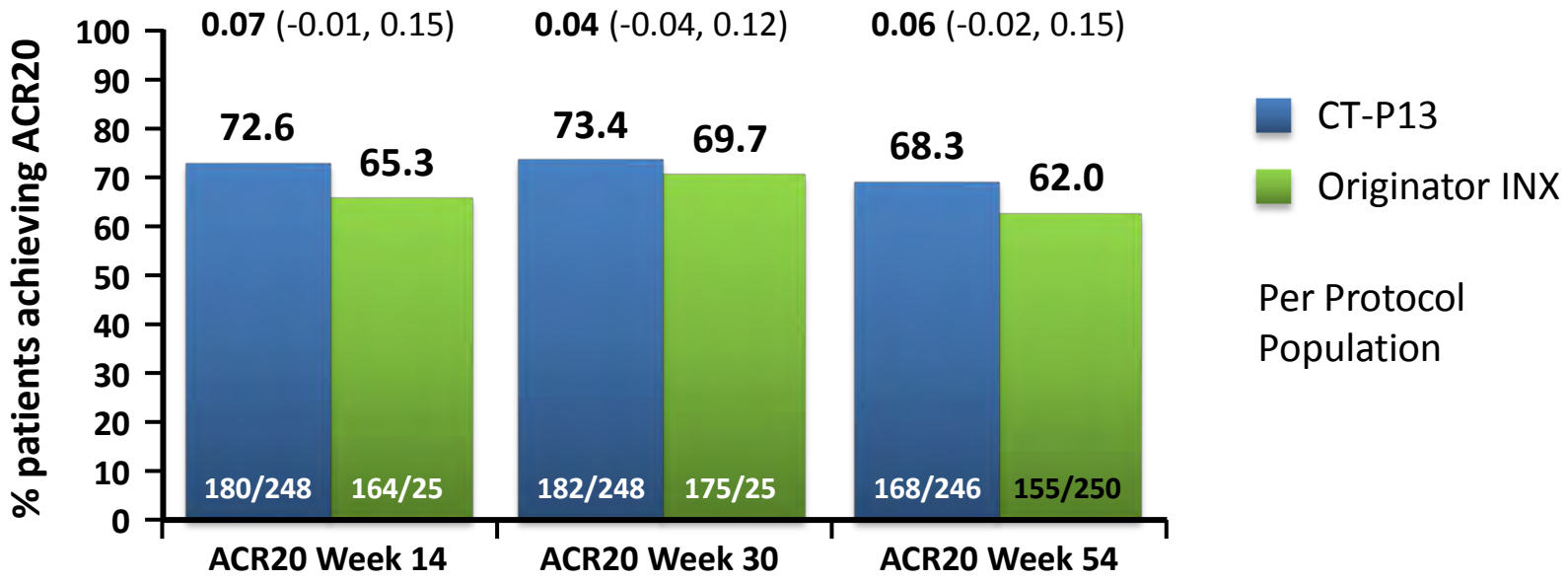


*Doses at weeks 0, 2 and 6 by 2-hr IV infusion.
**Doses every 8 weeks up to 54 weeks by 2-hr IV infusion.

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)



Primary endpoint:	**-15**	**Equivalence margin**		**+15**
ACR at Week 30:		**-4**	**CT-P13 result**	**+12**
ACR at Week 54:		**-2**	**CT-P13 result**	**+15**

Source: EMA Inflectra EPAR, June 2013

Clinical and epidemiological research

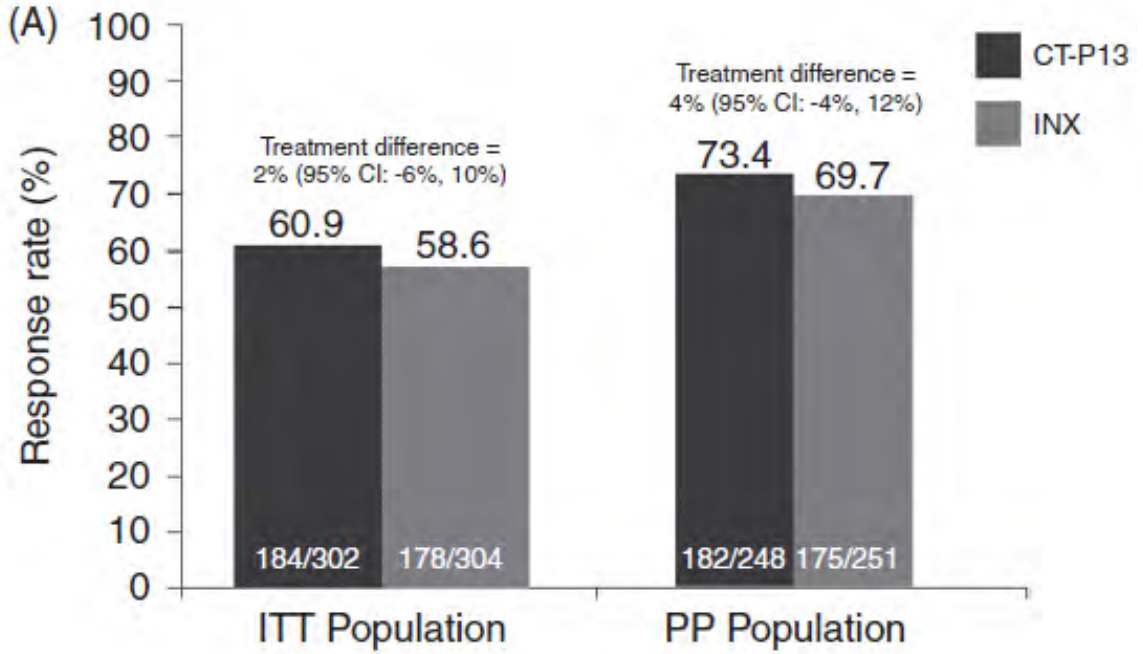
OPEN ACCESS

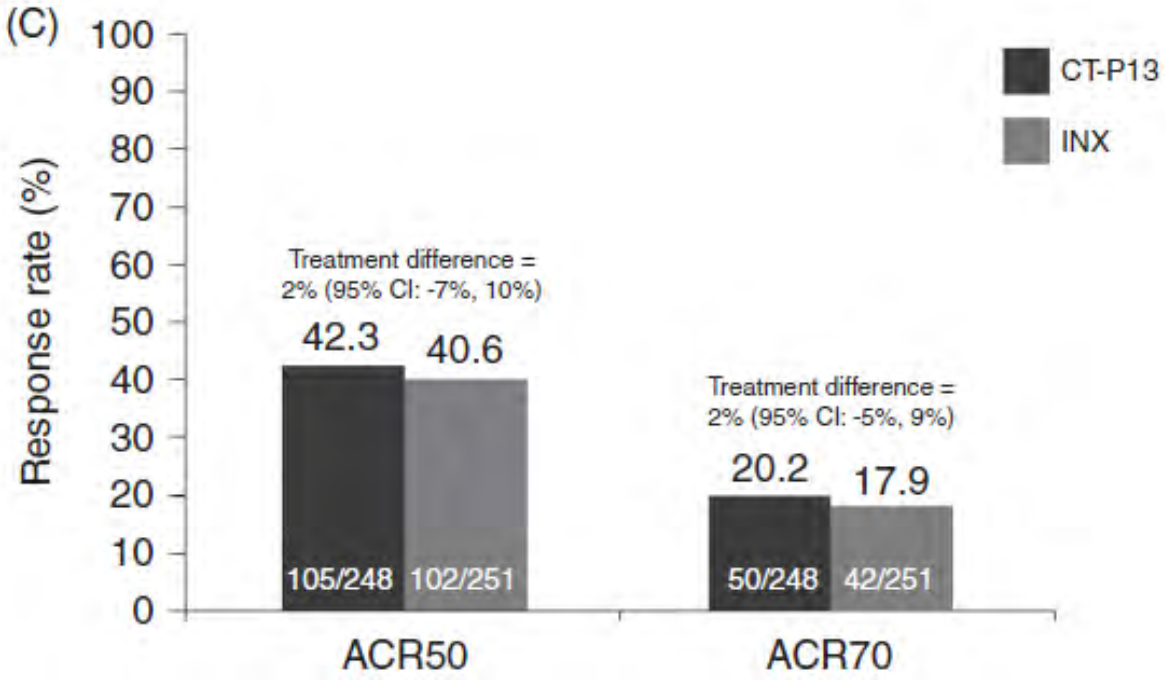
EXTENDED REPORT

A randomised, double-blind, parallel-group study to demonstrate equivalence in efficacy and safety of CT-P13 compared with innovator infliximab when coadministered with methotrexate in patients with active rheumatoid arthritis: the PLANETRA study

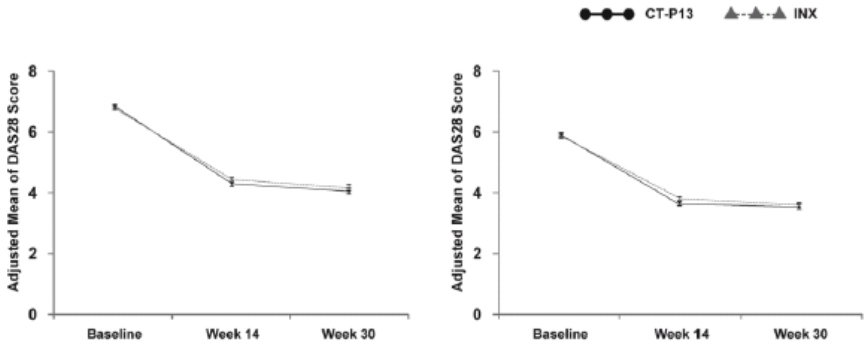
Dae Hyun Yoo,[1] Pawel Hrycaj,[2] Pedro Miranda,[3] Edgar Ramiterre,[4] Mariusz Piotrowski,[5] Sergii Shevchuk,[6] Volodymyr Kovalenko,[7] Nenad Prodanovic,[8] Mauricio Abello-Banfi,[9] Sergio Gutierrez-Ureña,[10] Luis Morales-Olazabal,[11] Michael Tee,[12] Renato Jimenez,[13] Omid Zamani,[14] Sang Joon Lee,[15] HoUng Kim,[16] Won Park,[17] Ulf Müller-Ladner[18]

Primary →





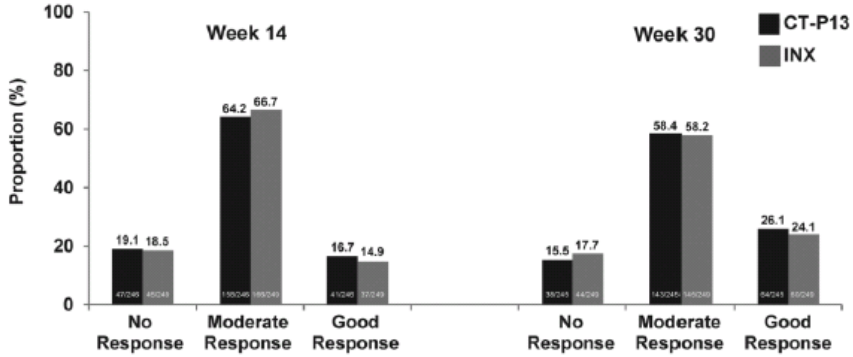
(A)



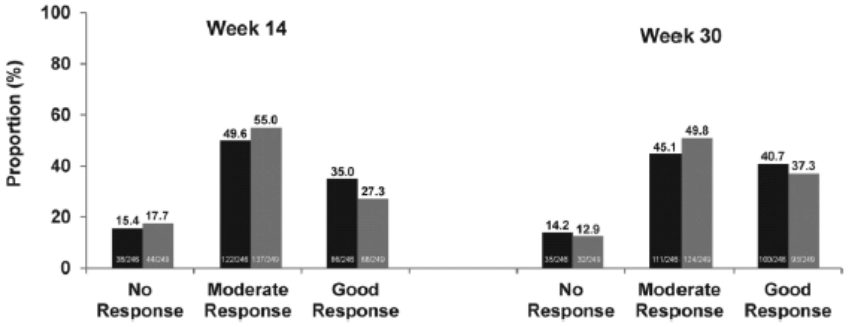
No. of Patients	Baseline	Week 14	Week 30
CT-P13	247	246	245
INX	251	249	249

No. of Patients	Baseline	Week 14	Week 30
CT-P13	248	246	246
INX	251	249	249

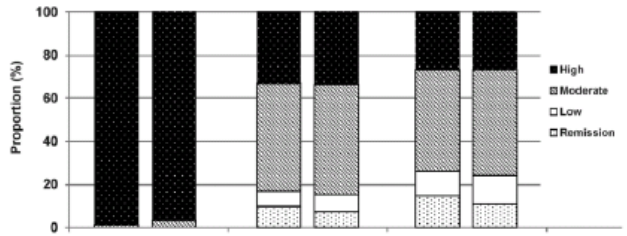
(B) EULAR (ESR)



EULAR (CRP)

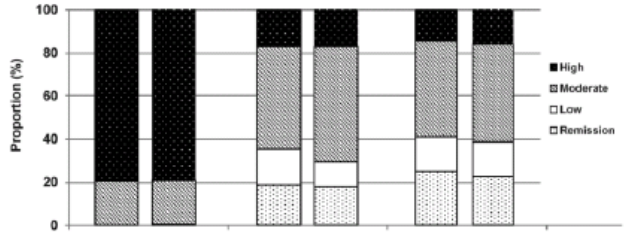


(C) DAS28 (ESR)



	Baseline		Week 14		Week 30	
	CT-P13	INX	CT-P13	INX	CT-P13	INX
High	243	243	82	84	66	67
Moderate	3	8	123	127	115	122
Low	0	0	17	20	28	33
Remission	0	0	24	18	36	27

DAS28 (CRP)



	Baseline		Week 14		Week 30	
	CT-P13	INX	CT-P13	INX	CT-P13	INX
High	196	199	42	43	35	40
Moderate	51	51	117	133	110	113
Low	0	1	41	29	40	40
Remission	0	0	46	44	61	56

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

OPEN ACCESS

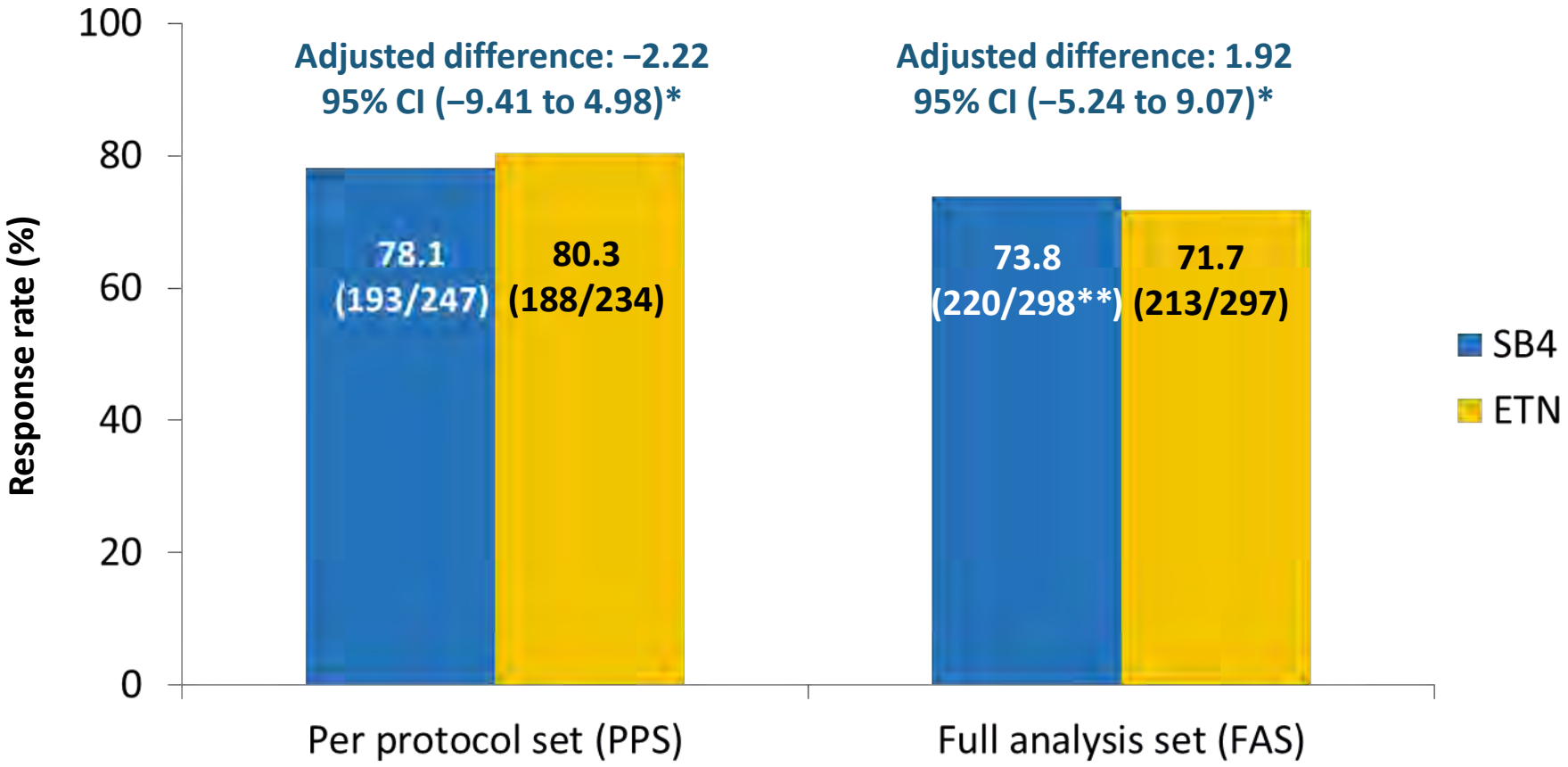
EXTENDED REPORT

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* Published Online First: [*please include* Day Month Year] doi:10.1136/annrheumdis-2015-207588

ACR20 Response Rate at Week 24 Equivalent between SB4 and ETN



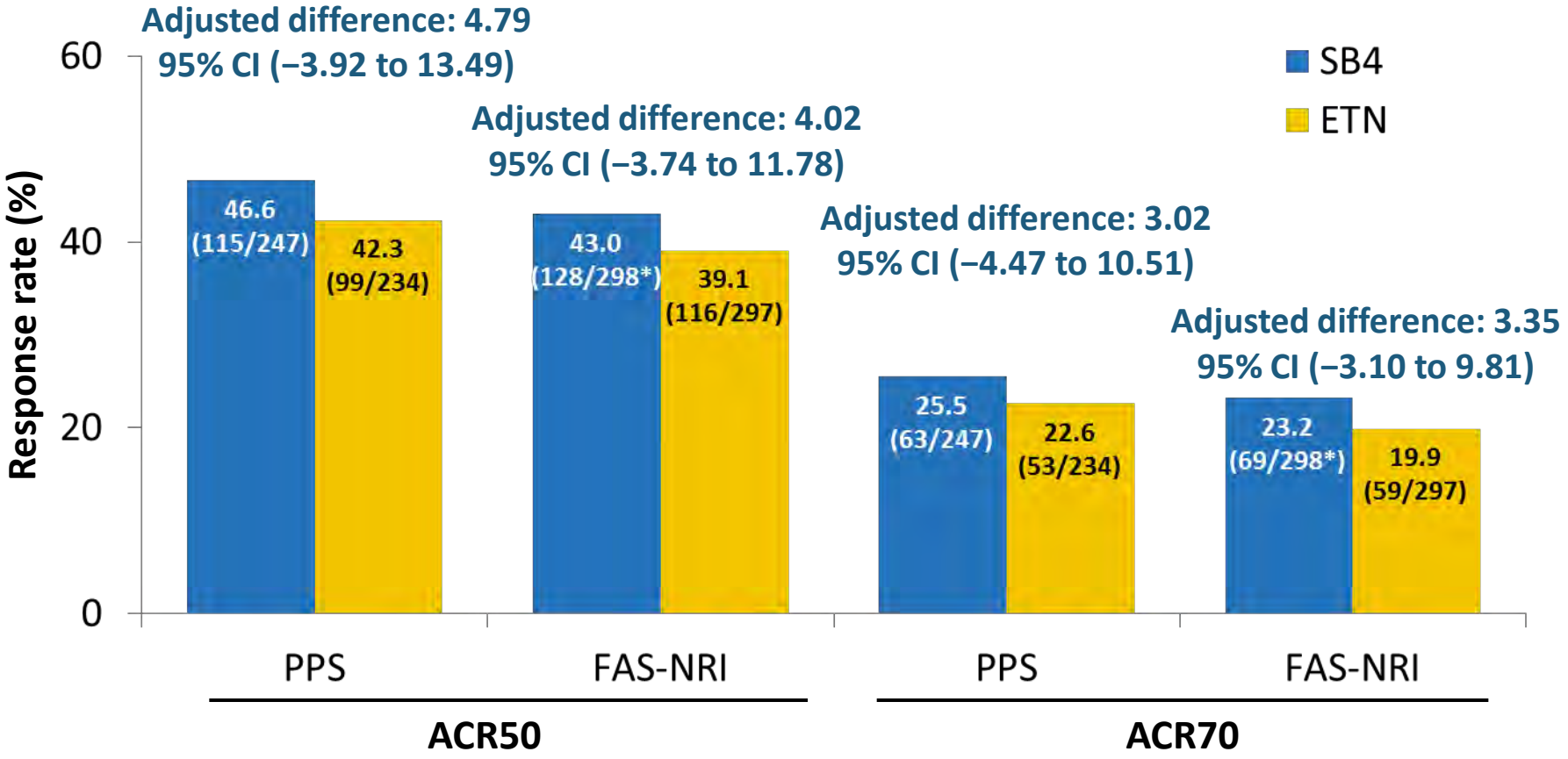
* Predefined equivalence margin -15% to 15%

**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.

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

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]

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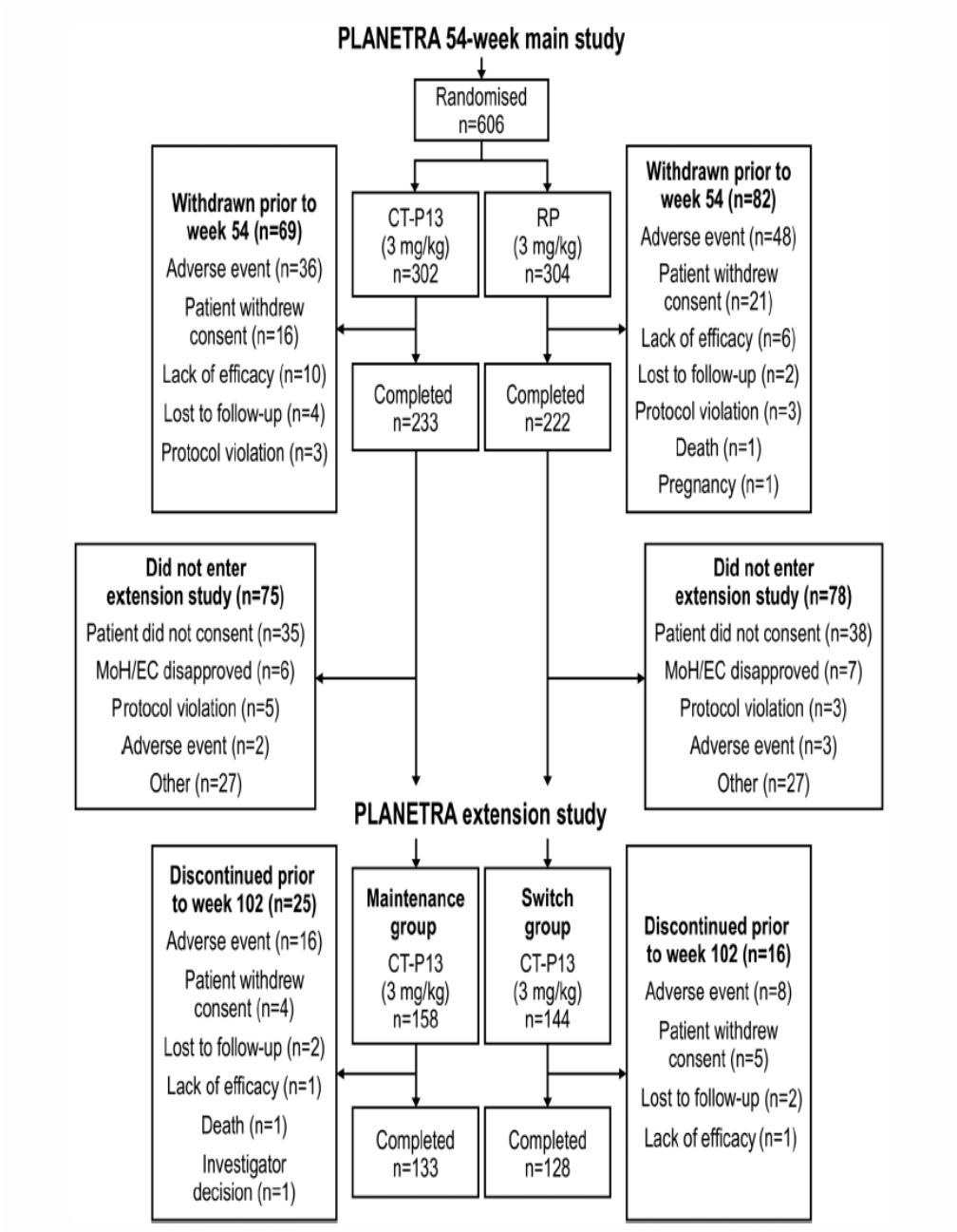
EXTENDED REPORT

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.

PLANETAS Extension Study

Safety

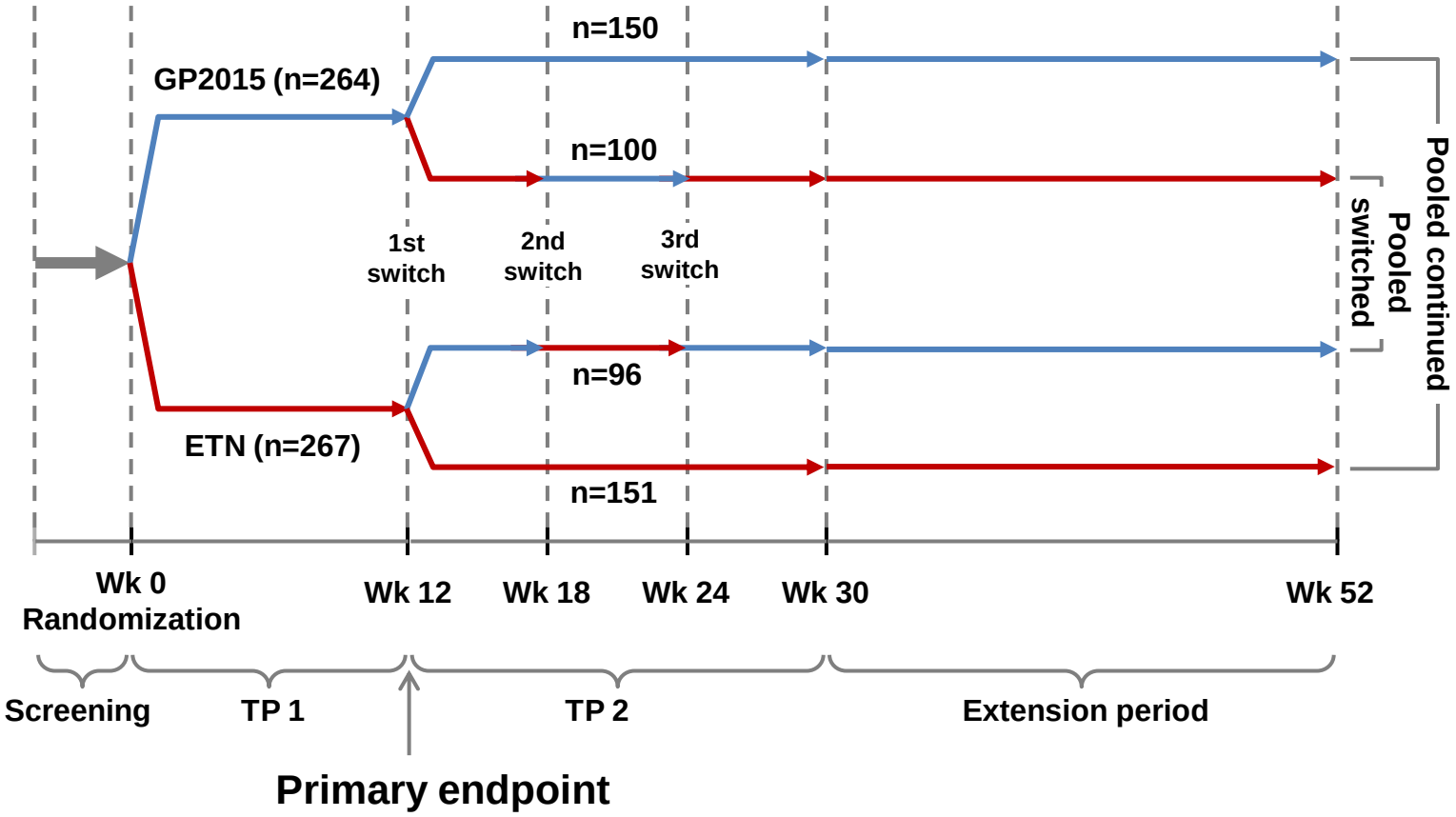
The proportion of patients who experienced at least one TEAE was 48.9% (n=44 of 90) in the maintenance group and 71.4% (n=60 of 84) in the switch group during the extension study, and 70.0% (n=63) and 61.9% (n=52) during the main study.

Table 4 Treatment-related TEAEs reported in at least 1% of patients in total, n (%) (safety population)

TEAE	Maintenance group* (n=90)	Switch group† (n=84)	Total (N=174)
Main study period			
Abnormal liver function test	9 (10.0)	8 (9.5)	17 (9.8)
Upper respiratory tract infection	8 (8.9)	6 (7.1)	14 (8.0)
Infusion-related reaction	4 (4.4)	7 (8.3)	11 (6.3)
Latent tuberculosis	6 (6.7)	3 (3.6)	9 (5.2)
Urinary tract infection	4 (4.4)	2 (2.4)	6 (3.4)
Neutropenia	3 (3.3)	2 (2.4)	5 (2.9)
Rash	2 (2.2)	3 (3.6)	5 (2.9)
Headache	3 (3.3)	1 (1.2)	4 (2.3)
Elevated serum creatine kinase	2 (2.2)	2 (2.4)	4 (2.3)
Sinusitis	2 (2.2)	1 (1.2)	3 (1.7)
Dizziness	1 (1.1)	1 (1.2)	2 (1.1)
Herpes virus infection	1 (1.1)	1 (1.2)	2 (1.1)
Hypertension	1 (1.1)	1 (1.2)	2 (1.1)
Weight increased	1 (1.1)	1 (1.2)	2 (1.1)
Leucopenia	0	2 (2.4)	2 (1.1)
Extension study period			
Infusion-related reactions	7 (7.8)	6 (7.1)	13 (7.5)
Abnormal liver function test	4 (4.4)	4 (4.8)	8 (4.6)
Latent tuberculosis	2 (2.2)	4 (4.8)	6 (3.4)
Upper respiratory tract infection	3 (3.3)	2 (2.4)	5 (2.9)
Elevated serum creatine kinase	2 (2.2)	1 (1.2)	3 (1.7)
Lower respiratory tract infection	2 (2.2)	1 (1.2)	3 (1.7)
Back pain	0	3 (3.6)	3 (1.7)
Cough	1 (1.1)	1 (1.2)	2 (1.1)
Hypophosphataemia	1 (1.1)	1 (1.2)	2 (1.1)
Tuberculosis	1 (1.1)	1 (1.2)	2 (1.1)
Weight decreased	1 (1.1)	1 (1.2)	2 (1.1)

Park W, et al. *Ann Rheum Dis* 2016. [Epub before print]. doi:10.1136/annrheumdis-2015-208783.

Study design – EGALITY study

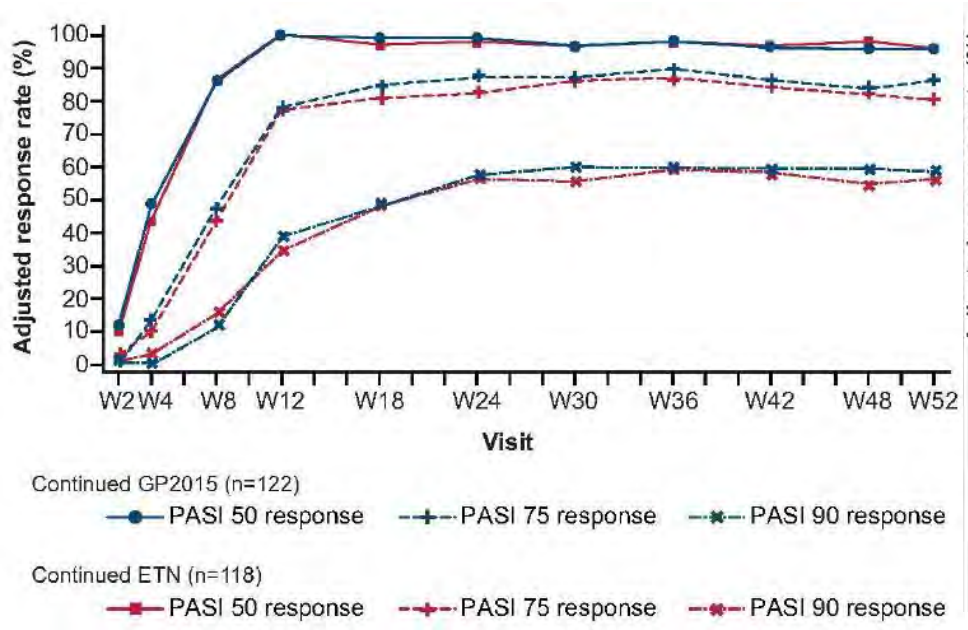


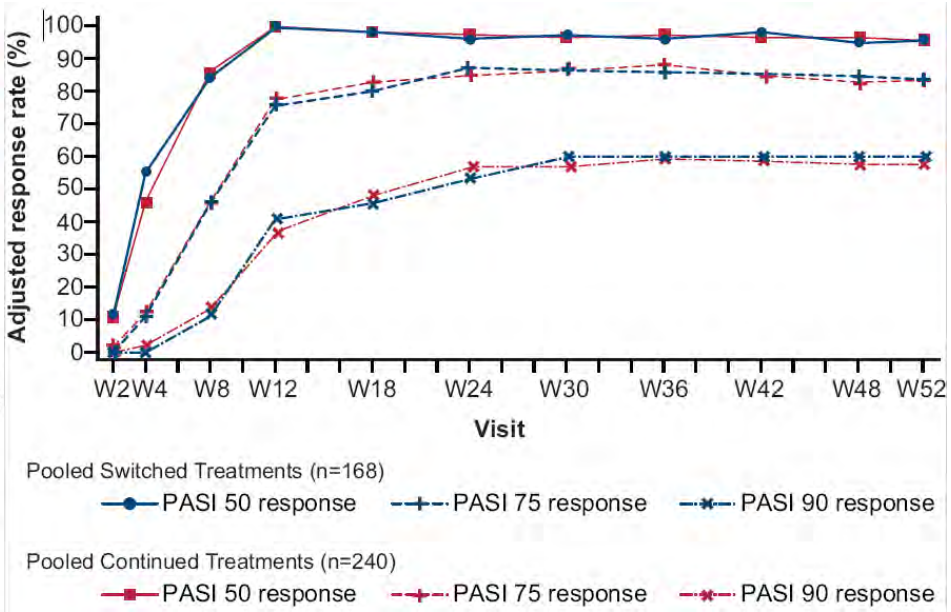
ETN, reference etanercept; TP, treatment period; Wk, week

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

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

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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)

Methods

Data from DANBIO were extracted regarding

1) Three months' disease activity and flare rates

- Disease activity

  ≈ 3 months before switch (pre-switch)

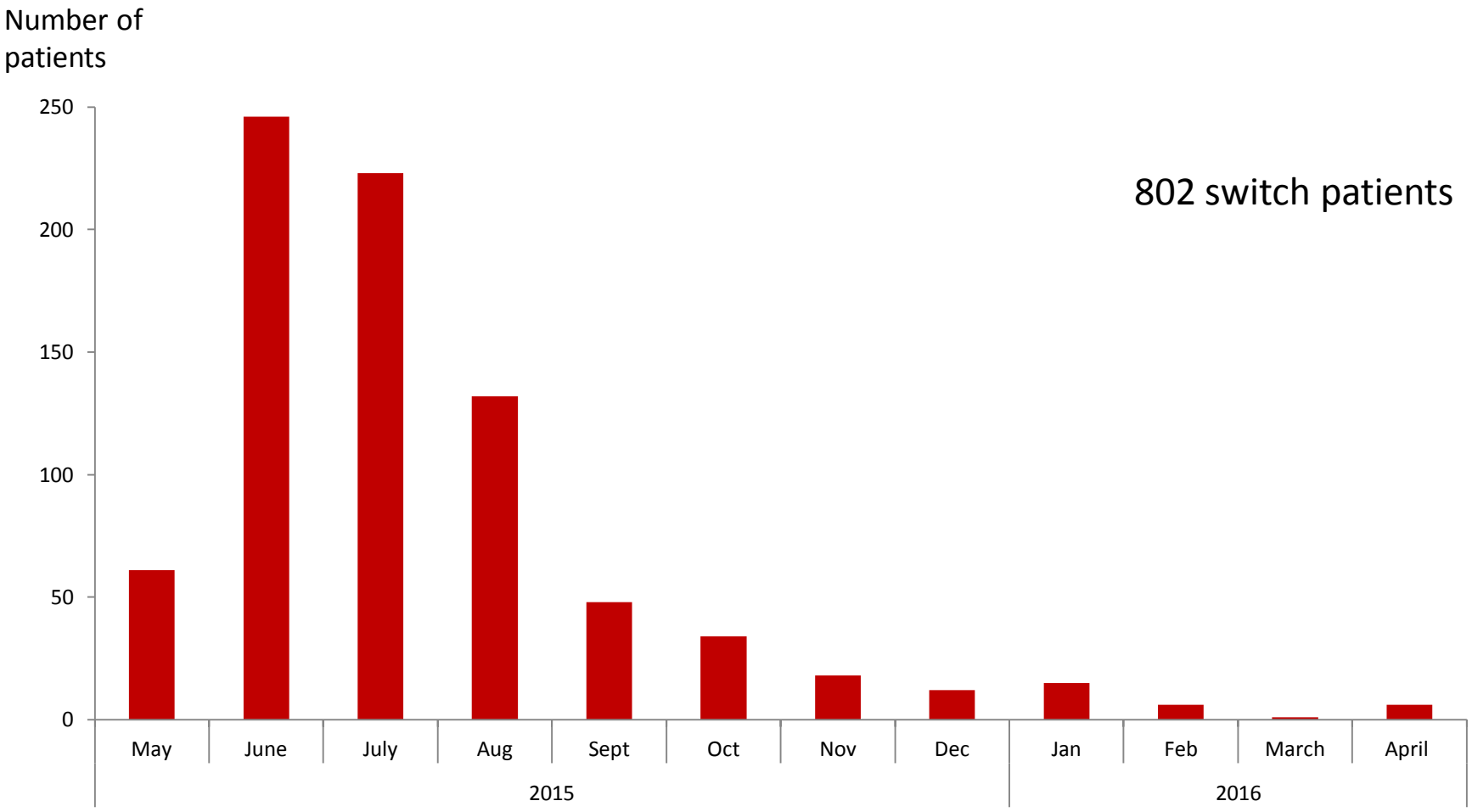
  At the time of switch

  ≈ 3 months after the switch (70-120 days) (post-switch)
- Changes in disease activity over time (Δpre-switch and Δpost-switch)
- Flare rates pre- and post-switch

2) Treatment retention for CT-P13

- Reasons for withdrawal
- Remsima retention rate compared to a historic cohort of Remicade treated patients

Date of infliximab switch, DANBIO



Baseline demographics

Patients switched from Remicade to Remsima		RA	PsA	AxSpA	Total
Number of patients, n		**403**	**120**	**279**	**802**
Women		70%	48%	26%	51%
Age, years		63	52	47	55
Number of comorbidities ≥ 1		25%	23%	17%	22%
Concomitant methotrexate		82%	69%	32%	62%
Start of Remicade, year, n (%)					
	2000-2004	19%	9%	13%	15%
	2005-2009	50%	48%	48%	49%
	2010-2015	31%	43%	39%	36%
Remsima dose, mg/kg		3.4	4.6	4.8	4.0
Remsima dose interval, weeks		8	7	8	8
Prior Remicade treatment duration, years		7.3	6.3	6.5	6.8

Numbers are medians unless otherwise stated
Remicade was the first biological drug in 76% of patients

Glintborg B, Sørensen IJ, Loft AG, et al.
Ann Rheum Dis, Online First May 8th 2017
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

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Withdrawal

- Median follow-up time after switching was 413 (339-442) days
- 132/802 patients (16%) stopped Remsima treatment
- Remicade treatment duration: 5.9 (2.9-9.2) years

Reason for Remsima withdrawal	Number of patients, n (%)
Lack of effect	71 (54)
Adverse events	37 (28)
Remission	5 (4)
Cancer	5 (4)
Death	2 (2)
Several reasons	3 (2)
Other reasons	8 (6)
Unknown	1 (1)
Total	132 (100)

Glintborg B, Sørensen IJ, Loft AG, et al.
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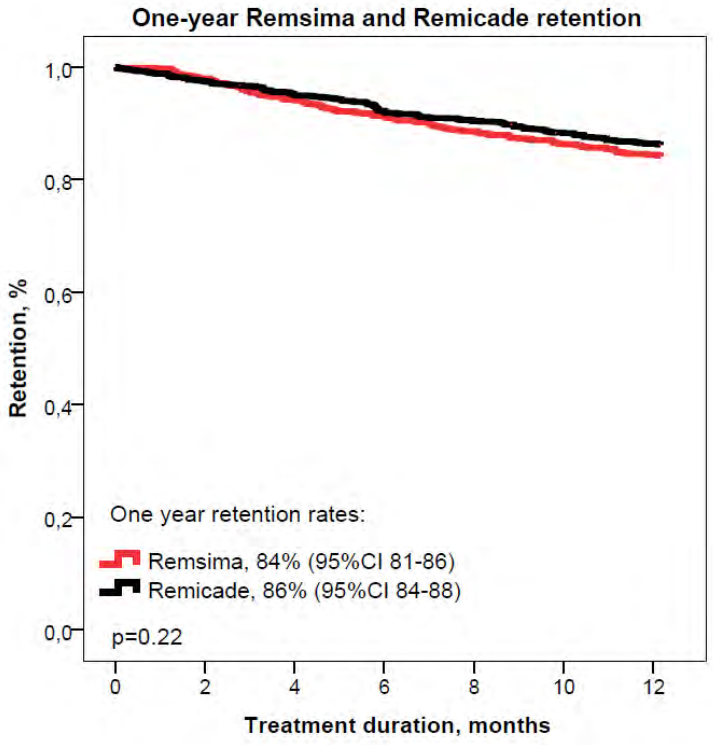
Retention of treatment

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



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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*

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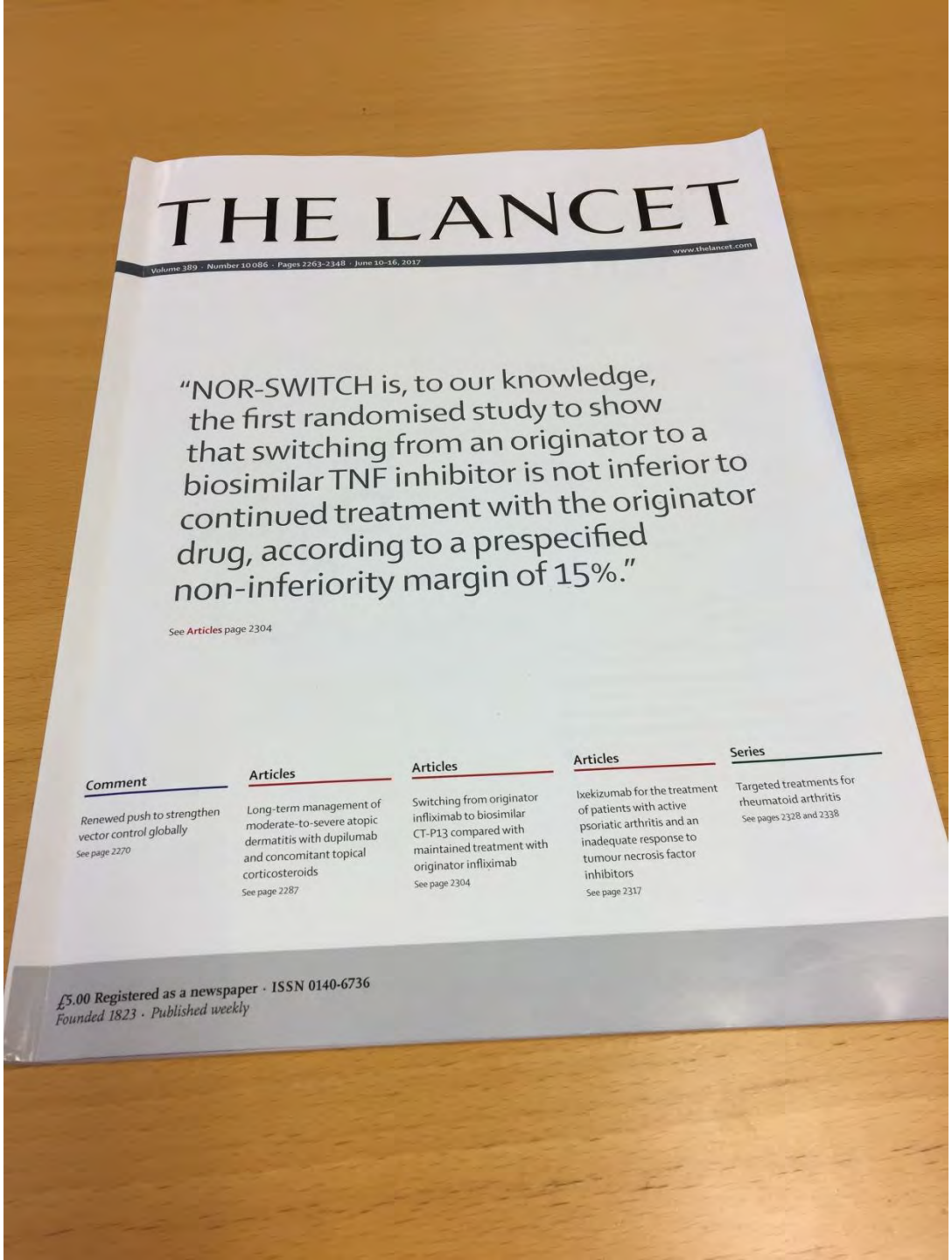
THE LANCET
Volume 389 · Number 10086 · Pages 2263–2348 · June 10–16, 2017
www.thelancet.com
"NOR-SWITCH is, to our knowledge, the first randomised study to show that switching from an originator to a biosimilar TNF inhibitor is not inferior to continued treatment with the originator drug, according to 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
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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

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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

Study Endpoints

Primary endpoint:

•Occurrence of **disease worsening** during the 52-week study period based on disease specific efficacy assessment scores

Secondary endpoints:

Generic:

•Time from randomization to disease worsening

•Patient and Physician Global assessment of disease activity

•Occurrence of drug discontinuation

•Time from randomization to drug discontinuation

Disease-specific:

•Inflammation assessed by biochemical parameters (CRP, faecal calprotectin)

•UC: Partial Mayo score, IBDQ

•CD: HBI, IBDQ

Exploratory endpoints:

•EQ-5D

•SF-36

•WPAI-GH

•Use of health care resources

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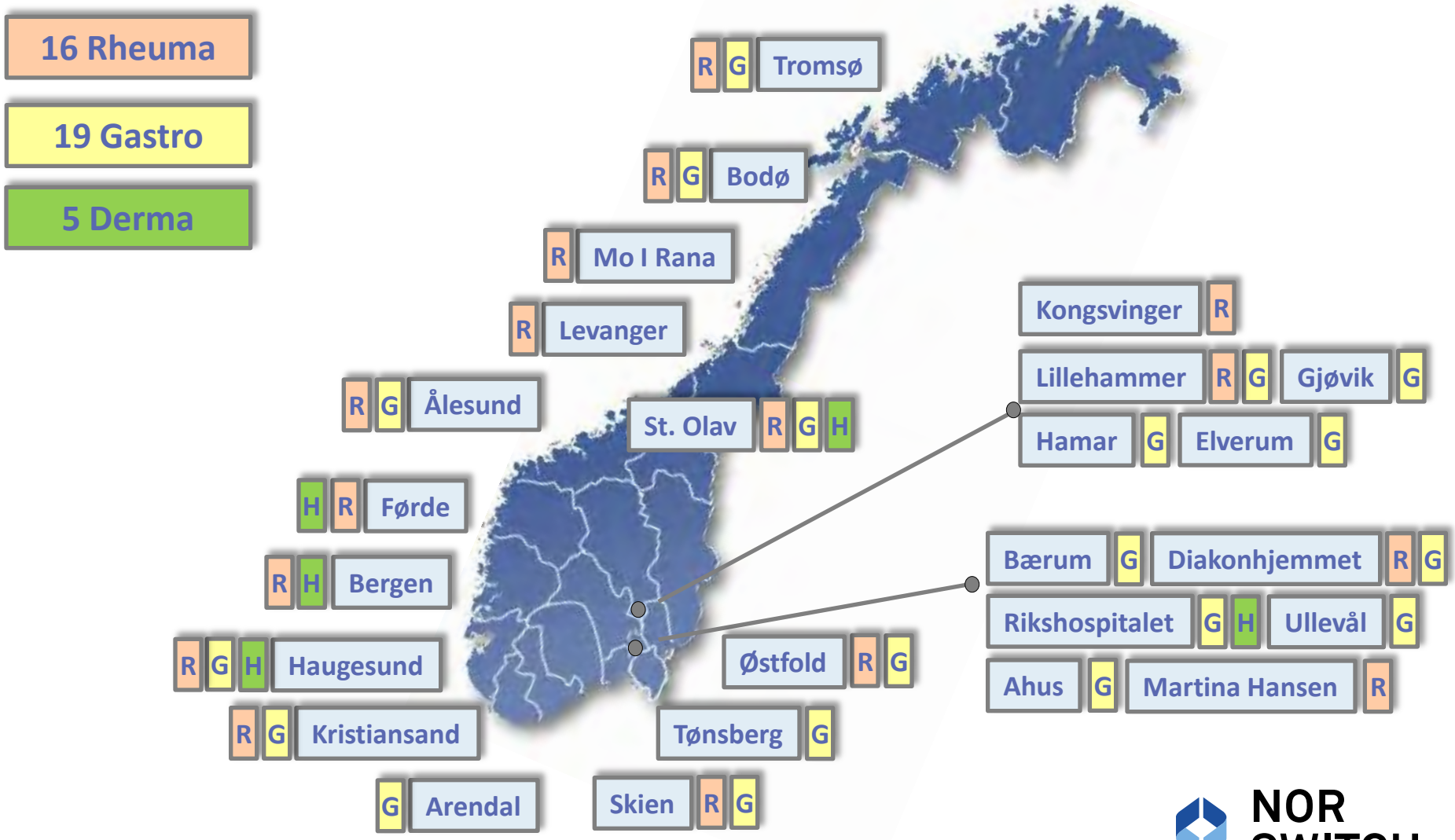
Table 1: The numbers in the cells represent the total number of patients needed in total. All calculations are based on a power of 80% and alpha 2.5%

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

National multi-center study n = 40



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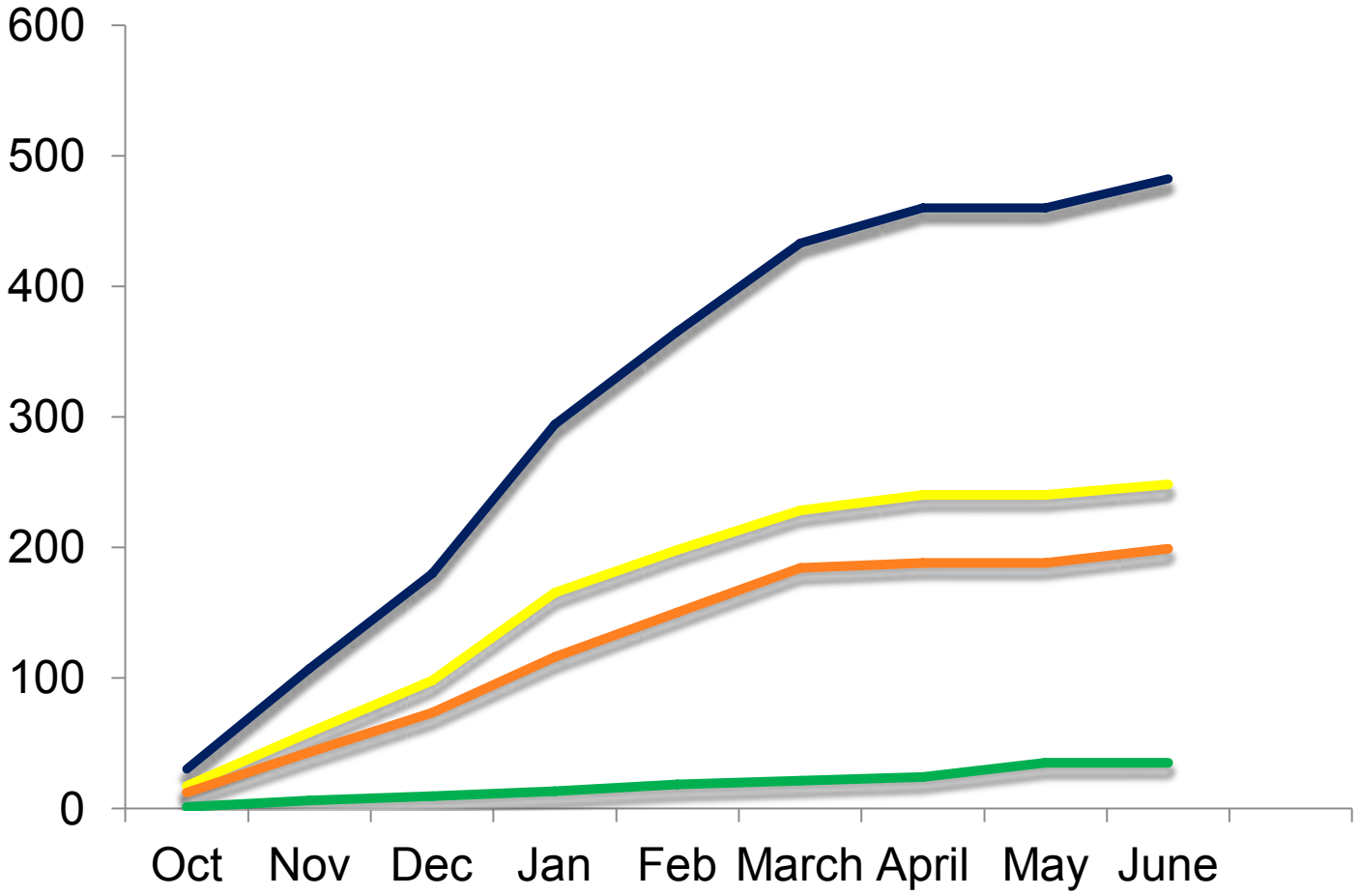
Randomized patients 2014–2015



482 in total

248 Gastro

199 Rheuma

35 Derma

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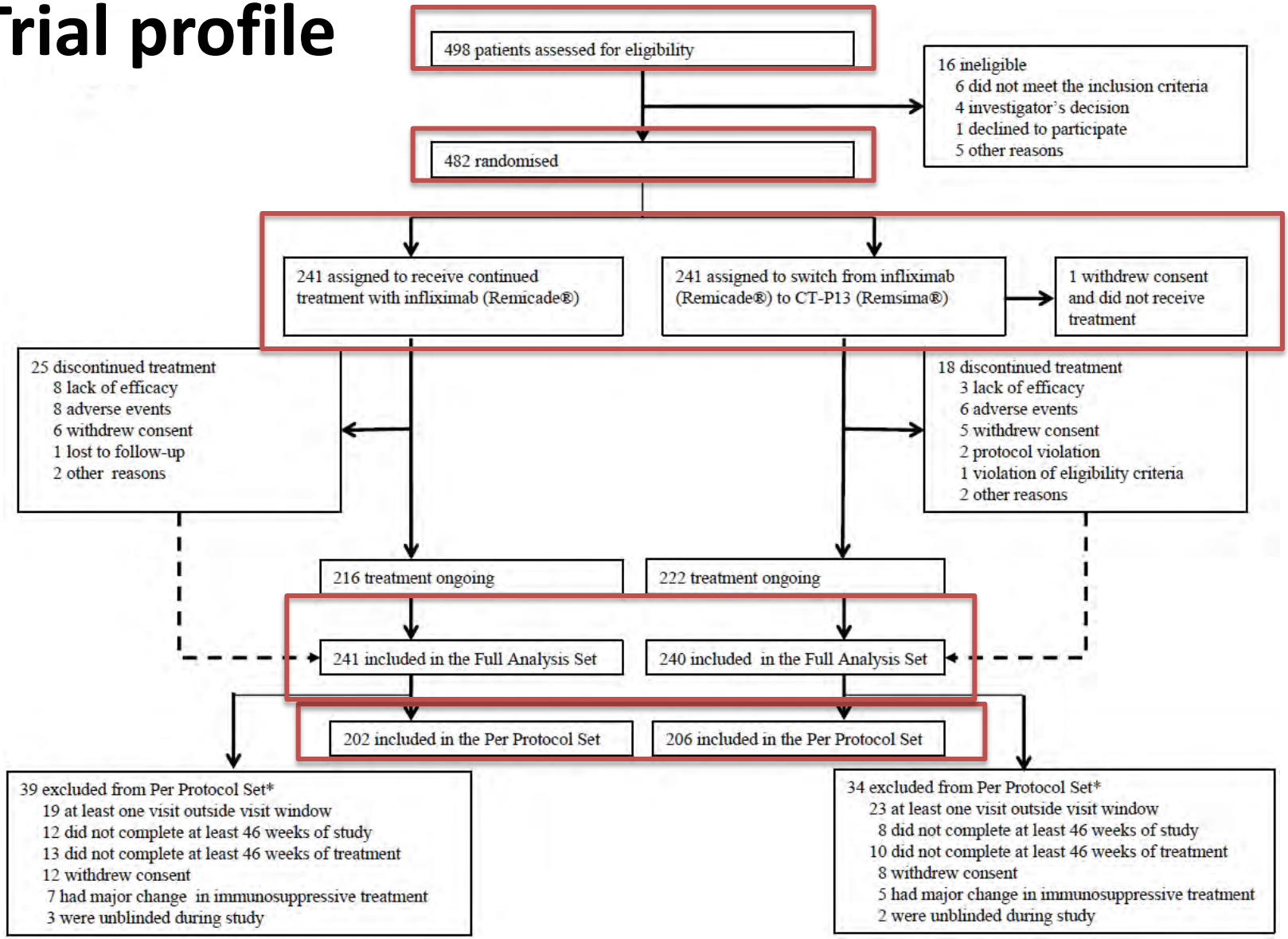
Trial profile



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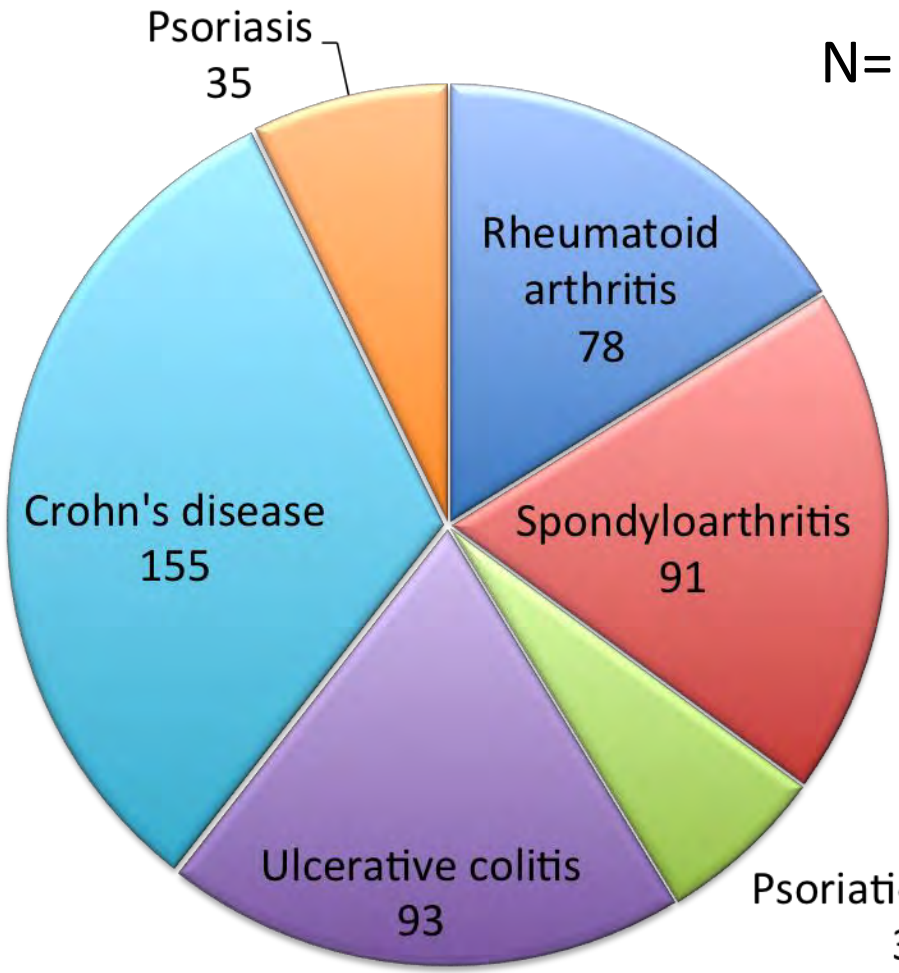
Kvien T. NOR-SWITCH Principal Investigator. Unpublished data.

Diagnosis distribution



N= 482

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Demographics and baseline characteristics

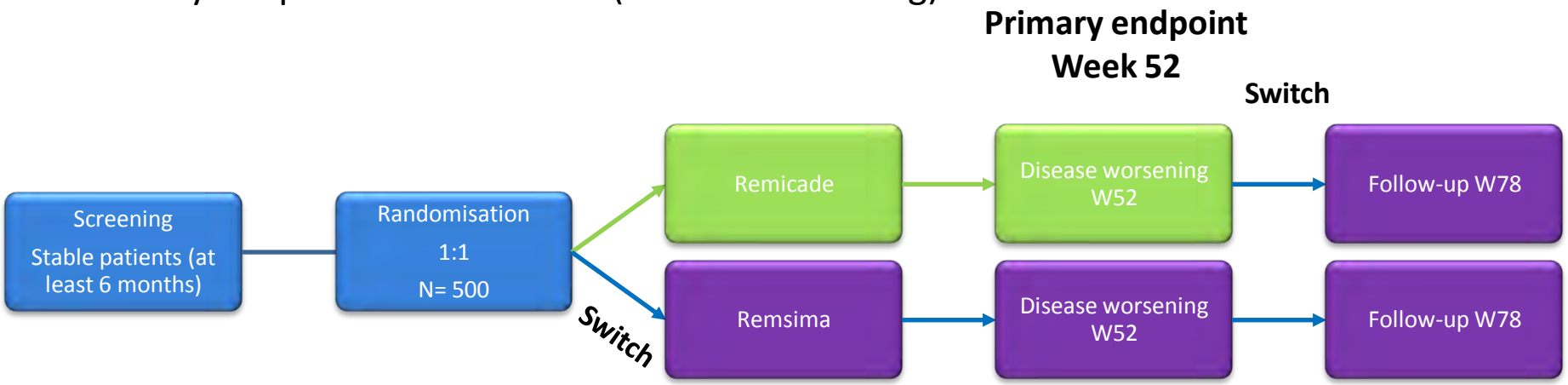
	INX (n=241)	CT-P13 (n=240)
Age (years)	47·5 (14·8)	48·2 (14·9)
Female	99 (41·1%)	87 (36·2%)
Disease duration (years)	16·7 (10·9)	17·5 (10·5)
Duration of ongoing INX treatment (years)	6·7 (3·6)	6·9 (3·8)
Previous therapy with biologics prior to INX		
TNFα inhibitors		
none	188 (78·0%)	188 (78·3%)
one	43 (17·8%)	40 (16·7%)
two	10 (4·1%)	9 (3·8%)
three or more	0 (0%)	3 (1·2%)
Other biologics	2 (0·8%)	1 (0·4%)
Concomitant immunosuppressive therapy *	113 (46·9%)	129 (53·8%)

* MXT, AZA, 6-MP, SASAP, leflunomide

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

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Results

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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

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Disease worsening

Diagnosis	INX (n= 202)	CT-P13 (n=206)	Rate difference (95% CI)
Crohns disease	14 (21.2%)	23 (36.5%)	-14.3% (-29.3 - 0.7%)
Ulcerative colitis	3 (9.1%)	5 (11.9%)	-2.6% (-15.2 - 10.0%)
Spondyloarthritis	17 (39.5%)	14 (33.3%)	6.3% (-14.5 - 27.2%)
Rhematoid arthritis	11 (36.7%)	9 (30.0%)	4.5% (-20.3 - 29.3%)
Psoriatic arthritis	7 (53.8%)	8 (61.5%)	-8.7% (-45.5 - 28.1%)
Psoriasis	1 (5.9%)	2 (12.5%)	-6.7% (-26.7 - 13.2%)
Overall	53 (26.2%)	61 (29.6%)	-4.4% (-12.7 - 3.9%)

CD: increase in HBI of ≥ 4 points and a HBI score of ≥ 7 points
UC: increase in p-Mayo score of ≥ 3 points and a p-Mayo score of ≥ 5 points

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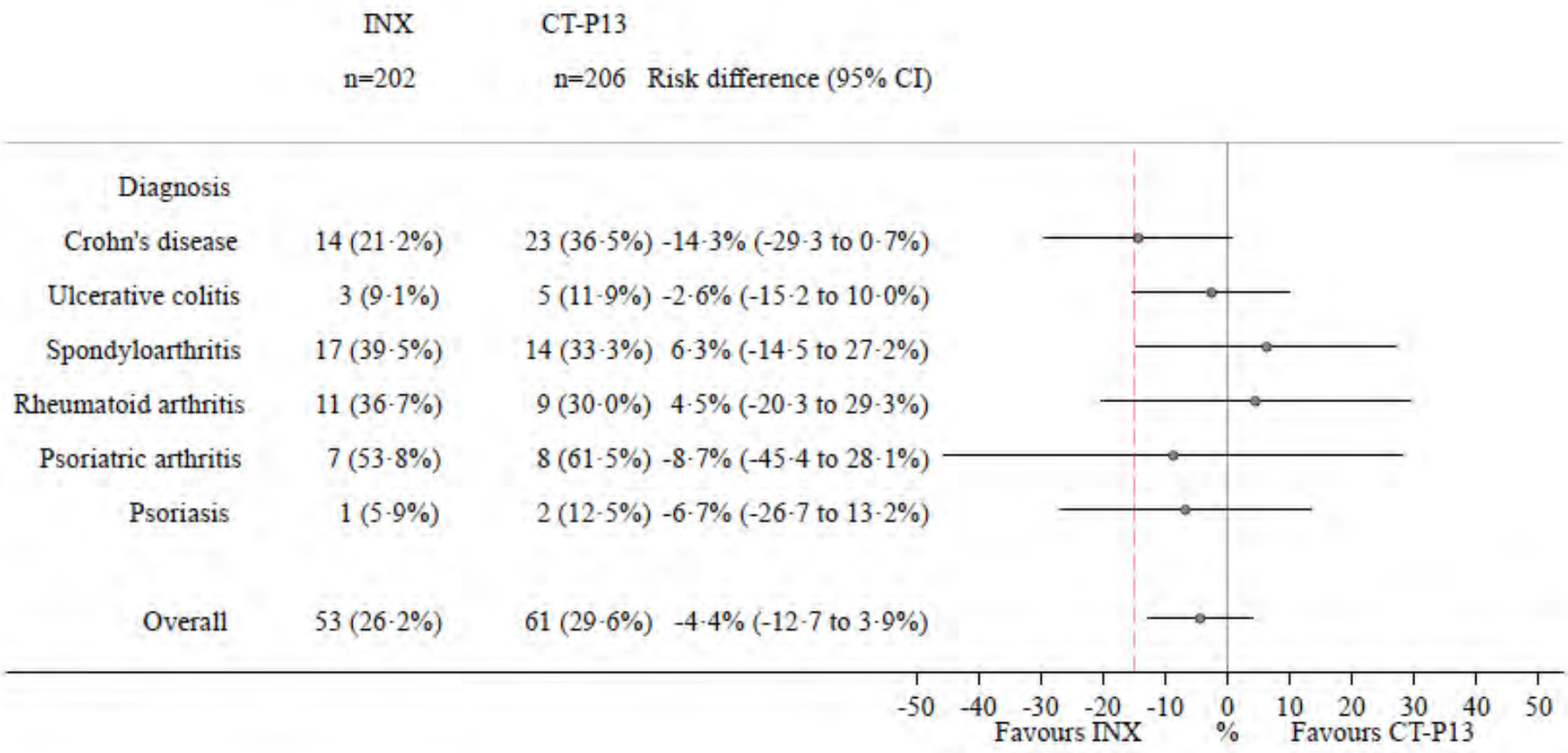
Disease Worsening



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Remission

Diagnosis	INX (n= 202)	CT-P13 (n=206)	Rate difference (95% CI)
Crohns disease	46 (69.7%)	41 (65.1%)	5.6% (-11.0 - 22.2%)
Ulcerative colitis	29 (87.9%)	39 (92.9%)	-5.9% (-21.7 - 9.9%)
Spondyloarthritis	10 (23.3%)	7 (16.7%)	7.2% (-11.2 - 25.5%)
Rhematoid arthritis	17 (56.7%)	19 (63.3%)	-9.8% (-33.5 - 13.9%)
Psoriatic arthritis	6 (46.2%)	6 (46.2%)	-1.8% (-39.9 - 36.3%)
Psoriasis	15 (88.2%)	14 (87.5%)	0.7% (-21.3 - 22.8%)
Overall	123 (60.9%)	126 (61.2%)	0.6% (-7.5 - 8.8%)

CD: HBI ≤ 4
UC: p-Mayo score ≤ 2

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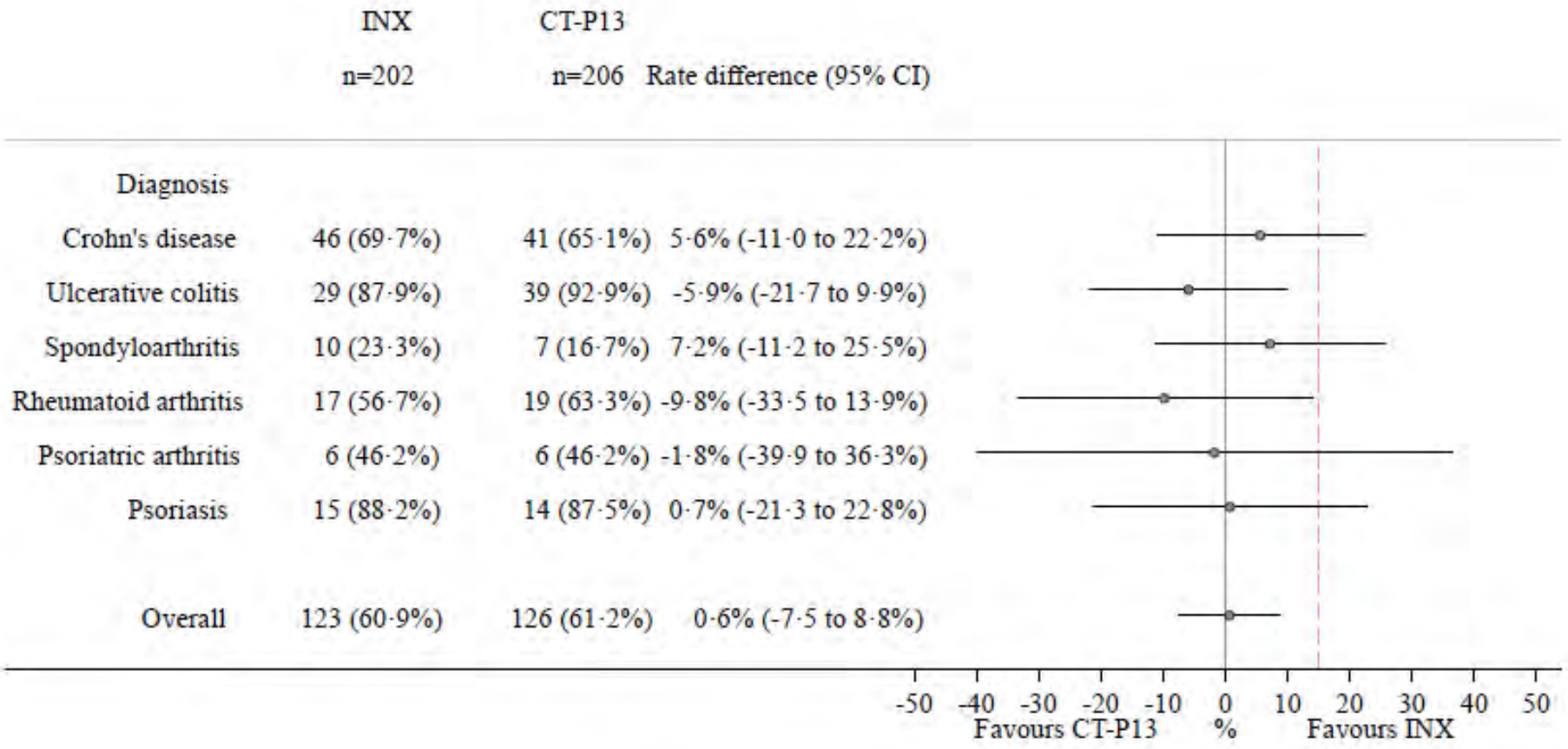
Remission



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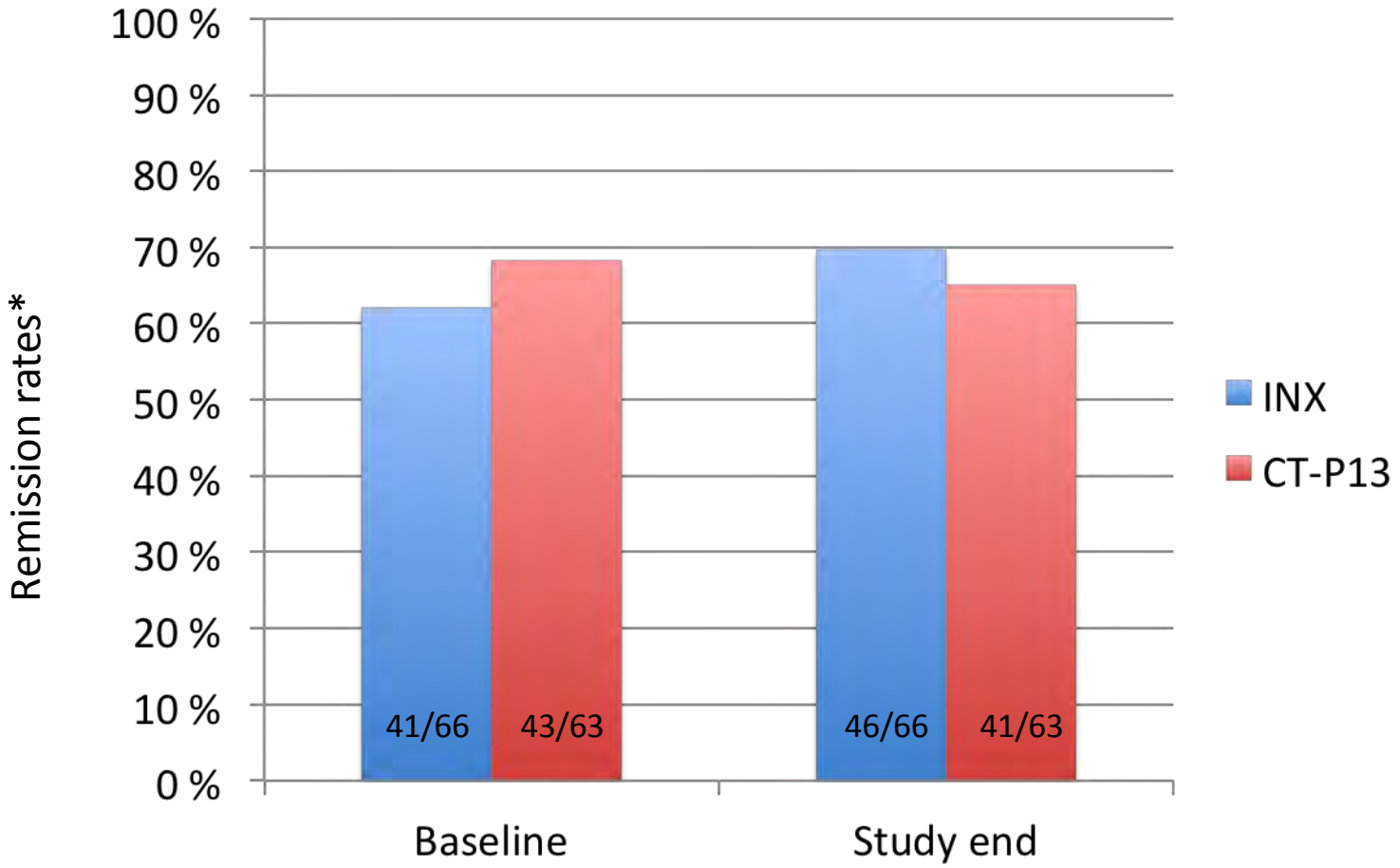
Crohns Disease



*Harvey Bradshaw Index ≤ 4

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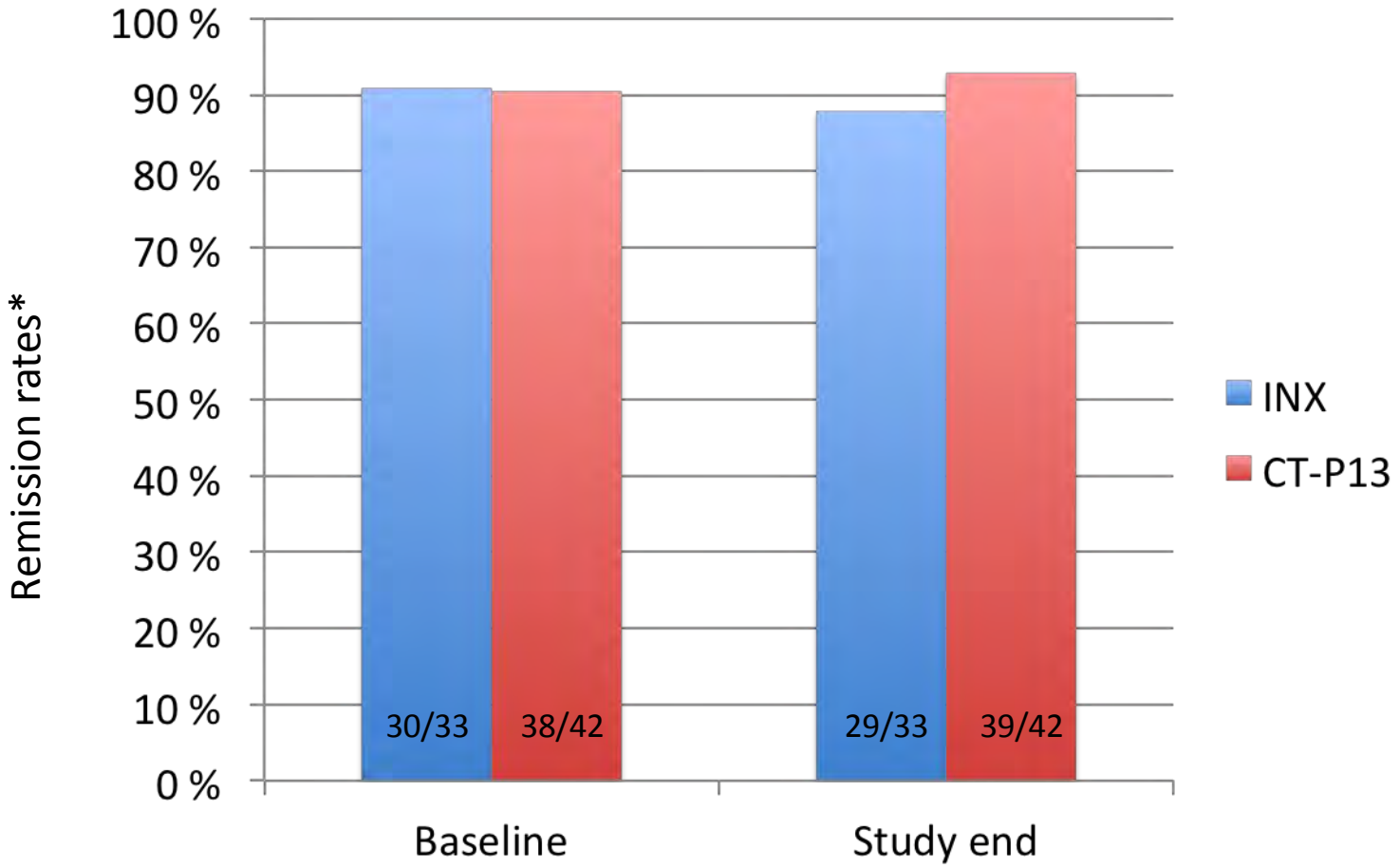
Ulcerative colitis



*p-Mayo score ≤ 2

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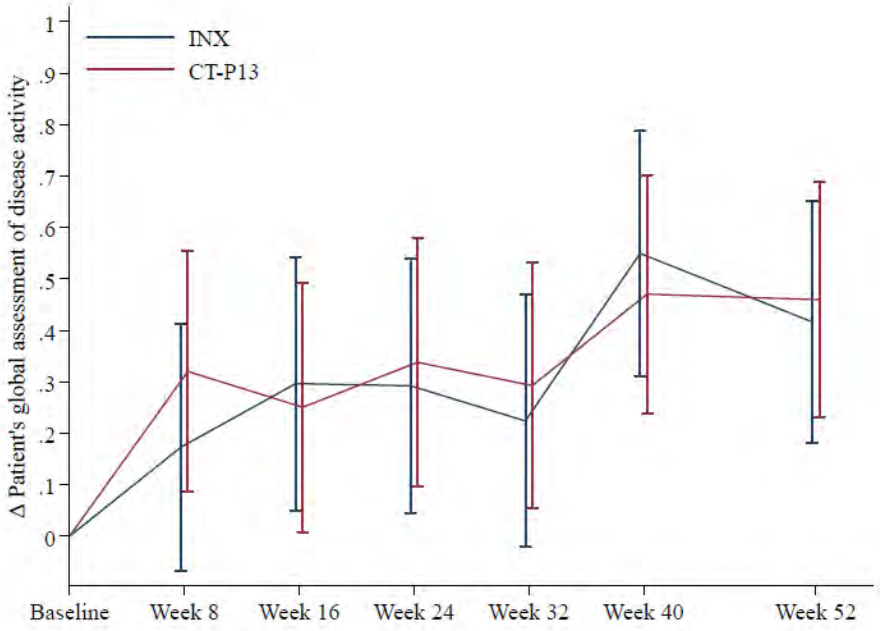
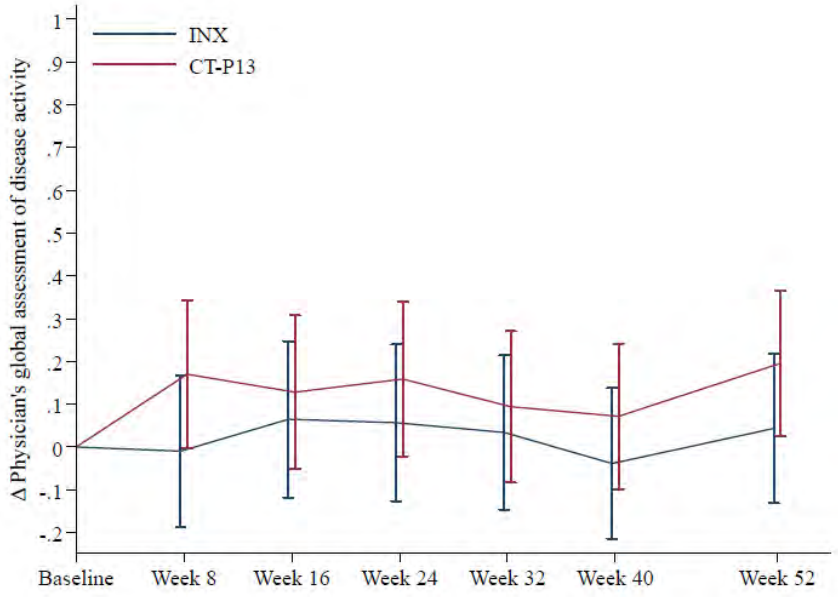
Global Assessment of Disease Activity



Patient



Physician

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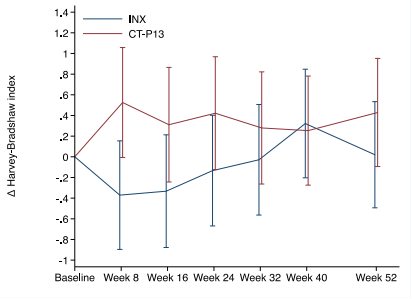
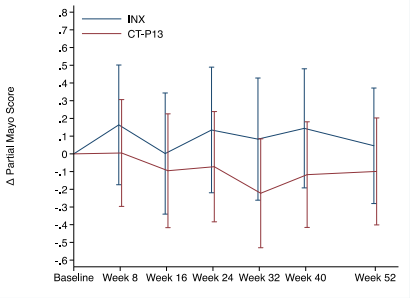
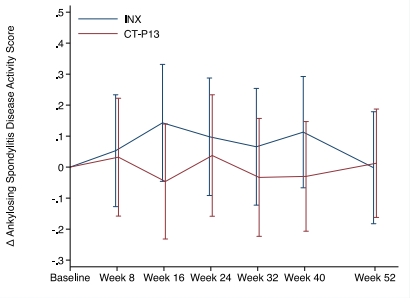
Disease Activity



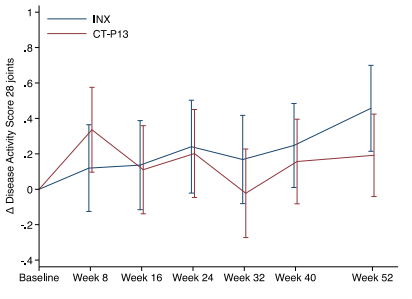
HBI



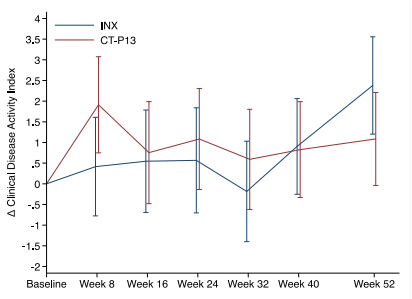
p-Mayo score



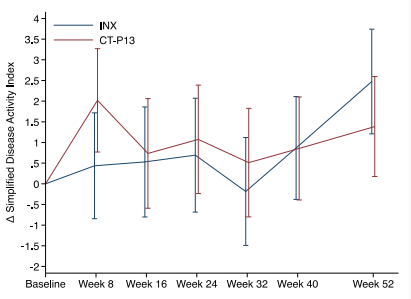
ASDAS



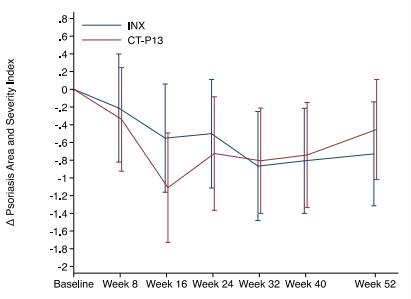
DAS28



CDAI



SDAI



PASI

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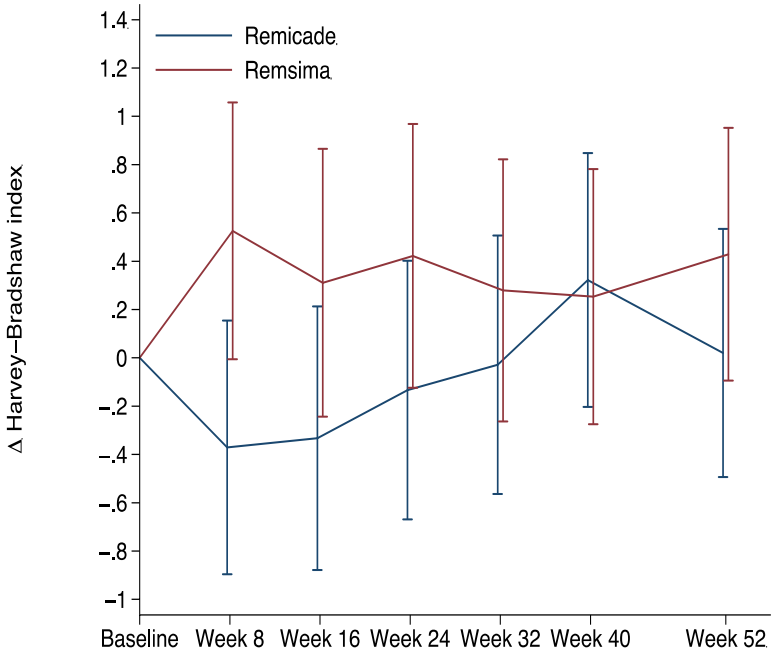
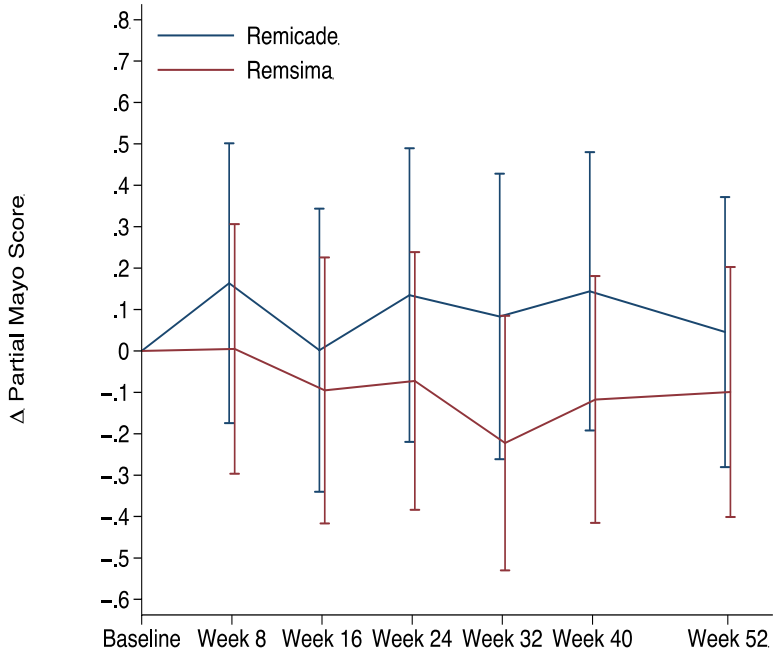
Disease Activity - IBD

Crohns disease



HBI

Ulcerative colitis



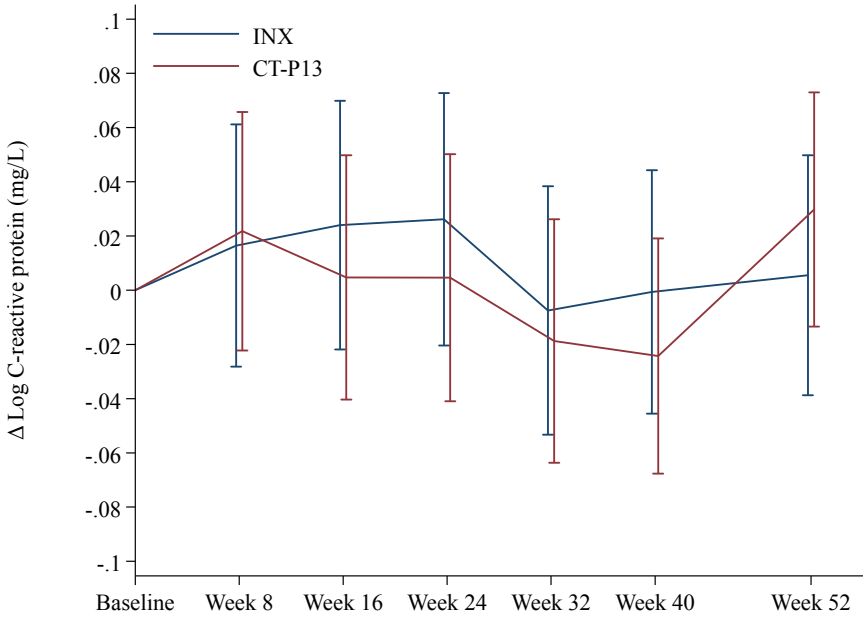
p-Mayo score

HBI = Harvey-Bradshaw index

NOR SWITCH

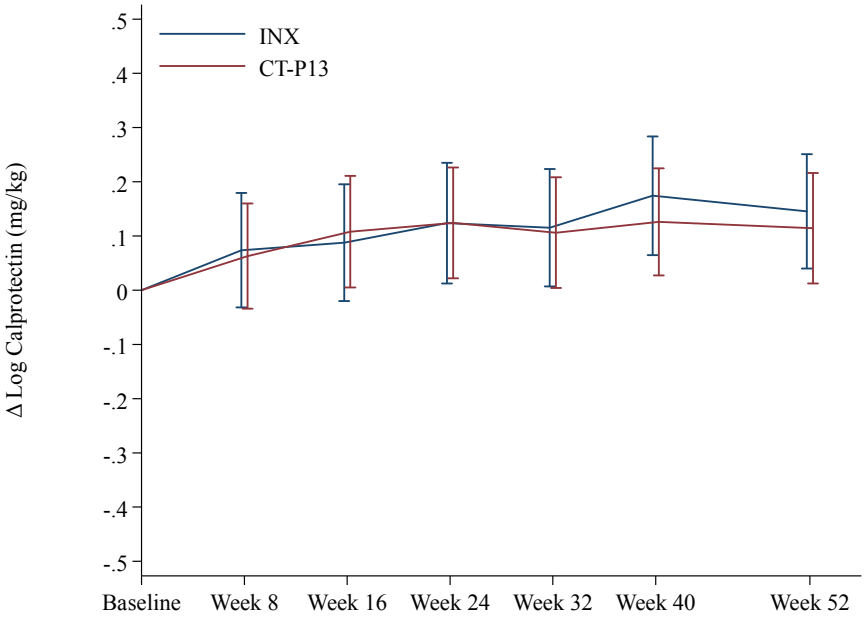
CRP and Calprotectin

Over all



CRP

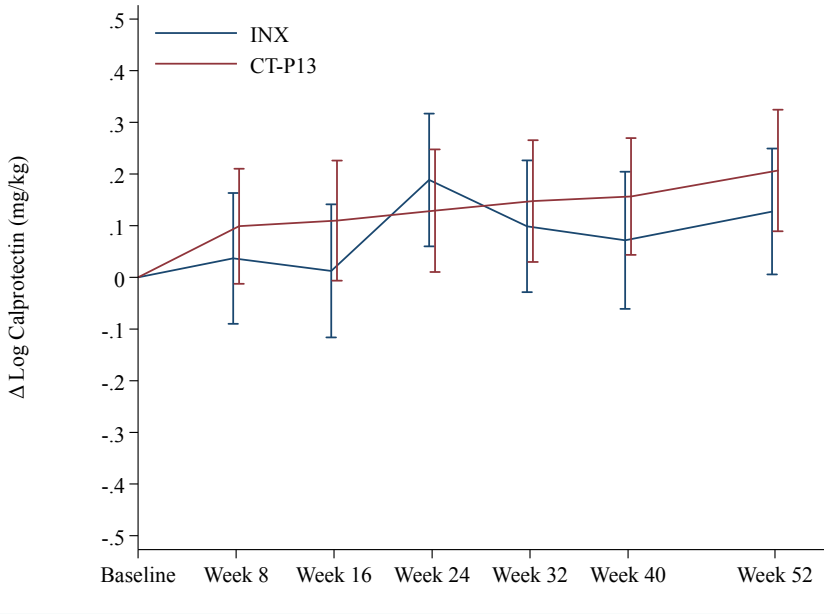
IBD



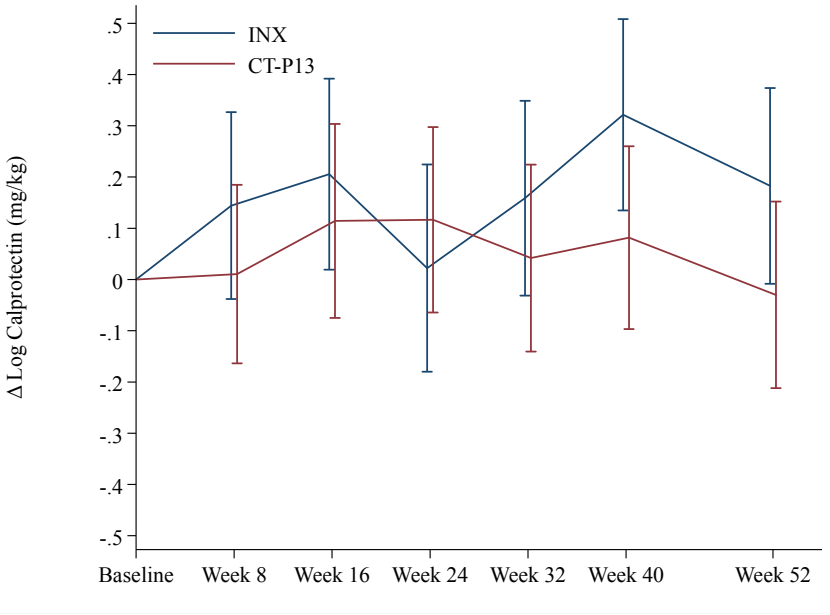
Calprotectin

NOR SWITCH

Calprotectin - IBD



Crohns disease



Ulcerative colitis

NOR SWITCH

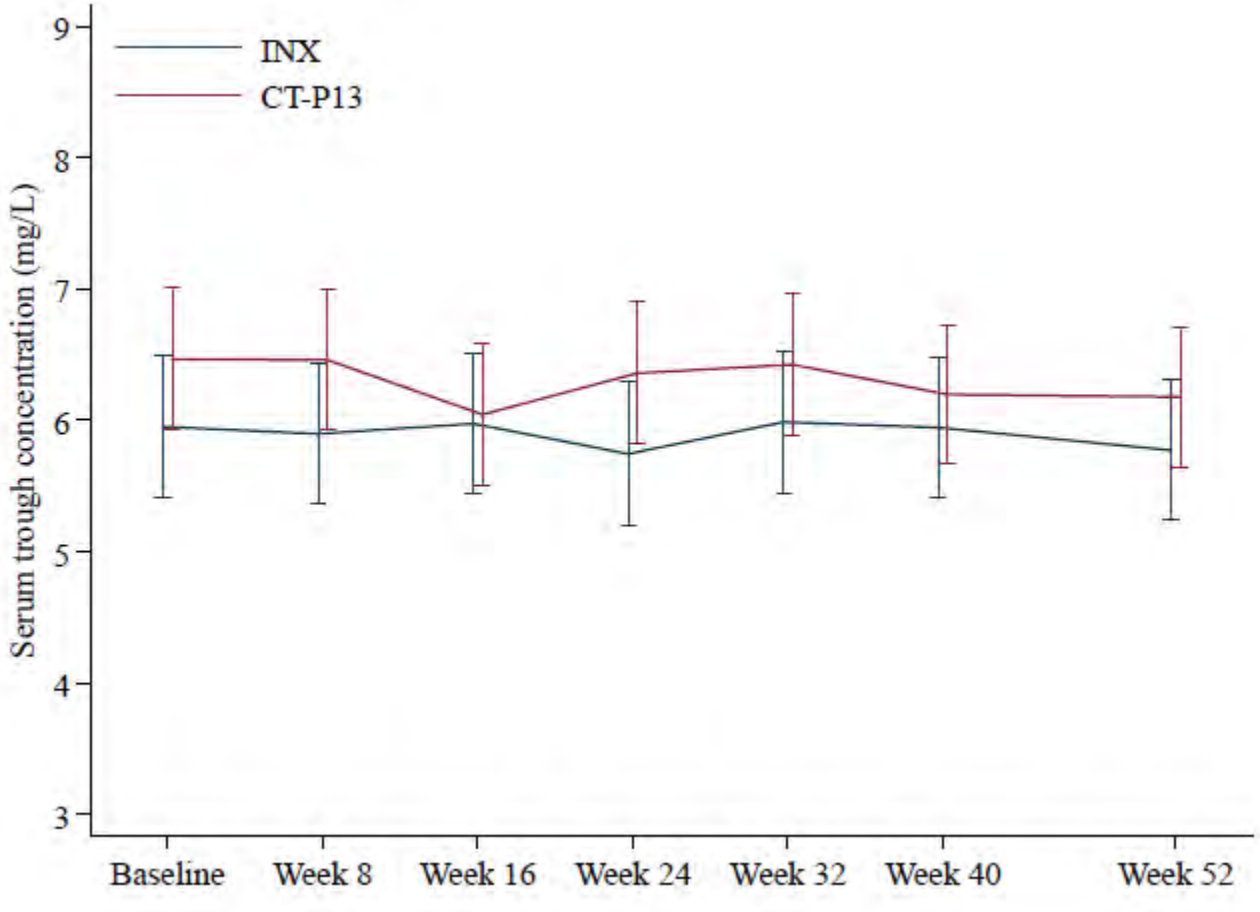
Patient Reported Outcome Measures

- **General:** SF-36, EQ-5D, WPAI
- **CD, UC:** IBD-Q
- **SpA, RA, PsA:** MHAQ, BASDAI, RAID, PsAID
- **Ps:** DLQI

- Changes (from baseline to study end) were similar in INX and CT-P13 group

NOR SWITCH

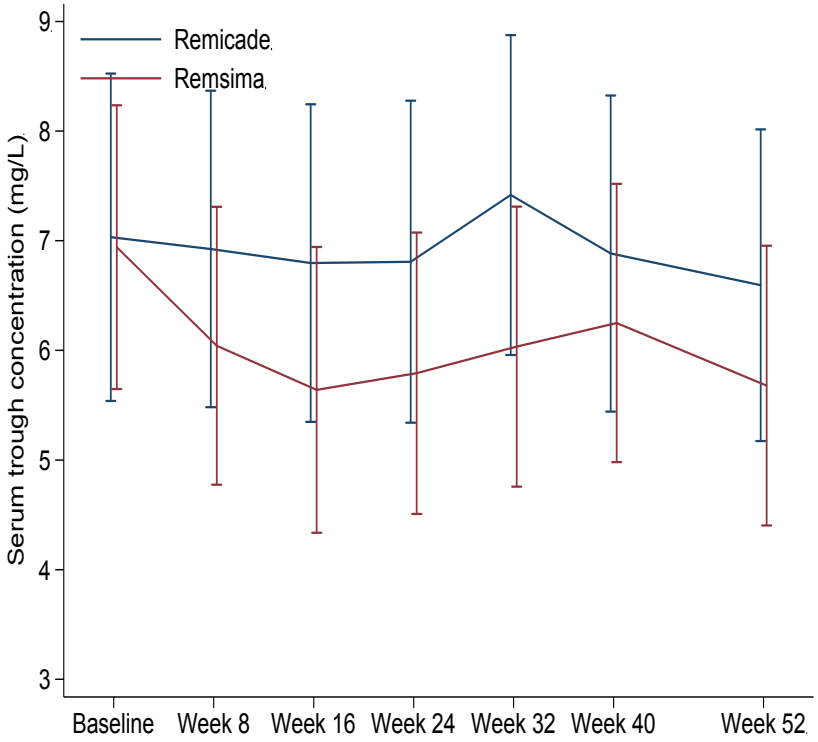
Drug trough levels



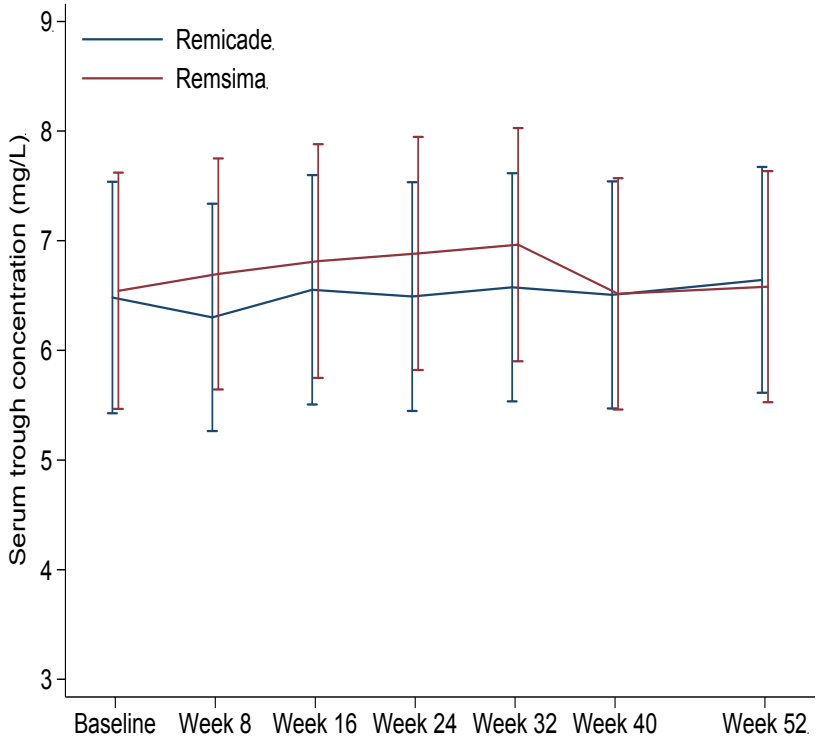
Over all

NOR SWITCH

Drug trough levels - IBD



Ulcerative colitis



Crohns disease

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

Methodological considerations

- Strengths
  - Design - RCT
  - Comprehensive data collection
  - Included sufficient number of patients according to power calculations
  - Patient representatives in project group
  - Financed by government, monitored within the health care system and no industry involvement
  - Drugs provided through the regular payment schedule
- Limitations
  - Not powered for non-inferiority within each diagnostic group
  - Blinding procedures
  - No data on patients who declined participation
  - Non-inferiority margin too large?
  - Results relevant also for other boDMARDs/bsDMARDs?

NOR SWITCH

Nor-Switch

Project group: Tore K Kvien, Jørgen Jahnsen, Kristin K Jørgensen, Guro Løvik Goll, Merete Lorentzen, Inge C Olsen, 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

Nor-Switch study group: Øivind Asak, Somyeh Baigh, Ingrid M Blomgren, Trude J Bruun, Katrine Dvergsnes, Svein O Frigstad, Clara G Gjesdal, Berit H J Grandaunet, Inger M Hansen, Ingvild S H Hatten, Gert Huppertz-Hauss, Magne Henriksen, Sunniva S Hoie, Jan Krogh, Julia R Kruse, Maud-Kristine A Ljoså, Irina P Midtgard, Pawel Mielnik, Bjørn Moum, Geir Noraberg, Armin Poyan, Ulf Prestegård, Haroon U Rashid, Liv Sagatun, Kathrine A Seeberg, Kristine Skjetne, Eldri K Strand, Hilde Stray, Njaal Stray, Roald Torp, Cecilia Vold, Carl M Ystrøm, Camilla C Zettel, Karoline Henanger, David Warren

Patient representatives: Bjørn Gulbrandsen, Jon Hagfors, Kenneth Waksvik

Data monitoring: Martha Colban, Nina Flatner, Trond Smedsrud, Bjørn Solvang, Inger Hilde Zahl, Cecilie Moe, Trude Langeng and NorCRIN

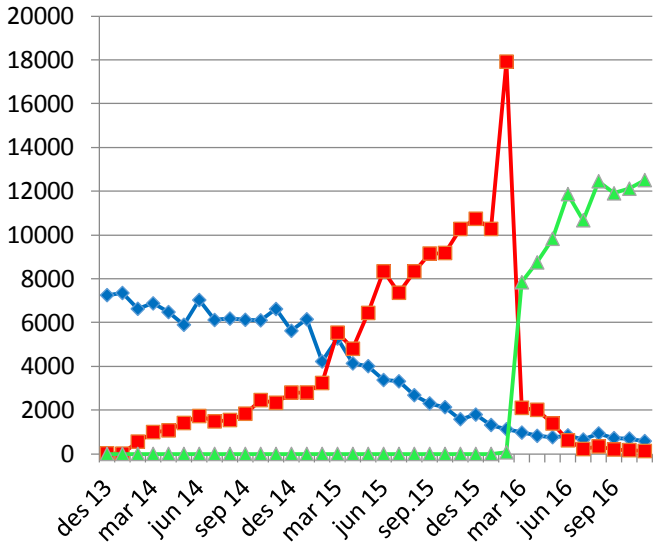
Study nurses: at each study centre

NOR SWITCH

Summary

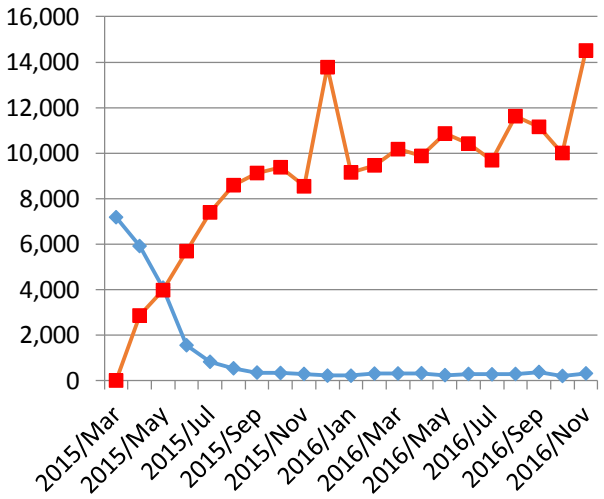
- Phase 3 equivalence trials support similarity between originator and approved biosimilar products regarding efficacy, safety and immunogenicity
- Switch (transition) data from extensions of RCTs and from registries have not raised concerns about switching
- The same is true for switching within phase 3 trials
- NOR-SWITCH is the only RCT and demonstrated that switching from the originator to biosimilar CT-P13 was not inferior to continued treatment with the originator infliximab product
- More switch RCTs are needed to increase confidence in switching from other reference molecules to biosimilars as well as between biosimilars and from biosimilars back to the reference product in patients with long-term originator treatment .

DDDs infliksimab – per Nov. 2016



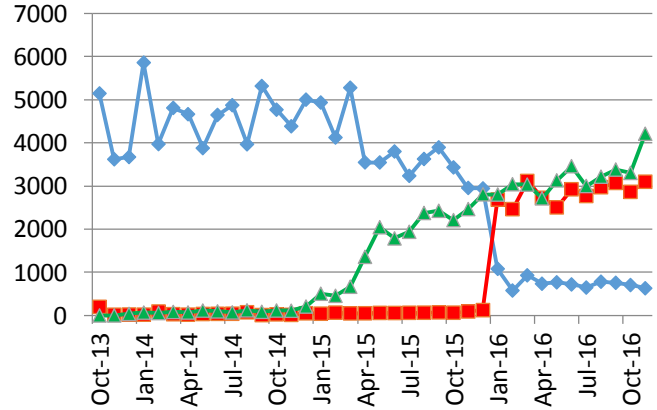
95,6%

REMICADE
REMSIMA
INFLECTRA



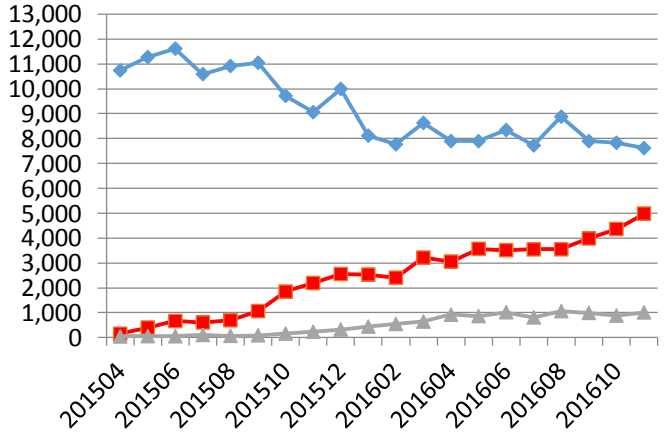
97,8%

Remicade
Remsima



92,1%

Remicade
Remsima
Inflectra



44,1%

Remicade
Remsima
Inflectra

References:

The development of the infliximab market is based from sales data from respective Nordic country. Norway: Farmastat AS https://farmastat.no/ ; Denmark: DLIMI AS https://www.dli-mi.dk/Pages/default.aspx ; Finland: IMS Health OY http://www.sld.fi/ ; Sweden: Reveal AB http://www.reveal.se/lakemedelsstatistik/