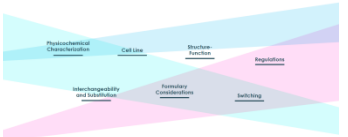


Professor Tore Kristian Kvien, MD, PhD, Norway

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

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'

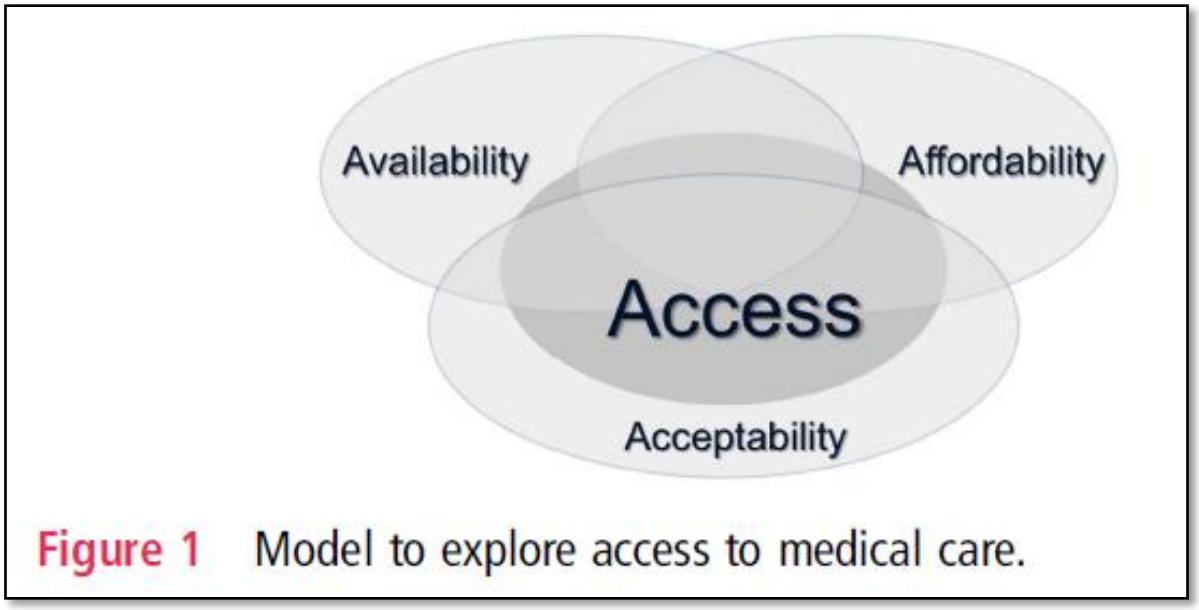


Figure 1 Model to explore access to medical care.

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

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

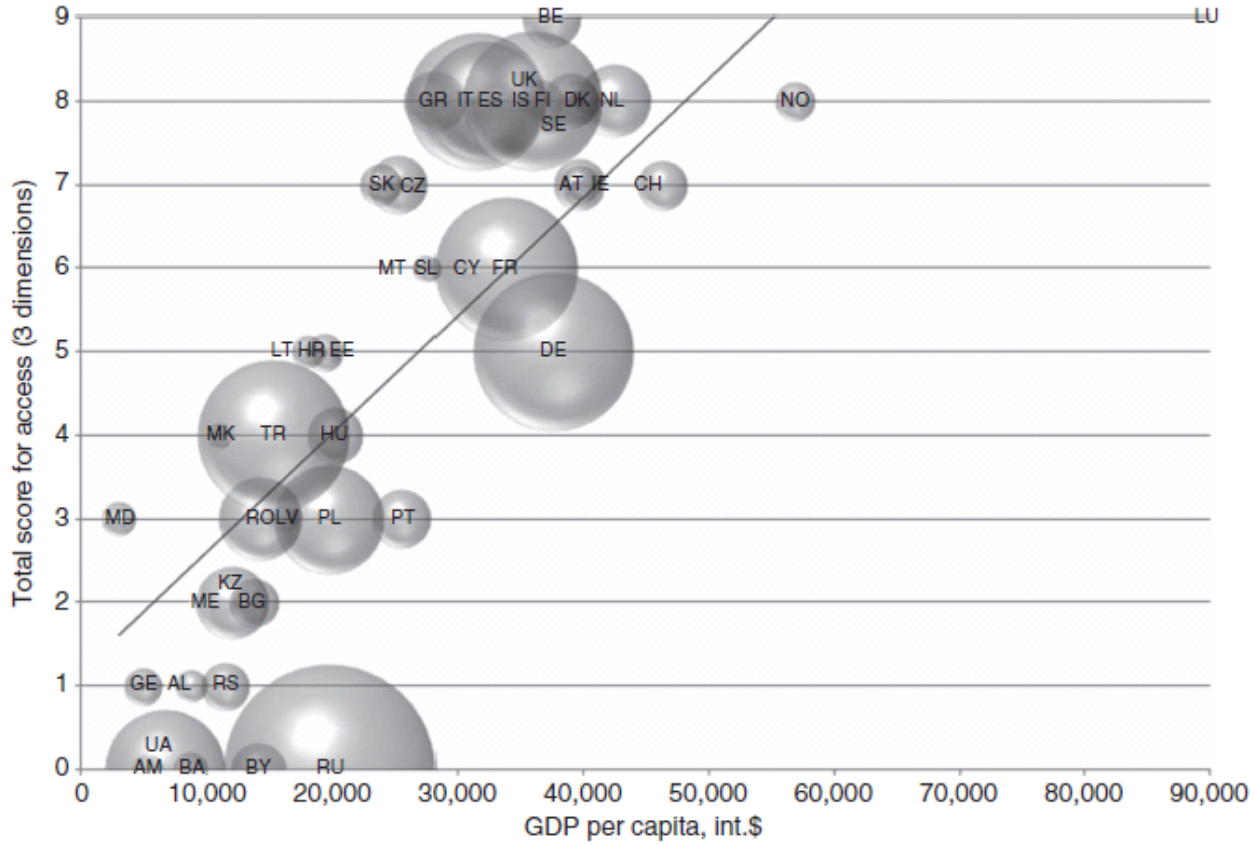


Figure 3 Access to biologic disease modifying antirheumatic drugs and gross domestic product per capita, international dollars (n=44). Size of the bubbles is proportional to the population size of the country. AL, Albania; AM, Armenia; AT, Austria; BA, Bosnia and Herzegovina; BE, Belgium; BG, Bulgaria;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

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

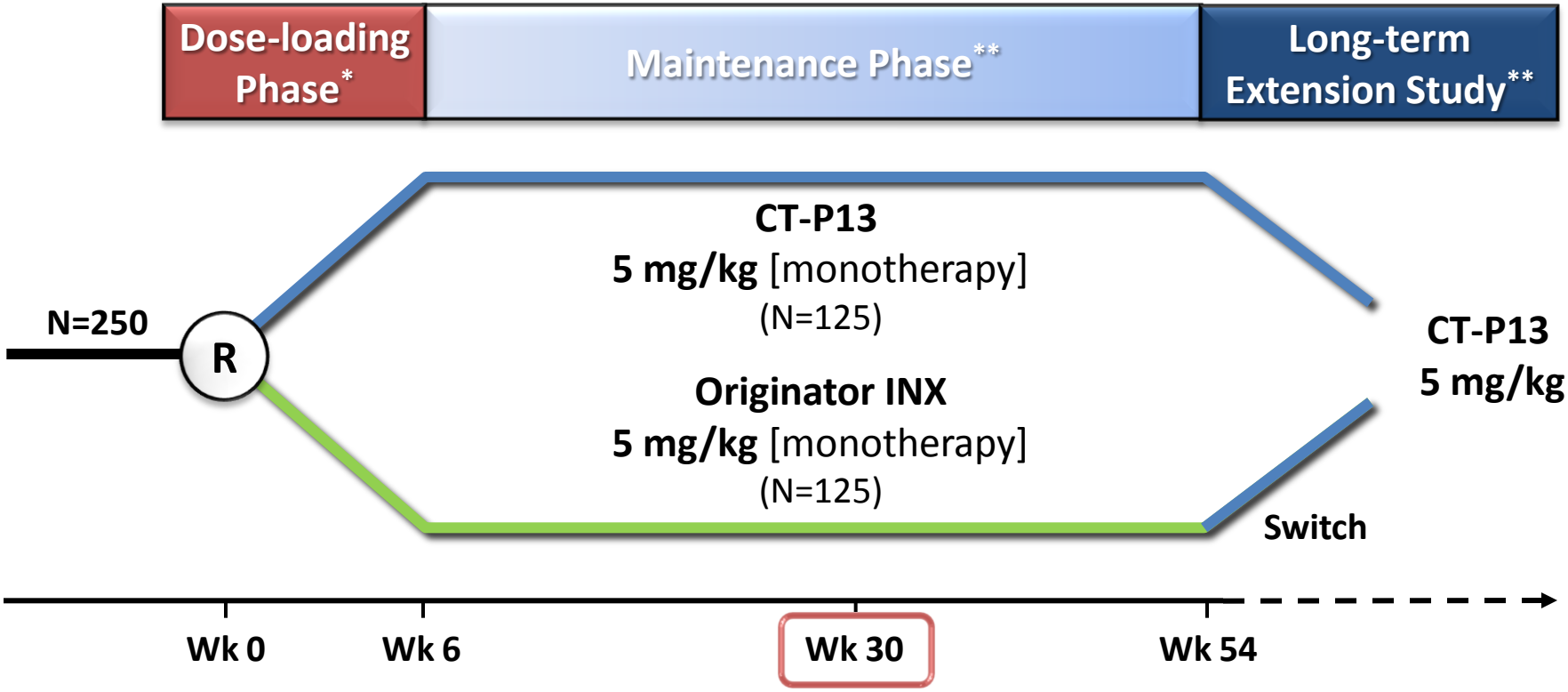
A randomised, double-blind, multicentre, parallel-group, prospective study comparing the pharmacokinetics, safety, and efficacy of CT-P13 and innovator infliximab in patients with ankylosing spondylitis: the PLANETAS study

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**(5mg/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%

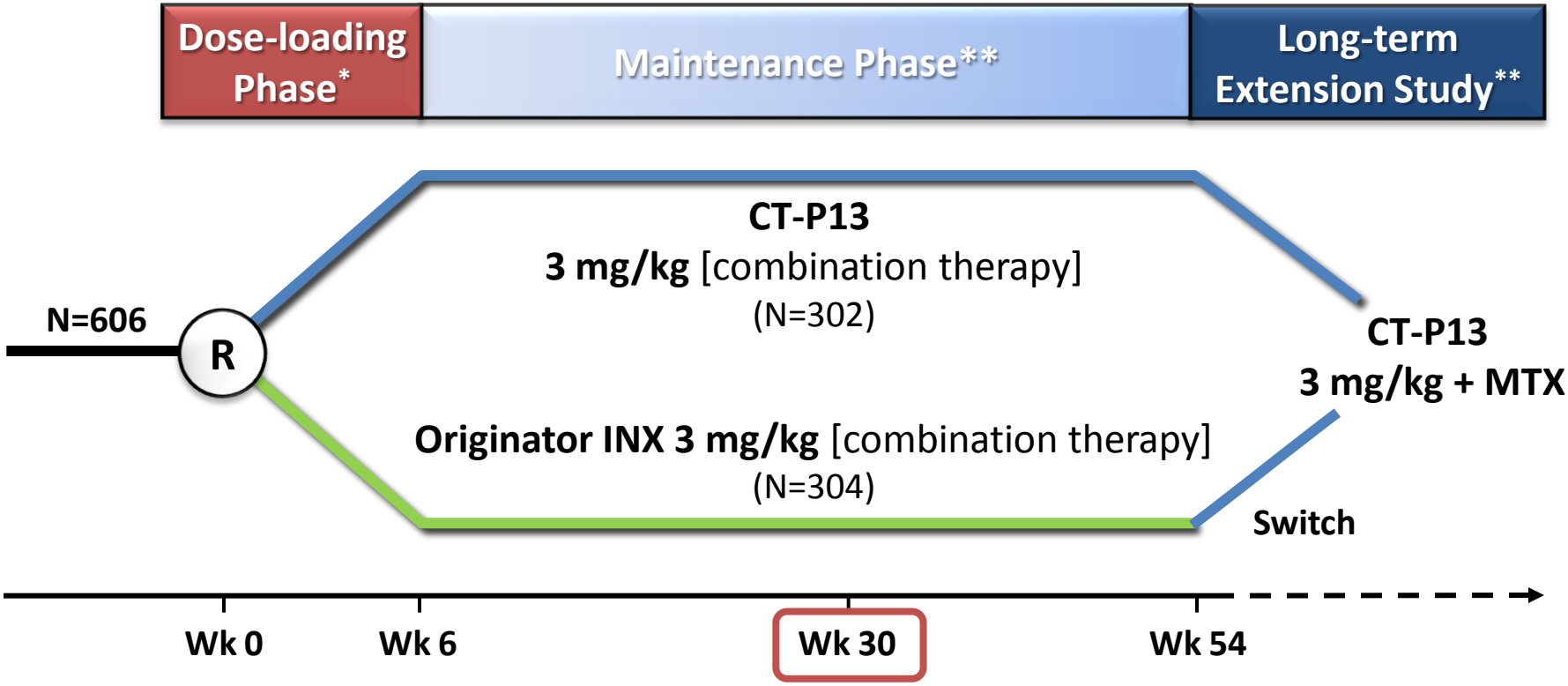
Source: EMA Inflectra EPAR, June 2013.

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

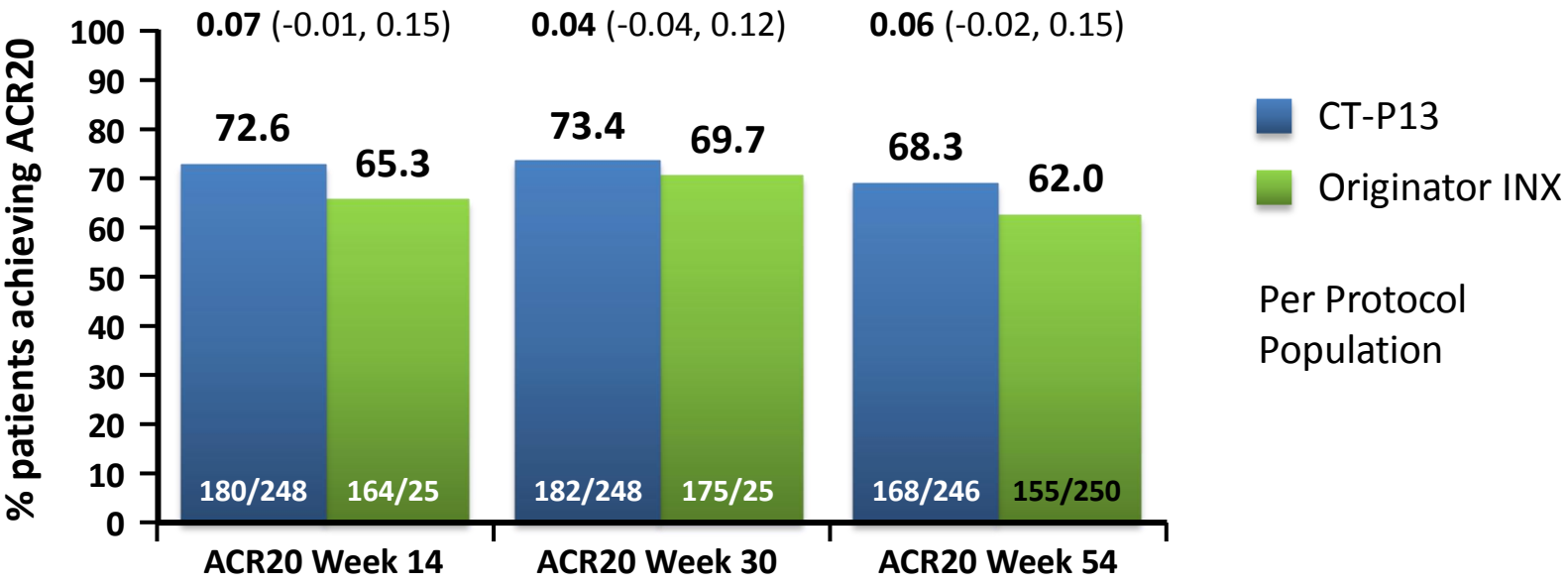


*Doses at weeks 0, 2 and 6 by 2-hr IV infusion.
**Doses every 8 weeks up to 54 weeks by 2-hr IV infusion.

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

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

OPEN ACCESS

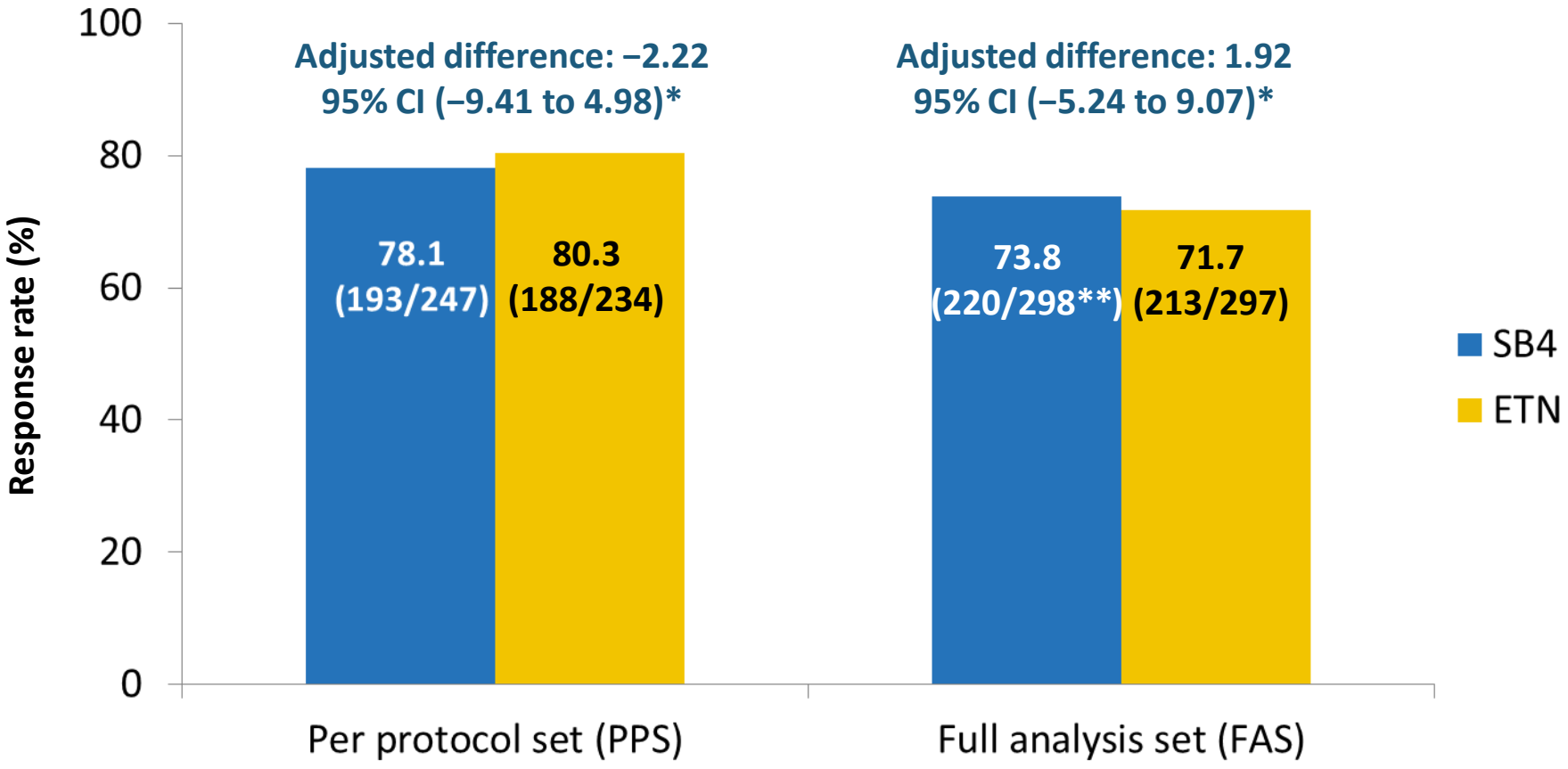
EXTENDED REPORT

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



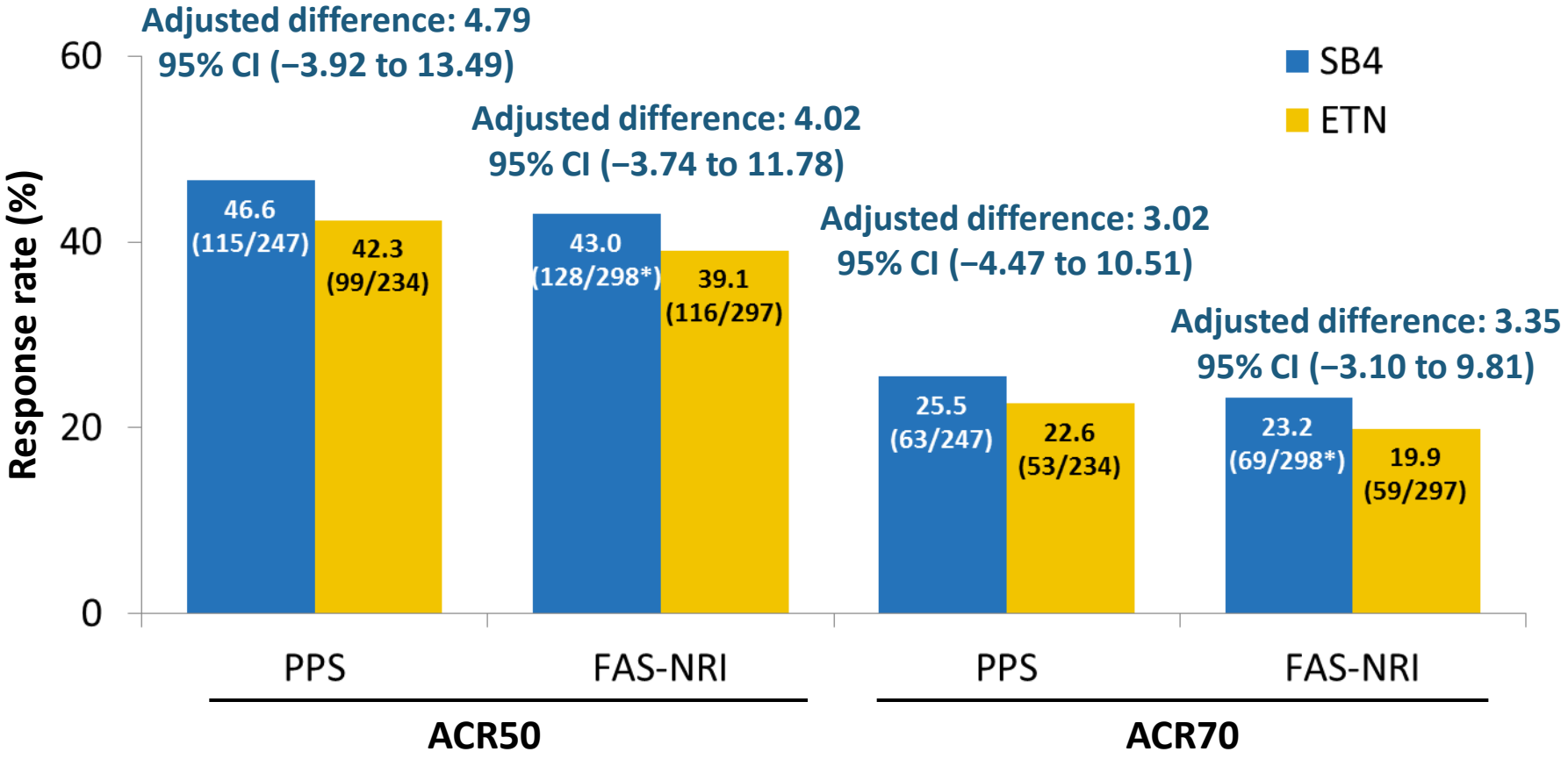
* Predefined equivalence margin -15% to 15%

**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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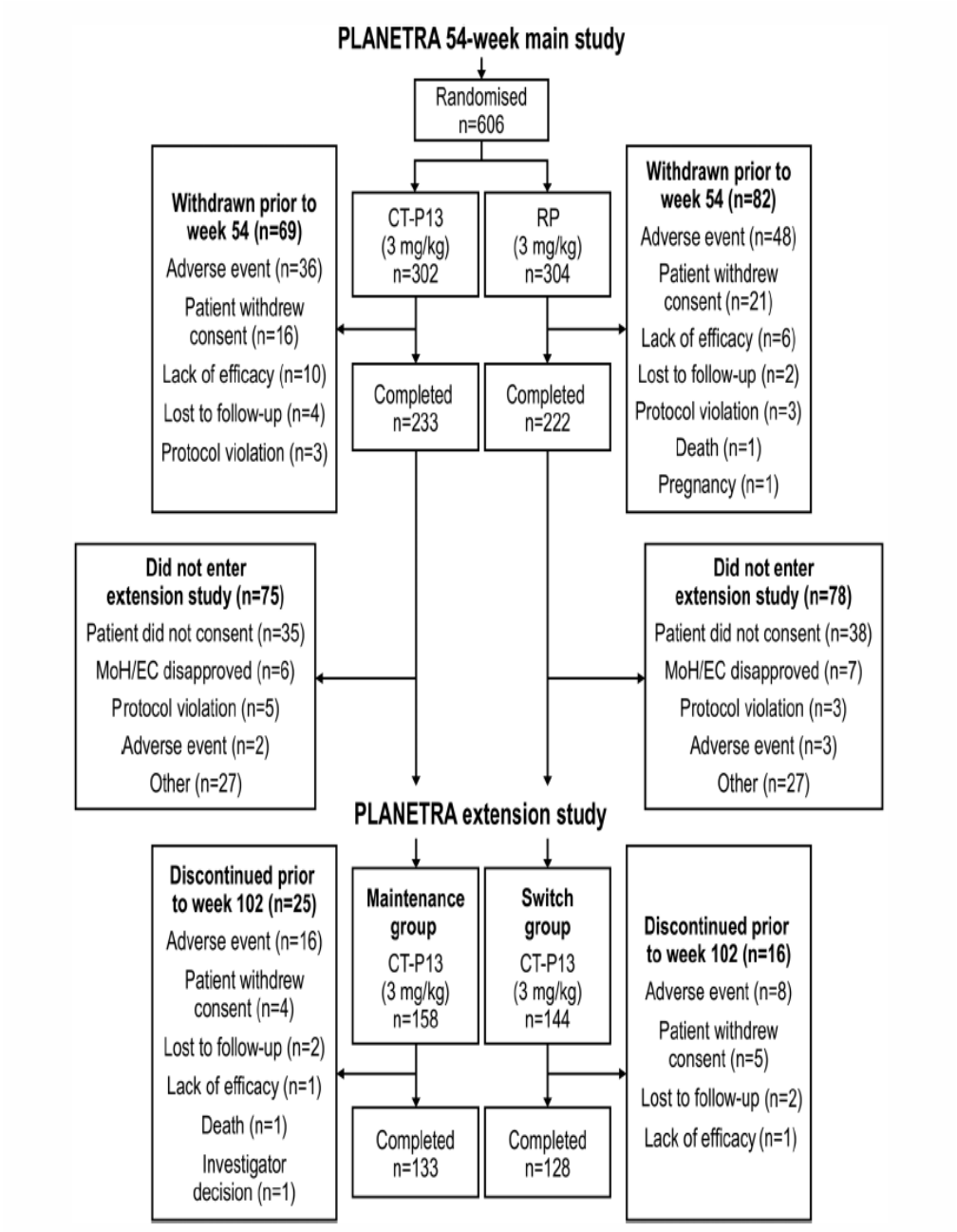
EXTENDED REPORT

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

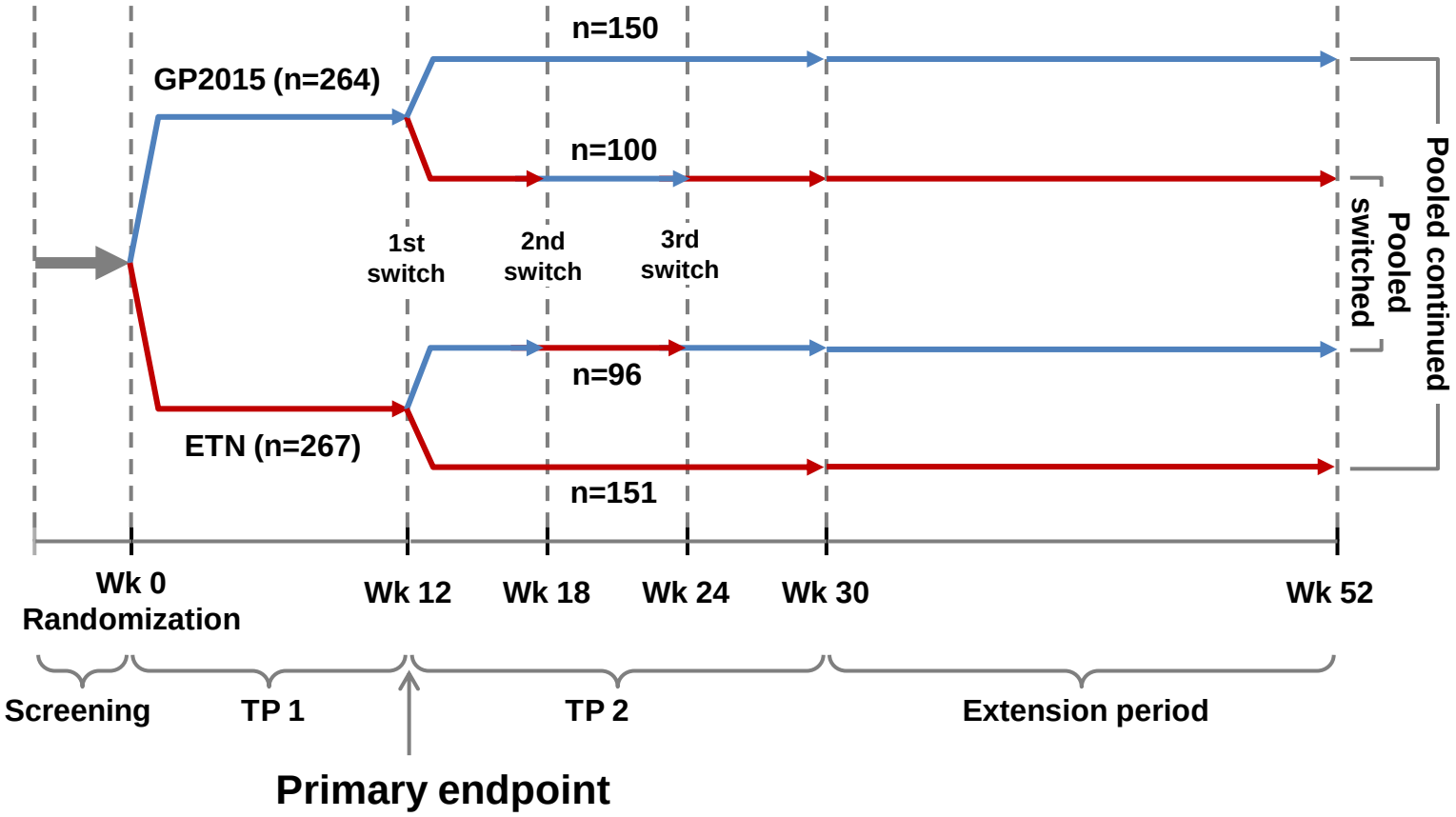
The proportion of patients who experienced at least one TEAE was 48.9% (n=44 of 90) in the maintenance group and 71.4% (n=60 of 84) in the switch group during the extension study, and 70.0% (n=63) and 61.9% (n=52) during the main study.

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

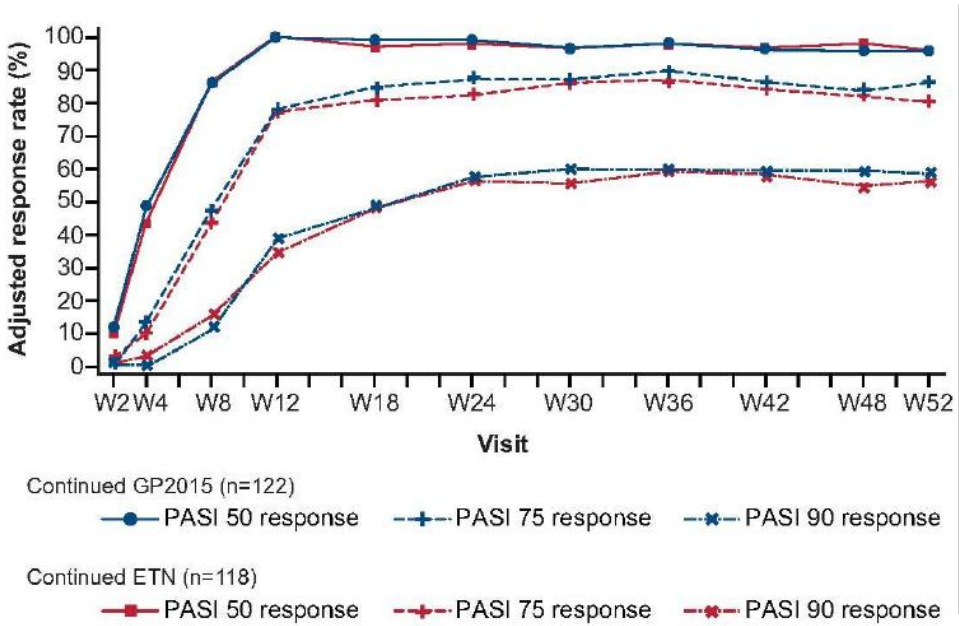


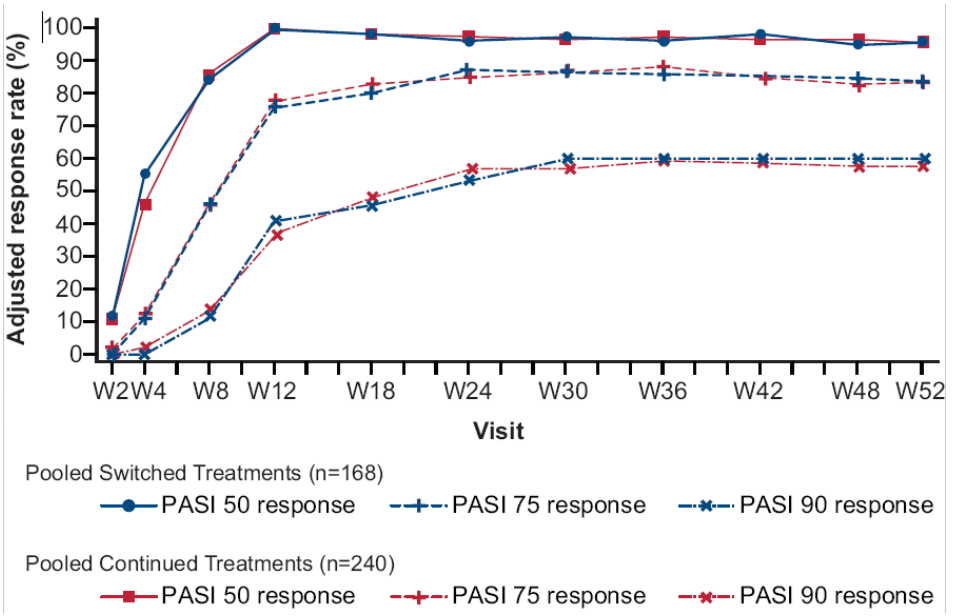
ETN, reference etanercept; TP, treatment period; Wk, week

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

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

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)

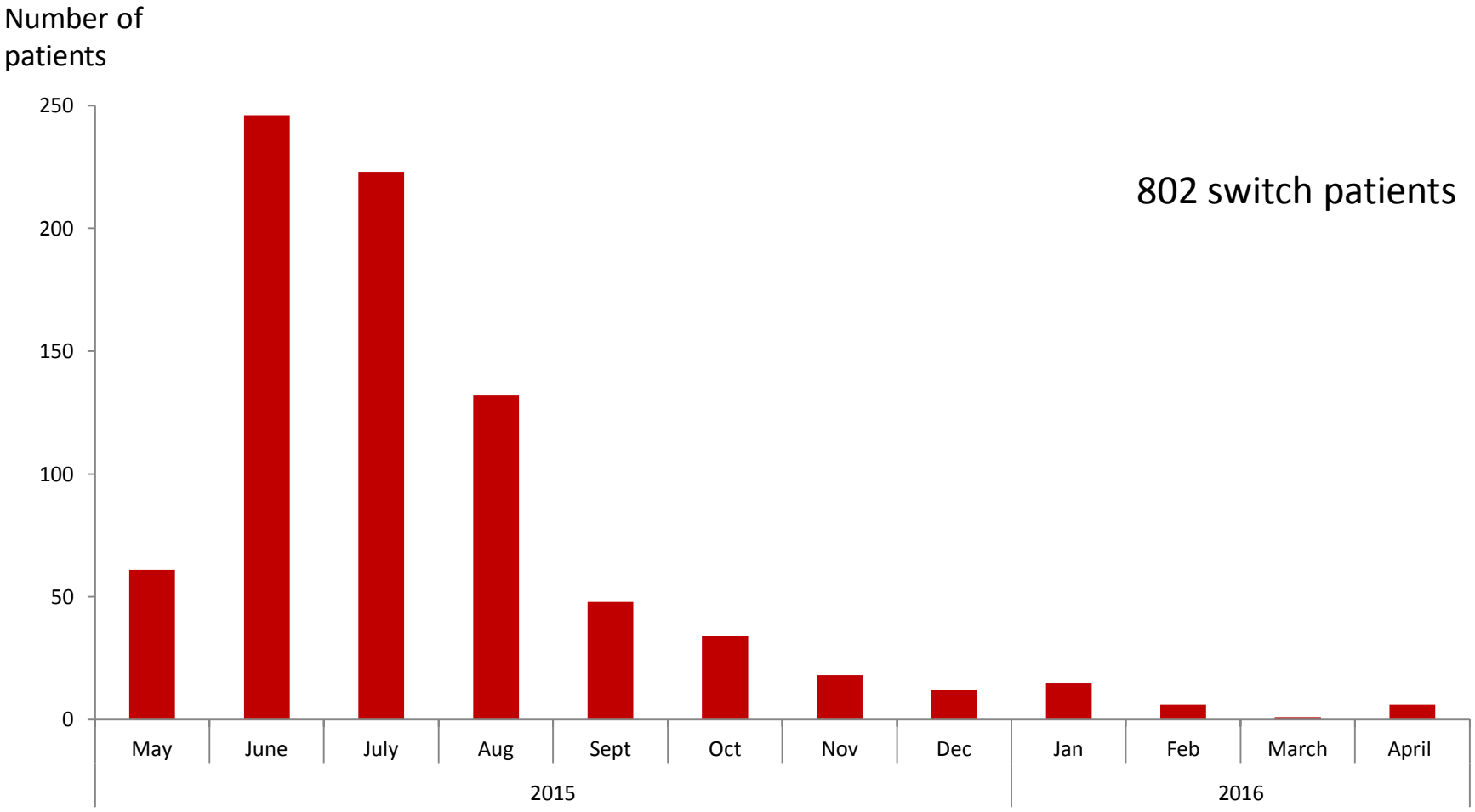
  At the time of switch

  ≈ 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

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

Withdrawal

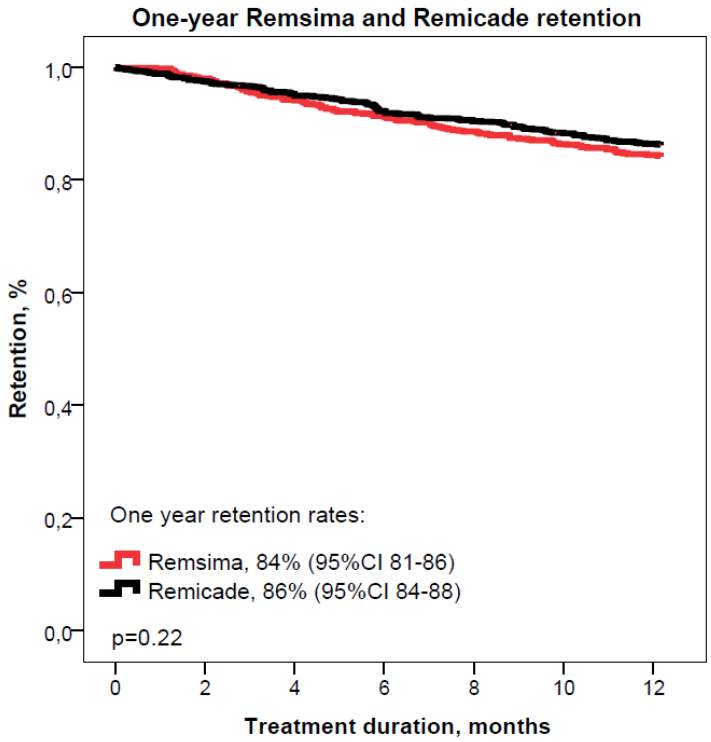
- Median follow-up time after switching was 413 (339-442) days
- 132/802 patients (16%) stopped Remsima treatment
- Remicade treatment duration: 5.9 (2.9-9.2) years

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.
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 1 January 2014



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

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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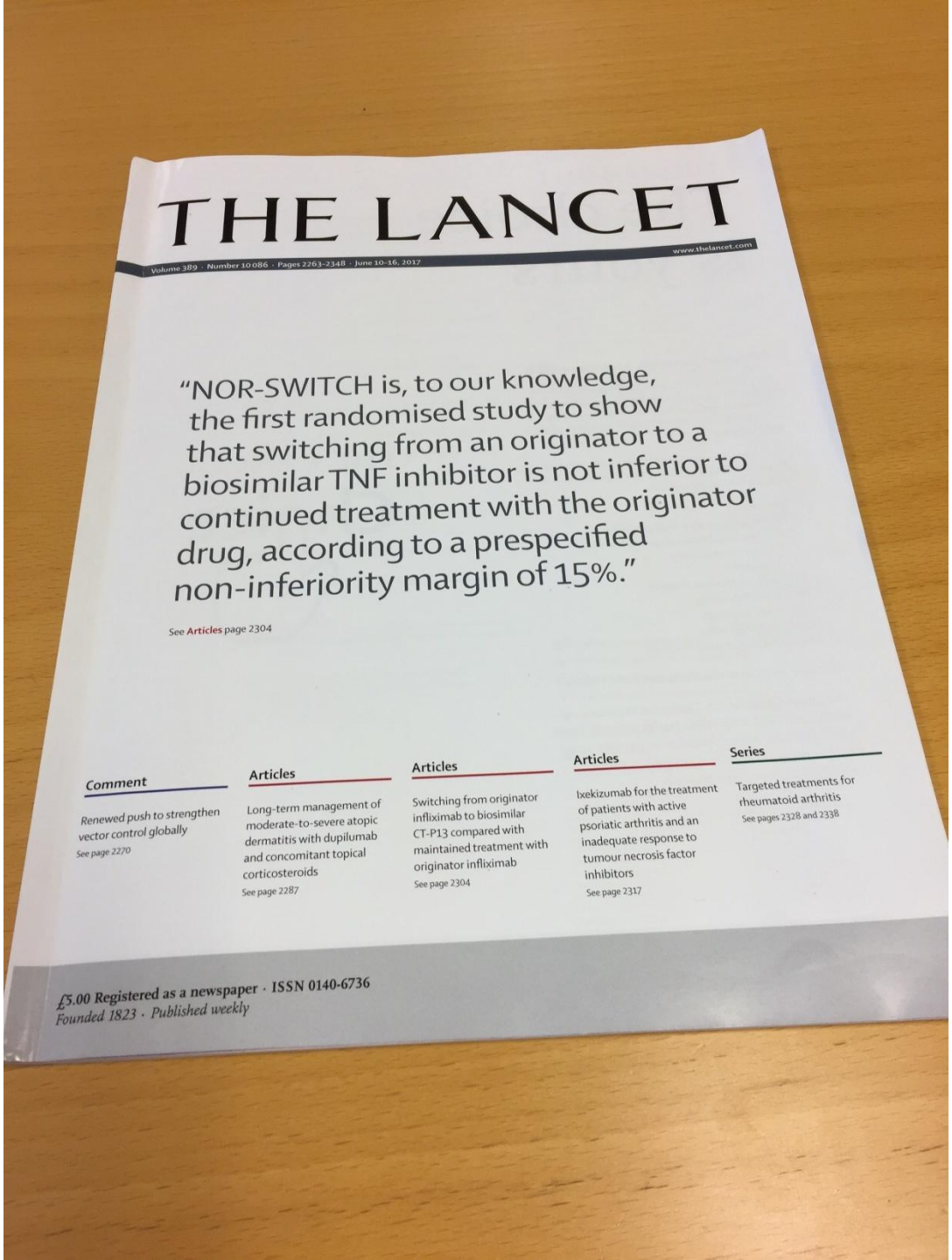
http://dx.doi.org/10.1016/S0140-6736(17)30068-5



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"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

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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

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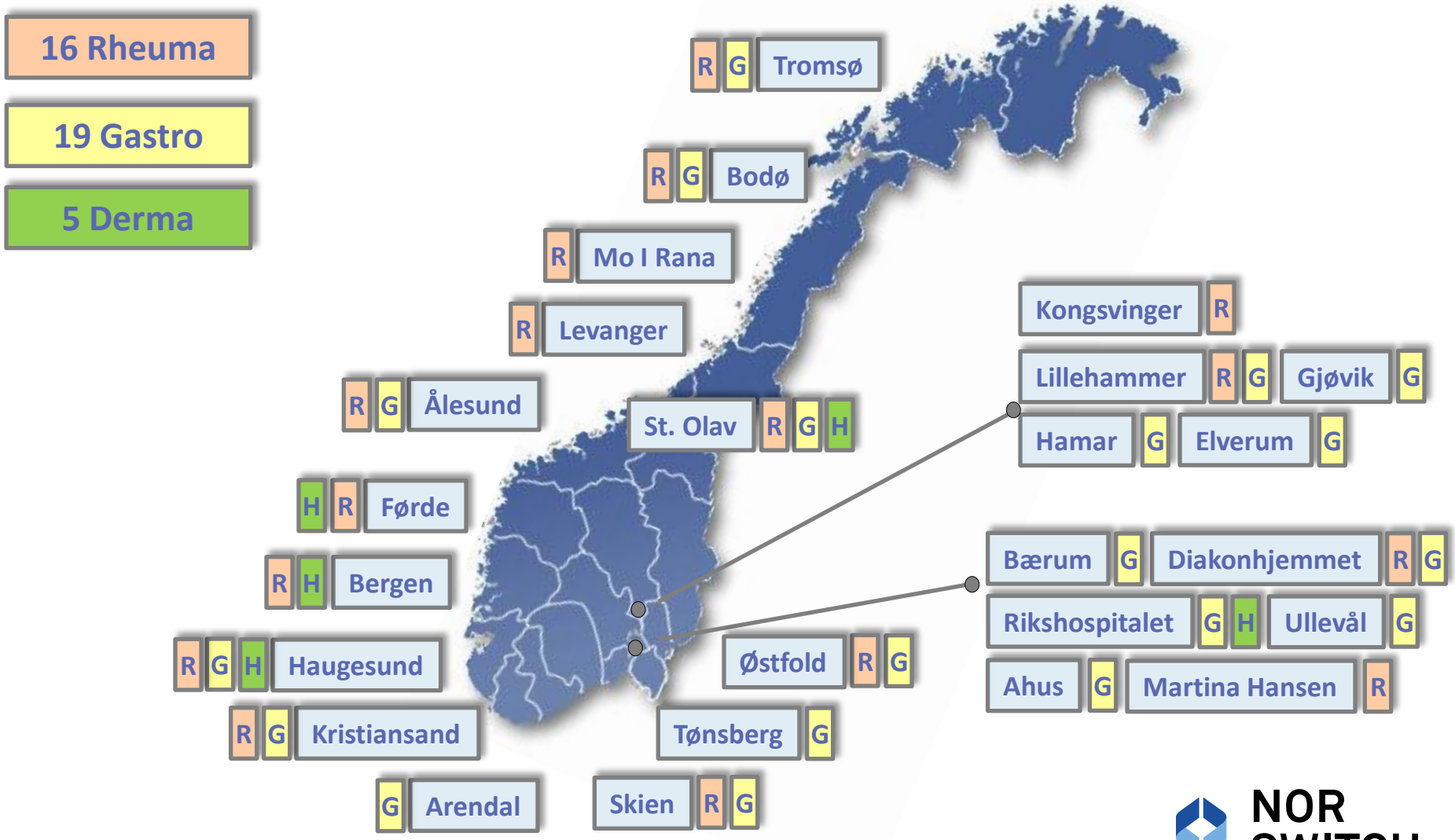
Table 1: The numbers in the cells represent the total number of patients needed in total. All calculations are based on a power of 80% and alpha 2.5%

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

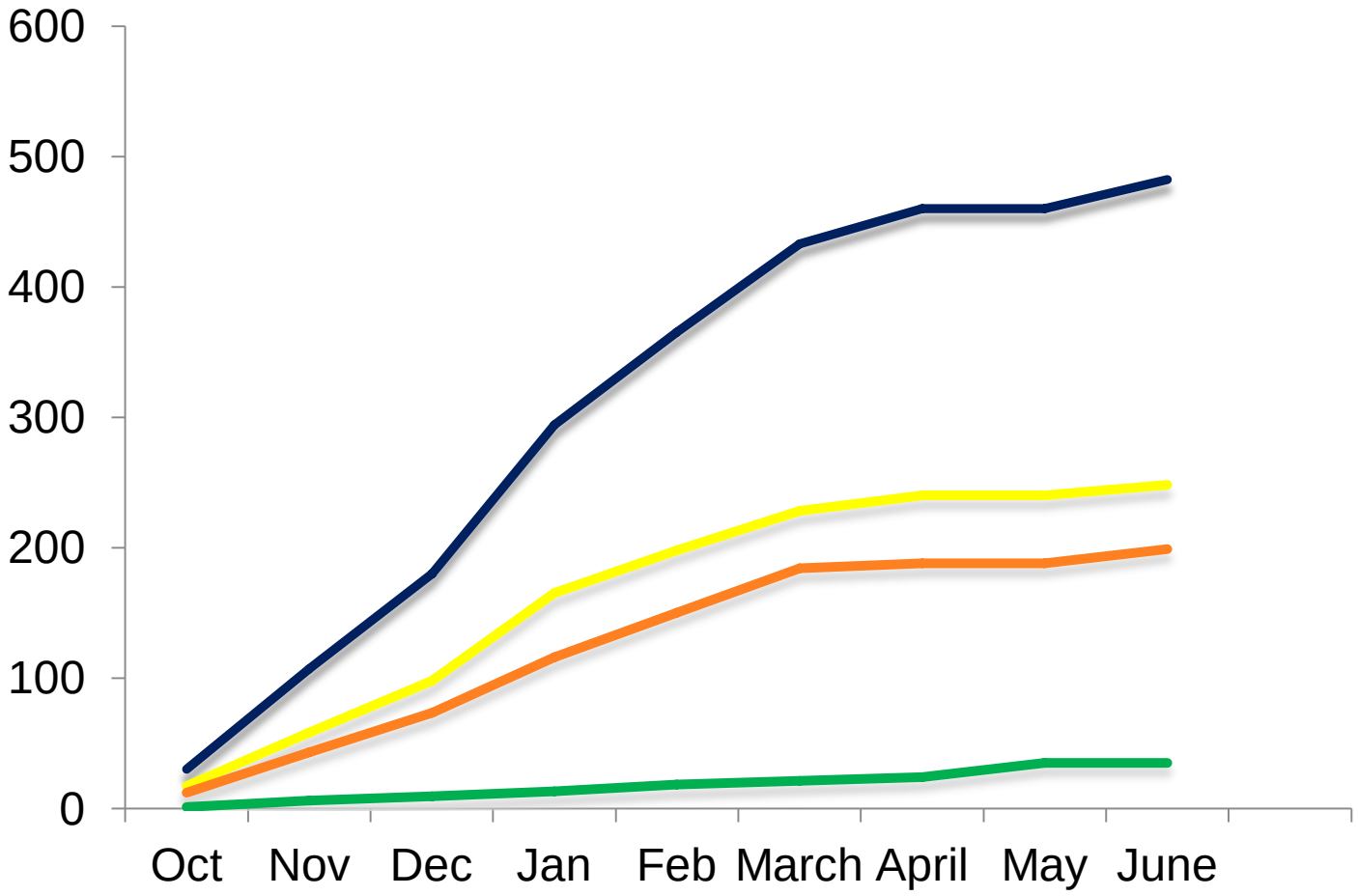
Table 2: The numbers in the cells represent the total number of patients needed in total. All calculations are based on a power of 90% and alpha 2.5%.

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



Randomized patients 2014–2015



482 in total

248 Gastro

199 Rheuma

35 Derma

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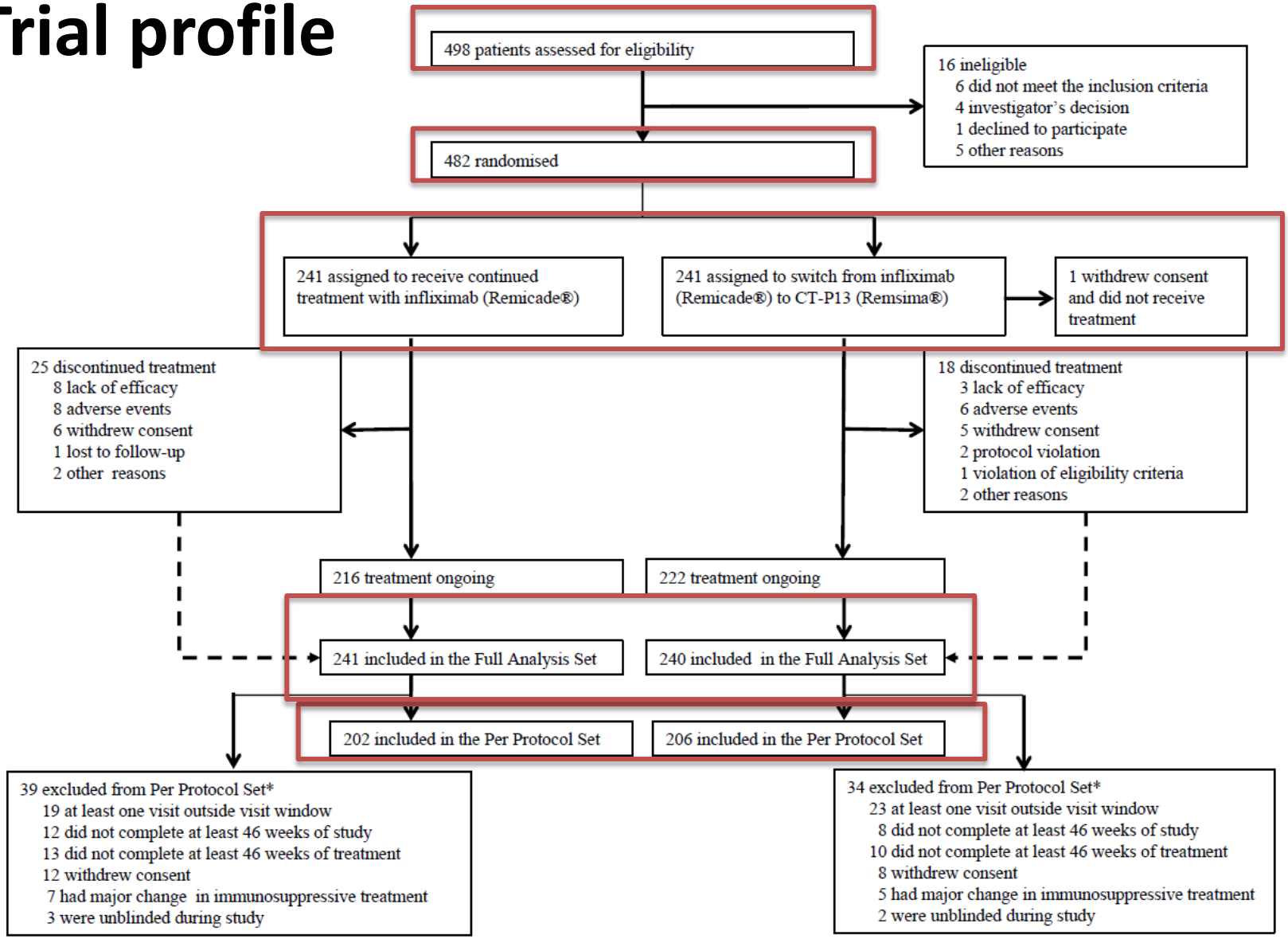
Trial profile



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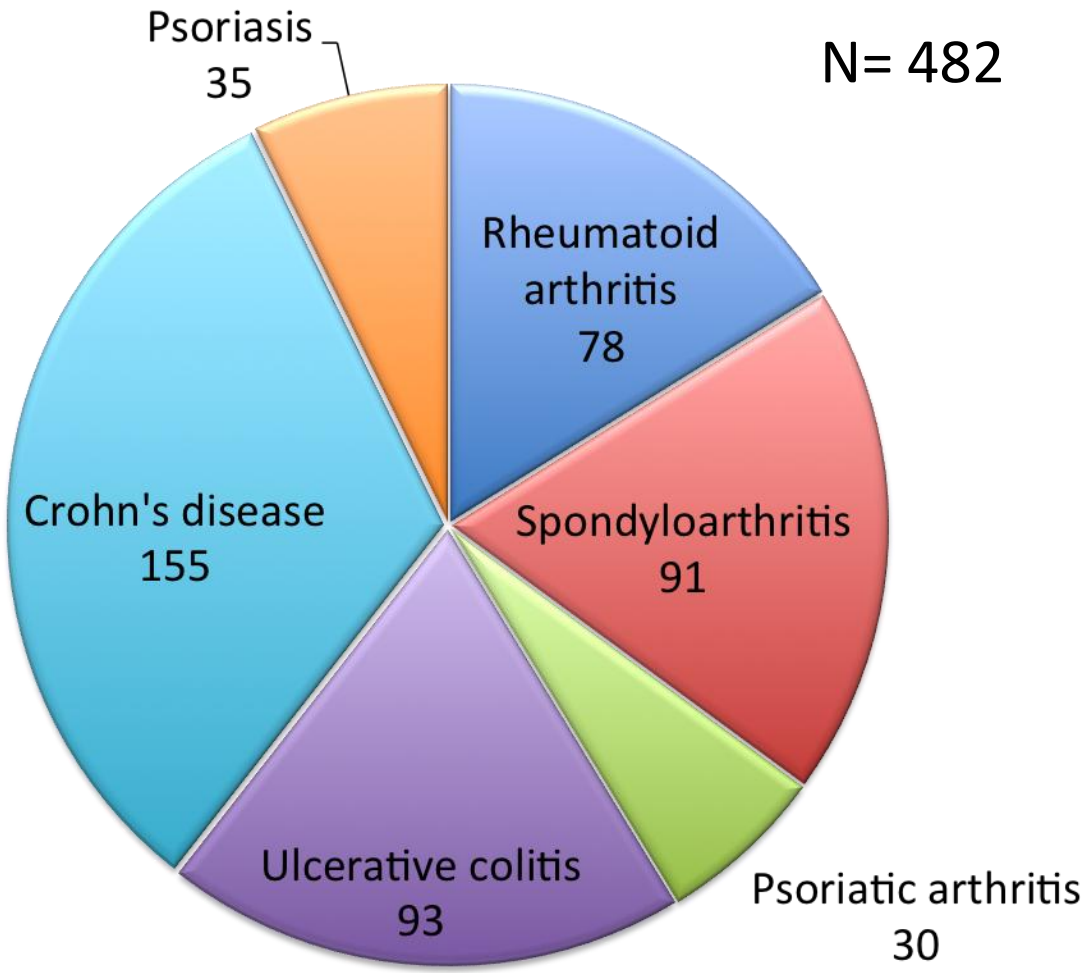
Kvien T. NOR-SWITCH Principal Investigator. Unpublished data.

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

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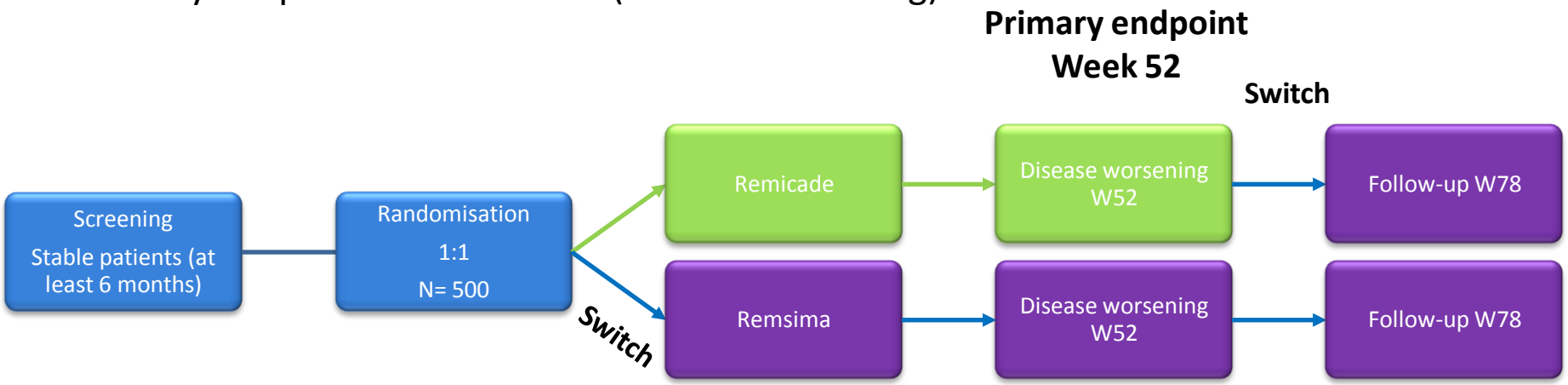
NOR- SWITCH Study design

- 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

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Results

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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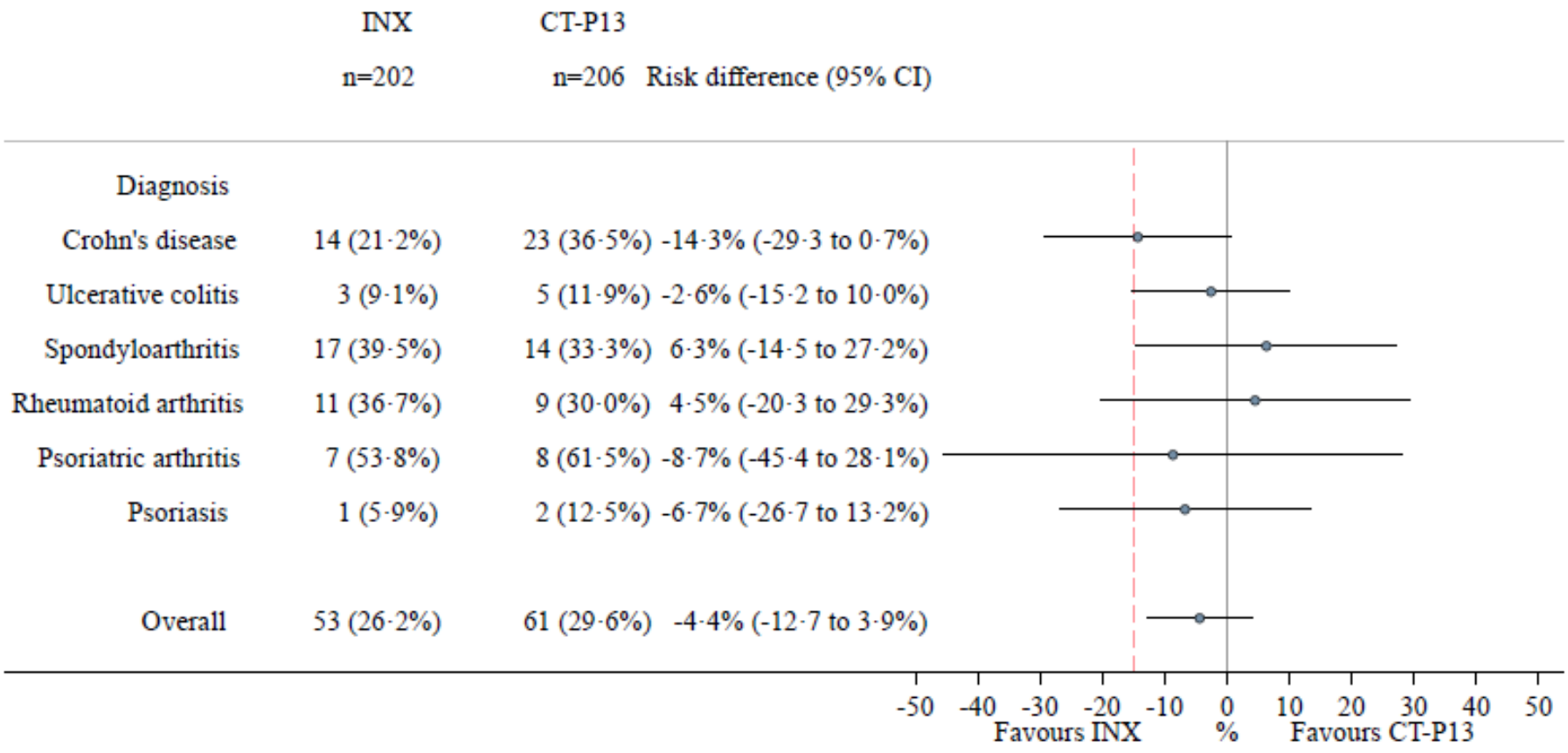
Disease Worsening



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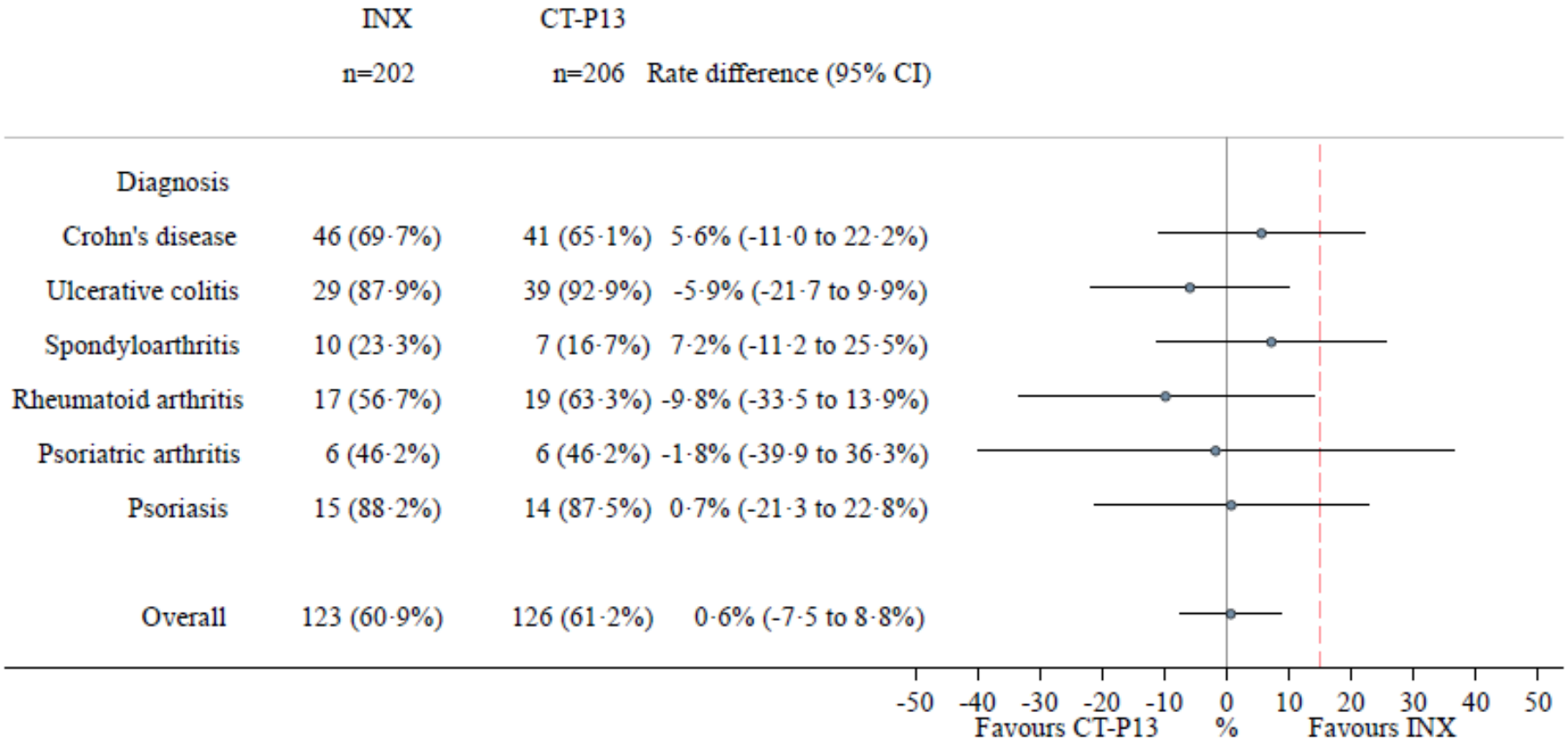
Remission



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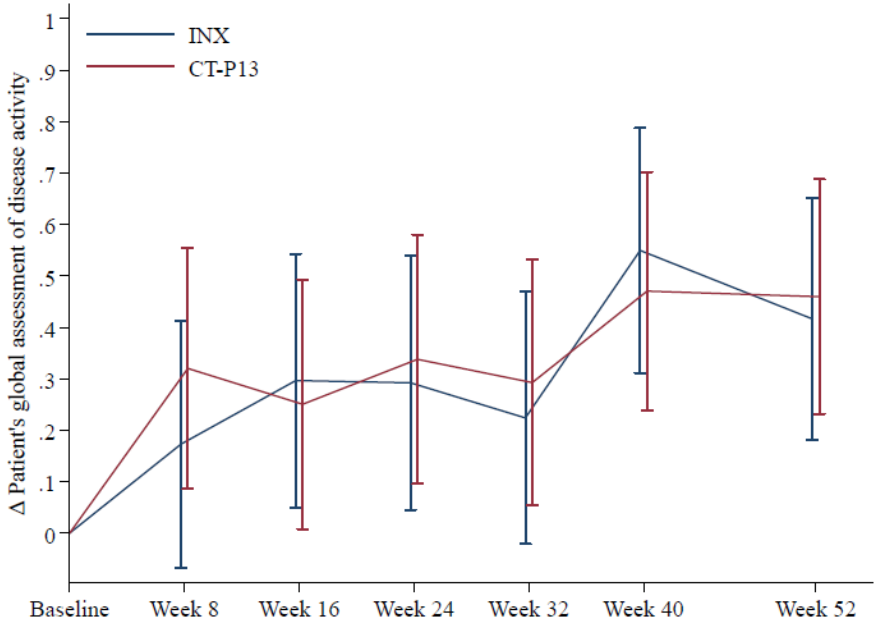
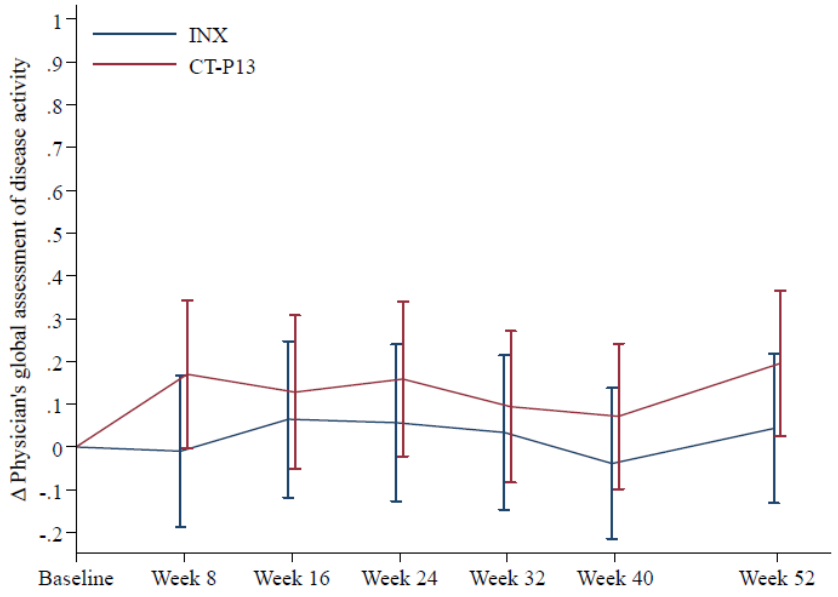
Global Assessment of Disease Activity



Patient



Physician

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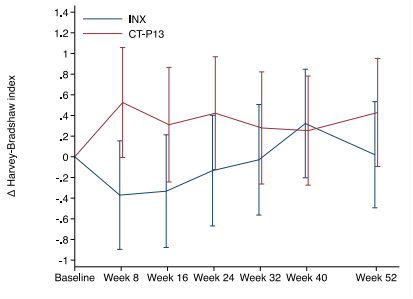
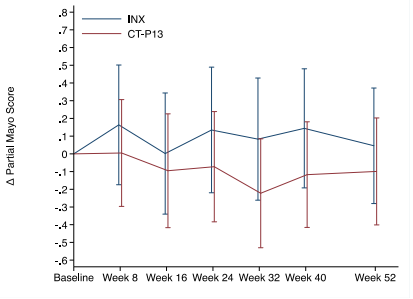
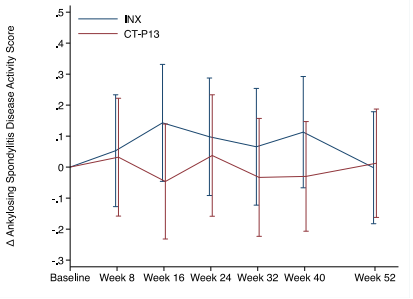
Disease Activity



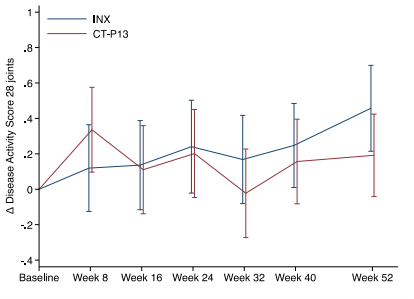
HBI



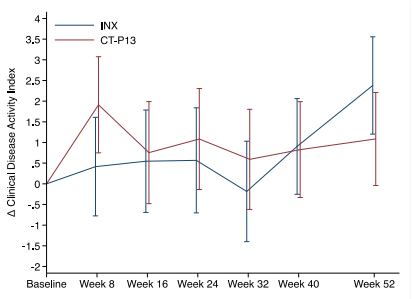
p-Mayo score



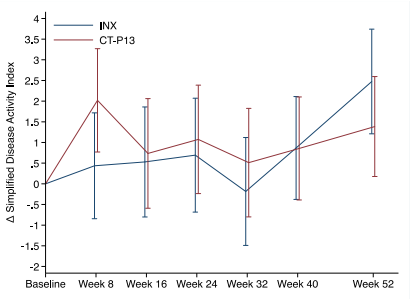
ASDAS



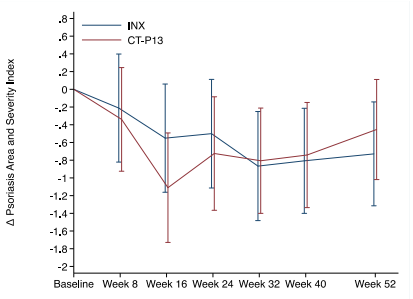
DAS28



CDAI



SDAI



PASI

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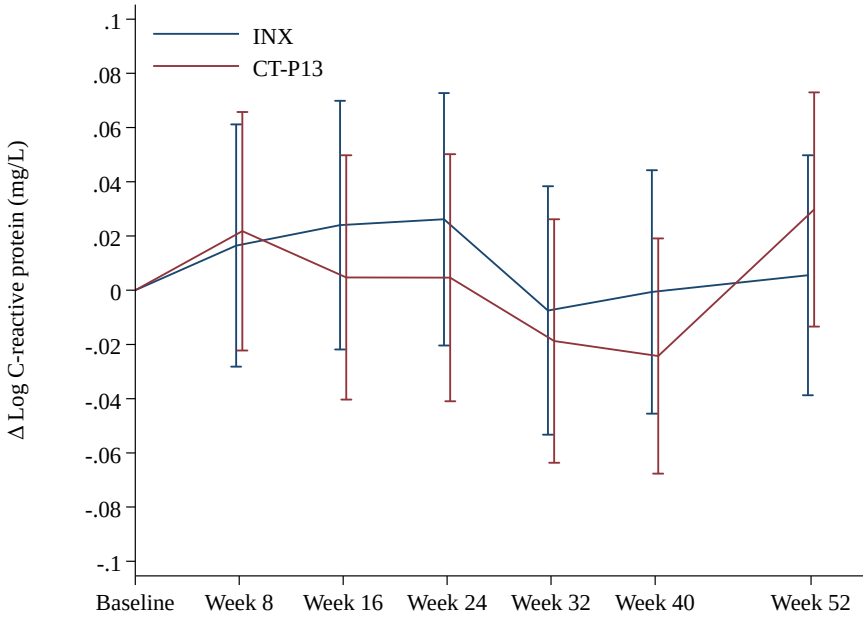
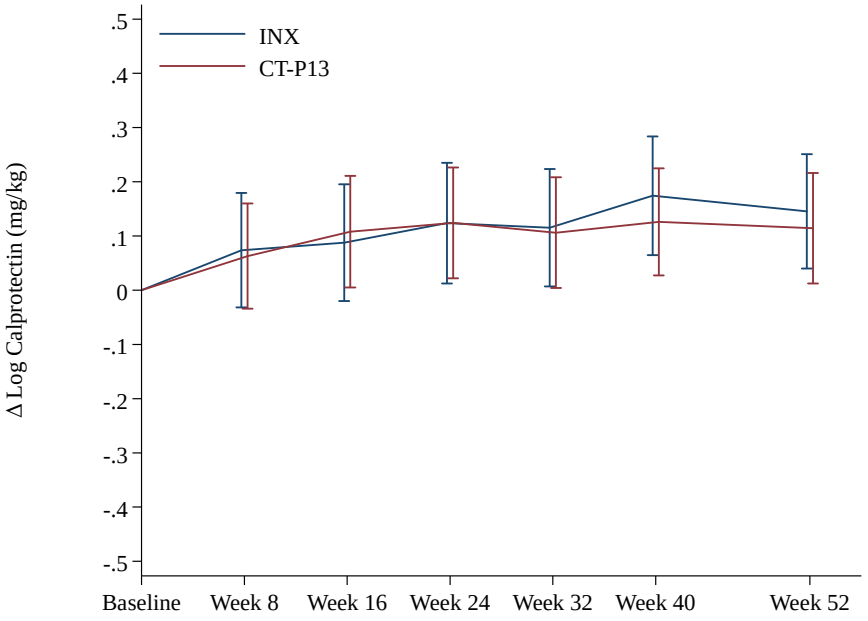
CRP and Calprotectin

Over all



CRP

IBD



Calprotectin

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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

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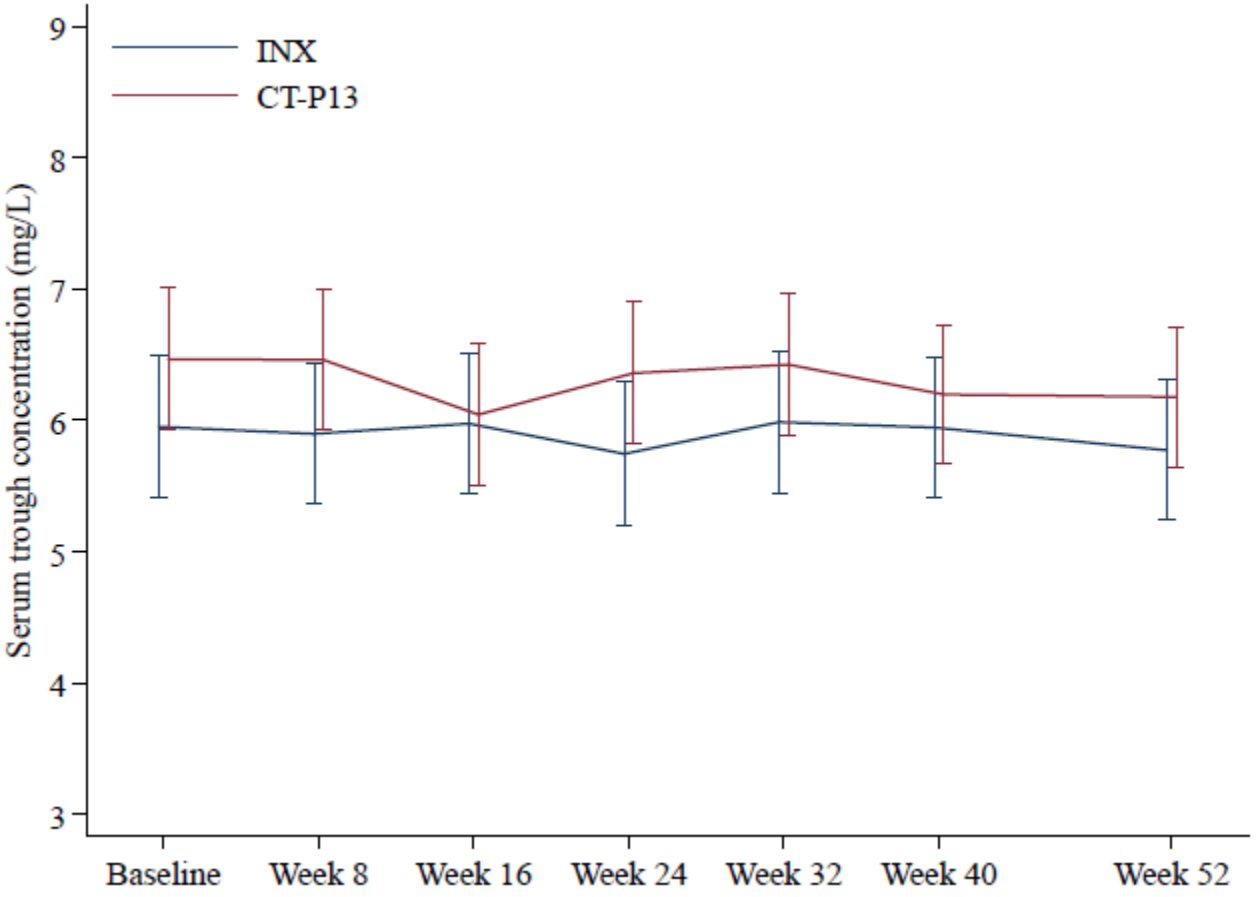
Drug trough levels



Over all

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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%)

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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 (%)

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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

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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?

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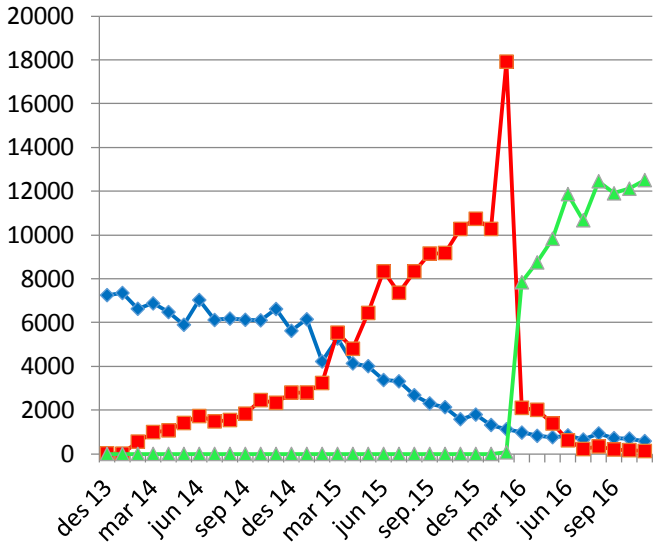
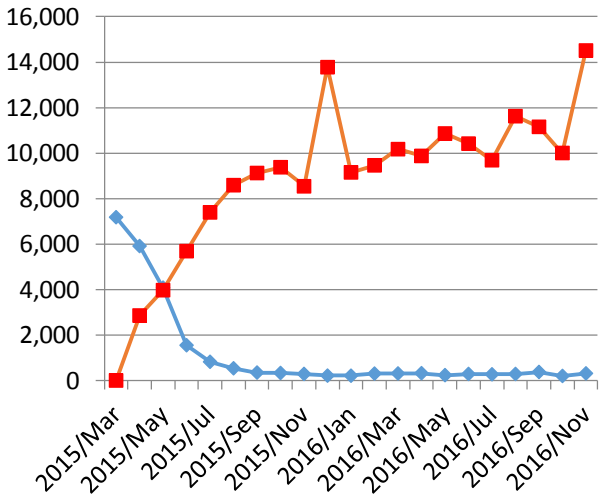
DDDs infliksimab – per Nov. 2016



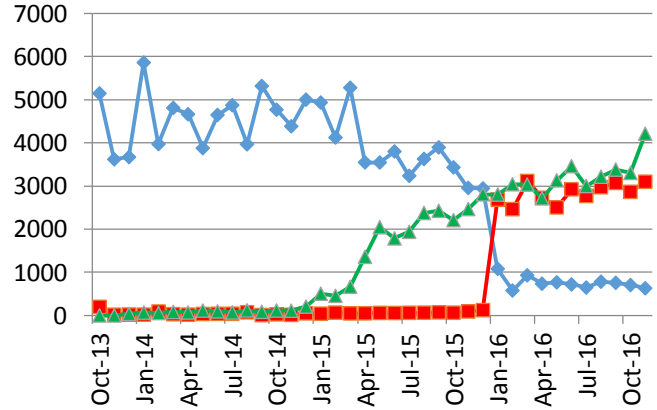
95,6%

REMICADE
REMSIMA
INFLECTRA



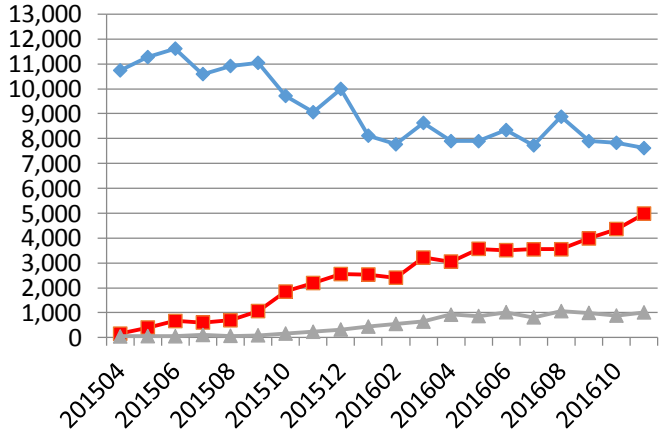
97,8%

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/

Table 1 Biosimilars for rheumatic diseases for which data have been published in peer-reviewed journals or presented at international scientific meetings

Reference product	Biosimilar molecules
Adalimumab	ABP501
	BI 695501
	CHS-1420
	GP-2017
	M923
	SB5
	ZRC-3197
Etanercept	CHS-0214
	GP2015
	HD203
	SB4*
Infliximab	BOW015†
	CT-P13*‡
	PF-06438179
	SB2
Rituximab	CT-P10
	GP2013
	PF-05280586

*Approved by EMA and multiple other countries.
†Approved in India.
‡Recommended for approval by FDA.
EMA, European Medicines Agency; FDA, Food and Drug Administration.

Dörner T et al
Ann Rheum Dis 2016

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

Jonathan Kay,[1] Monika M Schoels,[2] Thomas Dörner,[3] Paul Emery,[4] Tore K Kvien,[5] Josef S Smolen,[2,6] Ferdinand C Breedveld,[7] on behalf of the Task Force on the Use of Biosimilars to Treat Rheumatological Diseases

To cite: Kay J, Schoels MM, Dörner T, *et al*. *Ann Rheum Dis* Published Online First: [*please include* Day Month Year]. doi:10.1136/annrheumdis-2017-211937

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.