CURRENT PERSPECTIVES ON BIOSIMILARS IN IMMUNE MEDIATED INFLAMMATORY DISEASES

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Disclosures

- Research Grants: Abbvie, AstraZeneca, Lilly, Novartis and Roche
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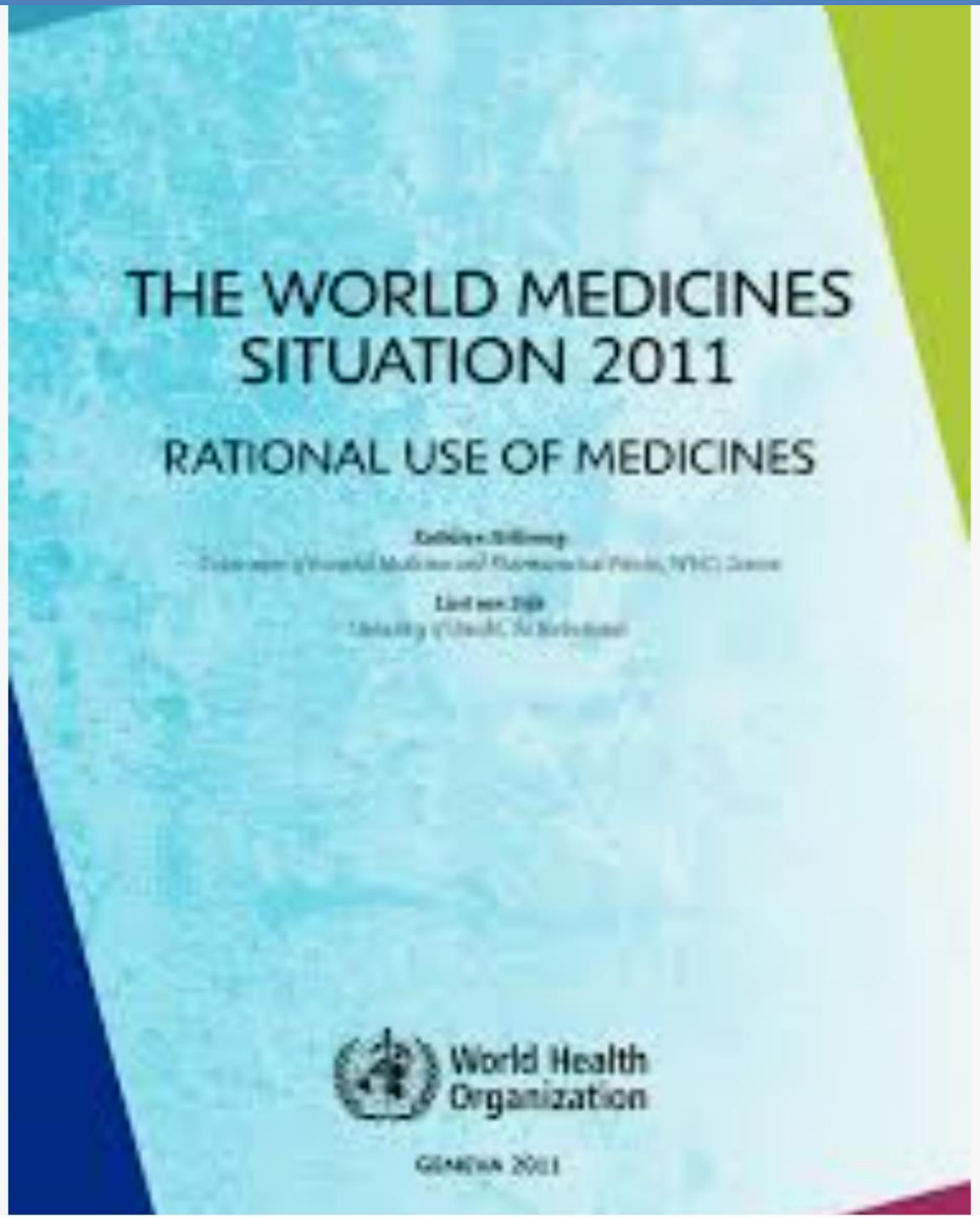
- Other: Co-Editor, Rheumatology 7E/8E; Convenor of EULAR Task Forces, Convenor of T2T Task Forces, Editor Annals of the Rheumatic Diseases

What governs my approach to RA therapy?

- The recommendation by WHO on rational use of medicines
- EULAR recommendations for the management of RA – 2019 update



INTRODUCTION

What is rational use?

Medicines use is rational (appropriate, proper, correct) when patients receive the appropriate medicines, in doses that meet their own individual requirements, for an adequate period of time, and at the lowest cost both to them and the community (*1*). Irrational (inappropriate, improper and incorrect) use of medicines is when one or more of these conditions is not met.

2021: 16 DMARDs Available to Treat RA!!!

- 3 csDMARDs
  - Methotrexate
  - Leflunomide
  - Sulfasalazine
- Glucocorticoids
  - For bridging

- 5 Anti-TNFs
  - Adalimumab
  - Certolizumab
  - Etanercept
  - Golimumab
  - Infliximab
- Biosimilars for Adalimumab Etanercept, Infliximab, and Rituximab

- 1 Costimulation inhibitor
- 2 Anti-IL-6R
- 1 Anti-B-Cell
- 4 JAK-inhibitors

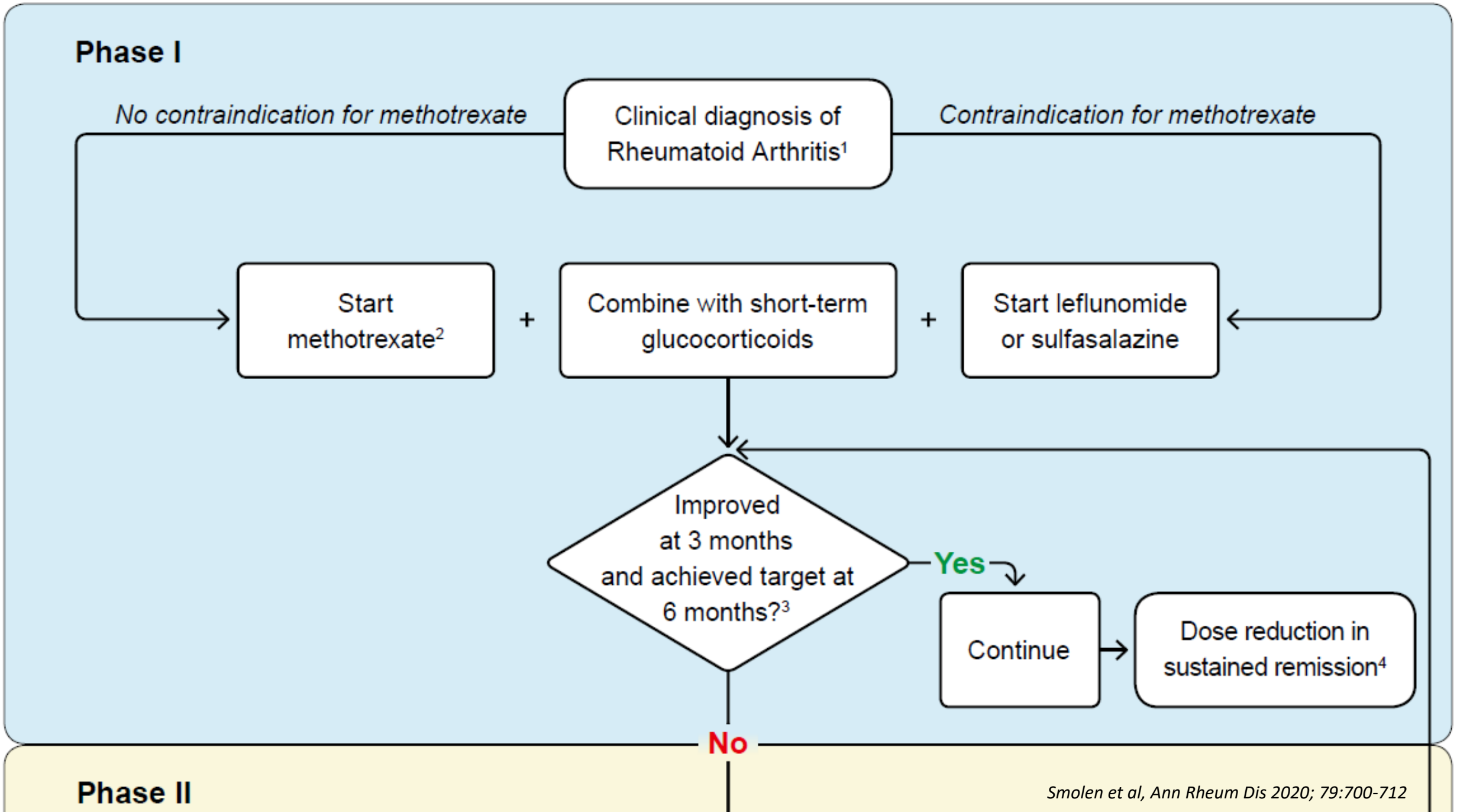
- And treatment strategies (T2T)

Recommendation

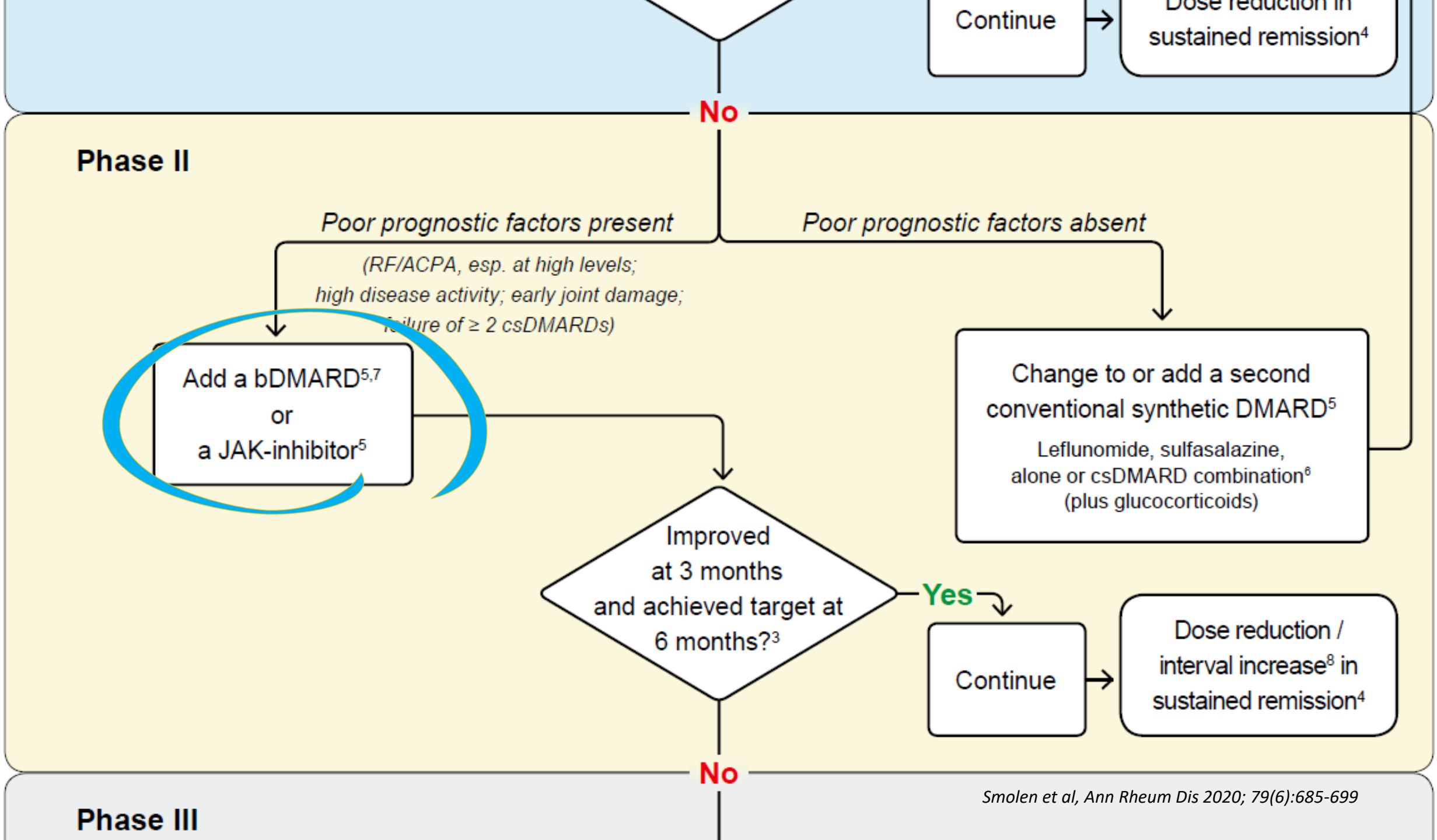
EULAR recommendations for the management of rheumatoid arthritis with synthetic and biological disease-modifying antirheumatic drugs: 2019 update

Josef S Smolen ,[1] Robert B M Landewé,[2,3] Johannes W J Bijlsma,[4] Gerd R Burmester,[5] Maxime Dougados,[6] Andreas Kerschbaumer ,[1] Iain B McInnes,[7] Alexandre Sepriano ,[8] Ronald F van Vollenhoven,[9] Maarten de Wit ,[10] Daniel Aletaha,[1] Martin Aringer ,[11] John Askling,[12] Alejandro Balsa,[13] Maarten Boers,[14] Alfons A den Broeder,[15] Maya H Buch ,[16] Frank Buttgereit,[5] Roberto Caporali,[17] Mario Humberto Cardiel,[18] Diederik De Cock,[19] Catalin Codreanu,[20] Maurizio Cutolo ,[21] Christopher John Edwards,[22] Yvonne van Eijk-Hustings ,[23] Paul Emery ,[24] Axel Finckh,[25] Laure Gossec ,[26] Jacques-Eric Gottenberg,[27] Merete Lund Hetland,[28] Tom W J Huizinga ,[29] Marios Koloumas,[30,31] Zhanguo Li,[32] Xavier Mariette,[33] Ulf Müller-Ladner,[34] Eduardo F Mysler,[35] Jose A P da Silva ,[36] Gyula Poór,[37] Janet E Pope ,[38] Andrea Rubbert-Roth ,[39] Adeline Ruyssen-Witrand,[40] Kenneth G Saag,[41] Anja Strangfeld,[42] Tsutomu Takeuchi,[43] Marieke Voshaar,[44] René Westhovens,[19] Désirée van der Heijde [29]

Ann Rheum Dis 2020; 79(6):685-699



Smolen et al, Ann Rheum Dis 2020; 79:700-712



Smolen et al, Ann Rheum Dis 2020; 79(6):685-699

EULAR recommendations for the management of rheumatoid arthritis with synthetic and biological disease-modifying antirheumatic drugs: 2013 update

Josef S Smolen,[1,2] Robert Landewé,[3,4] Ferdinand C Breedveld,[5] Maya Buch,[6,7] Gerd Burmester,[8,9] Maxime Dougados,[10] Paul Emery,[6,7] Cécile Gaujoux-Viala,[11] Laure Gossec,[12] Jackie Nam,[6,7] Sofia Ramiro,[13,14] Kevin Winthrop,[15] Maarten de Wit,[16] Daniel Aletaha,[1] Neil Betteridge,[16] Johannes W J Bijlsma,[17] Maarten Boers,[18] Frank Buttgereit,[8,9] Bernard Combe,[19] Maurizio Cutolo,[20] Nemanja Damjanov,[21] Johanna M W Hazes,[22] Marios Kouloumas,[16] Tore K Kvien,[23] Xavier Mariette,[24] Karel Pavelka,[25] Piet L C M van Riel,[26] Andrea Rubbert-Roth,[27] Marieke Scholte-Voshaar,[16] David L Scott,[28] Tuulikki Sokka-Isler,[29,30] John B Wong,[31] Désirée van der Heijde[5]

9. In patients responding insufficiently to MTX and/or other csDMARD strategies, with or without glucocorticoids, bDMARDs (TNF inhibitors*, abatacept or tocilizumab, and, under certain circumstances, rituximab†) should be commenced with MTX
10. If a first bDMARD has failed, patients should be treated with another bDMARD; if a first TNF inhibitor therapy has failed, patients may receive another TNF inhibitor* or a biological agent with another mode of action
11. Tofacitinib may be considered after biological treatment has failed
12. If a patient is in persistent remission after having tapered glucocorticoids, one can consider tapering‡ bDMARDs§, especially if this treatment is combined with a csDMARD
13. In cases of sustained long-term remission, cautious reduction of the csDMARD dose could be considered, as a shared decision between patient and physician
14. When therapy needs to be adjusted, factors apart from disease activity, such as progression of structural damage, comorbidities and safety issues, should be taken into account

*TNF inhibitors: adalimumab, certolizumab pegol, etanercept, golimumab, infliximab, biosimilars (as approved according to a thorough approval process, such as by EMA and/or FDA),

Smolen JS, et al. Ann Rheum Dis 2014;73:492–509

ACR-EULAR 2011 Definition of Remission

For Clinical Trials

Boolean

SJC, TJC, PtGA (0–10 scale), CRP (in mg/dL) all ≤1

Index-based

SDAI ≤3.3

SDAI = 28SJC + 28TJC + EGA + PtGA + CRP (mg/dL)

For Clinical Practice

Boolean

SJC, TJC, PtGA (0–10 scale) all ≤1

Index-based

CDAI ≤2.8

CDAI = 28SJC + 28TJC + EGA + PtGA

DAS28 should not be used to define remission !

Felson D et al. Arthritis Rheum, 2011;63:573–586, and Ann Rheum Dis. 2011;70:404–413

EGA = evaluator global disease activity
PtGA = patient global disease activity

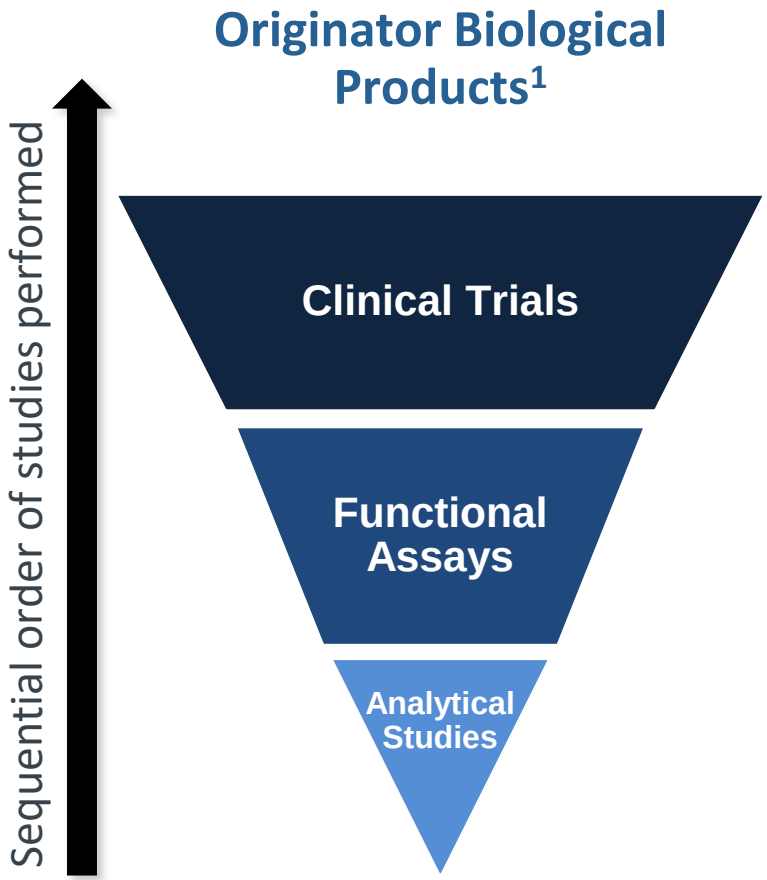
Biosimilars are truly similar to the originator in terms of efficacy and safety…

Approaching Biosimilars

A biosimilar is ‘a biotherapeutic product which is similar in terms of quality, safety and efficacy to an already licensed reference biotherapeutic product’, with similarity defined as ‘the absence of a relevant difference in the parameter of interest’

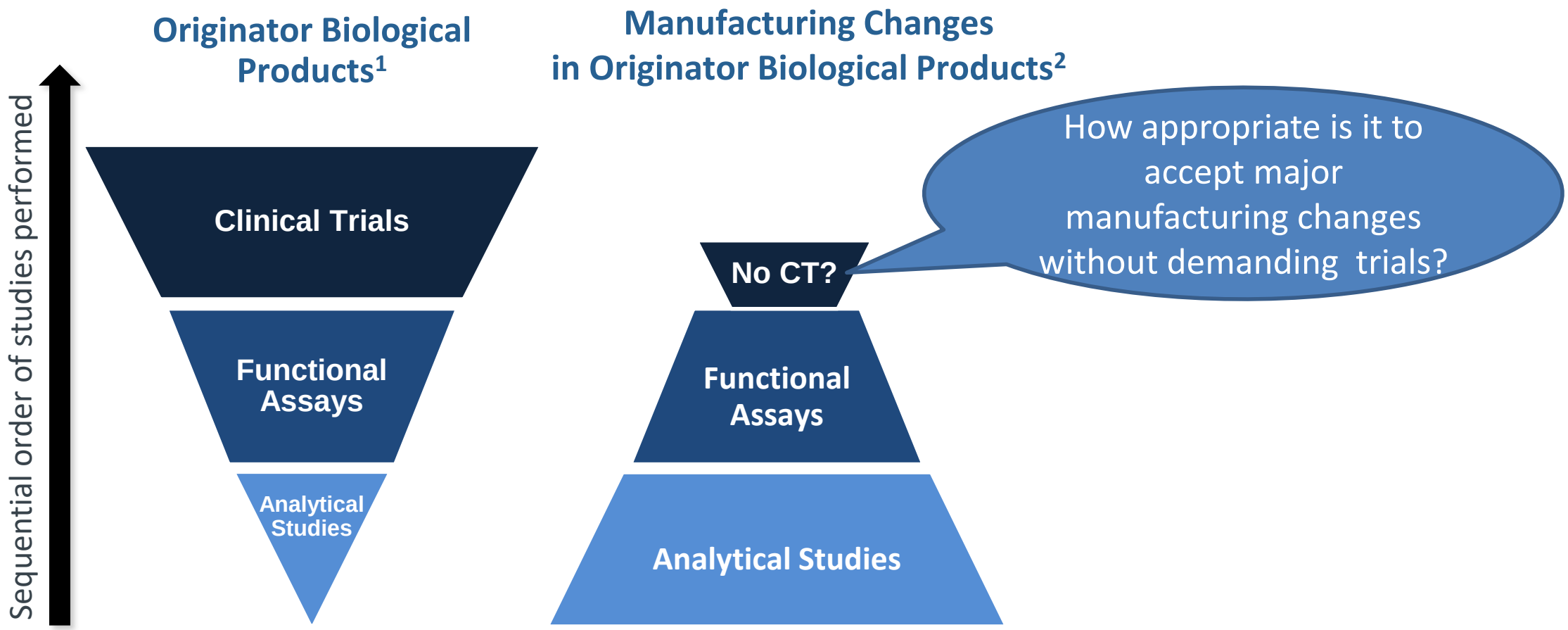
World Health Organization. Expert committee on biological standardization. Geneva, 19 to 23 October 2009. Guidelines on evaluation of similar biotherapeutic products (SBPs). http://www.who.int/biologicals/areas/biological_therapeutics/BIOTHERAPEUTICS_FOR_WEB_22APRIL2010.pdf (accessed 10 Sep 2012).

Development of a Biologic Drug



Kingham R. Key regulatory guidelines for the development of biologics in the United States and Europe. 2014.

Continued Production of a Biologic Drug



1. *Kingham R. Key regulatory guidelines for the development of biologics in the United States and Europe. 2014.*

2. *US FDA. Q5E comparability of biotechnological/biological products subject to changes in their manufacturing process. 2005.*

INTERNATIONAL CONFERENCE ON HARMONISATION OF TECHNICAL REQUIREMENTS FOR REGISTRATION OF PHARMACEUTICALS FOR HUMAN USE

ICH HARMONISED TRIPARTITE GUIDELINE

COMPARABILITY OF BIOTECHNOLOGICAL/BIOLOGICAL PRODUCTS SUBJECT TO CHANGES IN THEIR MANUFACTURING PROCESS

Q5E

November 2004

A determination of comparability can be based on a combination of analytical testing, biological assays, and, in some cases, nonclinical and clinical data. If a manufacturer can provide assurance of comparability through analytical studies alone, nonclinical or clinical studies with the post-change product are not warranted. However, where the relationship between specific quality attributes and safety and efficacy has not been established, and differences between quality attributes of the pre- and post-change product are observed, it might be appropriate to include a combination of quality, nonclinical, and/or clinical studies in the comparability exercise.

2.5.2 Type of Studies

The nonclinical and clinical studies referred to in this document might include, depending on the situation, PK studies, PD studies, PK/PD studies, clinical efficacy studies, specific safety studies, immunogenicity studies and pharmacovigilance studies. The purpose of these studies is to enable comparison of pre- and post-change product. Where appropriate, these studies should be direct comparative studies.

http://www.ich.org/fileadmin/Public_Web_Site/ICH_Products/Guidelines/Quality/Q5E/Step4/Q5E_Guideline.pdf

Variability is in the nature of glycoproteins

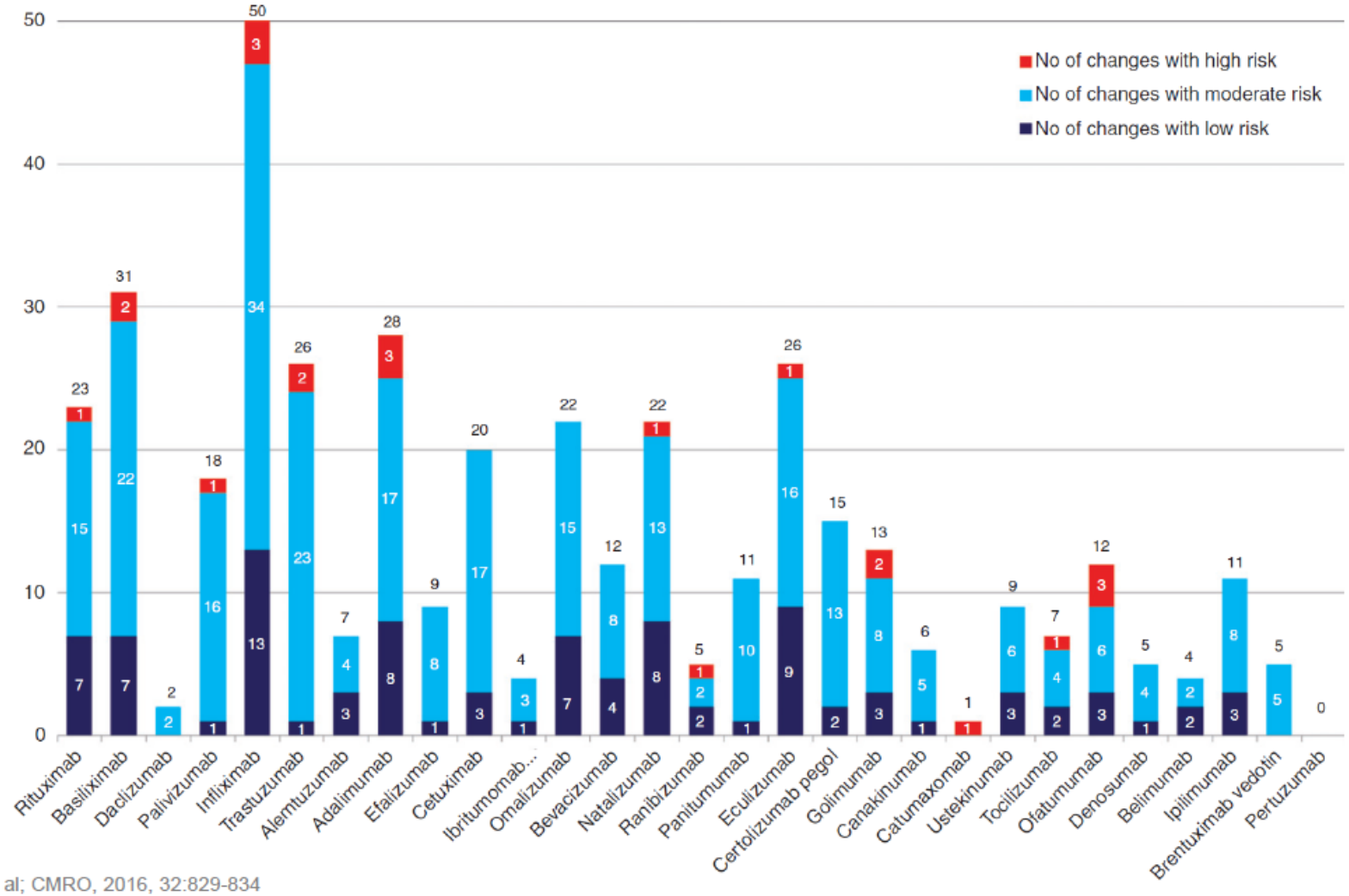
Batch-to-batch variations

- Non-identicality is a normal principle in glycosylated proteins
- **No batch of any biologic is "identical" to the other batches**
- Variability is natural even in the human body and usually not problematic

Manufacturing changes

- Manufacturing changes are made frequently
- Differences in attributes often larger than batch-to-batch variability
- **Such changes are stringently controlled by regulators and approved only if they do NOT lead to clinically meaningful differences**

Changes in the manufacturing process after originator approval

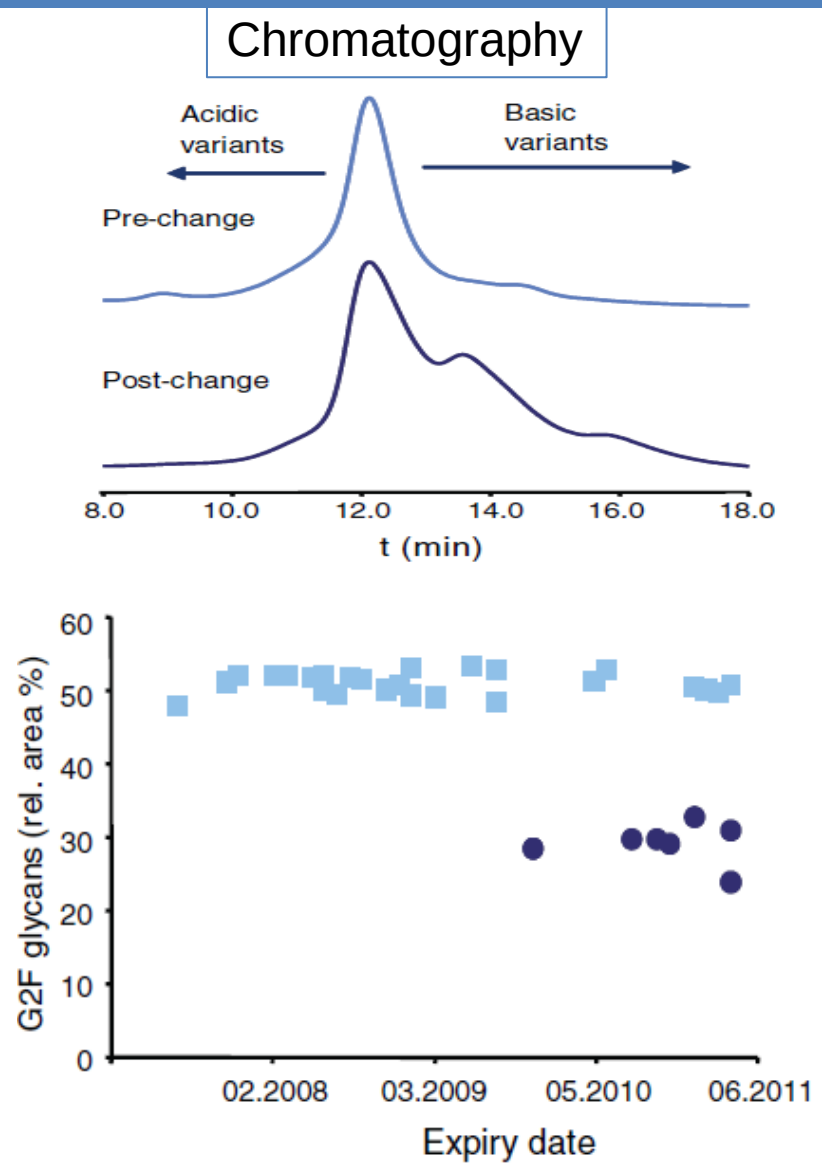


Vezér B, Zrubka Z et al; CMRO, 2016, 32:829-834

1. Weise et al. *Blood* 2012;120:5111-5117
2. Schiestl et al. *Nat Biotech* 2011; 29:310-312
3. Schneider *Ann Rheum Dis* 2013;72(3) 315-318

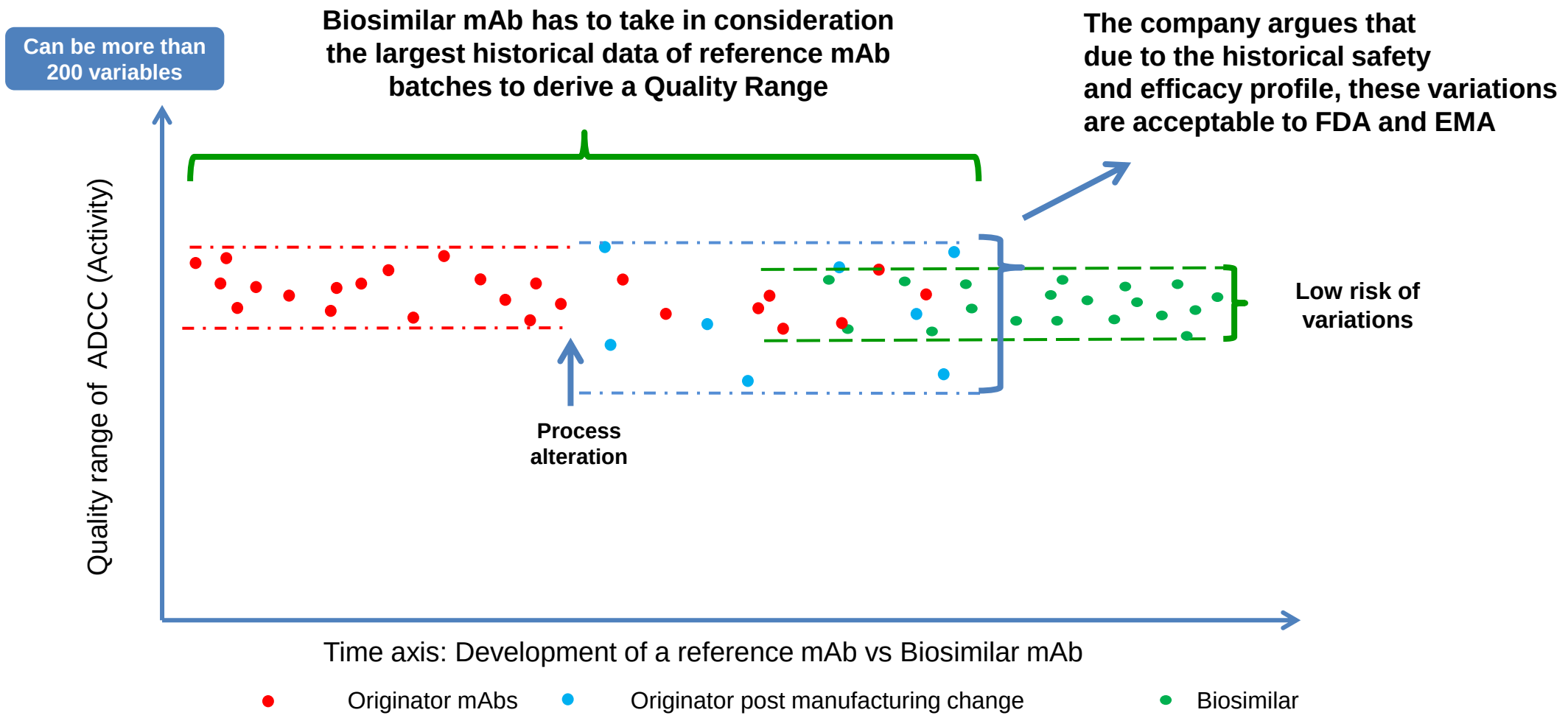
Etanercept

- Different batches tested
- Major differences were found in the glycosylation profile. The amount of variants containing the *N*-glycan G2F decreased from ~50% in the pre-change to ~30% in the post-change material



Schiestl et al, Nat Biotechol 2011; 29:310-2

The goal posts of biosimilarity:
The originator sets the rules for quality



IBD: ECCO issued its own position statement

SPECIAL ARTICLE

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

Silvio Danese [a,*], Fernando Gomollon [b,**] on behalf of the Governing Board and Operational Board of ECCO

[a] *IBD Center, Humanitas Clinical and Research Centre, Milan, Italy*
[b] *IIS, HCU Zaragoza, CIBEREHD, Spain*

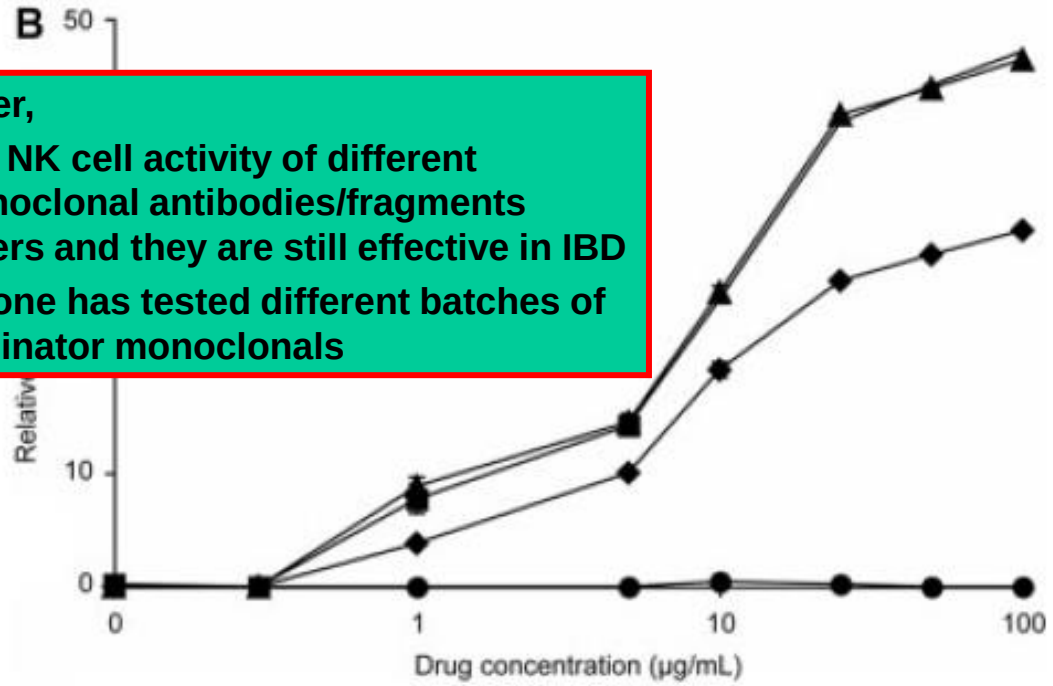
This position statement was drafted by Silvio Danese, Milan Italy and Fernando Gomollon, Zaragoza Spain and approved by the members of the Operational Board and Governing Board of ECCO: Simon Travis, Severine Vermeire, Axel Dignass, Floria Rieder, Marian O'Connor, Gerassimos Manzaris, Matthieu Allez, Peter Lakatos, Andre D'Hoore, Jannake van der Woude, Milan Lukas, and Daan Hommes.

Danese, *et al. J Crohns Colitis* 2013;7:586-589

Antibody Mediated Cytotoxicity (NK Cell)

However,

- **The NK cell activity of different monoclonal antibodies/fragments differs and they are still effective in IBD**
- **No one has tested different batches of originator monoclonals**



iments ± SEM. (B) Mediation of antibody-dependent cell-mediated cytotoxicity of TNFα-expressing TNF6.5 cells (targets) by infliximab (▲), adalimumab (■), etanercept (◆), and certolizumab pegol (●) in vitro in the presence of CD14-positive cell-depleted peripheral blood mononuclear cells (effectors), as assessed by uptake of PI by the target cells. Values shown are the percentages of PI-positive cells with the test agent minus the percentage of PI-positive cells achieved with the control. Results are the mean of 3 experiments ± SEM.

Nesbitt et al, Inflamm. Bowel Dis 2007; 13: 1323

LETTER TO THE EDITOR

ECCO position challenged by European drug regulators

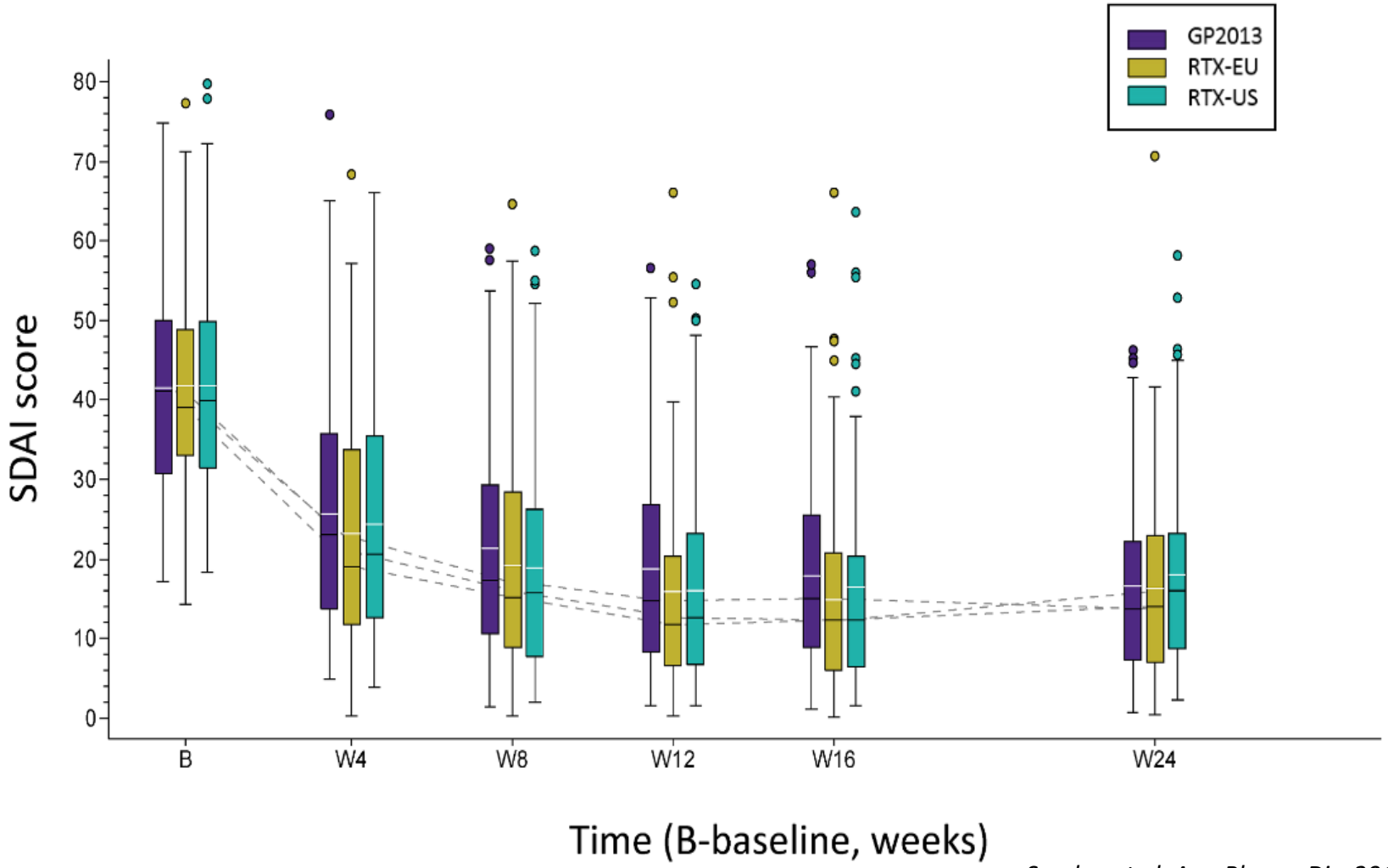
Kurki P, et al. Journal of Crohn's and Colitis (2014) 8, 258

NORWAY:
Switch study from originator Infliximab to biosimilar Infliximab has been published, addressing question of substitution

The scientific rationale for the extrapolation of efficacy to the indications not studied is based on the comprehensive characterisation and comparison of the physicochemical, binding and functional characteristics of the biosimilar and innovator products; indeed, similar effects were demonstrated in a wide range of *in vitro* and *ex vivo* functional assays, including experimental models tailored to IBD.

No pharmacokinetic or safety issues are known to be specific to IBD and the most responsive population (rheumatoid arthritis) was used to investigate immunogenicity; therefore, these clinical results enable the extrapolation of pharmacokinetics and safety data to patients with IBD.

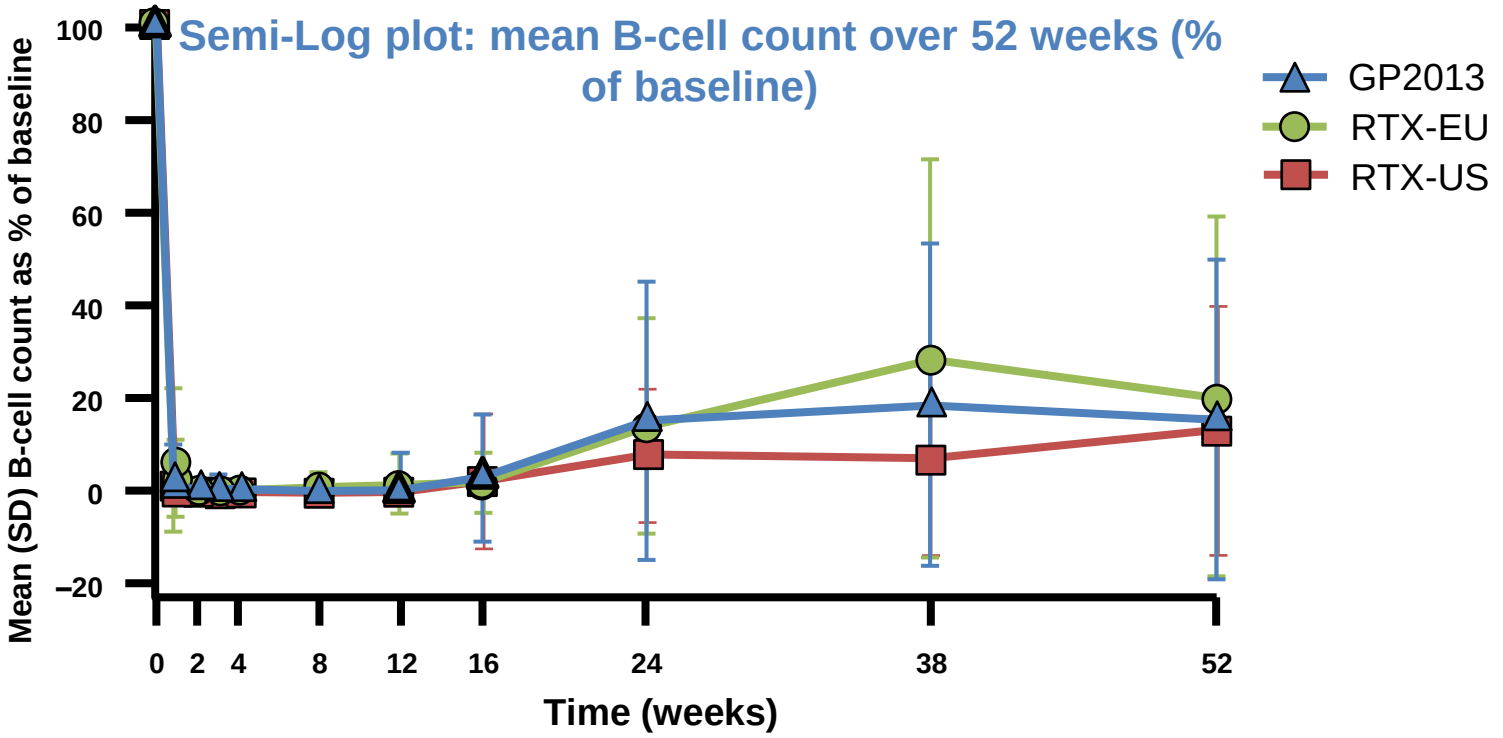
Originator Products and Biosimilar: SDAI



Smolen et al, Ann Rheum Dis. 2017;76:1598-1602

PD: B-Cell Depletion Until Week 52

(PK analysis set)

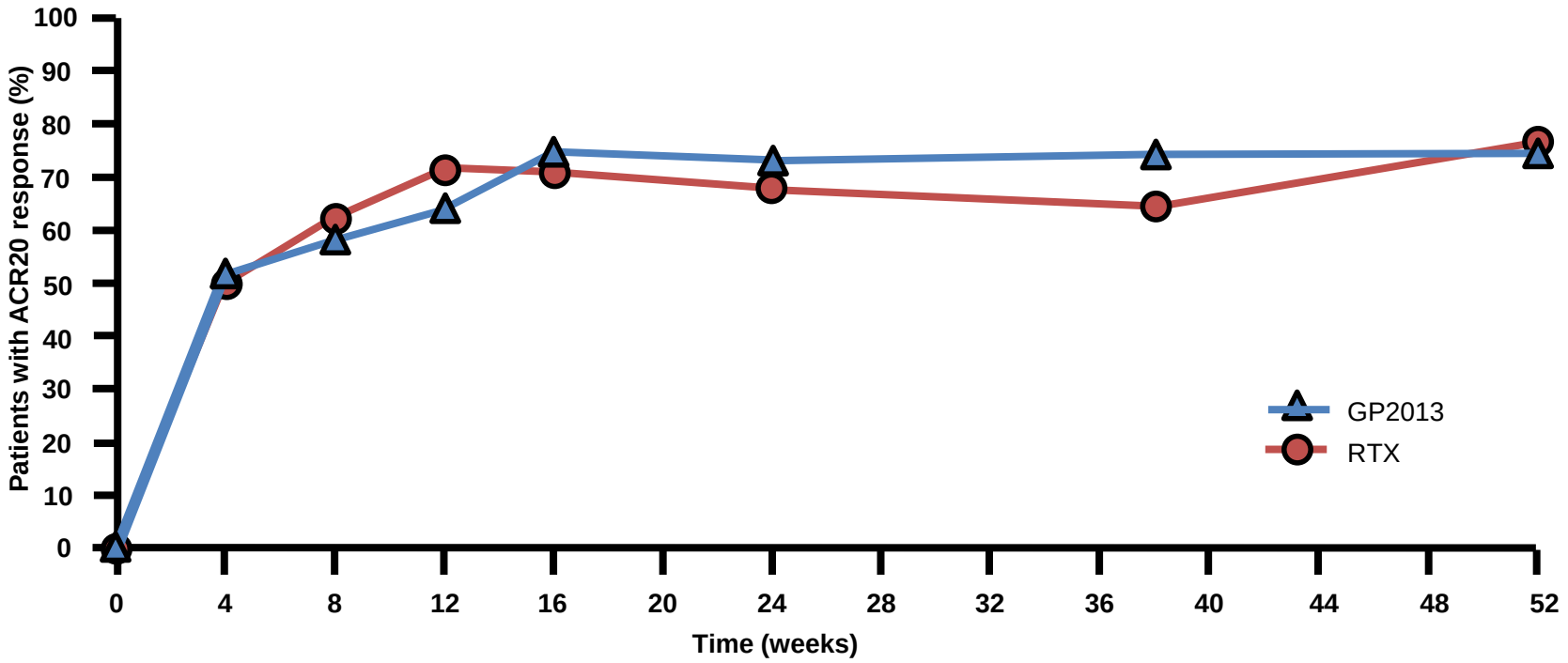


PD, pharmacodynamics; PK, pharmacokinetics; RTX, rituximab; SD, standard deviation

Smolen et al, Ann Rheum Dis. 2017 Sep;76(9):1598-1602

GP2013 (Rituximab) Efficacy: ACR20 response rate

(Per protocol set)



ACR20, 20% improvement in American College of Rheumatology criteria; RTX, rituximab

Smolen et al, Ann Rheum Dis. 2017 Sep;76(9):1598-1602

Immunogenicity: ADA incidence

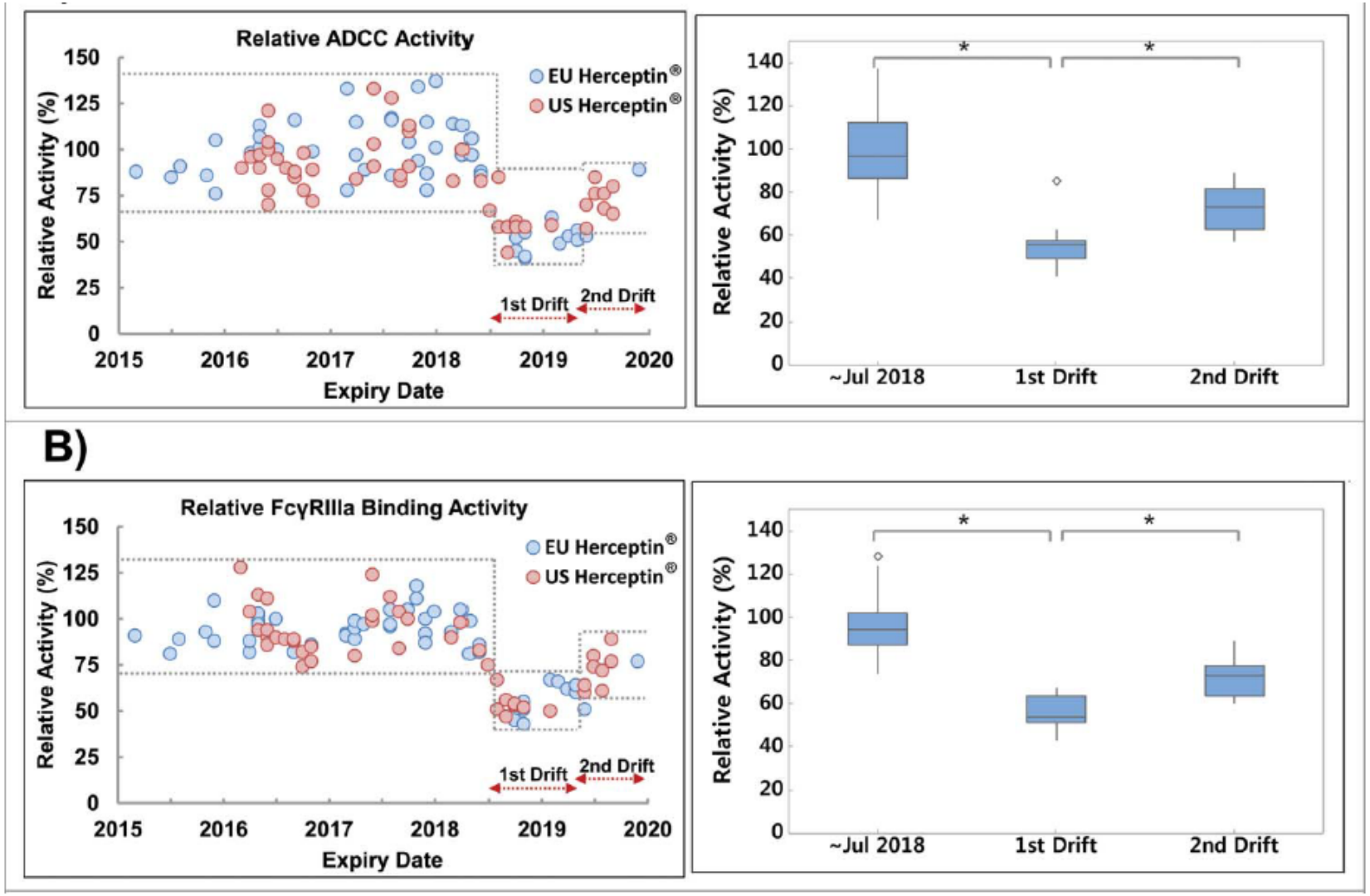
(Safety analysis set)

Result	GP2013 N=133	RTX-EU N=87	RTX-US N=92
ADA	16.5%	21.4%	13.4%
		15.1%	
NAb at any time	3.9%	1.2%	0
NAb at end of study	0	1.2%	0
Safety: IRR in NAb+ patients	1 - Throat tightness (IRR, AE)	2 - Gastroenteritis (IRR, AE) - Infusion reaction (IRR, SAE)	n/a
Efficacy: ACR20 response in NAb patients	Yes	No	n/a
Maximum ADA titer	40,000	800,000	800

ACR20, 20% improvement in American College of Rheumatology criteria; ADA, anti-drug antibody; AE, adverse event; IRR, infusion-related reaction; NAb, neutralizing antibody; RTX, rituximab; SAE, serious adverse event

Smolen et al, Ann Rheum Dis. 2017 Sep;76(9):1598-1602

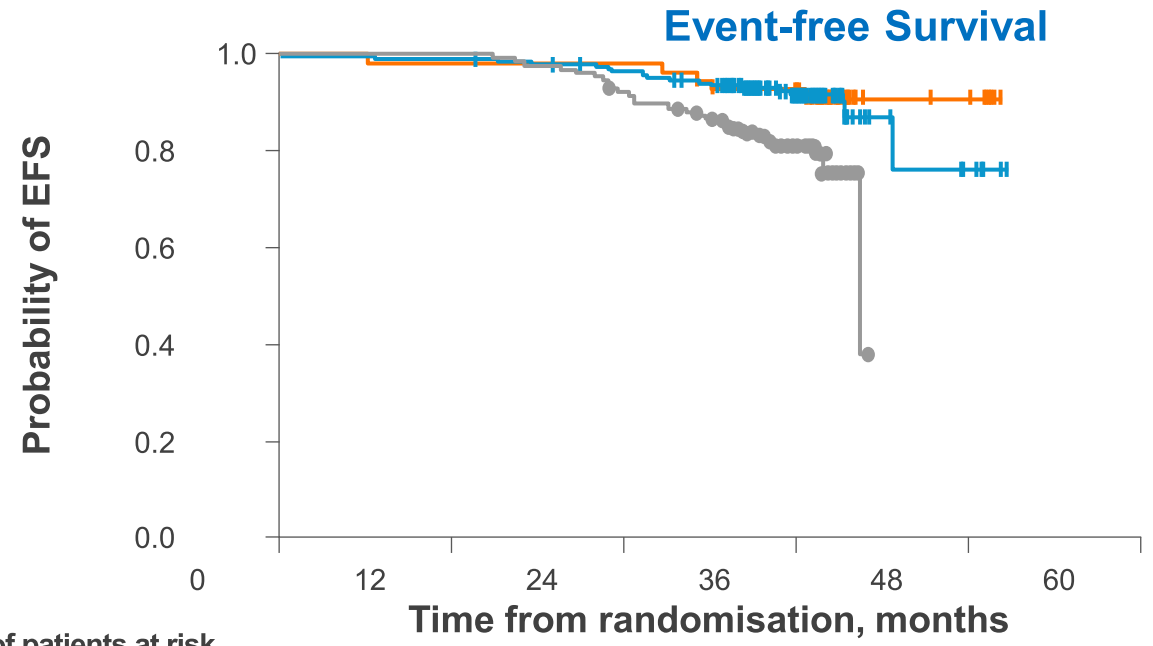
Herceptin: Changes of Fcγ-Binding and ADCC



Kim et al, MAbs 2017

Event-Free Survival With Originator Trastuzumab and Biosimilar Trastuzumab SB3: 3-year Follow-up by ADCC[1]

- **EFS rate was comparable between SB3 and non-drifted trastuzumab RP**
- **EFS rate was higher with non-drifted trastuzumab RP versus drifted trastuzumab RP, with post hoc analysis suggesting that a downward drift in ADCC activity as a contributing factor[1]**



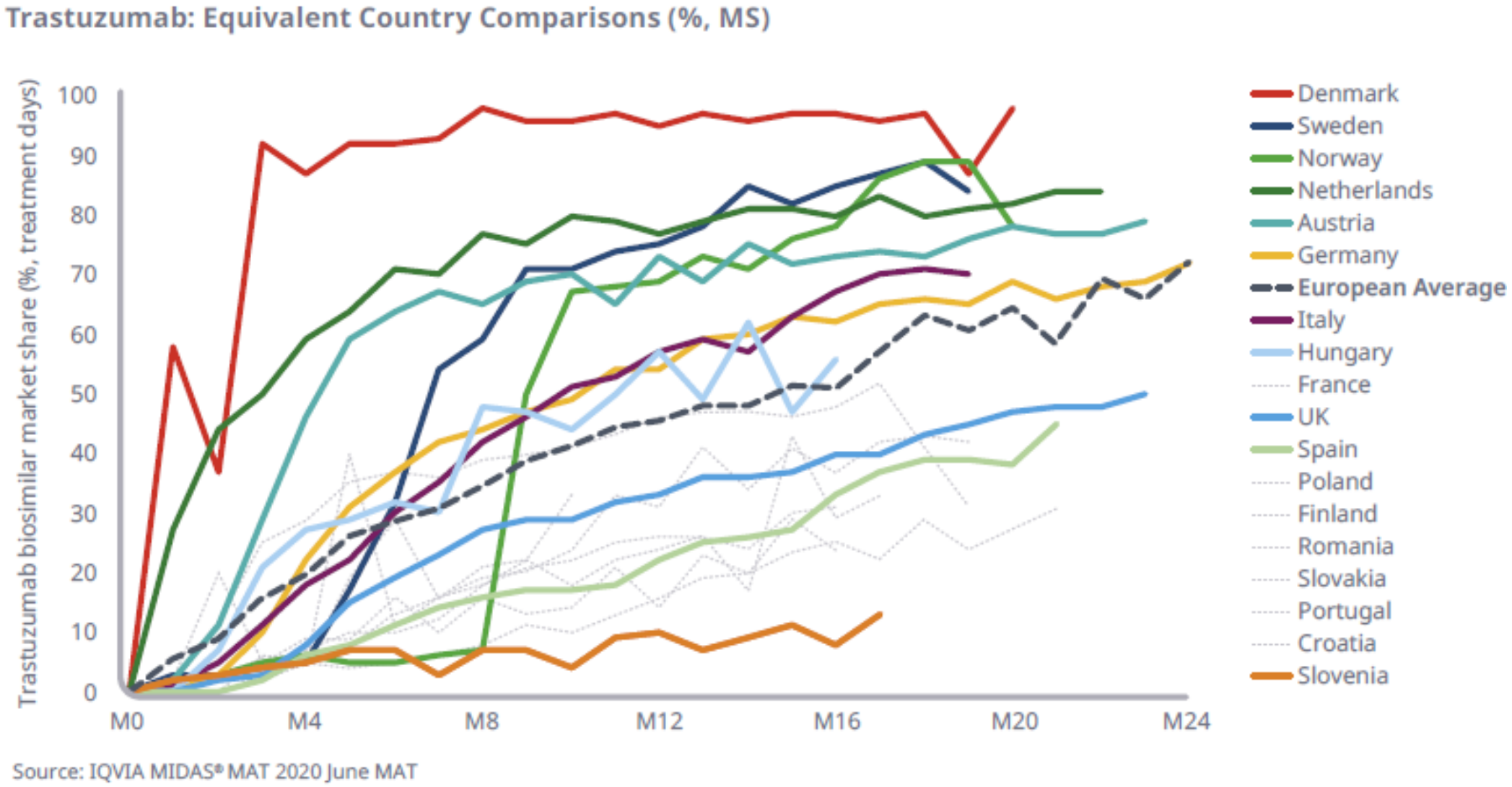
No. of patients at risk						
SB3	186	185	175	123	5	0
Non-drifted trastuzumab RP	55	54	54	48	7	0
Drifted trastuzumab RP	126	126	115	66	0	

	No. of Events (%)		HR (95% CI)
SB3	17 (9.1)	SB3/ Non-drifted TRZ	0.93 (0.31, 2.85)
Non-drifted TRZ	5 (9.1)		
Drifted TRZ	26 (20.6)	Drifted TRZ/ Non-drifted TRZ	5.31 (1.74, 16.25)

EFS, Event-free survival; HR, Hazard Ratio; SB3, Ontruzant®; TRZ, Trastuzumab RP; RP, reference product

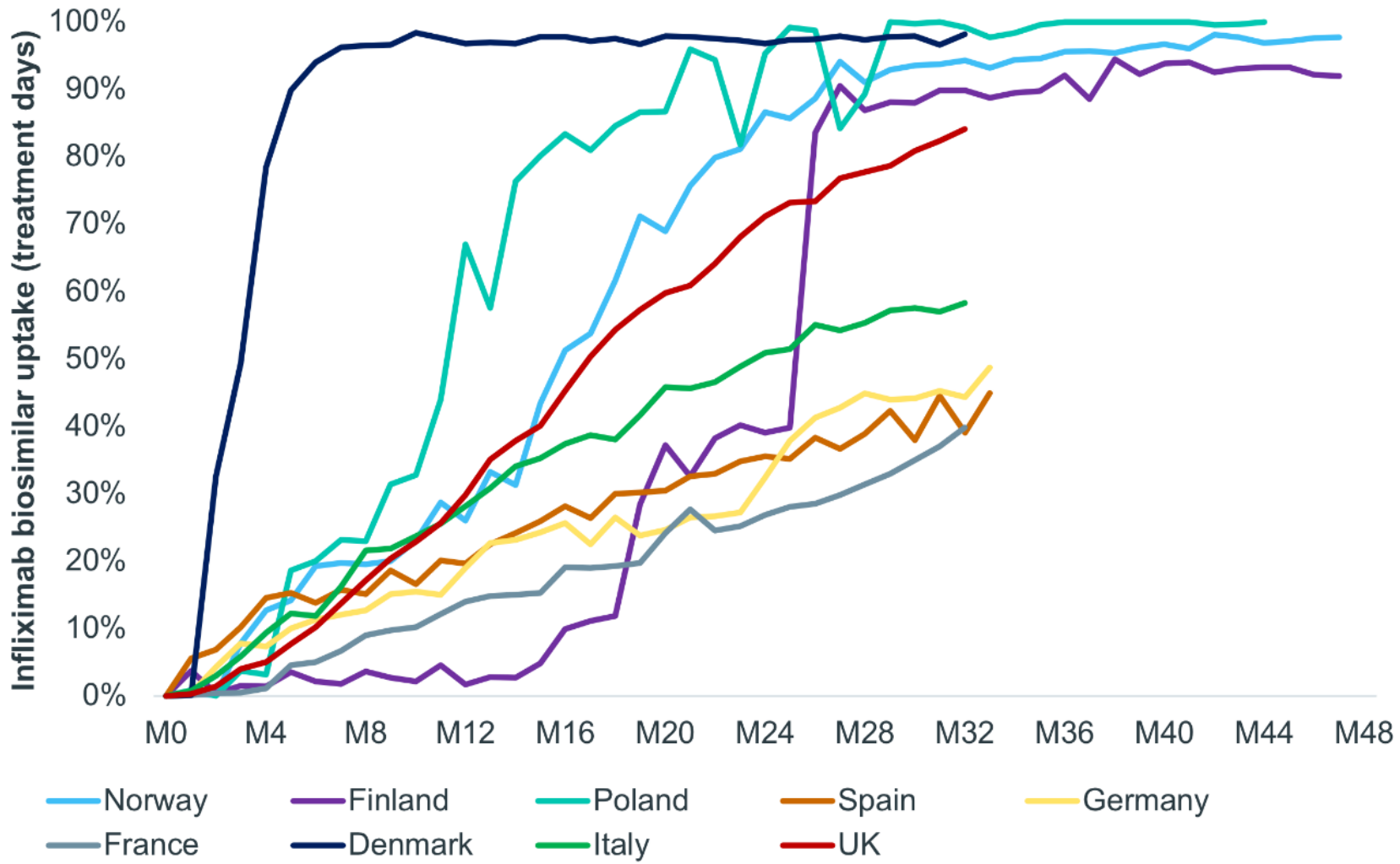
1. Pivot X, *et al*. Eur J Cancer. 2019;120:1-9. doi: 10.1016/j.ejca.2019.07.015.

Trastuzumab biosimilar uptake since launch across European markets



Source: IQVIA MIDAS® MAT 2020 June MAT

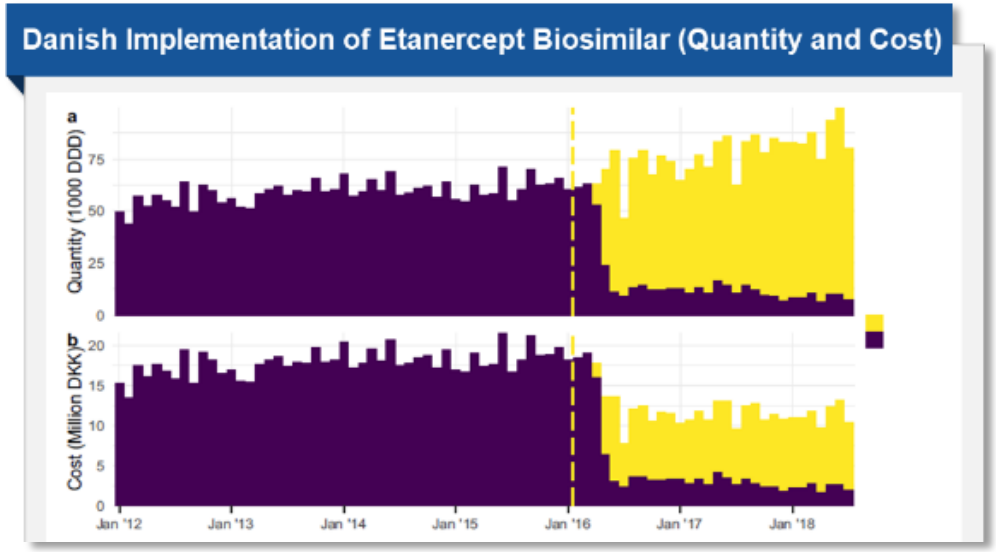
Infliximab biosimilar uptake since launch across European markets



Per Troein, IQVIA, March 2018

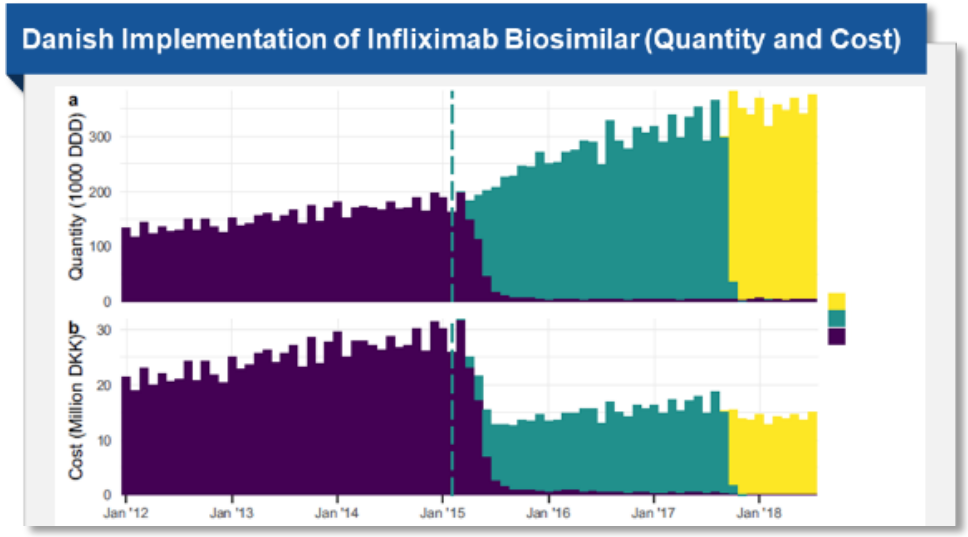
Cost Reduction due to Biosimilars

- In 2017, Etanercept biosimilar (SB4) accounted for 84.2% of total etanercept consumption in Denmark
- Example Denmark: The cost of infliximab was reduced by approximately two-thirds when changing from reference product to biosimilar, equivalent to a cost saving of 200 million DKK (approximately 30M USD) in 2015, which was the year biosimilars were introduced



The dashed vertical line on 1 Feb 2016 represents

Reference Etanercept | Etanercept Biosimilar



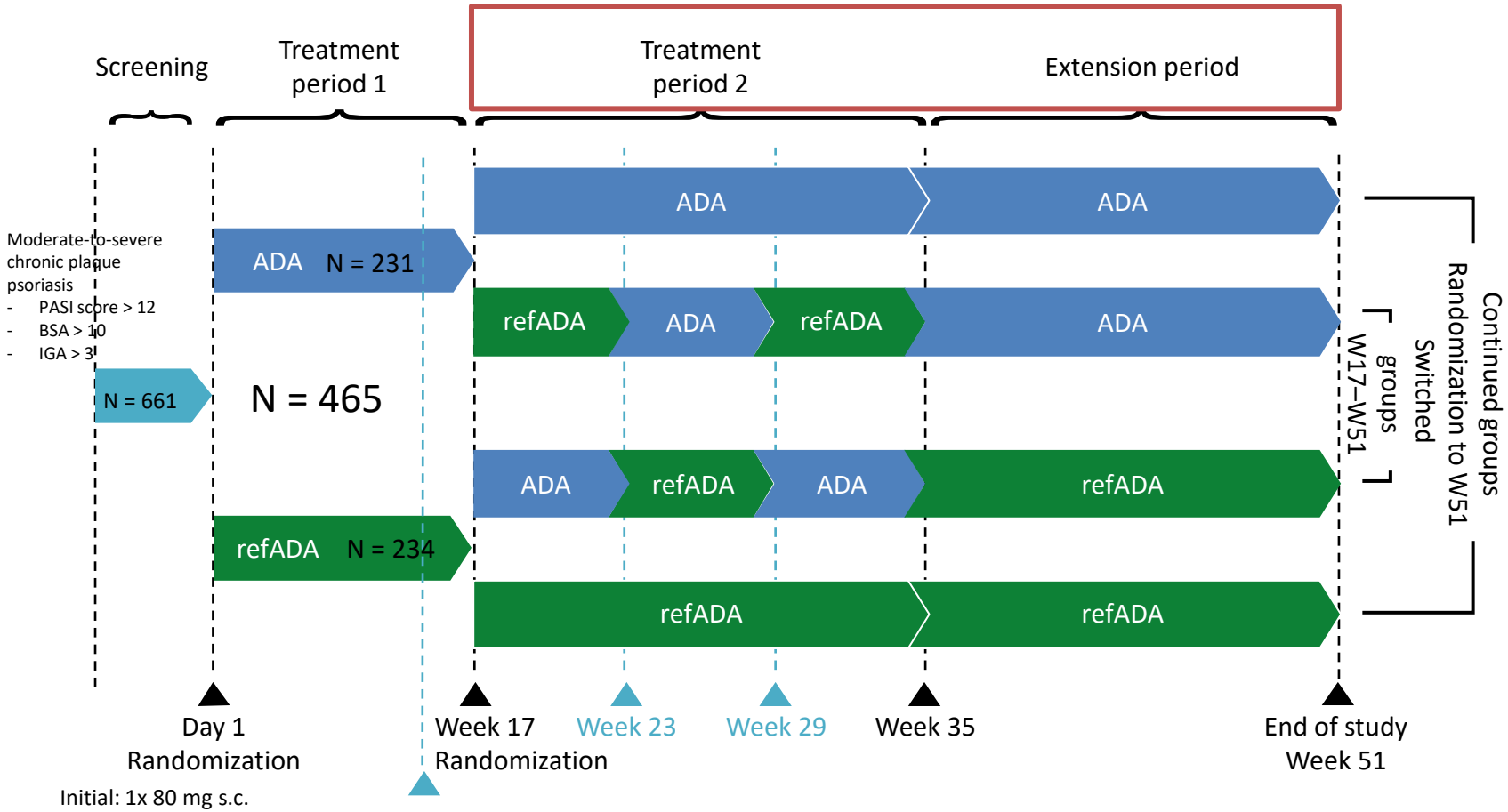
The dashed vertical line on 13 Feb 2015 represents

Reference Infliximab | Infliximab Biosimilar 1 | Infliximab Biosimilar 2

Jensen, TB (2019) European Journal of Clinical Pharmacology https://doi.org/10.1007/s00228-019-02765-3

But what about switching between originator and biosimilar?

Multicenter, Randomized, Double-Blind, Comparator-Controlled Phase III Study in Psoriasis With Four Study Periods

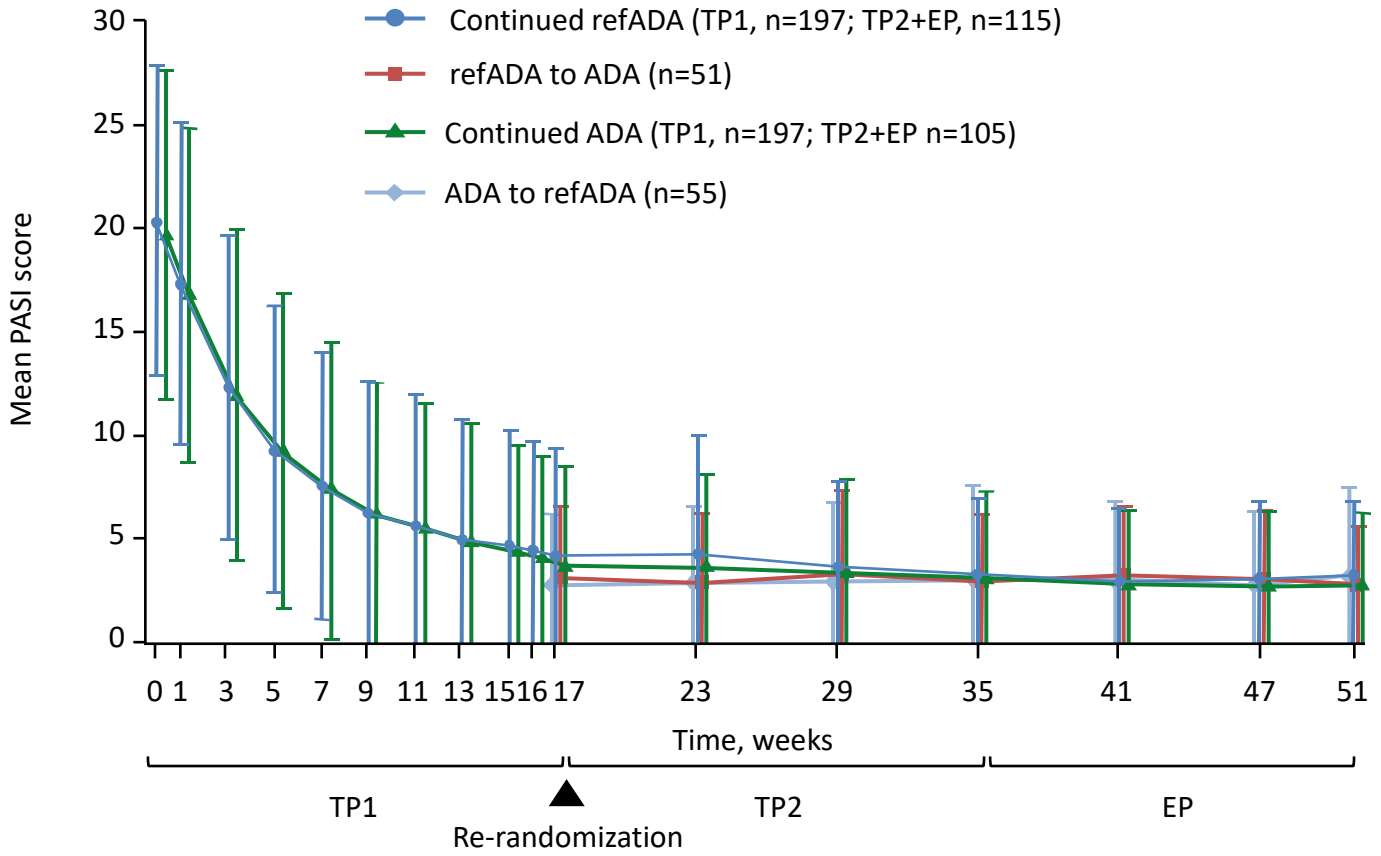


NCT02016105

ADA, proposed biosimilar adalimumab; refADA, reference adalimumab; N = 73 study centers in USA, Bulgaria, Slovakia, France

Blauvelt et al, Br J Dermatol. 2018 Sep;179(3):623-631

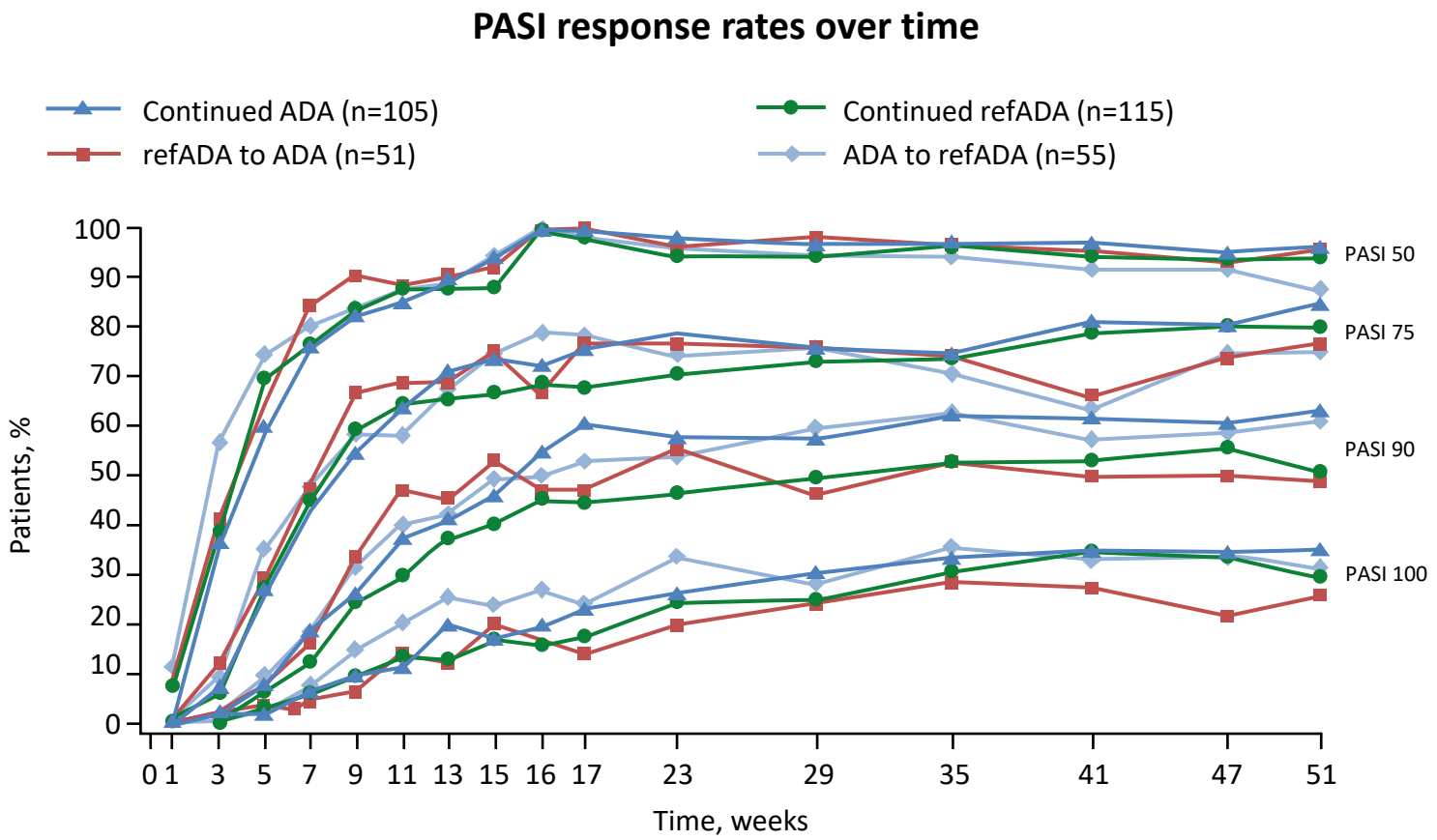
Mean absolute PASI score was similar over time



ADA, proposed biosimilar adalimumab; EP, extension period; PASI, Psoriasis Area and Severity Index; refADA, reference adalimumab; TP, treatment period

Blauvelt et al, Br J Dermatol. 2018 Sep;179(3):623-631

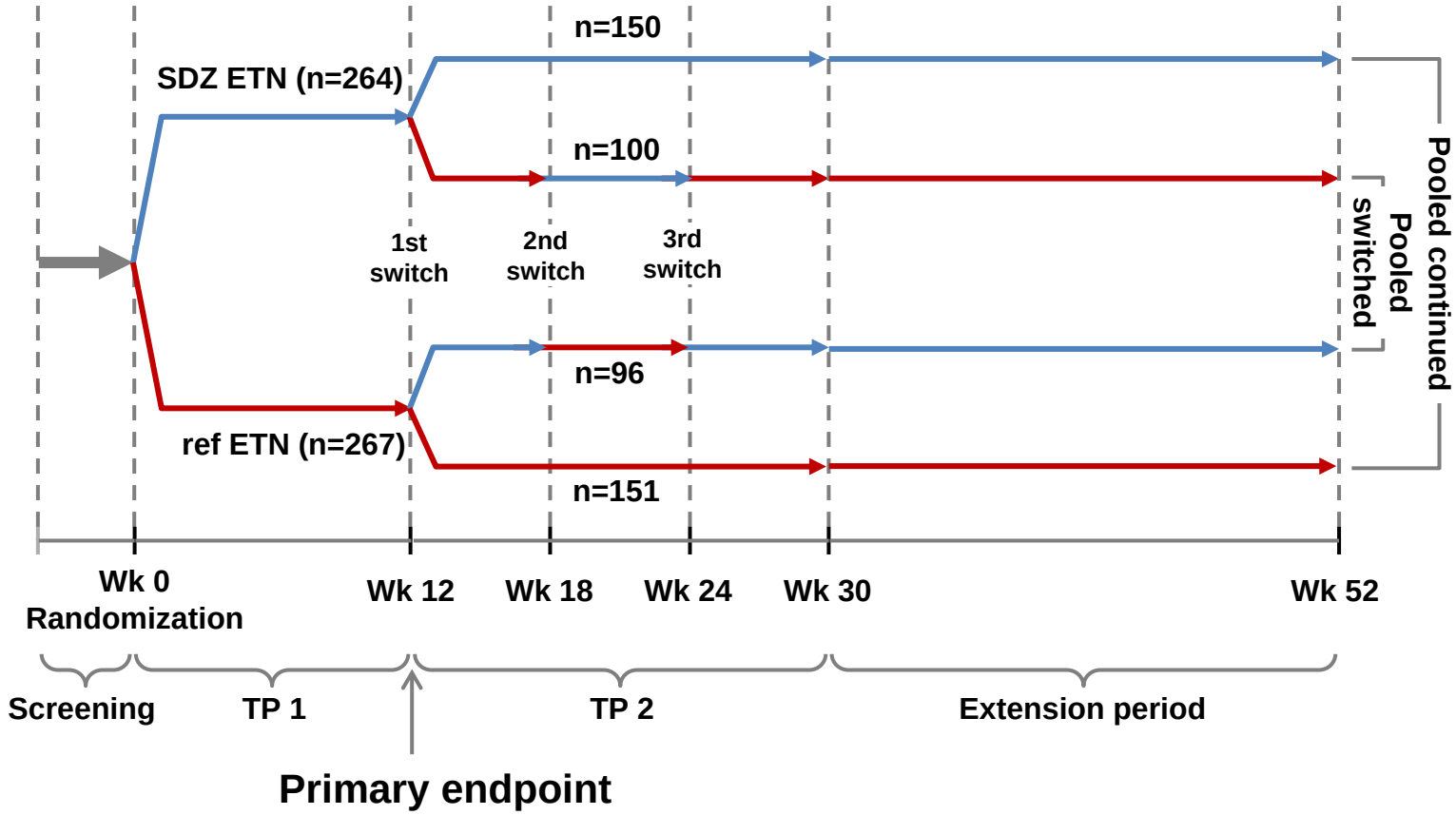
Efficacy Was Similar and Sustained in Patients Continuously Treated with ADA or refADA, or Switched Between ADA and refADA



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

Blauvelt et al, Br J Dermatol. 2018 Sep;179(3):623-631

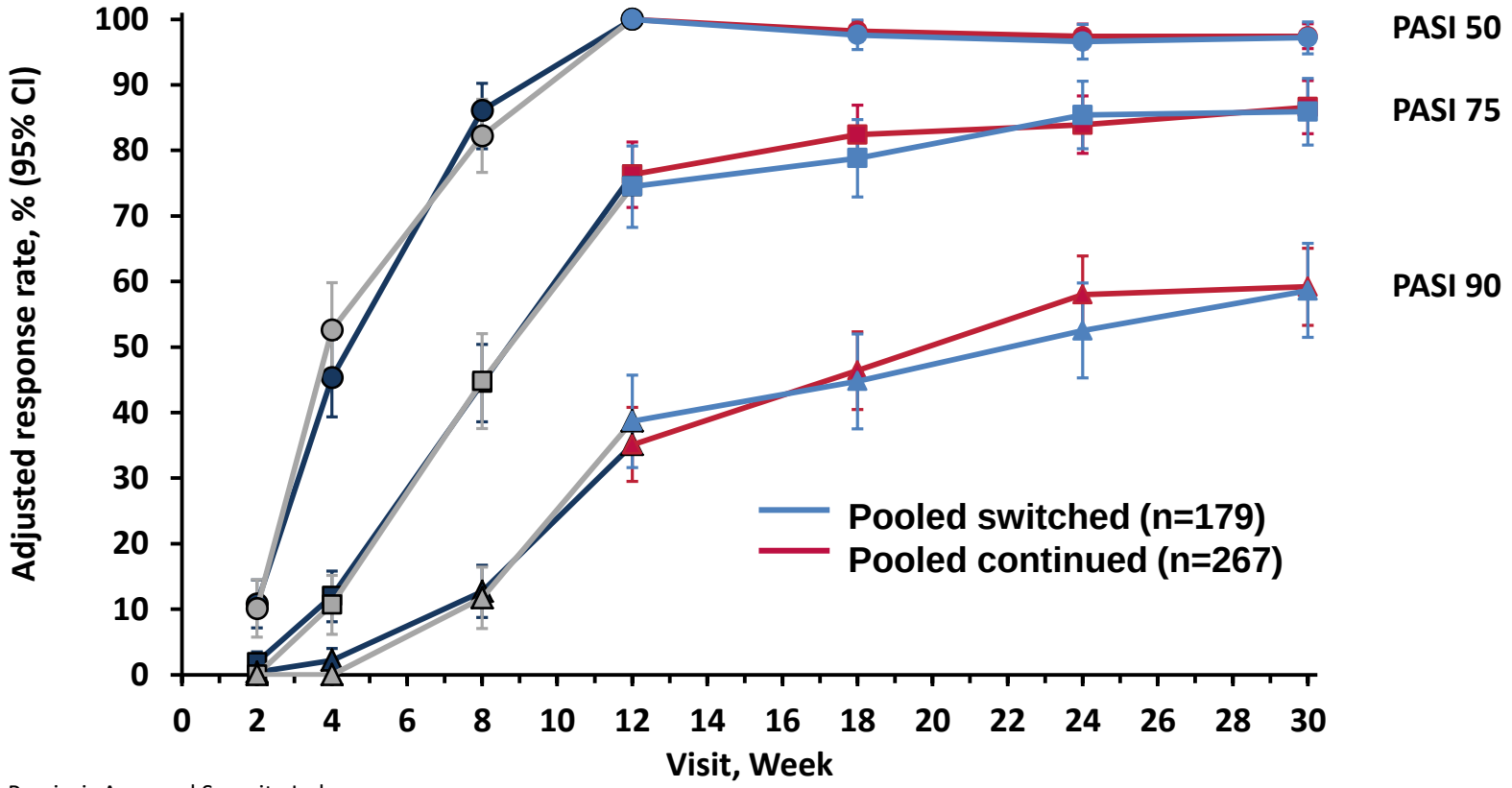
EGALITY-Trial in Psoriasis: Study design



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

Griffiths CEM, et al. Br J Dermatol 2017;176(4):928–38.

No Impact of Multiple Switching of GP2015 and Etanercept on PASI Response

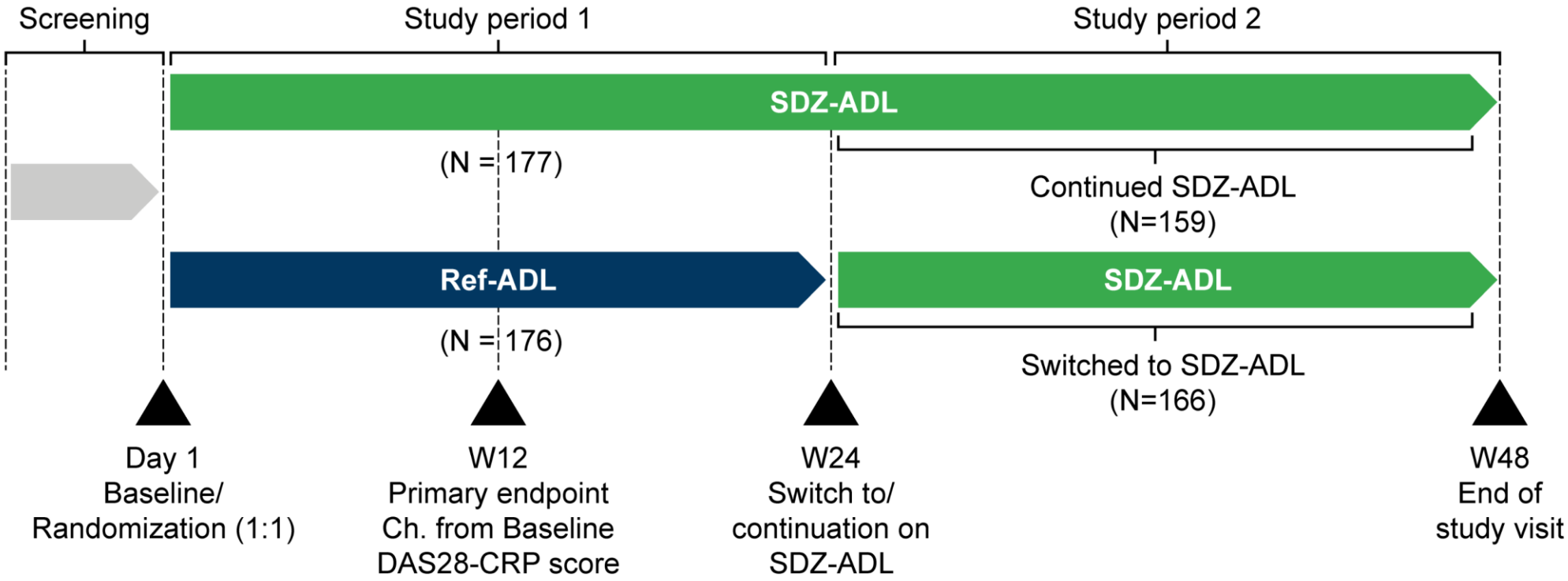


PASI, Psoriasis Area and Severity Index

FDA Arthritis Advisory Committee meeting presentation for GP2015 (2016). Available at: http://www.fda.gov/downloads/AdvisoryCommittees/CommitteesMeetingMaterials/Drugs/ArthritisAdvisoryCommittee/UCM513088.pdf [accessed 5 January 2017]

Gerdes et al, J Eur Acad Dermatol Venereol. 2018 Mar;32(3):420-427

ADMYRA: Study design

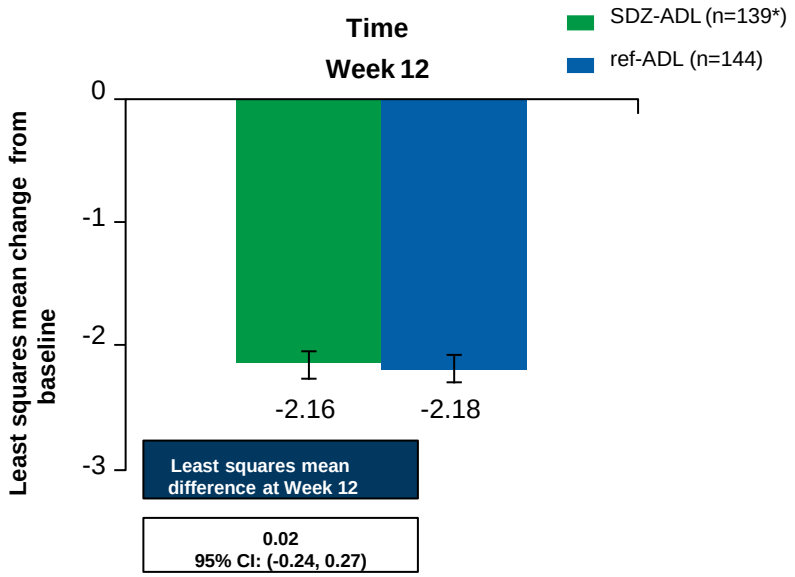


Study design was similar to ref-ADL ARMADA trial.[1]
Study treatment in Study Period 1: SDZ-ADL or ref-ADL 40 mg/0.8 mL s.c. injection from Day 1 to W22*
Study treatment in Study Period 2: Patients with at least moderate EULAR response switched to SDZ-ADL from W24 until W46*

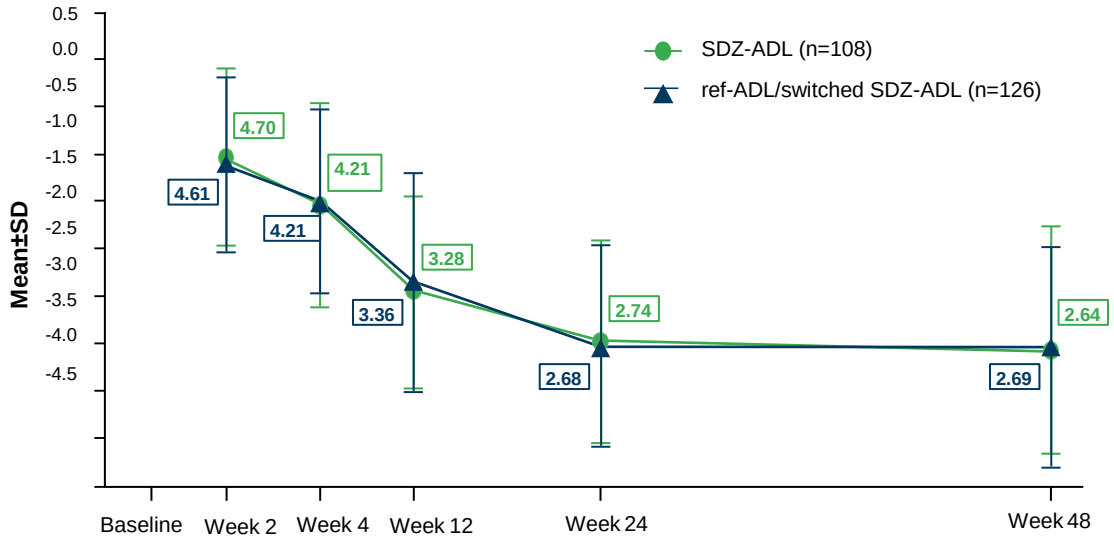
- *In Study Periods 1 and 2, last injections were administered at W22 and W46, respectively; last patient assessments were performed at W24 and W48, respectively.
- CRP = C-reactive protein; ch = change; DAS = disease activity score; EULAR = European League against Rheumatism; Ref-ADL = reference adalimumab;
  SDZ-ADL = Sandoz biosimilar adalimumab; s.c. = subcutaneous; W = Week

ADMYRA Trial: Primary and key secondary endpoint (DAS28-CRP)

Mean changes from baseline in DAS28-CRP scores over 12 Weeks (W12 PPS)



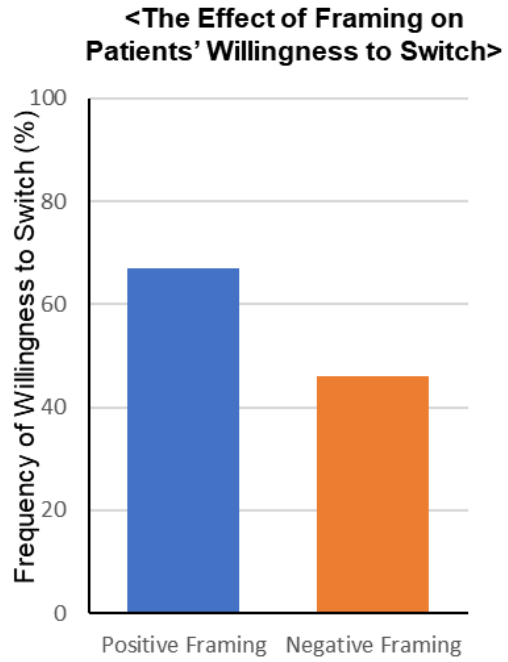
Absolute change in DAS28-CRP scores over 48 Weeks (SP2 PPS)



A mixed-model repeated measures analysis was performed for DAS28-CRP change from baseline including treatment, stratification factors, time (visits), the interaction between time (visits) and treatment, all as categorical variables, and baseline DAS28-CRP value as a continuous variable.*One patient had more than two joint assessments missing and therefore DAS28-CRP was not calculated. CI = confidence interval; CRP = C-reactive protein; DAS = disease activity score; n = number of patients per treatment group; PPS = per-protocol set; SD = standard deviation; ref-ADL = reference adalimumab; SDZ-ADL = Sandoz biosimilar adalimumab; SP2 PPS = study period 2 per protocol set; W = Week

Positive "Framing" can Improve Perceptions of Switching to Biosimilars

- **Study Purpose**
  - To measure the effect of differently framed explanations on patients' perceptions of and willingness to switch to a biosimilar
- **Method**
  - 96 patients with rheumatic disease taking a reference biologic were randomized to receive one of four biosimilar explanations, delivered by video positive/negative framing with and without an analogy
    - Positive: similarities between the biologics and biosimilars with positive body language and verbal cues
    - Negative: differences between the biologics and biosimilars with negative body language and verbal cues
- **Result**
  - Positive framing (67%) led to more participants being willing to switch than negative framing (46%)



Gasteiger, C. (2019). Arthritis Care & Research. doi: 10.1002/acr.24012

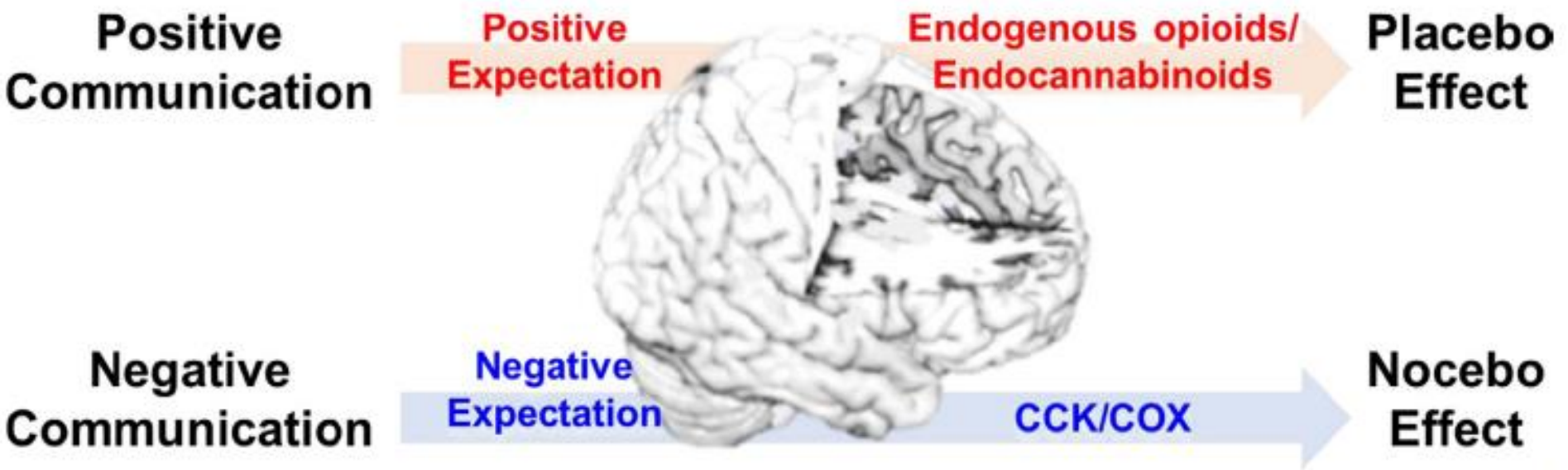


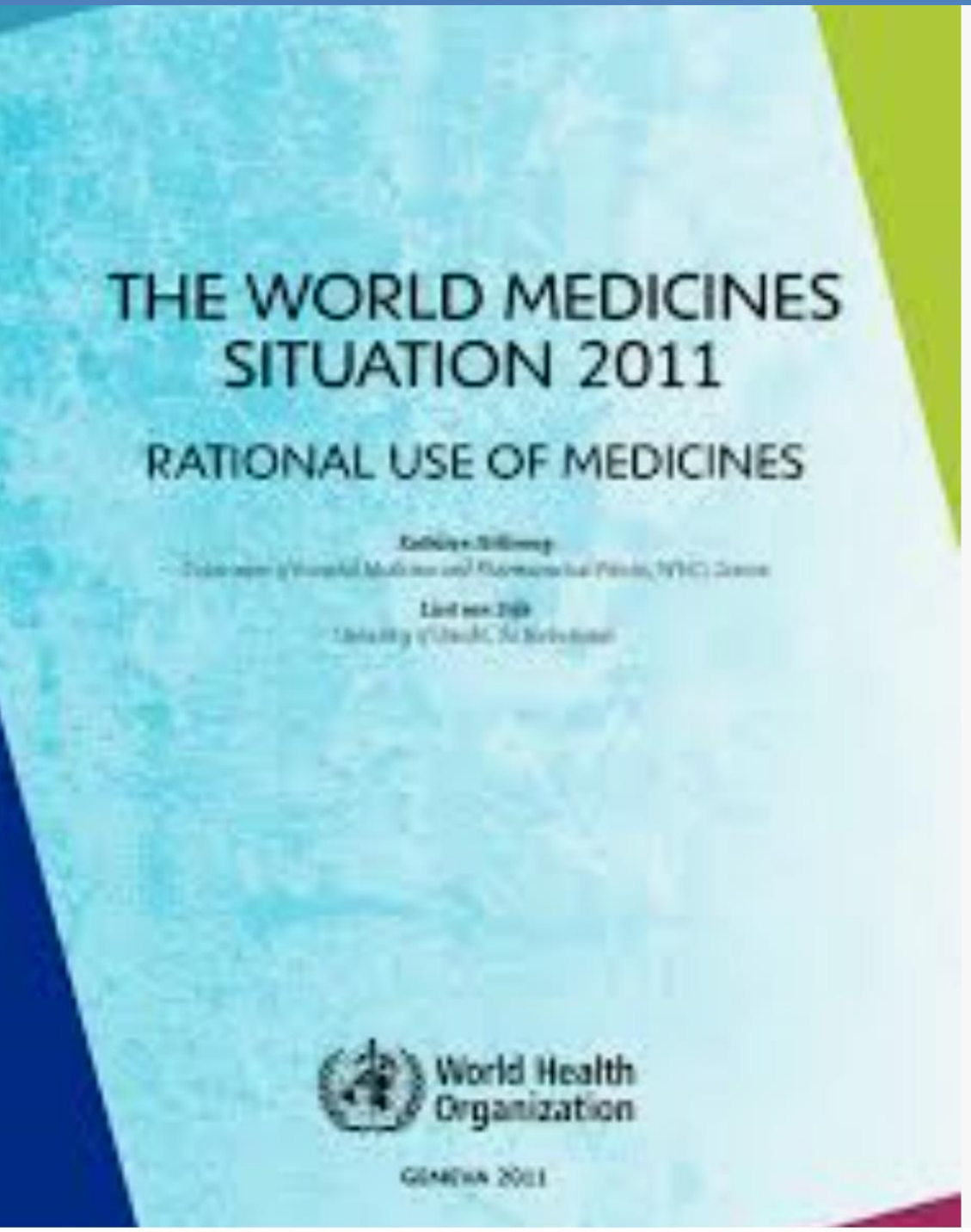
Figure 2 Neuroimaging of brain region activation in the positive/negative context. CCK, cholecystokinin ; COX, cyclooxygenase,

Smolen et al, RMD Open 2021 Jun;7(2):e001637. doi: 10.1136/rmdopen-2021-001637

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

Ann Rheum Dis 2018;**77**:165–174.



INTRODUCTION

What is rational use?

Medicines use is rational (appropriate, proper, correct) when patients receive the appropriate medicines, in doses that meet their own individual requirements, for an adequate period of time, and at the lowest cost both to them and the community (*1*). Irrational (inappropriate, improper and incorrect) use of medicines is when one or more of these conditions is not met.

Summary

- All bDMARDs have similar efficacy
  - JAK inhibitors are at least as efficacious as bDMARDs and show efficacy across many IMIDs
- bDMARDs and JAKinibs should be combined with MTX to convey optimal results
- T2T strategy (>50% improvement by 3 months and target attainment around month 6) leads to optimal outcomes
- Biosimilars approved in highly regulated areas are as efficacious and safe as originators and switching from originator to biosimilar is like using a different batch, such as post manufacturing change, of the originator
- **The prospects for RA patients become better with every year: we have good therapies and good treatment strategies – and there is more to come ☺**