CBG MEB

How to establish interchangeability??

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Biosimilar = Interchangeable?

- If a biosimilar is approved as such it is concluded by the regulatory authorities that the product is "highly similar" to its reference product in terms of Quality, Efficacy and Safety.

- The question is whether the conclusion on biosimilarity is in itself sufficient to conclude on interchangeability, or whether additional data is required to conclude this.

- There are different views between regulatory agencies (e.g. FDA and various EU Member states).
  - US legislation, makes a clear distinction between biosimilars and interchangeable biosimilars in terms of clinical evidence.

If more clinical data is needed to establish interchangeability, what kind of data should this be?

Depends on what is considered to be the key unknown to determine interchangeability:

Immunogenicity? PK? Safety? Efficacy? Usability?

Switching Induces Immunogenicity?

interchangeable. Switching between two similar biologic drugs increases the risk of anti-drug antibodies, which can lead to adverse immunologic reactions and decreased drug efficacy. Because the patient has received multiple drugs, the

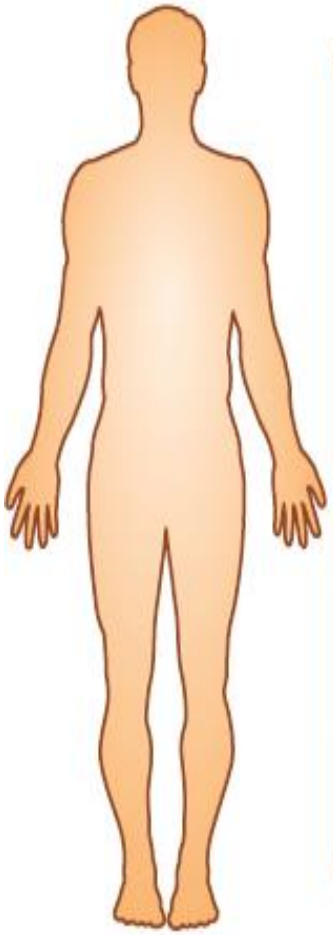
nal prescription. However, unlike small-molecule drugs, a biologic therapy that is repeatedly interchanged with a biosimilar agent might promote increased immunogenicity that could compromise the efficacy and safety of both medications.[29]

rules to prohibit the automatic substitution of biopharmaceuticals. Also, medical societies such as the French [33] and the Portuguese [34] Society of Nephrology have stated that there is no safe interchangeability of biopharmaceuticals. The main concern about switching from one biological medicine to another is the issue of immunogenicity.

qualified healthcare professional (8). As a consequence of their complexity, automatic substitution of biologics could give rise to different clinical consequences and should be ruled out for reasons of patient safety (9, 58).

4) Immunogenicity: repeated switches between biosimilars and originator products may increase immunogenicity with potentially negative effects.

Immunogenicity in Relation to Clinical Consequences of switching



What types of immunogenicity-related adverse clinical consequences are possible?

Acute adverse events:

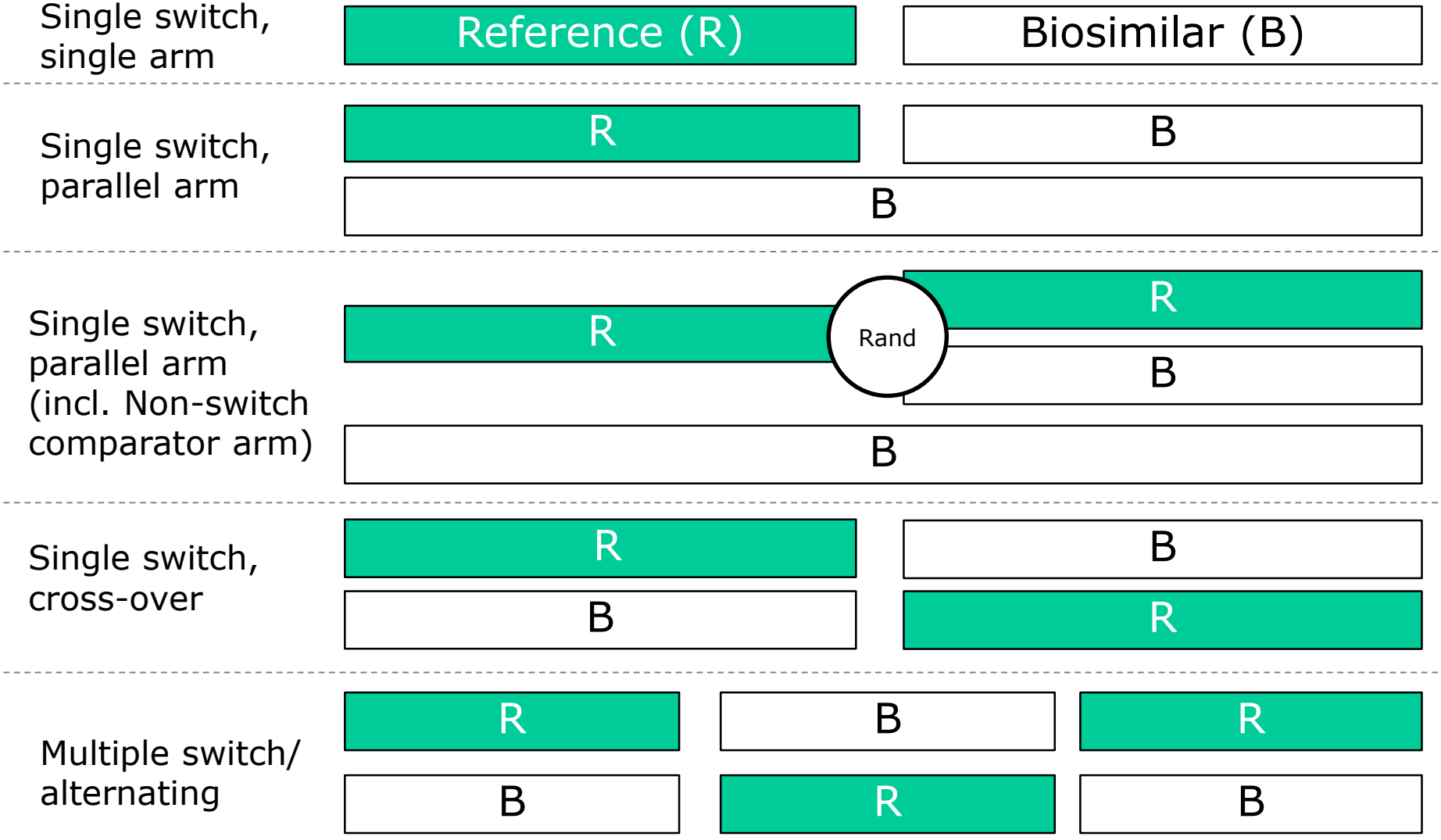
- Type-I hypersensitivity
- Injection-site reaction or infusion reaction

Non-acute adverse events:

- Type-III hypersensitivity
- Worsening of disease
- Increased drug toxicity
- Partial response (attenuated efficacy)
- Primary loss of response
- Secondary loss of response

Shankar et al. Nat Biotech 2015:33:334

Selection of Possible Designs of Switching Studies



Single arm Studies Are Hard To Interpret

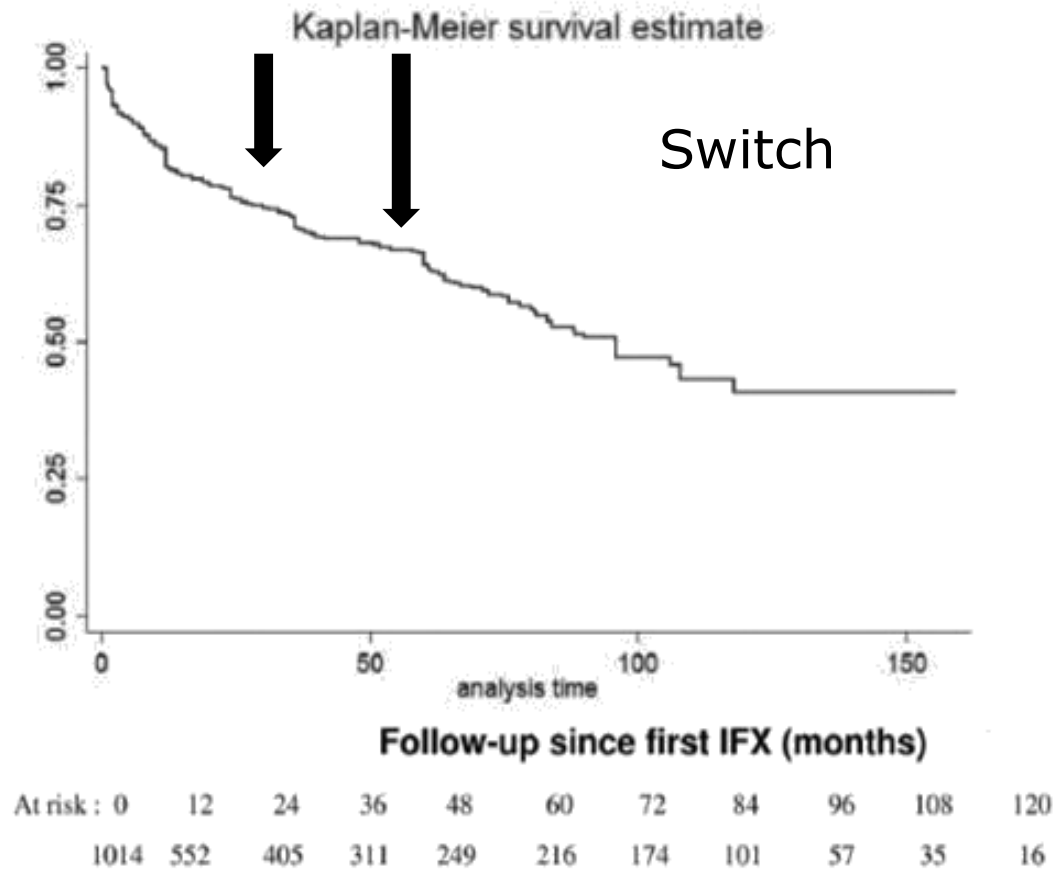


FIGURE 1. Kaplan–Meier survival curve based on the use of IFX in all patients with CD.

Patients and HCPs are aware of the switch
"hard endpoints" (e.g. trough levels) are less prone to bias

Pascal J *et al.* IBD 2015;21(1): 60

Even Well-designed Trials May Not be Sensitive to Detect Small Differences in Efficacy

Median time to relapse CD After Treatment Withdrawal in Infliximab Responders

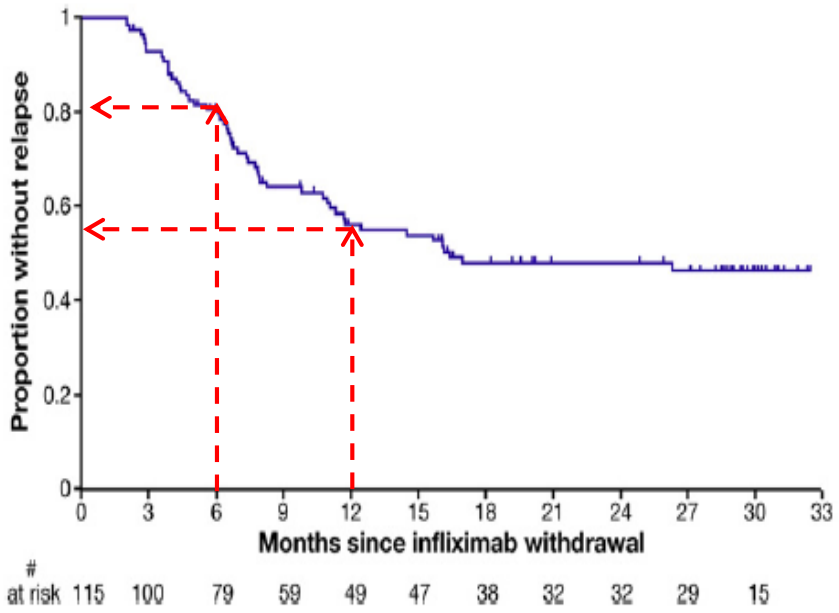
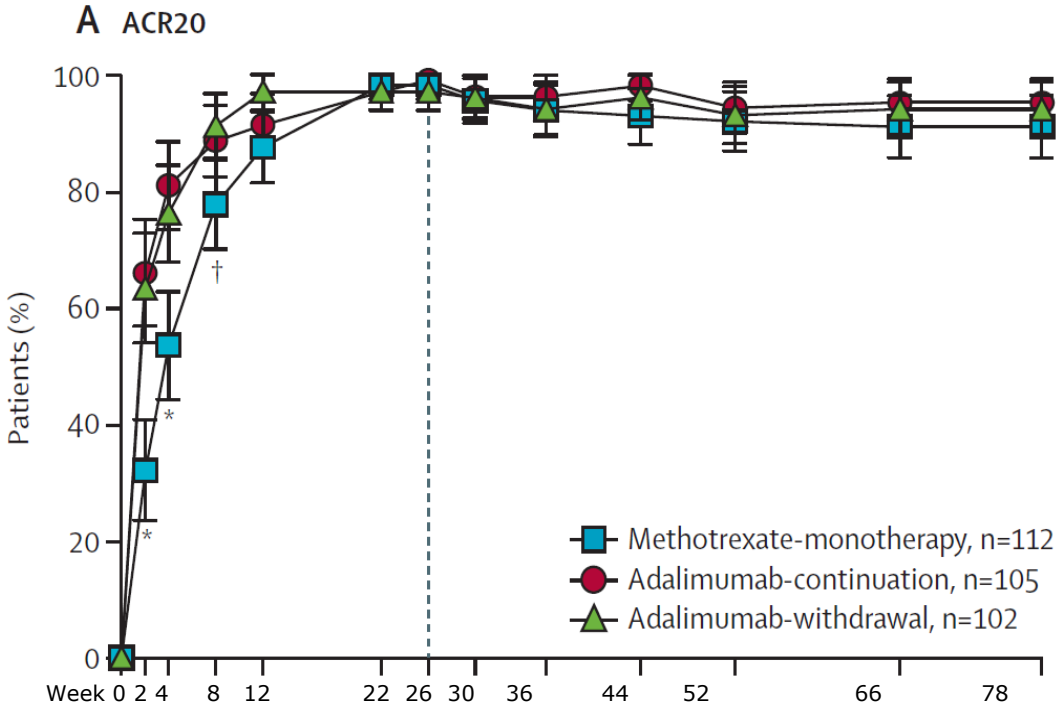


Figure 2. Kaplan–Meier time-to-relapse curve of the 115 included patients. The median ± SE follow-up time was 28 ± 2 months. There were 52 patients with confirmed relapse. The median time to relapse was 16.4 months.

Louis E, Gastroenterology. 2012;142(1):63-70

Randomized Withdrawal Study Adalimumab in Early RA

- 1032 randomised to MTX or adalimumab+MTX
  - ADA: 207 achieved stable low disease activity (randomised to continue or withdraw at Week 26)
  - MTX: 112: achieved stable low disease activity



Smolen Lancet 2014; 383: 321–32

Example of Reported AEs During OL Extension Study (48 Weeks) of CT-P13

Table 3 Treatment-related TEAEs that were reported in at least 1% of patients in either the maintenance group or the switch group

TEAE, n (%)	Maintenance group* (n=159)	Switch group† (n=143)	Total (n=302)
Extension study period			
Infusion-related reaction	11 (6.9)	4 (2.8)	15 (5.0)
Latent TB	9 (5.7)	4 (2.8)	13 (4.3)
Upper respiratory tract infection	6 (3.8)	3 (2.1)	9 (3.0)
Lower respiratory tract infection	4 (2.5)	4 (2.8)	8 (2.6)
Abnormal liver function test	1 (0.6)	4 (2.8)	5 (1.7)
Urinary tract infection	2 (1.3)	2 (1.4)	4 (1.3)
Bursitis	2 (1.3)	0	2 (0.7)
Urticaria	0	2 (1.4)	2 (0.7)

Yoo et al. Ann Rheum Dis. 2017;76(2):355-363

Review

EXPERT OPINION

The safety of switching between therapeutic proteins

Hans C Ebbers, Michael Muenzberg & Huub Schellekens†
†*Utrecht University, Utrecht Institute for Pharmaceutical Sciences (UIPS), Department of Pharmaceutics, TB Utrecht, The Netherlands*

"We have found no evidence from clinical trial data or post marketing surveillance data that switching to and from different biopharmaceuticals leads to safety concerns."

t years has
witching to
may lead to
f switching.
related to
thropoietins
rom clinical
ture on the
covers both
switching between innovator products within the same product class and switching to and from biosimilars.

Expert opinion: Data on the frequency of switching in clinical practice is scarce, but it seems most frequent for erythropoietins. We have found no evidence from clinical trial data or post marketing surveillance data that switching to and from different biopharmaceuticals leads to safety concerns.

Ebbers et al. Expert Opin Biol Ther. 2012;12(11):1473-85

Systematic literature review: Preliminary results

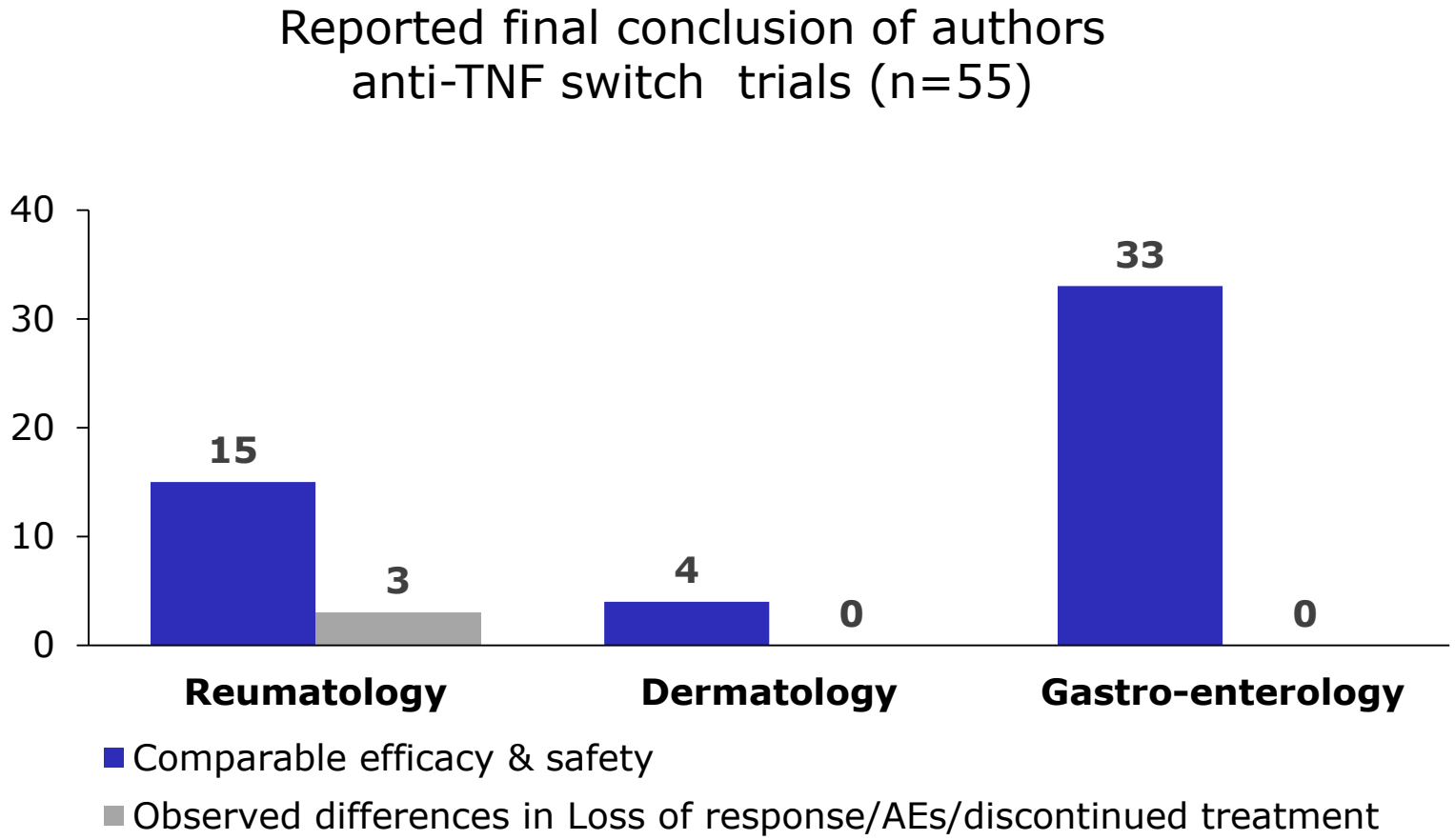
Overview anti-TNF switch trials classified by biosimilar

Disease	Infliximab	N*	Etaner-cept	N	Adalimu-mab	N
Rheumatology N=18	IFX→ CT-P13	8/6	ETN→SB4	1	ADA→SB5	1
	IFX→ SB2	1				
	IFX→ BOW015	1				
Dermatology N=4	IFX→ CT-P13	1/1	ETN→ GP2015	1	ADA→ ABP501	1
Gastro-enterology N=33	IFX→ CT-P13	20/ 13				

*prospective/retrospective

Courtesy of L. Barbier, manuscript in preparation

Systematic literature review: Preliminary results



Courtesy of L. Barbier, manuscript in preparation

Reports with a *Negative* Outcome — as Concluded by the Authors (3/55)

Indication	Study/ Design	Follow-up period	N	Outcome	ref
RA/SpA/ PsA	Registry (DANBIO)	3 months after switch	647	~6% of pts stopped treatment due to LOR/AE*	1
RA/SpA/ PsA	Obser-vational multicentre prospective cohort	6 months	192	23 % discontinued: mainly due to increase in BASDAI score and/of AE	2
RA	Retro-spective healthcare claims DB	9 months (IFX) 12 months CT-P13	269	Greater proportion of patients switching from to CT-P13 to IFX than vice versa	3

* A study from the same group/DB showed that switching had no negative impact on serum IFX or ADA 2–4 months following switch.

1.Glintborg et al. EULAR 2016 OP0225
2. Tweehuysen et al. ACR 2016 abstr. 627
3. Yacizi et al. ACR 2016 abstr. 1233

Courtesy of L. Barbier, manuscript in preparation

BioDrugs
DOI 10.1007/s40259-017-0210-0

CURRENT OPINION

Interchangeability of Biosimilars: A European Perspective

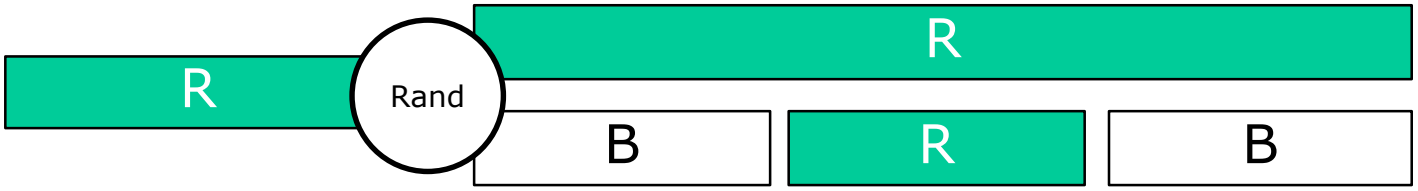
Pekka Kurki[1] · Leon van Aerts[2] · Elena Wolff-Holz[3] · Thijs Giezen[4] · Venke Skibeli[5] · Martina Weise[6]

"Our conclusion is that a state-of-the-art demonstration of biosimilarity, together with intensified post-marketing surveillance, is a sufficient and realistic way of ensuring interchangeability of EU-approved biosimilars under supervision of the prescriber."

Kurki et al. 2017 Gastroenterology. BioDrugs 2017 ePub

Some key Points from FDA approach to establish Interchangeability

- Generally Sponsors will be expected to conduct a switching study



- Non-US product would generally not be appropriate
- PK / trough levels as primary endpoint in switching studies

- Considerable focus on differences in presentation and device.
  - May need to be addressed in Human Factors studies

- Questions *not* answered in the guidance:
  - What to do with manufacturing changes? Innovator or biosimilar
  - How to deal with other interchangeable biosimilars?

Conclusions

- Thus far there is no evidence that switching to / from biosimilars causes safety issues
  - Differences in efficacy/safety may be hard to establish.
  - Hard to draw definitive conclusions from switching studies, other than a general reassurance that no problems have occurred as a result from the switch
- Mostly switching studies have been performed, alternating studies are rare.
  - May increase following US guidance
- If the key concern is immunogenicity, than ADAs in relation to clincial outcomes or trough levels should be determined
  - Limited data available, but no issues identified so far.
- More focus impact of differences in presentation (e.g. device) in relation to interchangeability?
  - Is not really addressed in EU guidance.

Thank you for your attention

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