The Science of Extrapolation

EBG Biosimilars 2015, London

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Federal Institute for Drugs and Medical Devices (BfArM), Germany

Frequent Concerns about Biosimilars [1]

- Fear of “low quality” biosimilars
- Safety database insufficient at time of licensing
- Increased immunogenicity
- Efficacy may be different from reference product
- **Most contentious issue: extrapolation of data**

[1] Weise et al. *Blood* 2012

Concerns have been expressed…

EDITORIALS & PERSPECTIVES

Key concepts and critical issues on epoetin and filgrastim biosimilars. A position paper from the Italian Society of Hematology, Italian Society of Experimental Hematology, and Italian Group for Bone Marrow Transplantation

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The term "biosimilars" ("follow-on biologics" in the USA) has been used by the European Medicines Agency (EMA) to describe officially-approved subsequent versions of innovator biotechnological products made by a different competitor after the patent and exclusivity rights have expired.[1] Biosimilars pose a problem to the clinician who is bound to require guidance on how best to capi- have first been 'engineered' to fulfill the best possible production and delivery characteristics. It is extremely important to note that such engineered cellular clones (the 'production clones') are not commercially available but that each company has to produce its own in-house, which *per se* represents an additional variability factor. Finally, differently to small molecular weight chemical drugs, depending upon specific

Biosimilar granulocyte-colony stimulating factor (G-CSF) for stem cell mobilization in related and unrelated donors

Biological products such as granulocyte-colony stimulating factor (G-CSF), erythropoetin, interferons and many others have revolutionized the treatment of patients with cancer. The recent and pending patent expirations for a number of biopharmaceuticals have prompted the ferred to as biosimilars.
he reference product,
aracteristics of which
il of biosimilars have
eral, the approval of
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o be demonstrated in
and extrapolation of
tion of stem cells) is
a biosimilar (500-600
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Journal of Crohn's and Colitis (2013) 7, 586–589

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SPECIAL ARTICLE

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

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Abstract

Biologics have become key agents for the management of Crohn's disease and ulcerative colitis. Biosimilars are biological medicines similar to previously authorized biologics and are already available in some countries. This ECCO Position Statement defines the collective view of European specialist in inflammatory bowel disease (IBD) concerning biosimilars. Biosimilars are not comparable to generic small molecules, since both efficacy and toxicity are difficult to predict due to subtle molecular changes that can have profound effects on clinical efficacy and immunogenicity. Direct evidence of safety and benefit from clinical trials in IBD, post-marketing pharmacoviligance, and unequivocal identification of the product as a biosimilar should be requirements before approval. Switching from an established biologic to a biosimilar to save costs is likely to be as inappropriate and ineffective as switching between current biologics that act on the same target, except when there is loss of response.

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Concerns about the use of biosimilar granulocyte colony-stimulating factors for the mobilization of stem cells in normal donors: position of the World Marrow Donor Association

Bronwen E. Shaw,[1,2] Dennis L. Confer,[3] William Y. Hwang,[4,5,6] Derwood H. Pamphilon,[7] and Michael A. Pulsipher[8,9]

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Lake City, Utah, USA. E-mail: bshaw@doctors.org.uk doi:

The World Health Organization (WHO) de
biosimilars or Similar Biotherapeutic Proc
(SBPs) as "a biotherapeutic product which is si
in terms of quality, safety and efficacy to an alr
licensed reference biotherapeutic product (RBP)".[1] A
patents for several of the RBP have recently expired,
has been a surge of interest in developing SBP to bro
access to these drugs through increased global availa
and reduced cost. However, manufacturing processe
RBP remain proprietary and, therefore, SBP are man

WMDA World Marrow Donor Association	Concerns about the use of biosimilars G-CSF			
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	Version:	1	Approved by:	Board
	Drafting Date:		Approval date:	2011-04-01
	Status	Public		

Concerns about the use of Biosimilar Granulocyte Colony Stimulating Factors for the mobilization of stem cells in normal donors

Position of the World Marrow Donor Association

Recombinant Granulocyte Colony Stimulating Factor (G-CSF) is routinely used for the mobilisation of haematopoietic stem cells (HSC) from the bone marrow into peripheral blood for collection by apheresis for transplantation. Since the late 1990s, HSC collection from related and unrelated healthy donors has been routine in Europe and North America. Two branded forms of G-CSF have been marketed since the early 1990s and there is extensive data concerning their use in normal donors.

Since 2002, the World Marrow Donor Association (WMDA) has maintained a centralised database collecting both short and long-term adverse events in unrelated donors receiving G-CSF. Recently, G-CSF biosimilar agents have become available. Biosimilars can be licensed based on data showing comparability to the reference product for the primary indication. Here we present the available evidence for the licensing of biosimilar G-CSF for mobilisation of HSC in Europe. As the efficacy for mobilisation is extrapolated, with little safety analysis and no long-term follow-up, the WMDA recommends that biosimilars must not be used for mobilisation in normal donors unless the donor is followed on a study addressing this question. Only when comprehensive data to confirm safety and efficacy is available should use of G-CSF biosimilars be considered routine.

Dietger Niederwieser
President of the EBMT on behalf of the Executive Committee

Extrapolation of data: not a new concept

Based on the totality of the evidence to demonstrate „comparability“ of different versions of the active substance of a biological

Scenario 1: Change in the manufacturing process of a given product (comparison of pre- and post-change product from the same manufacturer) (ICH guideline Q5E)

Scenario 2: Biosimilarity exercise (comparison of two products from different manufacturers)

The extent of the comparability exercise depends on the type of change

- The change has an impact on in-process controls but not on the specifications of the product
- The change has an impact on the specifications but not on safety or efficacy

Physico-chemical& biological testing

- An impact on safety and efficacy is possible

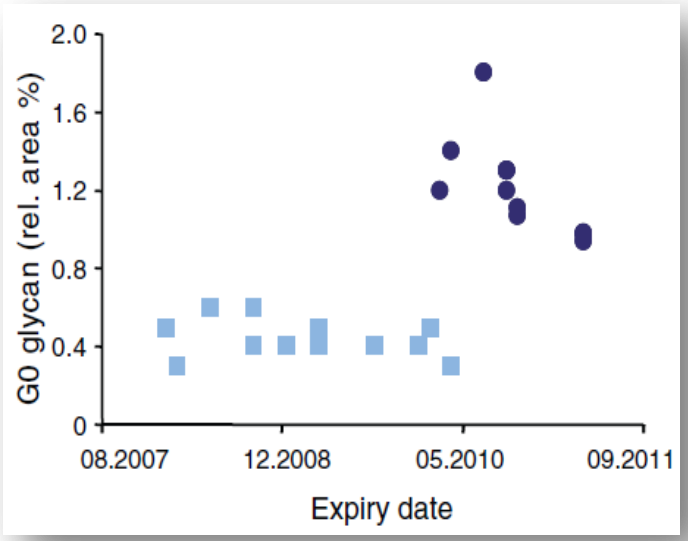
Additional (non) clinical tests

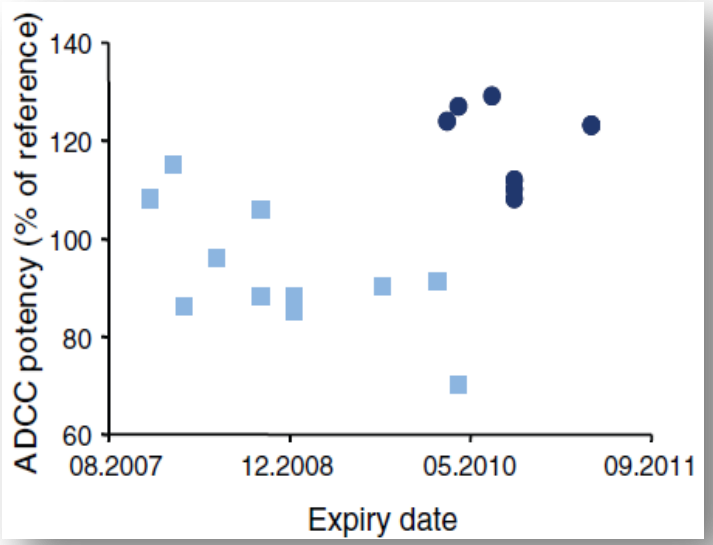
Sensitivity to detect differences:

Analytical tests > functional assays > clinical studies

Accepted differences in quality attributes

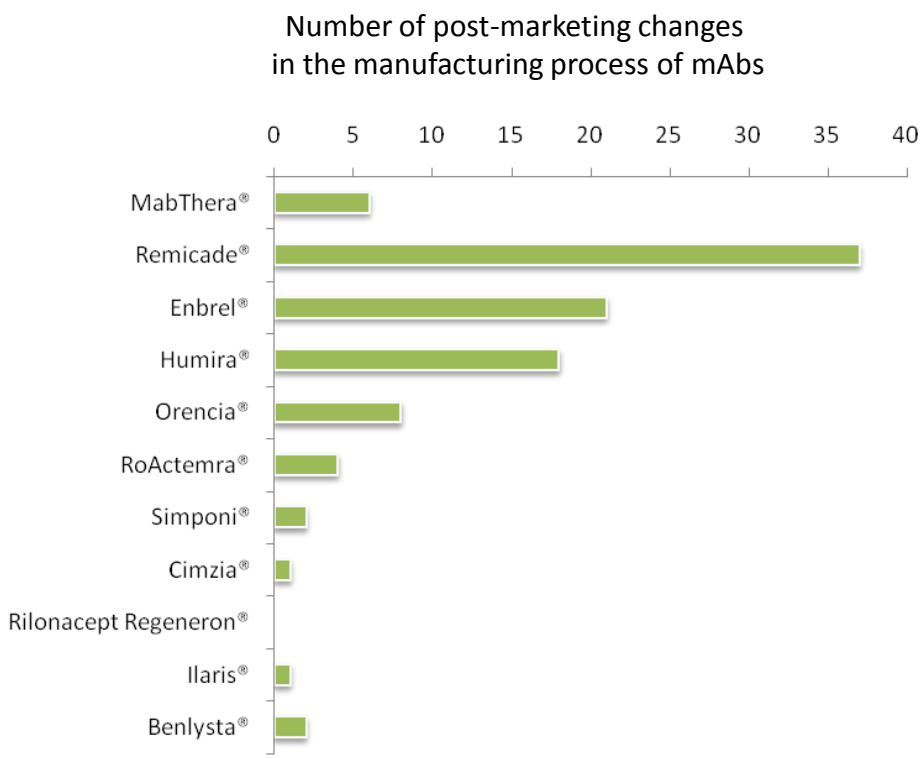
Change in the manufacturing process





Schiestl et al, Nat Biotech 2011

Changes in the manufacturing process of biologicals



Schneider CK: Biosimilars in rheumatology: the wind of change. Ann Rheum Dis. 2013 Mar;72(3):315-8. (Data source: EPARs on EMA website)

Biosimilars: the science of extrapolation

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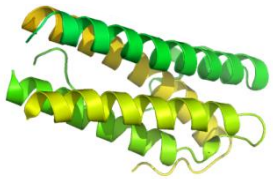
(*Blood.* 2014;124(22):3191-3196)

Extrapolation of data is already an established scientific and regulatory principle that has been exercised for many years, for example, in the case of major changes in the manufacturing process of originator biologicals. In such cases, clinical data are typically generated in one indication and, taking into account the overall information gained from the comparability exercise, may then be extrapolated to the other indications. In fact, the authors are not aware of any case where additional clinical studies with the changed product in other or even all approved indications have been provided by the marketing authorisation holders, or have been considered necessary by regulators.

Considerations for Extrapolation

- Usually unproblematic when MoA/receptor involved is the same and no unique safety concern, esp. regarding immunogenicity
- Different target-cell specific downstream signalling of the same receptor is no reason to request additional data
- If different active sites of the biological or different target receptors are involved, additional data necessary (e.g. functional assays and/or PD parameters)

Filgrastim: extrapolation



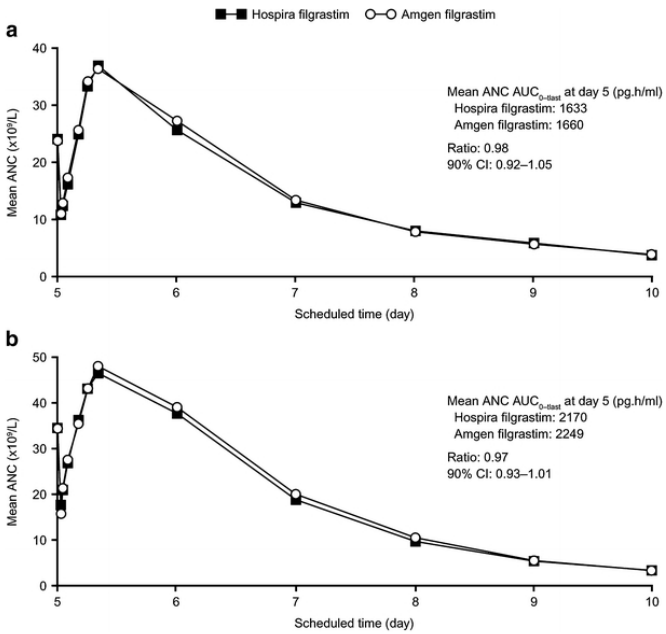
175 AA, 18.8 kDa

Concern: use for stem cell mobilisation in healthy donors

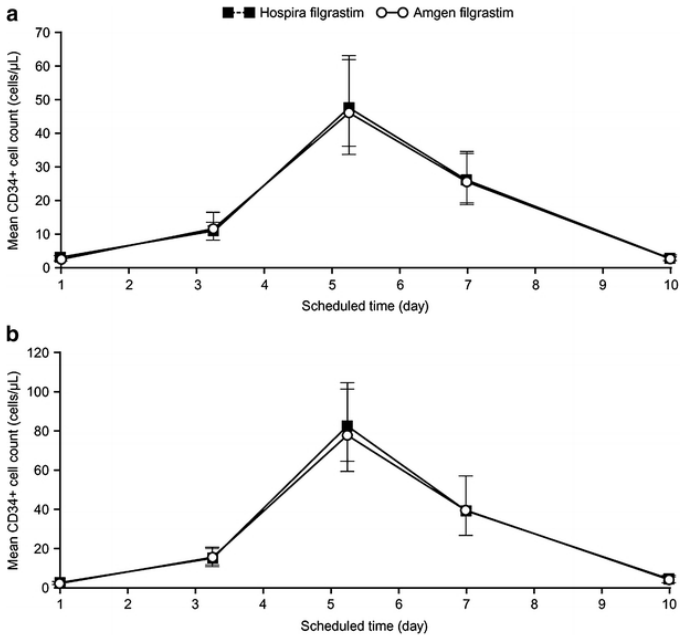
- Very well characterizable non-glycosylated protein
- Binding to CSF3R
- Data on stimulation of CD34+ cell count provide additional evidence for extrapolation from “neutropenia” to “stem cell mobilisation” indication
- Immunogenicity no particular issue
- Post-marketing studies confirmed efficacy and safety*

* (F Lefrére 2011, JC Ianotto 2012, A Publicover 2013, P Gascón 2013, M Schmitt 2014, P Reményi 2014)

Biosimilar Filgrastim (Nivestim®)



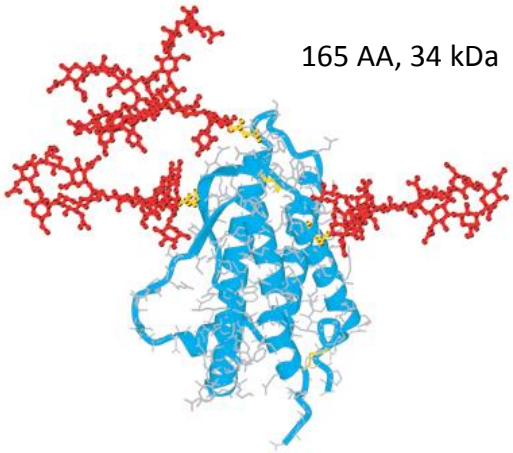
Mean ANC over time in subjects given Hospira filgrastim or Amgen filgrastim; **a** 5-µg/kg dose group and **b** 10-µg/kg dose group. Data shown are geometric means. Samples taken outside each schedule timepoint window have been excluded. *ANC* absolute neutrophil count, $AUC_{0–tlast}$ area under the curve from time 0 to the last time point, *CI* confidence interval



Mean CD34+ cell count over time in subjects given Hospira filgrastim or Amgen filgrastim; **a** 5-µg/kg dose group and **b** 10-µg/kg dose group. Data shown are geometric mean values with lower and upper 95% confidence intervals

Waller, Ann Hematol 2010

Epoetin: Extrapolation



Concern: use in cancer patients

- Complex glycoprotein but well characterizable
- Binding to EpoR
- Same MoA in haematopoiesis, regardless of the cause of anaemia
- Sensitive “model indication” to be studied: renal anaemia
- Risk of PRCA esp. with s.c. use in patients with renal anaemia

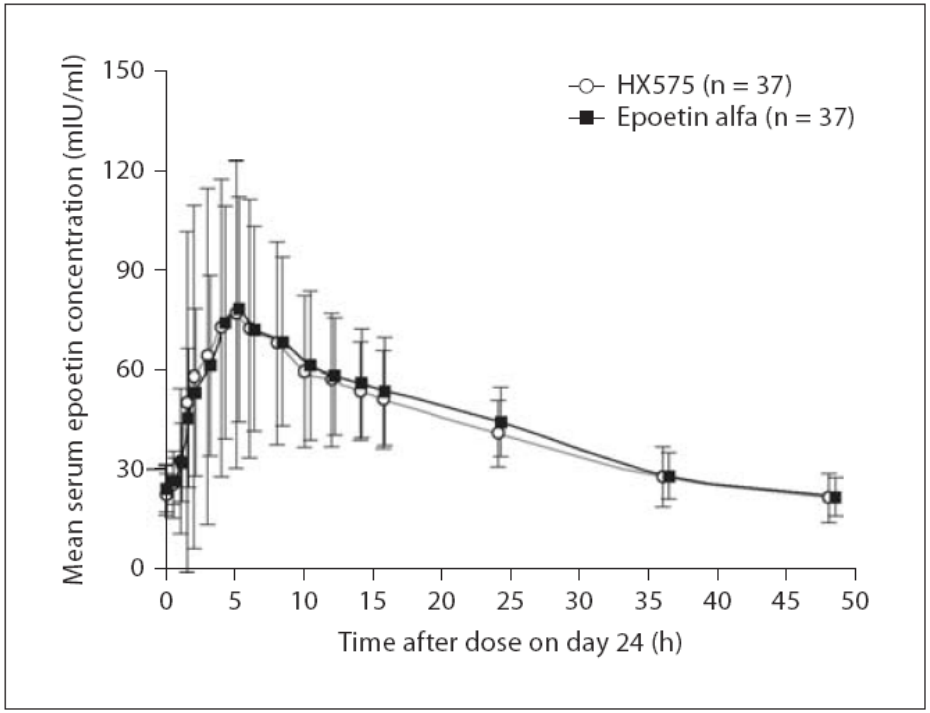
  ➔ extrapolation of immunogenicity data from renal to chemotherapy-induced anaemia and from s.c. to i.v. use, not vice versa
- Post-marketing studies confirmed efficacy and safety*

* (G Lonnemann 2011 , L Kerkhofs 2012 , F Hörbrand 2013)

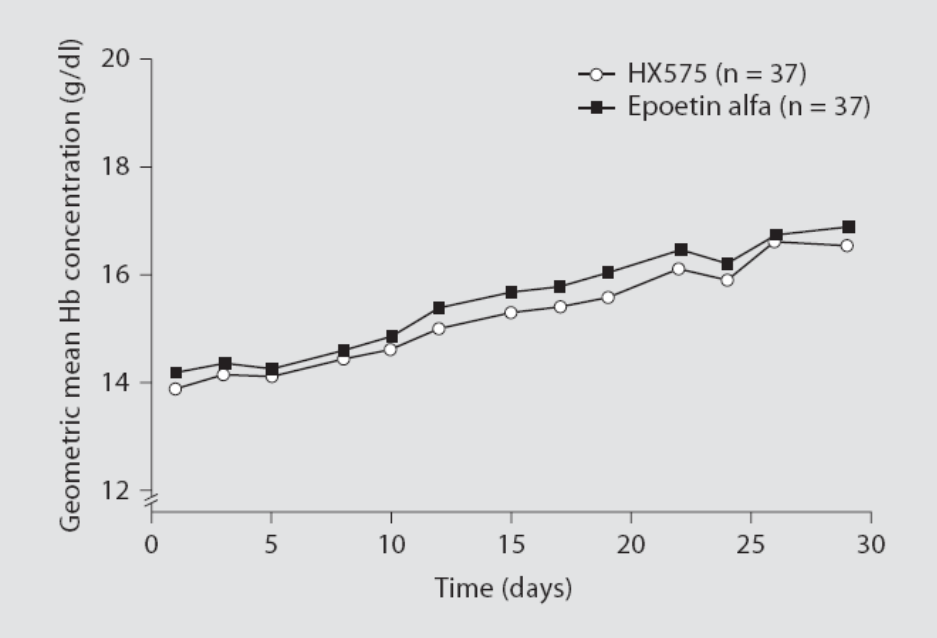
Biosimilar Epoetin (Binocrit®)

Multiple dose PK/PD study (SC)

Mean serum epoetin concentrations (± SD)



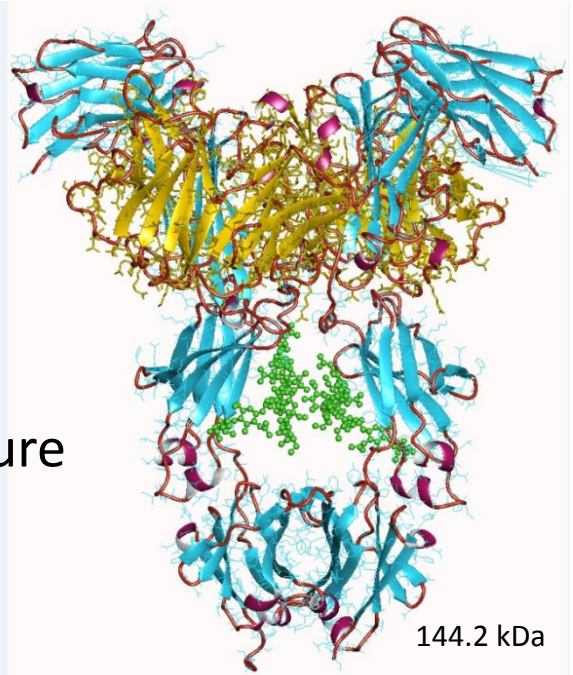
Mean Hb concentrations



Sörgel et.al., Pharmacology 2009;83:122–130

Similar efficacy and safety (compared to originator epoetin) confirmed in clinical trial

Biosimilar Infliximab*



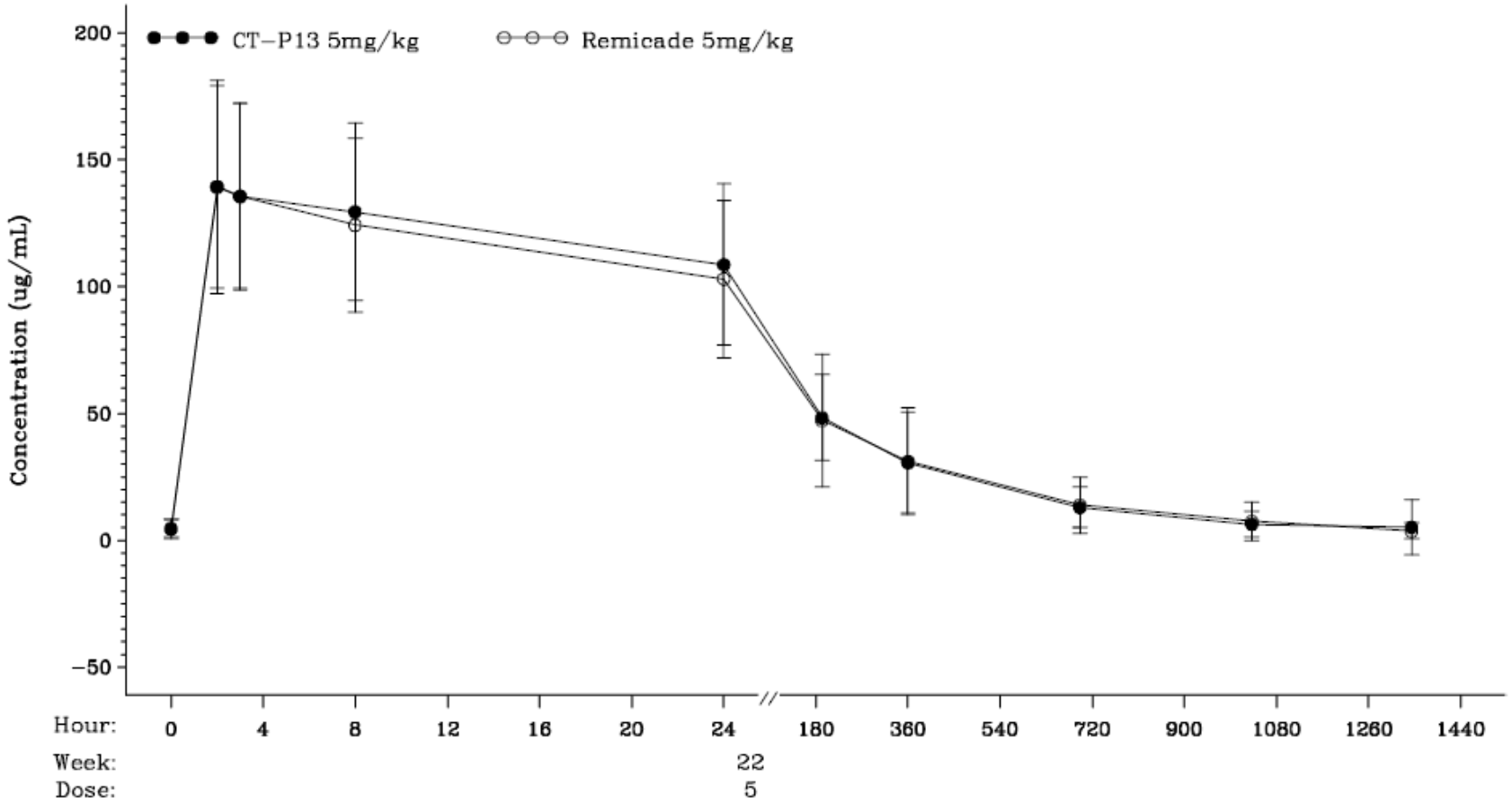
Concern: use in inflammatory bowel disease

- Identical primary, secondary and tertiary structure
- Comparable post-translational profiles
- Comparable *in vitro* functional characteristics
- Comparable pharmacokinetic profiles (250 patients with ankylosing spondylitis, 54 weeks, supportive efficacy and safety data)
- Comparable efficacy, safety and immunogenicity (606 patients with rheumatoid arthritis, 30+24 weeks)

* See European Public Assessment Report @ www.ema.europa.eu

Biosimilar infliximab*

Mean (±SD) serum concentrations (µg/ml) of infliximab vs time (h) by treatment for dose 5; PK population*



* See European Public Assessment Reports @ www.ema.europa.eu

Biosimilar infliximab*

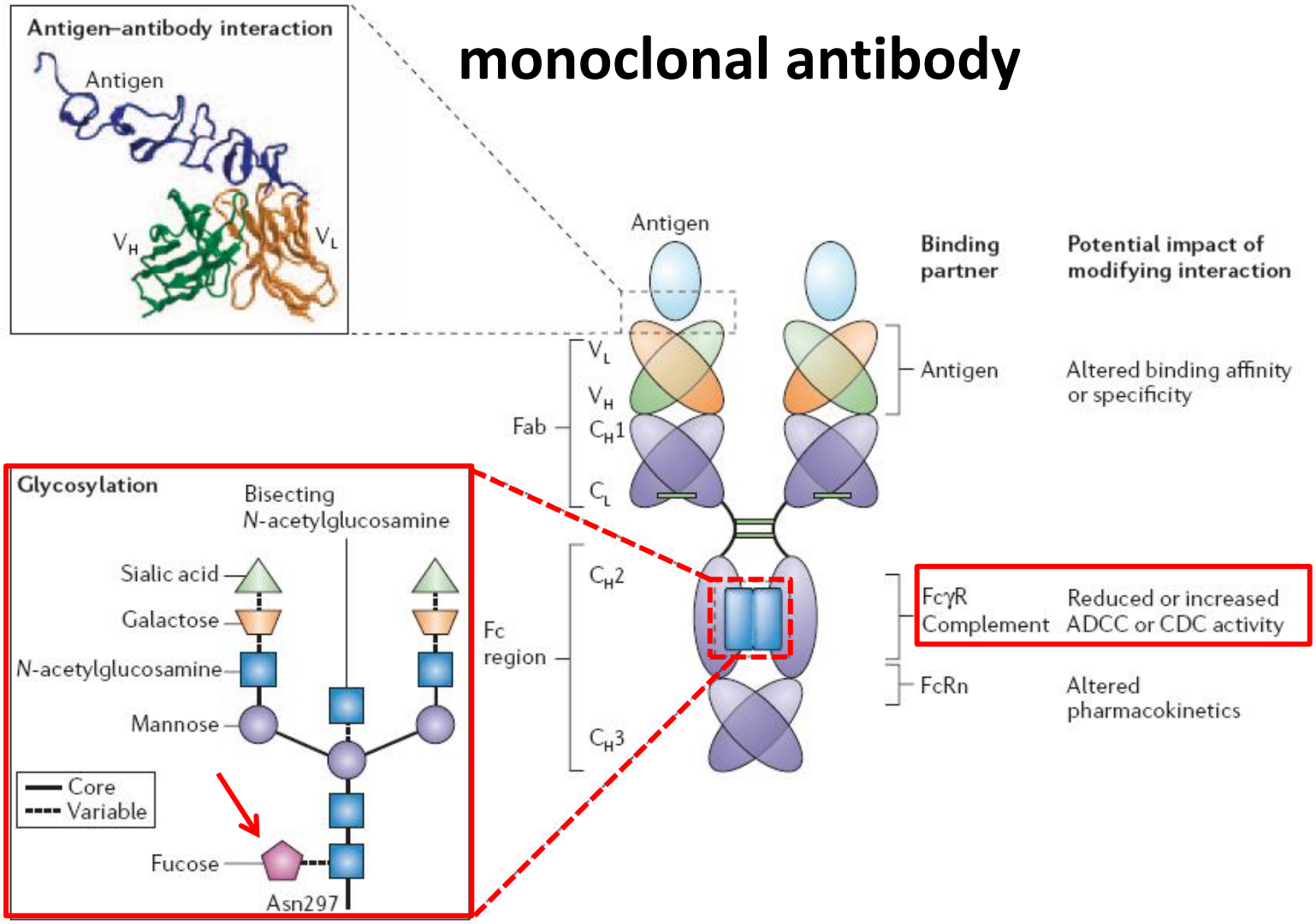
Efficacy (ACR20 at week 30)*

Treatment arm	n/N' (%)	Estimate of Treatment Difference	95% CI of Treatment Difference
All-randomised Population			
Biosimilar	184/302 (60.9)	0.02	(-0.06, 0.10)
Remicade	178/304 (58.6)		

The primary analysis was supported by the secondary efficacy endpoints (ACR50, ACR70, DAS28, ADL etc.)
Comparable safety profile, including immunogenicity

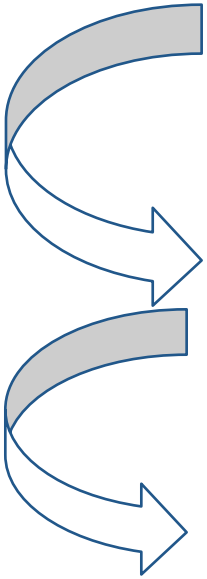
* See European Public Assessment Reports @ www.ema.europa.eu

monoclonal antibody



Carter PJ: Potent antibody therapeutics by design, Nature Rev Immunol 6, 343 (2006)

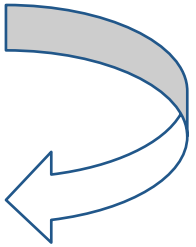
Biosimilar infliximab
Functional studies



Lower % of afucosylated glycoforms

Lower FcγRIIIa/b-binding

Lower ADCC activity



Impact on extrapolation to IBD?

Infliximab: Relevance of difference in ADCC*

- Difference in ADCC activity observed in the most sensitive *in vitro* test using Jurkat cells (expressing abnormally high levels of tmTNFα) as target cells and NK cells as effector cells
- Difference in ADCC activity not seen in more physiological conditions
  - Adding diluted serum or whole blood to the NK-cell assay or using PBMCs abrogated the difference in ADCC
  - No ADCC response when using lipopolysaccharide-stimulated monocytes as target cells → ADCC likely limited in inflammation
  - No difference in binding to neutrophils (high levels of FcγRIIIb)
  - Similar blocking of TNFα effects on human epithelial cells (suppression of inflammatory cytokine secretion and inhibition of apoptosis)
  - Similar induction of regulatory macrophages, inhibition of T-cell proliferation and promotion of wound healing of human colorectal epithelium cells

* See European Public Assessment Reports (EPARs) at www.ema.europa.eu

CHMP decision on Extrapolation*

All indications of the reference product approved

- Neutralisation of sTNFα and tmTNFα mediates efficacy in RA and other forms of autoimmune arthritis
- By using a range of experimental models that are considered representative of the pathophysiological conditions and MoA of infliximab, convincing evidence has been provided that the observed difference in afucosylated species is not clinically relevant

* See European Public Assessment Reports (EPARs) at www.ema.europa.eu

Conclusion

- Extrapolation of data is not a new concept and is based on sound scientific principles
- Extrapolation takes into account the totality of the evidence from the comparability exercise
- In case of doubt, additional (non)clinical data are necessary

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Thank you

BfArM