Ready Or Not, Here They Come
Anti-TNF Biosimilars For IBD

Fadi Hamid, M.D.
Assistant Professor of Medicine-
University of Missouri-Kansas City

Saint Luke's HOSPITAL OF KANSAS CITY

UMKC UNIVERSITY OF MISSOURI KANSAS CITY

Disclosures

- None

Learning Objectives

- Clarify the definition of Biosimilars
- Appreciate the changing landscape that led to the emergence of Biosimilars
- Understand the abbreviated FDA approval pathway for Biosimilars
- Appreciate the rationale for extrapolation of indications and understand the concept of interchangeability
- Consider clinical scenarios where Biosimilars can be safely utilized

What Are Biosimilars?

- The World Health Organization defines a biosimilar as a "product that is similar in terms of quality, safety and efficacy to an already licensed reference product"

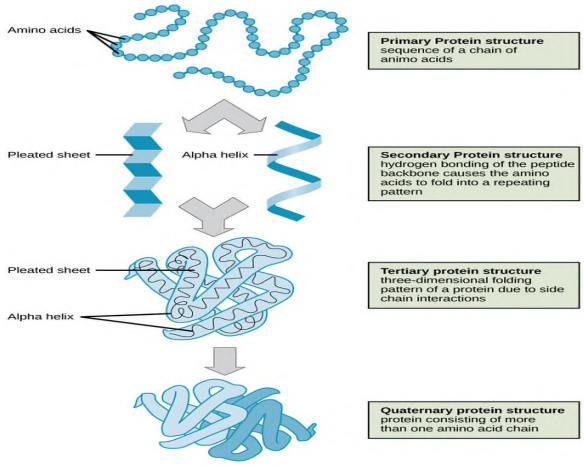
- Biosimilars are not "generic" biologic drugs

- World Health Organization. **Guidelines on evaluation of monoclonal antibodies as biosimilar biotherapeutic product (SBPs), Annex 2**. Technical report series No. 1004, 2016.

Biosimilars Key Issues

- A biosimilars has the same amino acid sequence as the originator but they are not identical
- These are complex substances synthesized in cells and are 1000 times larger than chemically synthesized drugs
- They have tertiary and quaternary folding and post-translational modifications such as glycosylation

Protein Structure Levels



Adapted from Boundless Biology

"No Two Snowflakes Are Alike"

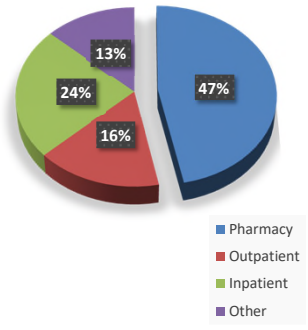
Economic Burden of Anti-TNF Therapy

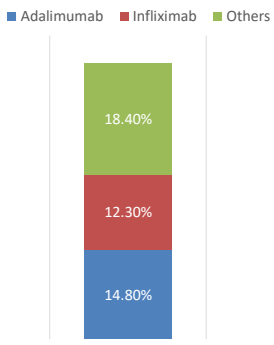
Annual Mean Expenditures per Person

$10,364 for CD
$7,827 for UC

vs.
$4,314 for non-IBD
$p < 0.05$

Health Plan Paid Costs by Cost-driver Category and Pharmacy Cost for CD





- Park MD *et al.*, *PeerJ*. 2014;2:e587.
- Park KT *et al.*, *Am J Gastroenterol.* 2016;111(1):15-23.

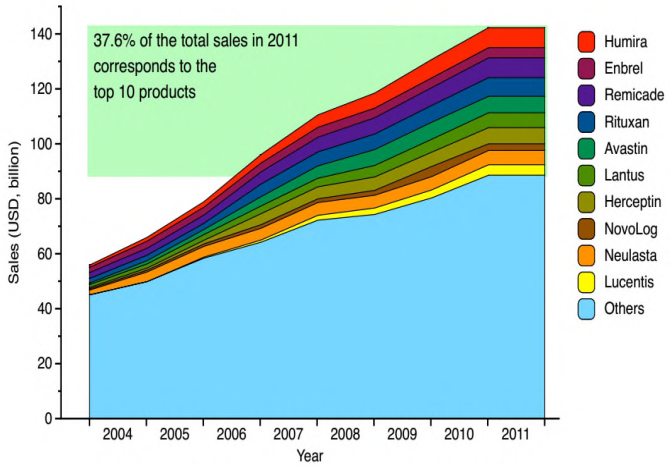
How Much Do Biologics Cost?

- Biologics cost an estimated $1.2 B. to develop
- Biologic manufacturing costs are not publicly disclosed
- Insurance discounts and rebates are confidential

- DiMasi JA, Grabowski HG. *Oxford Handbooks Online*. 2012.
- IMS Institute for Healthcare Informatics. IMS_InsAtute_Biosimilar_Brief_March_2016.pdf. March 2016. Accessed August 12, 2016

Global Sales of Biologic Drugs 2004-2011

Global expenditure on biologics in 2012 was $169 B., representing 18% of all medicines prescribed



Calo-Fernandez B, Martinez-Hurtado J. *Pharmaceuticals* 2012, *5*, 1393-1408; doi:10.3390/ph5121393

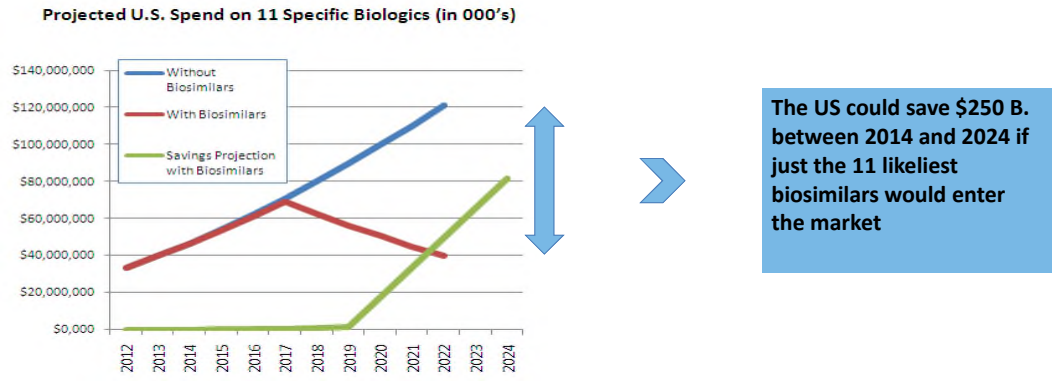
How Much Will Biosimilars Cost?

- Biosimilar prices in the EU have been on average approximately 30% less expensive than their reference products

- Due to lack of a single payor system in the U.S., the relative costs of biosimilars will be determined by negotiations between the manufacturers and payors. At least a 20% saving is expected by switching to biosimilars

- Pharmaceutical Commerce, Biosimilars: why deep discounts may become the dominant paradigm, Feb 22, 2016.
- Blackstone EA *et al.*, *Am Health Drug Benefits*, 2013 Sep-Oct; 6(8): 469–478.

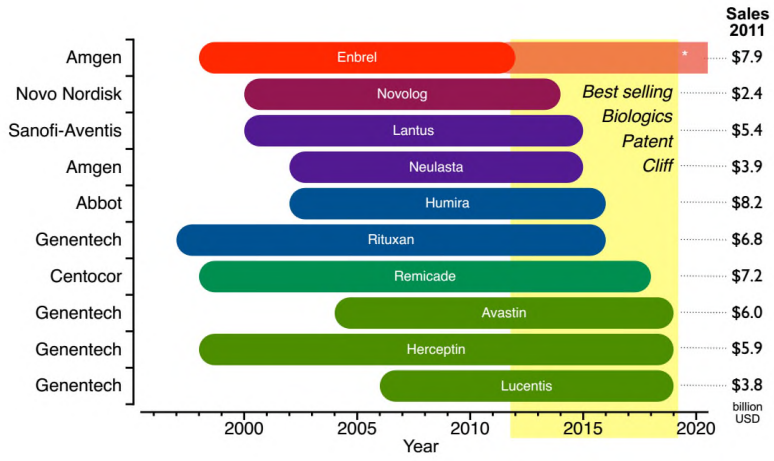
Global Socioeconomics And Potential Savings With Biosimilars



The US could save $250 B. between 2014 and 2024 if just the 11 likeliest biosimilars would enter the market

Steve Miller, The $250 Billion Potential of Biosimilars, Express Scripts, Apr 2013.

The Looming Biologics Patent Cliff



Calo-Fernandez B, Martinez-Hurtado J. Pharmaceuticals 2012, *5*, 1393-1408; doi:10.3390/ph5121393

Biologics Price Competition And Innovation Act of 2009

SEC. 7002. APPROVAL PATHWAY FOR BIOSIMILAR BIOLOGICAL PRODUCTS.

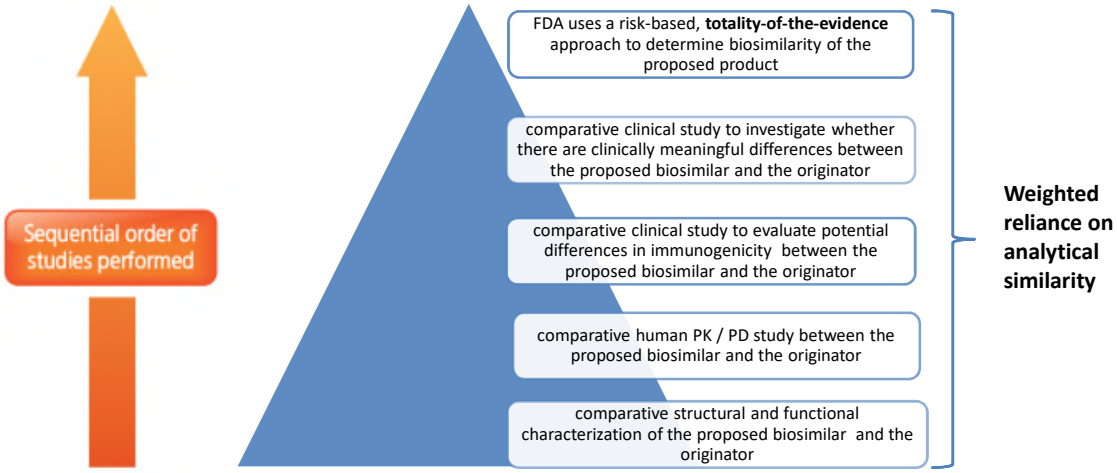
(a) LICENSURE OF BIOLOGICAL PRODUCTS AS BIOSIMILAR OR INTERCHANGEABLE.—Section 351 of the Public Health Service Act (42 U.S.C. 262) is amended—

"(2) The term 'biosimilar' or 'biosimilarity', in reference to a biological product that is the subject of an application under subsection (k), means—

"(A) that the biological product is highly similar to the reference product notwithstanding minor differences in clinically inactive components; and

"(B) there are no clinically meaningful differences between the biological product and the reference product in terms of the safety, purity, and potency of the product.

FDA Abbreviated Approval Pathway For Biosimilars



FDA, Beyond the Finish Line: Biosimilars in the US, Presented on Oct 2015

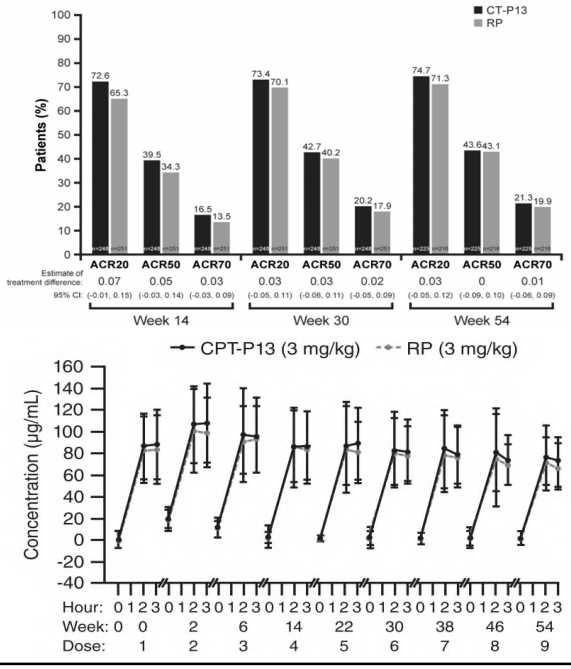
Yoo et al. Arthritis Research & Therapy (2016) 18:82
DOI 10.1186/s13075-016-0981-6

Arthritis Research & Therapy

RESEARCH ARTICLE Open Access

A phase III randomized study to evaluate the efficacy and safety of CT-P13 compared with reference infliximab in patients with active rheumatoid arthritis: 54-week results from the PLANETRA study

Dae Hyun Yoo[1], Artur Racewicz[2], Jan Brzezicki[3], Roman Yatsyshyn[4], Edgardo Tobias Arteaga[5], Asta Baranauskaite[6], Carlos Abud-Mendoza[7], Sandra Navarra[8], Vladimir Kadinov[9], Irmgadt Goecke Sariego[10], Seung Suh Hong[11], Sung Young Lee[11] and Won Park[12*]



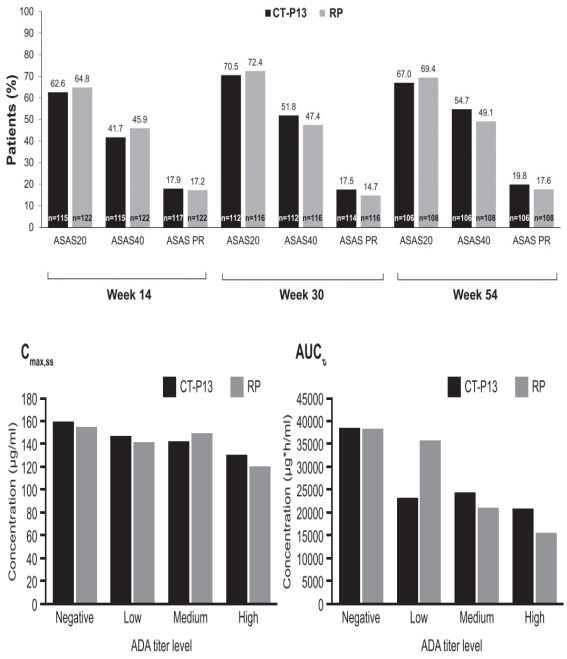
Park et al. Arthritis Research & Therapy (2016) 18:25
DOI 10.1186/s13075-016-0930-4

Arthritis Research & Therapy

RESEARCH ARTICLE Open Access

Comparable long-term efficacy, as assessed by patient-reported outcomes, safety and pharmacokinetics, of CT-P13 and reference infliximab in patients with ankylosing spondylitis: 54-week results from the randomized, parallel-group PLANETAS study

Won Park[1], Dae Hyun Yoo[2*], Janusz Jaworski[3], Jan Brzezicki[4], Andriy Gnylorybov[5], Vladimir Kadinov[6], Irmgadt Goecke Sariego[7], Carlos Abud-Mendoza[8], William Jose Otero Escalante[9], Seong Wook Kang[10], Daina Andersone[11], Francisco Blanco[12], Seung Suh Hong[13], Sun Hee Lee[13] and Jürgen Braun[14*]



Extrapolation

- Clinical trials in one indication used as rationale for clinical use in other indications for which the originator biological product is approved
- Requires appropriate scientific justification
- FDA approved the two Infliximab biosimilars for the treatment of IBD even in the absence of randomized data

Are Providers Comfortable With Extrapolation?

Published Studies on The Efficacy And Safety of CT-P13 in IBD

TABLE 7. Summary of Published Studies and Abstracts on CT-P13 in IBD

Author Reference	Country, Year	CD	UC	Switch CD/UC	Fail, %	LOR	Follow-up, wk	Stop, %	SAEs, %	ADA, %
Kang et al[28]	Korea, 2014	8	9	3/5	12.5	11	8	6	6	ng
Jung et al[29]	Korea, 2015	57	69	25/27	10.8	14	54	5.5	8	ng
Gecse et al[30]	Hungary, 2016	126	84	na	20.5	—	14	7.5	17 1 death	ng
Park et al[31]	Korea, 2015	95	78	44/16	25.5	11	30	3	22	ng
Sieczkowska et al[32]	Poland, 2016	32	7	32/7	—	18	12	2.5	2.5	ng
Farkas et al[33]	Hungary, 2015	18	21	na	30	ng	8	ng	ng	ng
Jahnsen et al[34]	Norway, 2015	46	32	na	21	ng	14	6.5	7.5	ng
Keil et al[35]	Czech R, 2016	30	22	—	4.5	ng	14	ng	7.7	ng
Gecse et al,[47] Golovics et al,[48] Lovasz et al[49]	Hungary, 2016	184	107	na	49	ng	30	ng	21.3	28
Bettey et al[50]	United Kingdom, 2016	134		134	1.5	0	16	1.5	41	ng
Smits et al[51]	Netherlands, 2016	57	24	57/24	6	0	16	6	7	8.6
Kolar et al[52]	Czech R, 2016	56	18	56/18	4	19	24	4	20.2	11.6
Farkas et al[53]	Hungary + Czech R, 2016	—	63	na	17.5	ng	14	ng	ng	11.8
Murphy et al[54]	Ireland, 2015	14		—	28.5	—	24	28.5	Surg and Hosp	ng

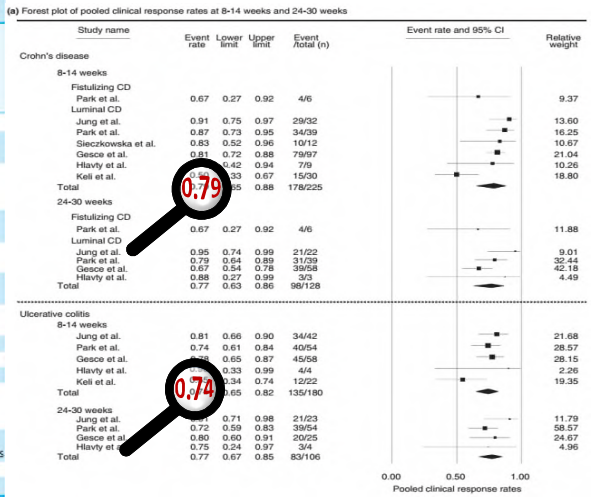
Fail, primary failure; Hosp, hospitalization; LOR, loss of response; na, not applicable; ng, not given; Surg, surgery.

In general, no clear signal of difference was seen between Infliximab and CT-P13

Systematic Review With Meta-Analysis: The Efficacy And Safety of CT-P13 in IBD

Table 1 | Characteristics of observational studies of biosimilar of anti-tumour necrosis factor-α agents (infliximab) in IBD

Diseases	Study, year (reference)	Study design	Name of biosimilar	Numbers of biosimilar patients (enrolled numbers) (n)	Age at study (year)	Dosage and schedule of biosimilar
CD	Jahnsen et al. 2015[31]	Prospective	CT-P13	46	39.0	5 mg/kg on weeks 0, 2, 6, 14
	Jung et al. 2015[32]	Retrospective	CT-P13	32	N.A.	5 mg/kg on week 0, 2, 6, then every 8 weeks
	Park et al. 2015[33]	Retrospective	CT-P13	43	31.8	5 mg/kg 53.5%, 5–7 mg/kg 37.2%, 7–10 mg/kg 2.2%, 10 mg/kg 7%
	Park et al. 2015 (fistulizing CD)[33]	Retrospective	CT-P13	8	27.9	5 mg/kg 87.5%, 5–7 mg/kg 12.5%.
	Sieczkowska et al. 2015[34]	Prospective	CT-P13	12	15.1	5 mg/kg on weeks 0, 2, 6
	Gecse et al. 2016[35]	Prospective	CT-P13	126	N.A.	5 mg/kg on weeks 0, 2, 6, 14, then every 8 weeks
	Hlavaty et al. 2016[36]	Retrospective	CT-P13	9	33.9	5 mg/kg on week 0, 2, 6
	Keli et al. 2016[37]	Prospective	CT-P13	30	37.9*	5 mg/kg on weeks 0, 2, 6, 14
UC	Jahnsen et al. 2015[31]	Prospective	CT-P13	32	40.0	5 mg/kg on weeks 0, 2, 6, 14
	Jung et al. 2015[32]	Retrospective	CT-P13	42	N.A.	5 mg/kg
	Park et al. 2015[33]	Retrospective	CT-P13	62	45.2	5 mg/kg 61.3%, 5–7 mg/kg 35.5%, 7–10 mg/kg 2.2%
	Gecse et al. 2016[35]	Retrospective	CT-P13	84	N.A.	5 mg/kg on weeks 0, 2, 6, 14, then every 8 weeks
	Hlavaty et al. 2016[36]	Retrospective	CT-P13	4	40.3	5 mg/kg on weeks 0, 2, 6
	Keli et al. 2016[37]	Prospective	CT-P13	22	37.9*	5 mg/kg on weeks 0, 2, 6, 14

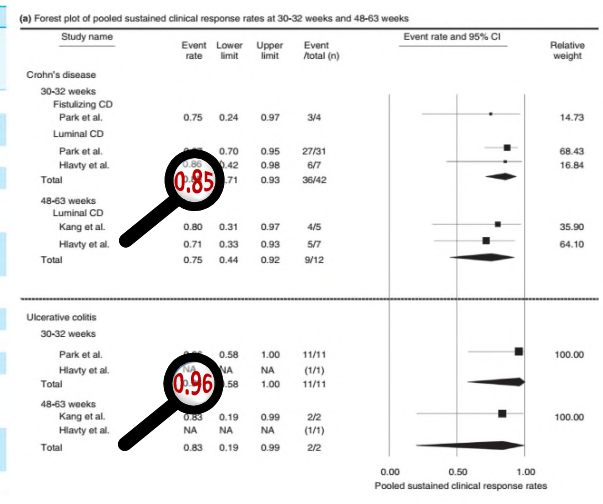


Komaki Y et al. Systematic review with meta-analysis: the efficacy and safety of CT-P13, a biosimilar of anti-tumor necrosis factor-a agent (infliximab), in inflammatory bowel diseases. Aliment Pharmacol Ther 2017; 45: 1043–1057

Systematic Review With Meta-Analysis: The Efficacy And Safety of CT-P13 in IBD

Table 2 | Characteristics of observational studies switching from infliximab to biosimilar

Diseases	Study, year (reference)	Study design	Name of biosimilar	Dosage and schedule of biosimilar	Concomitant medication
CD	Kang et al. 2015[38]	Retrospective	CT-P13	5 mg/kg every 8 weeks	5ASA 80%, steroids 80%, IM 80%
	Park et al. 2015[33]	Retrospective	CT-P13	5 mg/kg 57.5%, 5–7 mg/kg 25%, 7–10 mg/kg 5%, 10 mg/kg 12.5%	Steroids 30%, AZA 45%
	Park et al. 2015 (fistulizing CD)[33]	Retrospective	CT-P13	5 mg/kg 87.5%, 5–7 mg/kg 12.5%.	AZA 50%
	Hlavaty et al. 2016[36]	Retrospective	CT-P13	5 mg/kg every 8 weeks (every 4 weeks if any LOR)	AZA 50%
	Kolar et al. 2016[39]	Prospective	CT-P13	N.A.	AZA 46%*
	Sieczkowska et al. 2016[40]	Prospective	CT-P13	N.A. (30/32 were given every 8 weeks till 16 weeks)	5ASA 3%, 5ASA+AZA 34%, AZA 25%, MTX 3%, 5ASA+MTX 25%
	Smits et al. 2016[41]	Prospective	CT-P13	N.A. (dosing and interval remained unchanged unless need of adjustment)	5ASA 4%, steroids 7%, thiopurines 60%, MTX12%
UC	Kang et al. 2015[38]	Retrospective	CT-P13	5 mg/kg	5ASA 50%, steroids 100%
	Park et al. 2015[33]	Retrospective	CT-P13	5 mg/kg 61.3%, 5–7 mg/kg 35.5% 7–10 mg/kg 2.2%	5ASA 79%, steroids 55%, AZA 60%
	Hlavaty et al. 2016[36]	Retrospective	CT-P13	5 mg/kg every 8 weeks (every 4 weeks if any LOR)	AZA 50%
	Kolar et al. 2016[39]	Prospective	CT-P13	N.A.	AZA 46%*
	Sieczkowska et al. 2016[40]	Prospective	CT-P13	N.A.	5ASA 43%, AZA 14%, 5ASA+AZA 43%
	Smits et al. 2016[41]	Prospective	CT-P13	N.A. (dosing and interval remained unchanged unless need of adjustment)	5ASA 65%, steroids 15%, thiopurines 54%



Komaki Y et al. Systematic review with meta-analysis: the efficacy and safety of CT-P13, a biosimilar of anti-tumor necrosis factor-a agent (infliximab), in inflammatory bowel diseases. Aliment Pharmacol Ther 2017; 45: 1043–1057

The **PROSIT-BIO** Cohort: A Prospective Observational Study of Patients with IBD Treated with Infliximab Biosimilar

- 680 consecutive IBD patients (373 CD, 307 UC) were enrolled from 25 centers
- 400 patients were anti-TNF naive, 171 had a previous exposure and 109 were switched to CT-P13 after a mean of 18 +/- 14 infusions of infliximab
- A total number of over 4,000 infusions were recorded
- One of the largest prospective cohort of IBD patients treated with CT-P13… **no signals of difference in safety and clinical efficacy has been observed**

Fiorino G et al. Inflamm Bowel Dis. Vol 23, Number 2, February 2017.

Randomized, DB, Phase III Study Conducted in Patients With Moderate to Severe CD

- 220 patients in 58 study centers across 16 countries randomized to CT-P13 or Infliximab
- At Week 6, CDAI-70 response rate of CT-P13 was quite similar to that of Infliximab
- The number of patients with at least one treatment-emergent adverse event (TEAE) showed a similar proportion in the 2 treatment groups

Table 1. Efficacy Results at Week 6 for Per-Protocol Population

	CT-P13 (N=105)	INX (N=101)
CDAI-70 response n (%), CI*	75 (71.4%) [61.8, 79.8]	76 (75.2%) [65.7, 83.3]
CDAI-100 response n (%), CI*	65 (61.9%) [51.9, 71.2]	65 (64.4%) [54.2, 73.6]
Clinical remission n (%), CI*	45 (42.9%) [33.2, 52.9]	45 (44.6%) [34.7, 54.8]

*95% confidence interval

Kim Y.H. et al. Ecco 2017: Digital Oral Poster 061

Cross-immunogenicity: Antibodies to Infliximab in Remicade-Treated Patients With IBD Similarly Recognize The Biosimilar Remsima

- 125 patients' and controls' sera were tested. All 56 anti-Remicade ATI-negative were also negative for anti-Remsima ATI. All 69 positive anti-Remicade IBD sera were cross-reactive with Remsima. Anti-Remicade ATIs of patients with IBD (n=10) exerted similar functional inhibition on Remsima or Remicade TNF-α binding capacity

- **Conclusions-**
  - Anti-Remicade antibodies in patients with IBD recognize and functionally inhibit Remsima to a similar degree, suggesting similar immunogenicity and shared immunodominant epitopes

Ben-Horin S, et al. Gut; 2016, Vol. 65 Issue: Number 7 p1132-1138, 7p.

Interchangeability

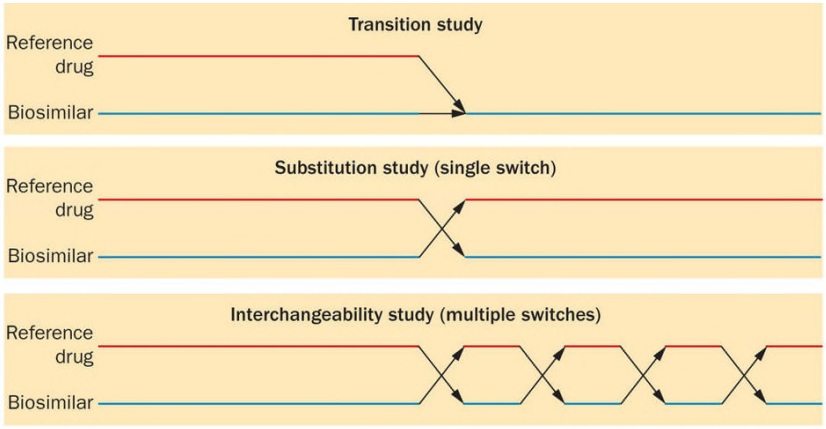
- FDA defines as “Substitution for the reference product by a pharmacist without the intervention of the health care provider who prescribed the reference product”

- **No** biosimilar in the U.S. yet has **interchangeability** designation

Interchangeability

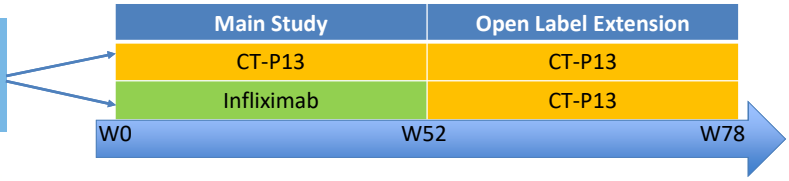
- No data to support interchangeability
- Break of tolerance and development of immunogenicity which can cause hypersensitivity reactions, neutralization with loss of response and autoimmunity
- Safety surveillance for individual drugs becomes very challenging when making multiple switches

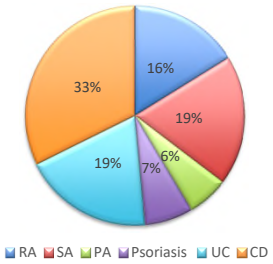
Switching vs. Substitution



NOR-SWITCH

482 pts stable on Infliximab for at least 6 months randomized 1:1





- **Primary Endpoint**:
Occurrence of disease worsening at W52
- **Assumptions**:
  - 30% disease worsening in the Infliximab arm
  - Non-inferiority margin: 15%

Jørgensen K, et al. UEGW 2016, Abstract LB15, Latebreaker Oral Presentation

NOR-SWITCH

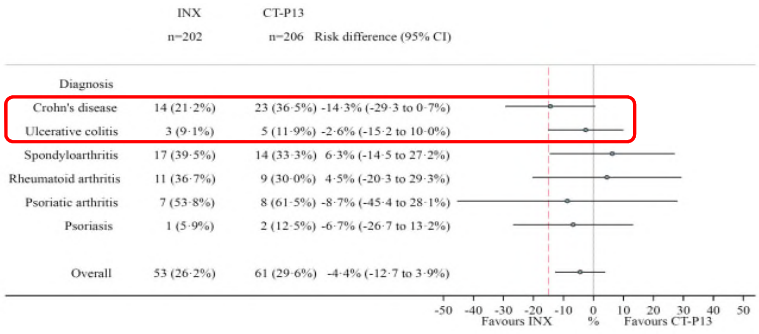


Figure. Occurrence of disease worsening during 52 weeks follow-up, overall and within the diagnoses in the Per Protocol Set.

Comparable trough serum levels, ADA (Remicade 7.1%, CT-P13 7.9%) and reported adverse events between Remicade and CT-P13

Jørgensen K, et al. UEGW 2016, Abstract LB15, Latebreaker Oral Presentation

Status of U.S. Biosimilars For IBD

- **Biosimilars for Remicade**
  - **Inflectra (infilixmab-dyyb)**
    - FDA approval: April 2016
    - Available: Nov. 2016
  - **Renflexis (infliximab-abda)**
    - FDA approval: April 2017
- **Biosimilars for Humira**
  - **Amjevita (adalimumab-atto)**
    - FDA approval: Sep. 2016
  - **Cyletezo (adalimumab-adbm)**
    - FDA approval: Oct. 2016

Biosimilars Nomenclature

- In August 2015 FDA proposed a rule for naming biosimilars. The names include distinguishing suffixes (devoid of meaning), composed of four random lowercase letters (infliximab-**hjmt**, infliximab-**dyyb** and infliximab-**abda**)
- Intention- to avoid inaccurate perception of biosimilars efficacy
- Influences prescribing practice of biosimilars

Practical Considerations For Biosimilars

- Dosing is the same as the reference product
- Prior-authorization is expected to be the same for these agents
- Existing commercial therapeutic drug monitoring (**TDM**) assays **will work** with biosimilars
- **Anti-drug antibody will cross react** between a reference product and its biosimilar (and vice versa)
- **No** biosimilar in the U.S. yet has **interchangeability** designation

Clinical Scenarios For Biosimilars Use

New Start	• Prescriber choice of originator or biosimilar
Primary Nonresponder	• Switching to a biosimilar **SHOULD NOT BE CONSIDERED** because it has the same MOA • Prescriber should switch to another biologic with a different MOA
Stabilized Responder	• Prescriber elects to maintain the originator • Prescriber elects to switch to a biosimilar
Loss of Response	• If attributed to high ADA titer then switching to a biosimilar **SHOULD NOT BE CONSIDERED** • Prescriber should switch to another therapy

Real Life Experience

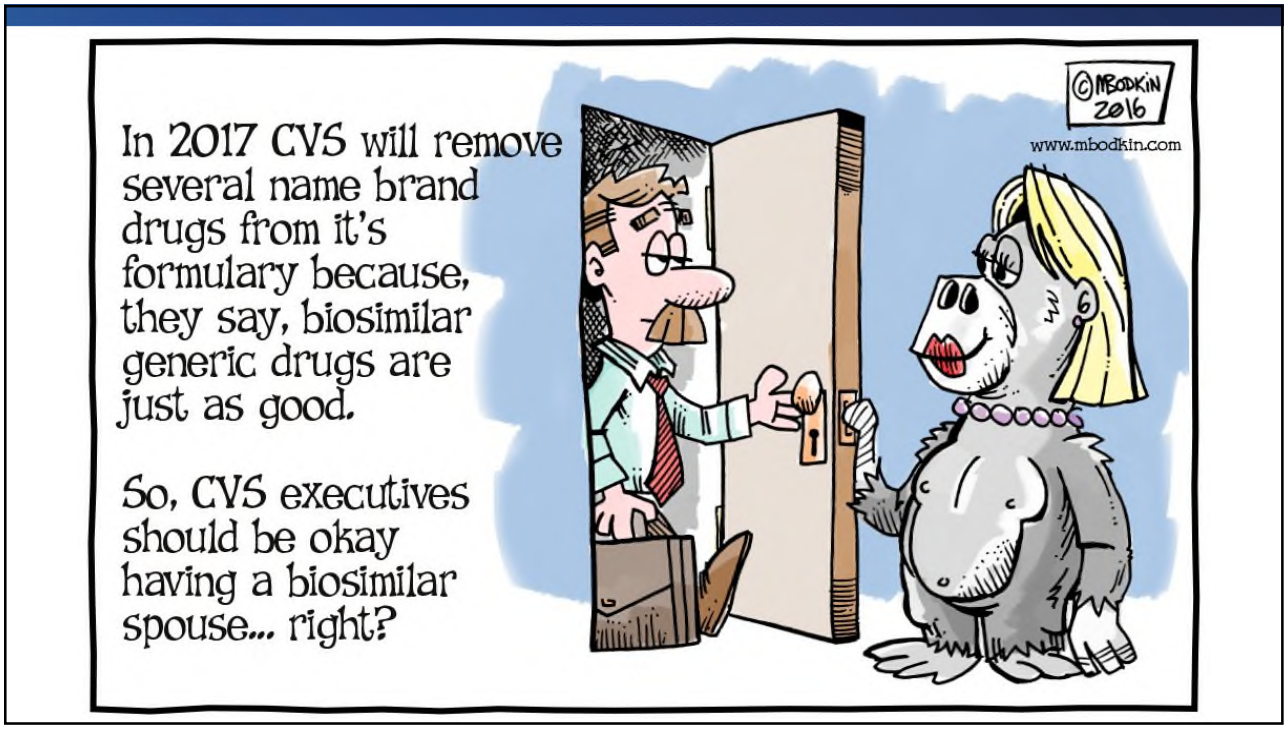
CHANGES TO INFLIXIMAB THERAPY OFFERINGS FOR SLHS INFUSION CENTERS – TRANSITION FROM REMICADE TO INFLECTRA
GO-LIVE November 1, 2017

IMPORTANT TO KNOW: **On November 1,** Saint Luke's Health System (SLHS) will be transitioning to Inflectra as the "preferred" product for patients requiring infliximab therapy in our outpatient infusion centers. For any new patient being initiated on infliximab therapy, providers should order Inflectra (infliximab-dyyb) rather than Remicade (infliximab). Remicade will remain available for only those outpatients already stabilized on Remicade and receiving maintenance therapy in our infusion centers.

Due to lower costs, Inflectra will be the preferred infliximab product for SLHS patients who are being initiated on this therapy. Remicade will remain on formulary for outpatients already stabilized on the drug but eventually will be phased out.

Other Resources

- American Gastroenterological Association- Biosimilars: www.gastro.org/biosimilars
- U.S. Food & Drug Administration- Information for Healthcare Professionals (Biosimilars): www.fda.gov/Drugs/DevelopmentApprovalProcess/HowDrugsareDevelopedandApproved/ApprovalApplications/TherapeuticBiologicApplications/Biosimilars/ucm241719.htm
- Crohn's & Colitis Foundation: Biosimilars- What IBD Patients Should Know: www.crohnscolitisfoundation.org/resources/biosimilars.html


In 2017 CVS will remove several name brand drugs from it's formulary because, they say, biosimilar generic drugs are just as good.
So, CVS executives should be okay having a biosimilar spouse... right?
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