SERBIAN IBD ASSOCIATION

Biosimilari. Gde je njihovo mesto?

Doc Dr Marijana Protic

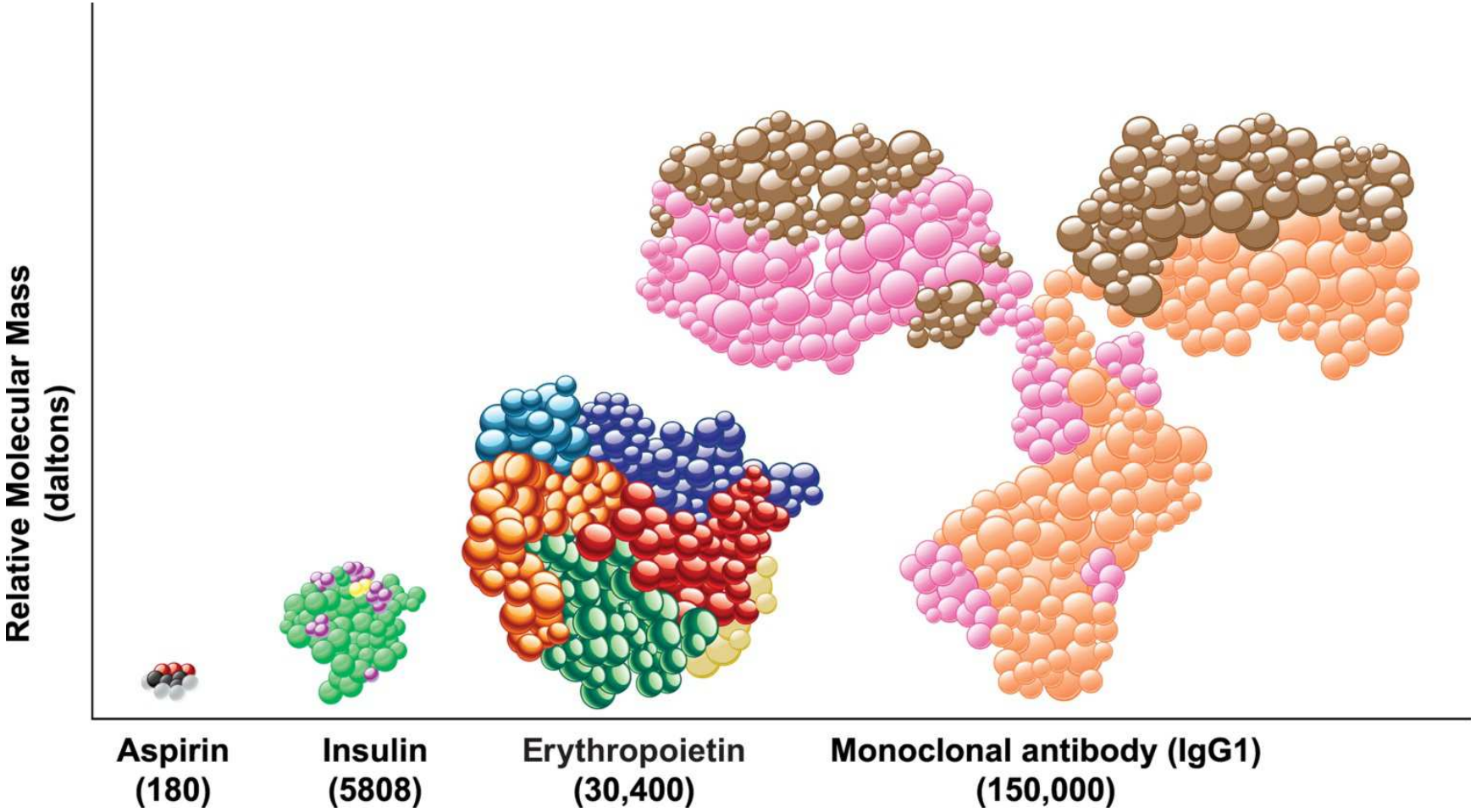
Odeljenje za Gastroenterologiju I hepatolgiju

KBC "Zvezdara"

Aranđelovac, 05.11.2016.

ADSBIO 160155

O sličnostima i razlikama…



Mellstedt H. *EJC Supplements* 2013;11:1-11.

REGULATORNI ZAHTEVI:

INOVATIVNI (ORIGINALNI) LEK vs BIOLOŠKI SLIČAN LEK

Klasično odobrenje za inovativni lek

Dokaz **"koristi za pacijenta"**

Faza I
Faza II
Faza III za sve indikacije
Plan minimizacije rizika

Skraćeno odobrenje za biološki sličan lek

Dokaz **"sličnosti"**

Faza I , PK/PD
Bez Faze II
Faza III za jednu reprezentativnu indikaciju
Plan minimizacije rizika

European Medicines Agency (EMA): Guideline on similar biological medicinal products containing monoclonal antibodies – non-clinical and clinical issues .
Available at: http://www.ema.europa.eu/docs/en_GB/document_library/Scientific_guideline/2012/06/WC500128686.pdf. Accessed 25 September 2014.

NEDOUMICE
PRAVNE REGULATIVE

Prenošenje indikacija (EXTRAPOLATION)

Prenošenje odobrenja upotrebe sa indikacije na kojoj je potvrđena biosličnost, na ostale indikacije odobrene za originalni biološki lek .

Medjusobna zamenljivost (INTERCHANGEABILITY)

Jedan lek može biti zamenjen drugim lekom (više puta) na osnovu karakteristika leka potvrđenih putem kliničkih studija koje dokazuju da je ovakva zamena moguća bez povećanog rizika u pogledu bezbednosti i efikasnosti u odnosu na korišćenje isključivo jednog leka.

Zamena *(SUBSTITUTION)*

Zamena originalnog biološkog leka biosličnim lekom u kliničkoj praksi, bez odluke lekara (farmaceut)

Promena (SWITCH)

Zamena jednog biološkog leka biosličnim lekom u kliničkoj praksi, prema odluci lekara uz isti cilj lečenja

European Medicines Agency. Available at: http://www.ema.europa.eu/docs/en_GB/document_library/Scientific_guideline/2010/11/WC500099361.pdf. Published November 18, 2010. Accessed November 29, 2011.
US DHHS, FDA, CDER, CBER. Available at:www.fda.gov/downloads/Drugs/GuidanceComplianceRegulatoryInformation/Guidances/UCM291128.pdf. Published February 2012. Accessed March 8, 2012.

Ipak realnost…

- CT-P13 biosimilar IFX – registracija 2013. EU; 2015. Srbija
- Jun 2016. C lista RFZO
- Registracione studije za indikacije u IBD-u ne postoje
- Ekstrapolacija podataka iz reumatoloskih studija
- Male prospektivne I retrospektivne studije [1, 2, 3]
- NOR-SWITCH konacno

1. Gecse KB,et al. Efficacy And Safety Of The Biosimilar Infliximab CT-P13 Treatment In IBD: A Prospective, Multicentre, Nationwide Cohort. JCC 2015.
2. Keil R, et al. Clinical monitoring: infliximab biosimilar CT-P13 in the treatment of CD &UC. *Scand. J. Gastroenterol.* 2016

BIOSIMILARI – EFIKASNOST I KRATKOROČNA BEZBEDNOST

PLANETRA

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]

PLANETAS

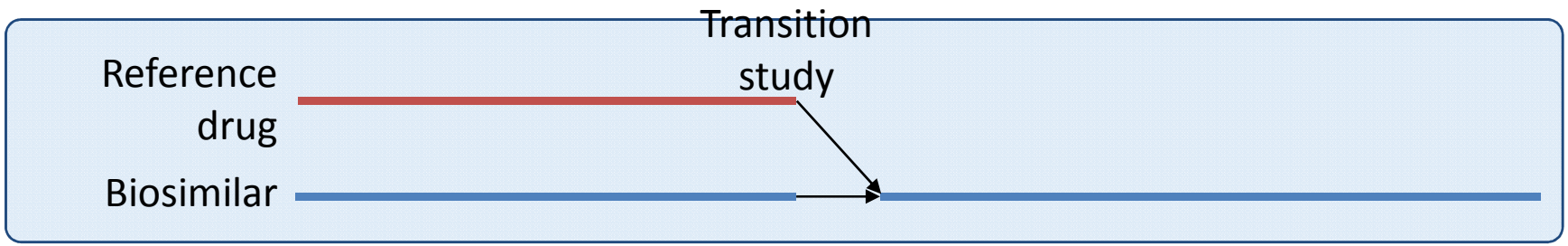
EXTENDED REPORT

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

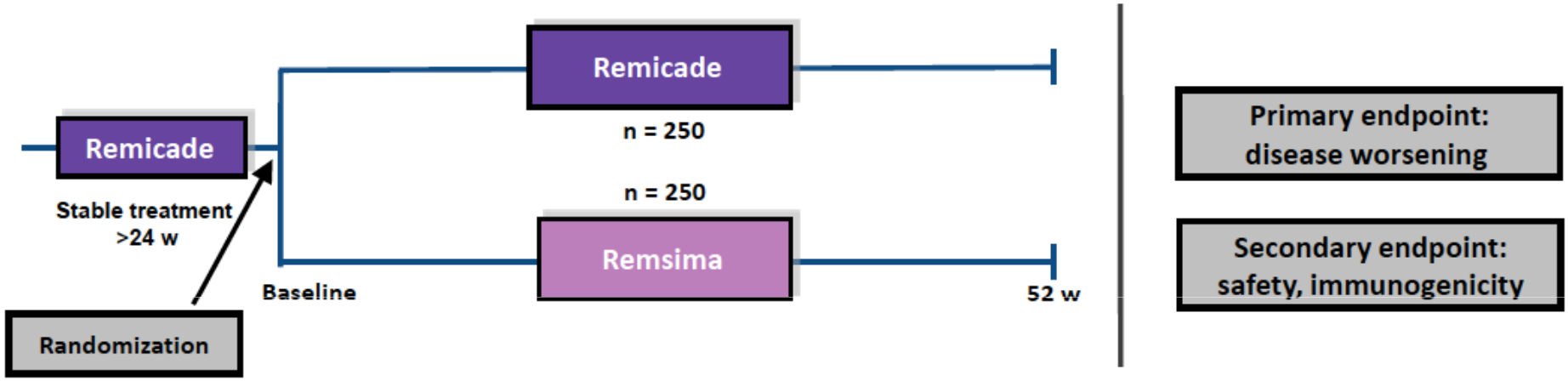
Won Park,[1] Pawel Hrycaj,[2] Slawomir Jeka,[3] Volodymyr Kovalenko,[4] Grygorii Lysenko,[5] Pedro Miranda,[6] Helena Mikazane,[7] Sergio Gutierrez-Ureña,[8] MieJin Lim,[1] Yeon-Ah Lee,[9] Sang Joon Lee,[10] HoUng Kim,[11] Dae Hyun Yoo,[12] Jürgen Braun[13]

NOR-SWITCH Study

- From Remicade® (infliximab) to Remsima™ (CT-P13)[1]: ***NOR-SWITCH Study***
- 500 patients, <u>100 in each indication</u>-
- Rheumatoid arthritis, Spondyloarthritis, Psoriatic arthritis, Ulcerative colitis, Crohn's disease, and Psoriasis
- ***Non-inferiority*** margin ± 15%



The Nor-Switch study



- A national, randomized, double-blind, parallel-group study
- Evaluate the efficacy and safety of switching from innovator infliximab (Remicade) to biosimilar infliximab (Remsima)
- Ulcerative colitis, Crohn's disease, rheumatoid arthritis, spondyloarthritis, psoriatic arthritis, psoriasis

NOR SWITCH

1. Goll LG. NOR-SWITCH, April 2016

Primary Endpoint [1]

- Occurrence of disease worsening during the 52w study period based on disease specific efficacy assessment scores

Secondary Endpoints [2]

Generic

- Time from randomization to disease worsening
- Patient and physician global assessment of disease activity
- Occurrence of drug discontinuation

Disease-specific

- Inflammation assessed by biochemical parameters
- UC: partial Mayo score, IBDQ
- CD: HBI, IBDQ

1. **Kvien, et al, UEGW 2016, Abstract LB15, Late Breaker Oral Presentation.**
2. ***clinicaltrials.gov/ct2/show/NCT02148640***

Disease worsening [1]

- **RA and PsA :** ↑ DAS 28 ≥1.2 from randomization, a min. DAS 28 ≥ 3.2.
- **SpA:** ↑ ASDAS of ≥1.1 from randomization and a minimum ASDAS ≥ 2.1
- ***Ulcerative colitis : ↑ par. Mayo score of ≥ 3 from randomization and a min. par. Mayo ≥ 5***
- ***Crohn's disease: ↑ HBI of ≥ 4 from randomization and a min HBI ≥7***
- **Psoriasis** Increase in PASI of ≥ 3 from randomization and a min. PASI ≥ 5

- **Patient and investigator consensus on disease worsening** :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.

1. Goll LG. NOR-SWITCH, April 2016

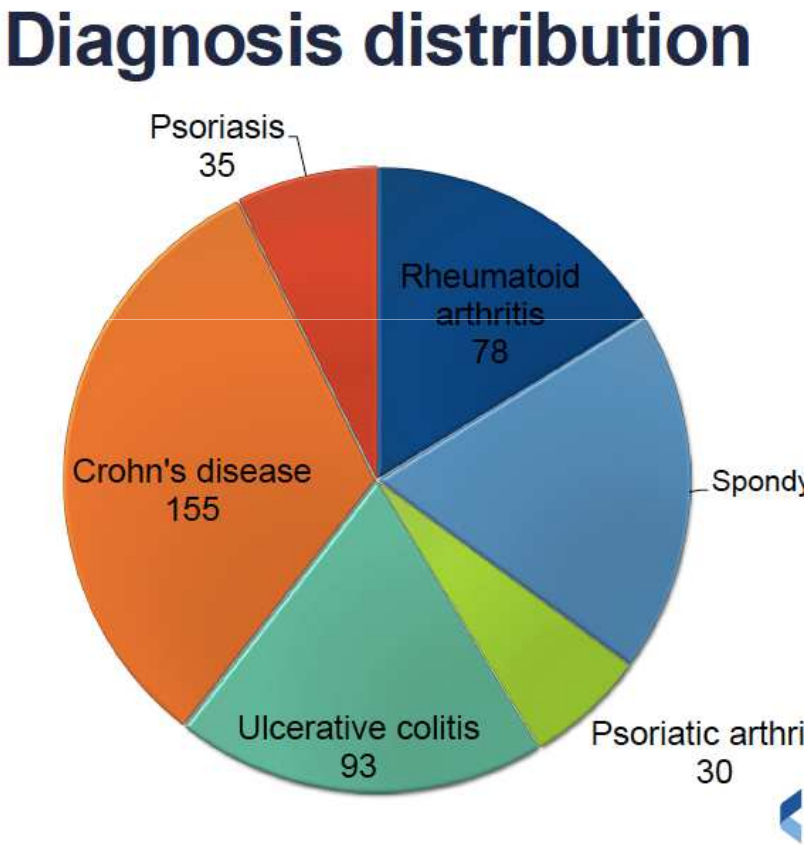
Šta kažu brojevi ?

Non-Inferiority Margin	10% Disease Worsening at 48 W	20% Disease Worsening at 48 W	30% Disease Worsening at 48 W
10%	380	674	884
15%	170	300	394
20%	96	170	222

Table 1. Numbers in the cells represent the total number of patients needed. All calculations are based on a power of **90%** and alpha 2.5%

Kvien, et al, UEGW 2016, Abstract LB15, Late Breaker Oral Presentation

The Nor-switch study



	IFX	CTP 13
Diagnoses		
Crohn's disease	***78 (32.4%)***	***77 (32.1%)***
Ulcerative colitis	***47 (19.5%)***	***46 (19.2%)***
Spondyloarthritis	45 (18.7%)	46 (19.2%)
Rheumatoid arthritis	39 (16.2%)	38 (15.8%)
Psoriatic arthritis	14 (5.8%)	16 (6.7%)

1. Goll LG. NOR-SWITCH, April 2016

Demografski podaci [1]

	INX	CT-P13
Number of patients (FAS)	241	240
Age (years)	47.5 (14.8)	48.2 (14.9)
Females	99 (41.1%)	87 (36.2%)
Disease duration (years)	16.7 (10.9)	17.5 (10.5)
Duration of ongoing infliximab treatment (years)	***6.7 (3.6)***	***6.9 (3.8)***
Concomitant immunosuppressive comedication	113(46.9%)	129 (53.8%)

Tabela 1. Demografski podaci za celu grupu pacijenata

1. **Kvien, et al, UEGW 2016, Abstract LB15, Late Breaker Oral Presentation.**

Demografija -CB i UK [1]

Crohn'disease	Remicade (n=77)	CT-P13 (n=78)
Concomitant IS rx (MTX, AZA/6-MP)	30 (38%)	36 (47%)
Harvey Bradshaw Index (HBI)	2 (1-4)	2 (0-4)
C-reactive protein (mg/L)	2.8 (1.0-5.0)	1.3 (1.0-5.0)
Fecal calprotectin (mg/kg)	70 (32-190.5)	65 (27-210)

Tabela 1. Crohn-ova bolest

Ulcerative colitis	Remicade (n=47)	CT-P13 (n=46)
Concomitant IS rx (MTX, AZA/6-MP)	19 (40%)	20 (43%)
Partial Mayo Score (p-Mayo)	0 (0-1)	0 (0-1)
C-reactive protein (mg/L)	1.4 (1-5)	1.1 (1-5)
Fecal calprotectin (mg/kg)	44 (19-110.5)	39.5 (19-208)

Tabela 2. Ulcerozni kolitis

1. **Kvien, et al, UEGW 2016, Abstract LB15, Late Breaker Oral Presentation**

Rezultati [1]

Diagnosis	Remicade (n=202)	CT-P13 (n=206)	Adjusted Rate Difference (95% CI)
Crohn's disease	***14 (21.2%)***	***23 (36.5%)***	***-14.3% (-29.3-0.7%)***
Ulcerative colitis	***3 (9.1%)***	***5 (11.9%)***	***-2.6% (-15.2-10.0%)***
Spondyloarthritis	17 (39.5%)	14 (33.3%)	6.3% (-14.5-27.2%)
Rheumatoid arthritis	11 (36.7%)	9 (30.0%)	4.5% (-20.3-29.3%)
Psoriatic arthritis	7 (53.8%)	8 (61.5%)	-8,7% (-45.5-28.1%)
Psoriasis	1 (5.9%)	2 (12.5%)	6.7% (-26.7-13.2%)
Overall	*53 (26.2%)*	*61 (29.6%)*	*-4.4% (-12.7-3.9%)*

Diagnosis	Remicade	CT-P13	Adjusted Rate Difference (95% CI)
Harvey-Bradshaw Index (CD)	0.26 ***(2.35)***	0.49 (***3.15)***	-1.14 - 0.33
Partial Mayo Score (UC)	0.09 ***(1.28)***	-0.17 ***(1.68)***	-0.30 - 0.59

1. Kvien, et al, UEGW 2016, Abstract LB15.

Zaključak autora Nor-Switch studije[1]

- "The NOR-SWITCH trial demonstrated that switch from Remicade to CT-P13 was not inferior to continued treatment with Remicade"

Study limitations

- Non inferiority design
- ***Not powered for non-inferiority within each diagnostic group***
- Blinding procedures

Kvien, et al, UEGW 2016, Abstract LB15

Ipak...

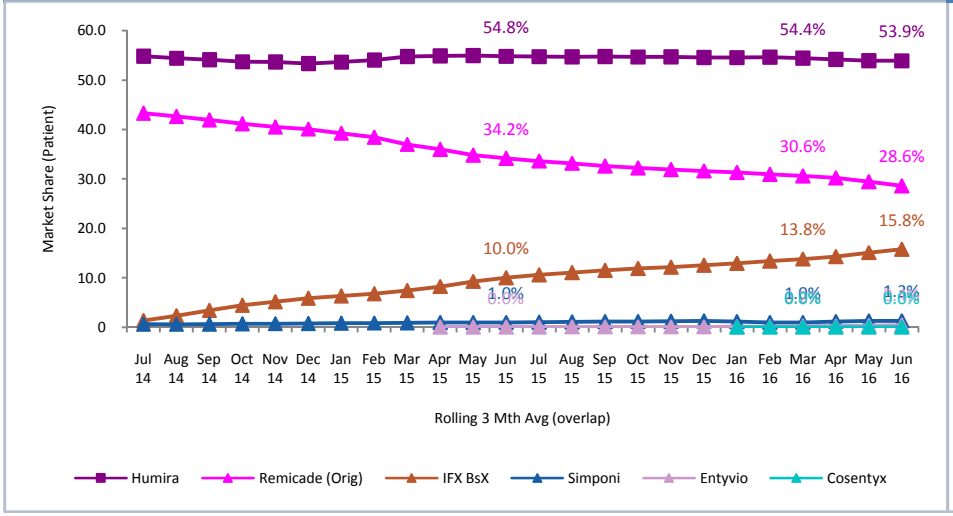
- **<u>Evropska agencija za lekove EMA</u>** -

1. Primena kod biološki naivnih pacijenata
2. Ne preporučuje se zamena originalnog leka biosimilarom/ obrnuto

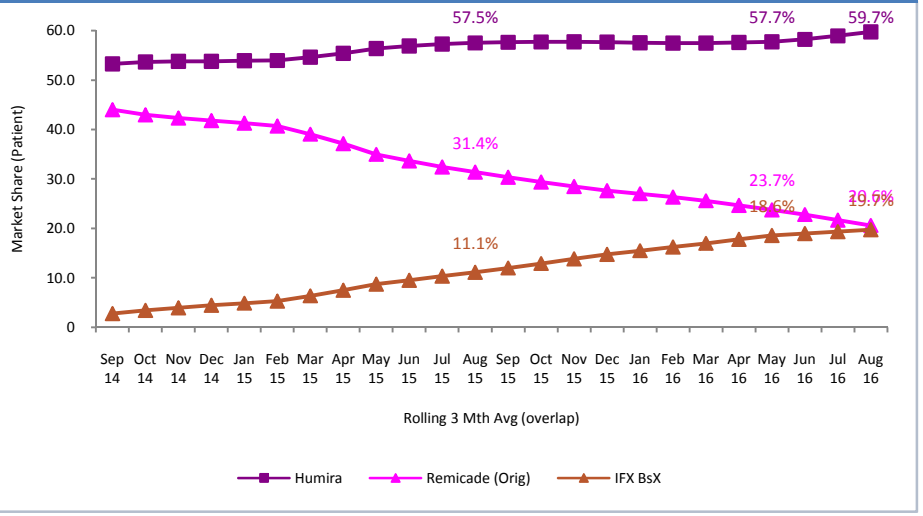
✧ Sobzirom da je nacionalna regulativa jedina obavezujuća:

- ***U većini zemalja EU 2015./16. godine – biosimilari,***
- Kod bio-naivnih pacijenata ali I “switching”
- Formiranje MDT
- Poštujući želju/potrebu za subkutanim originalnim anti TNF lekovima

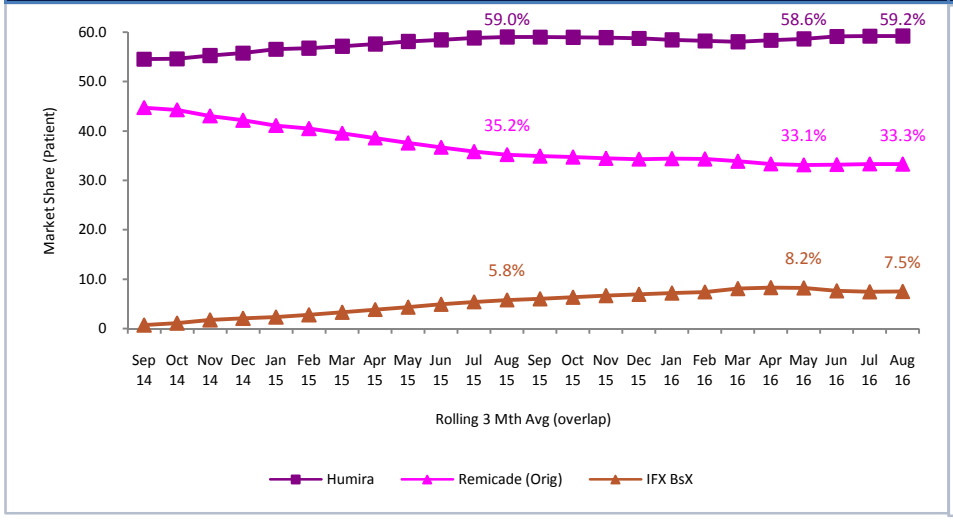
Total Gastro Market Share (CD + UC) Central Europe



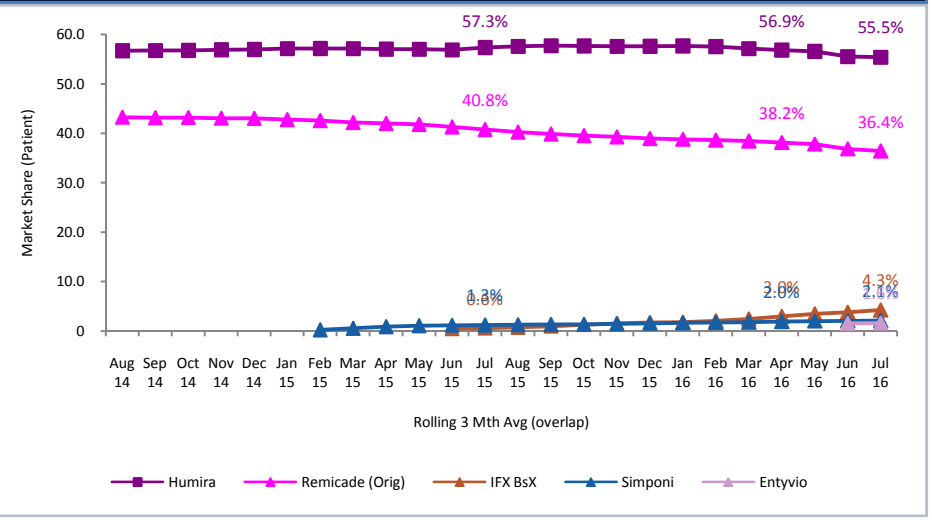
Total Gastro Market Share (CD + UC) Hungary



Total Gastro Market Share (CD + UC) Romania



Total Gastro Market Share (CD + UC) Slovenia



Vreme ce pokazati …

- *Beurer L et al. JCC 2016.*
- Prospective, “open label”- single center
- Switching Remicade ® ➔ Remsima ®
- ***The primary endpoints***

✓ the proportion of patients remaining on medication 6 months after switching

✓ adverse events during the 6 months after switching

➢ ***Results: 143 IBD pts – 97% remained on the Remsima 6 months after switching***

✧ ***BUT, 23% (33 pts) needed therapy optimization + 1 additional Vedolizumab***

✧ **13%/ yearly LOR anti TNF drugs**

➢ **What is the real cost?**

❖ **NO DATA ON ENDOSCOPY so far – What’s about mucosal healing?**

SIBDA I URES- 2016.

1. Terapija biološki sličnim lekom može se primeniti samo kod bolesnika koji ***predhodno nisu lečeni nijednim originalnim biološkim lekom*** kako bi se obezbedila pouzdanost podataka o efikasnosti i bezbednosti

2. U skladu sa regulatornim aktima EMA prenošenje ***indikacija na populaciju dece nije dozvoljeno*** ukoliko nisu dostavljeni podaci o studijama u kojima je ispitivana PK i PD u dece, kao i podaci o bezbednosti primene

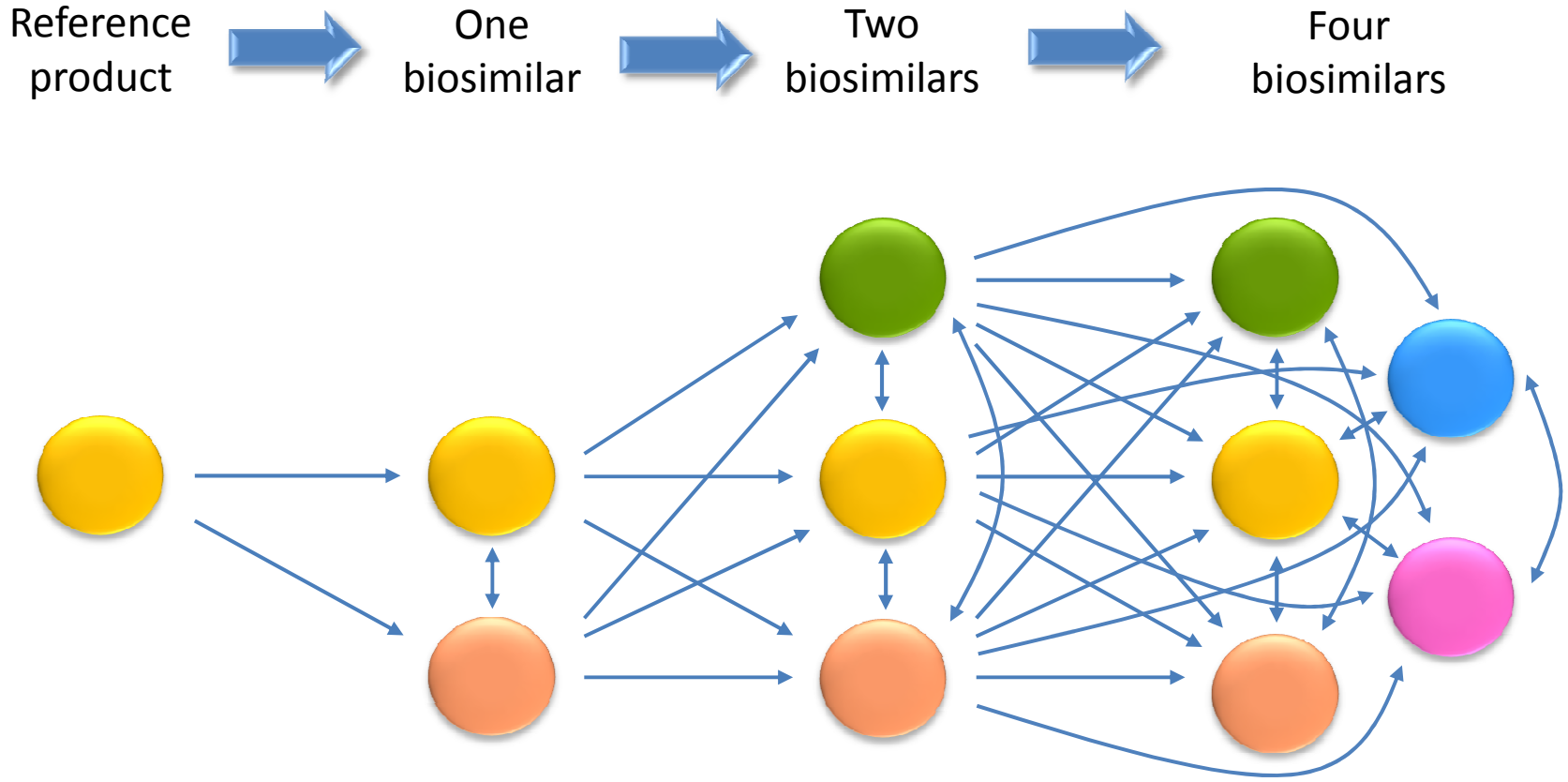
3. Iako biološki sličan lek u osnovi ima isti klinički efekat kao originalni biološki lek, ***ovi se lekovi ne mogu direktno međusobno zamjenjivati***. ***Nije dozvoljena:***

   a) međusobna zamenljivost ***od strane farmaceuta*** ili bilo kog drugog lica

   b) Zamena kod ***bolesnika koji su započeli lečenje originalnim biološkim lekom***

   c) ***u slučaju neefikasnosti biološkog leka***, promena i nastavak lečenja biološki sličnim lekom na isti originalni biološki lek

Pitanje na koje nema odgovora



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