EAFS
Eesti Akadeemiline Farmaatsia Selts

Geneeriline ja võrdlusravim
Võrdlevad uuringud

Kristian Semjonov

„Geneerilised ravimid“

Tallinn, 30 mai 2019

Huvidekonflikt

- Terve Pere Apteek OÜ, proviisor

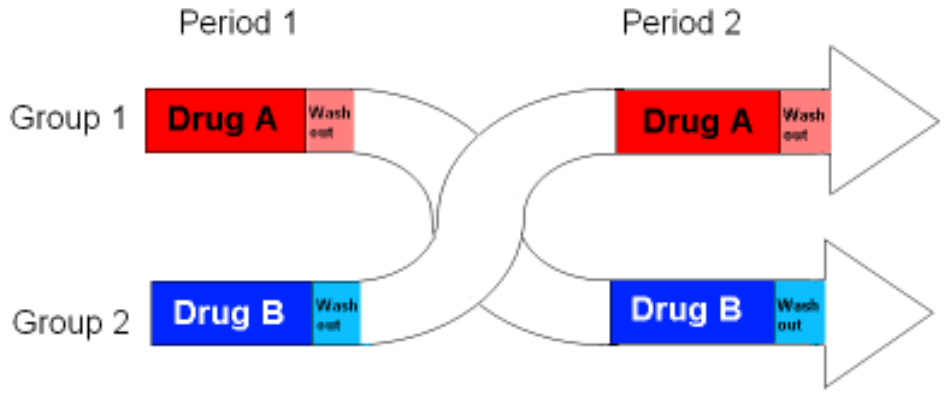
EAFS
Eesti Akadeemiline Farmaatsia Selts

Medline (Pubmed)
Scopus
ScienceDirect
Cochrane Library
Clinicaltrials.gov
Google Scholar
.....

generic, brand, bioequivalence, meta-analysis, review, biosimilar, switching....

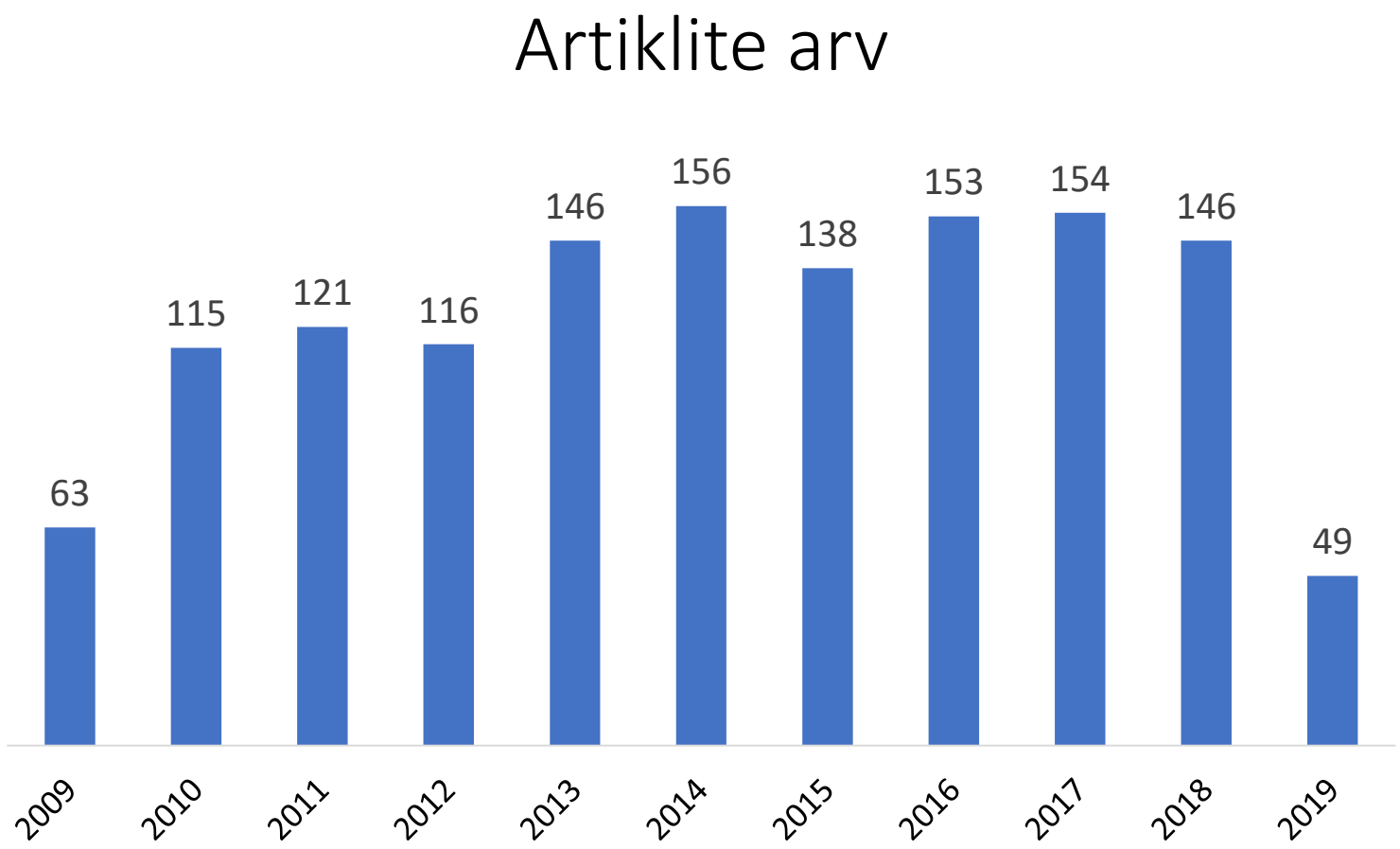
Terminoloogia

- Meta-analüüs
- Ristuv uuring (*cross-over study*)
- Randomiseeritud kontrollrühma uuring (RCT)
- Vaatlusuuring



http://en.citizendium.org/wiki/Cross-over_study

Pubmed 2009-2019 „generic brand drug“



https://www.ncbi.nlm.nih.gov/pubmed

Kas geneeriline ravim on bioekvivalentne?

- FDA e Ameerika Toidu- ja Ravimiamet
  - Office of Generic Drugs
  - Office of Testing and Research
- Retrospektiivne BE uuringute analüüs, n=2070 (1997-2007)
- Lühi- ja pikatoimelised ravimpreparaadid
- Cmax, AUC, Tmax

Barbara M Davit, Patrick E Nwakama, Gary J Buehler, Dale P Conner, Sam H Haidar, Dewrat T Patel, Yongsheng Yang, Lawrence X Yu, and Janet Woodcock. **Comparing Generic and Innovator Drugs: A Review of 12 Years of Bioequivalence Data from the United States Food and Drug Administration.** Annals of Pharmacotherapy, Volume 43, 2009, p1583-97

EAFS
Eesti Akadeemiline Farmaatsia Selts

Table 2. Average Percent Differences Between Generic and Innovator Drug Product Bioequivalence Parameter Geometric Means[a]

Solid Oral Dosage Form Type	C_{max} BE Studies, n	C_{max} Average Percent Difference	AUC_{0-t} BE Studies, n	AUC_{0-t} Average Percent Difference	AUC_{∞}[b] BE Studies, n	AUC_{∞}[b] Average Percent Difference
All drug products	2070	4.35 ± 3.54	2070	3.56 ± 2.85	1939	3.52 ± 2.86
IR drug products	1788	4.43 ± 3.50	1788	3.15 ± 2.66	1693	3.08 ± 2.61
MR drug products	282	5.44 ± 3.99	282	3.79 ± 3.12	246	3.81 ± 3.16

AUC = area under the concentration-time curve; BE = bioequivalence; C_{max} = peak drug plasma concentration; IR = immediate release; MR = modified release.
[a]Mean ± SD.
[b]There are fewer observations for AUC_{∞} because in some studies it was not possible to extrapolate AUC_{0-t} to infinity.

PK parameetrite erinevus: 4.35% (Cmax) ja 3.56% (AUC_{0-t})

91.6% BE uuringutes erines Cmax > 10%

97.6% BE uuringutes erines AUC > 10%

Table 3. Distribution of Percent Absolute Differences Between Generic and Innovator Bioequivalence Parameter Geometric Means

Range of Percent Differences	Percent of Total BE Studies (Studies, n) All Drug Products (n = 2070)[a] C_{max}	All Drug Products (n = 2070)[a] AUC_{0-t}	IR Drug Products (n = 1788) C_{max}	IR Drug Products (n = 1788) AUC_{0-t}	MR Drug Products (n = 282) C_{max}	MR Drug Products (n = 282) AUC_{0-t}
0–5	64.1 (1327)	80.8 (1673)	66.1 (1182)	81.5 (1457)	51.4 (145)	76.3 (215)
6–10	27.5 (569)	16.8 (348)	26.2 (468)	16.3 (291)	36.2 (102)	19.8 (56)
11–15	8.0 (166)	2.3 (47)	7.3 (131)	2.1 (38)	12.1 (34)	3.5 (10)
>15	0.4 (8)	0.1 (2)	0.4 (7)	0.1 (2)	0.3 (1)	0.4 (1)

AUC = area under the concentration-time curve; BE = bioequivalence; C_{max} = peak drug plasma concentration; IR = immediate release; MR = modified release.
[a]Total number of studies in which the bioequivalence parameter was measured.

Geneerikud on bioekvivalentsed võrdlusravimitega!

Barbara M Davit, Patrick E Nwakama, Gary J Buehler, Dale P Conner, Sam H Haidar, Dewrat T Patel, Yongsheng Yang, Lawrence X Yu, and Janet Woodcock. **Comparing Generic and Innovator Drugs: A Review of 12 Years of Bioequivalence Data from the United States Food and Drug Administration.** Annals of Pharmacotherapy, Volume 43, 2009, p1583-97

Kardioloogilised ravimid – geneerik vs võrdlusravim

- 74 randomiseeritud kliinilist uuringut
  - 3 uuringut (n=667) tulemusnäitajaks (hard) MACE või surm
  - 52 uuringut (n=2609) tulemusnäitajaks (soft) RR, LDL

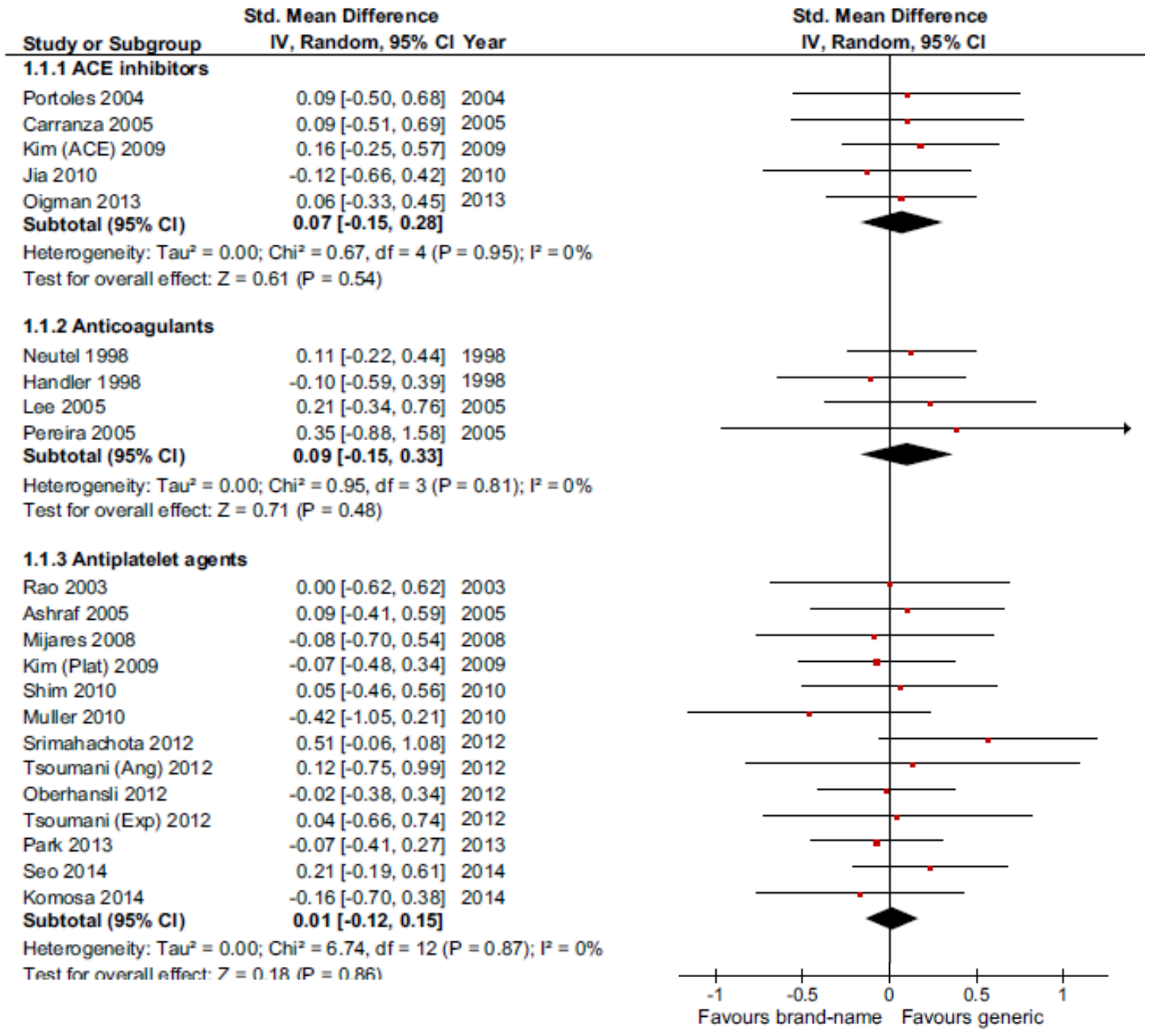
  - 1/3 uuringutest publitseeritud peale 2005a.

AKE inhibiitorid (12), antikoagulandid/antiagregandid (22), ß-blokaatorid (11), kaltsiumikanali blokaatorid (7), diureetikumid (13), statiinid (6), teised (3)

Lamberto Manzoli, Maria Elena Flacco, Stefania Boccia, Elvira D'Andrea, Nikola Panic, Carolina Marzuillo, Roberta Siliquini, Walter Ricciardi, Paolo Villari, John P. A. Ioannidis. **Generic versus brand-name drugs used in cardiovascular diseases.** Eur J Epidem, Volume 31, 2016, p351-368

Table 1 continued

First author	Year	Country	Active principle	Patient's status	Mean age (years)	Follow-up duration[a]	Design	Total sample (generics)	Extracted outcomes	Funding	Protocol registration
Antiplatelet agents											
Oberhänsli [75]	2012	Swiss	Clopidogrel	CVD	69	10 days	Cross-over	60 (60)	Platelet aggr. inhibition (E), sAEs (S)	Non profit	No
Srimahachota [78]	2012	Thailand	Clopidogrel	CVD	NR	6 h	Parallel-group	49 (25)	Platelet aggr. inhibition (E), mAEs (S)	Not reported	No
Tsoumani (A) [79]	2012	Greece	Clopidogrel	ACS	70	6 months	Parallel-group	86 (45)	Platelet aggr. inhibition (E)	Generic manufacturer	No
Tsoumani (E) [80]	2012	Greece	Clopidogrel	ACS	64	4 weeks	Parallel-group	96 (51)	Platelet aggr. inhibition (E)	Non profit	No
Zou [81]	2012	China	Clopidogrel	Healthy	24	36 h	Cross-over	20 (20)	sAEs (S)	Not reported	No
Park (J) [76]	2013	Korea	Clopidogrel	CVD	62	4 weeks	Parallel-group	130 (65)	Platelet aggr. inhibition (E), MACE and death (E), mAEs (S), sAEs (S)	Generic manufacturer	NCT01584791
Komosa [72]	2014	Poland	Clopidogrel	CVD	49	8 days	Parallel-group	53 (28)	Platelet aggr. inhibition (E), mAEs (S)	Not reported	No
Seo [77]	2014	Korea	Clopidogrel	ACS	58	24 h (4 weeks for AEs and MACE)	Parallel-group	95 (47)	Platelet aggr. inhibition (E), MACE and death (E), sAEs (S)	Generic manufacturer	NCT02060786



Lamberto Manzoli, Maria Elena Flacco, Stefania Boccia, Elvira D'Andrea, Nikola Panic, Carolina Marzuillo, Roberta Siliquini, Walter Ricciardi, Paolo Villari, John P. A. Ioannidis**Generic versus brand-name drugs used in cardiovascular diseases.** Eur J Epidem, Volume 31, 2016, p351-368

1.1.4 Beta-Blockers

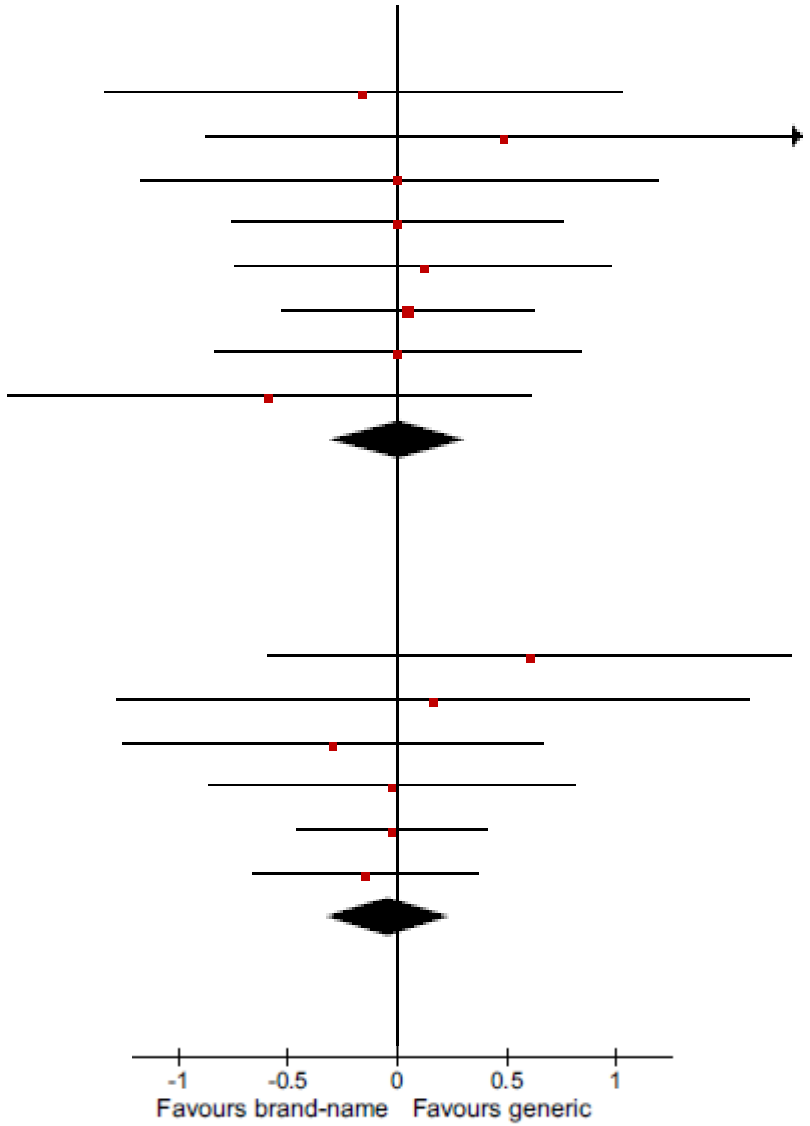
El-Sayed 1989	-0.11 [-0.91, 0.69]	1989
Biswas 1989	0.33 [-0.60, 1.26]	1989
Carter 1989	0.00 [-0.80, 0.80]	1989
Sarkar 1995	0.00 [-0.51, 0.51]	1995
Chiang 1995	0.08 [-0.50, 0.66]	1995
Bongers 1999	0.03 [-0.36, 0.42]	1999
Cuadrado 2002	0.00 [-0.57, 0.57]	2002
Mirfazaelian 2003	-0.40 [-1.21, 0.41]	2003
Subtotal (95% CI)	**0.00 [-0.21, 0.21]**	

Heterogeneity: Tau² = 0.00; Chi² = 1.59, df = 7 (P = 0.98); I² = 0%
Test for overall effect: Z = 0.01 (P = 0.99)

1.1.5 Calcium channel blockers

Usha 1997	0.41 [-0.40, 1.22]	1997
Saseen 1997	0.11 [-0.87, 1.09]	1997
Park 2004	-0.20 [-0.85, 0.45]	2004
Mignini 2007	-0.02 [-0.59, 0.55]	2007
Kim 2007	-0.02 [-0.31, 0.27]	2007
Kim 2008	-0.10 [-0.45, 0.25]	2008
Subtotal (95% CI)	**-0.03 [-0.22, 0.16]**	

Heterogeneity: Tau² = 0.00; Chi² = 1.63, df = 5 (P = 0.90); I² = 0%
Test for overall effect: Z = 0.31 (P = 0.75)



1.1.6 Diuretics

Grahnen 1984	0.16 [-0.82, 1.14]	1984
Garg 1984	0.13 [-0.56, 0.82]	1984
Martin 1984	-0.14 [-0.95, 0.67]	1984
Pan 1984	0.09 [-1.15, 1.33]	1984
Meyer 1985	-0.49 [-1.15, 0.17]	1985
Singh 1987	-0.13 [-1.18, 0.92]	1987
Sharoky 1989	0.08 [-0.64, 0.80]	1989
Kaojarern 1990	-0.60 [-1.66, 0.46]	1990
Awad 1992	-0.35 [-0.97, 0.27]	1992
Murray 1997	0.31 [-0.24, 0.86]	1997
Subtotal (95% CI)	**-0.07 [-0.31, 0.17]**	

Heterogeneity: $Tau^2 = 0.00$; $Chi^2 = 5.94$, df = 9 (P = 0.75); $I^2 = 0\%$
Test for overall effect: Z = 0.58 (P = 0.56)

1.1.7 Statins

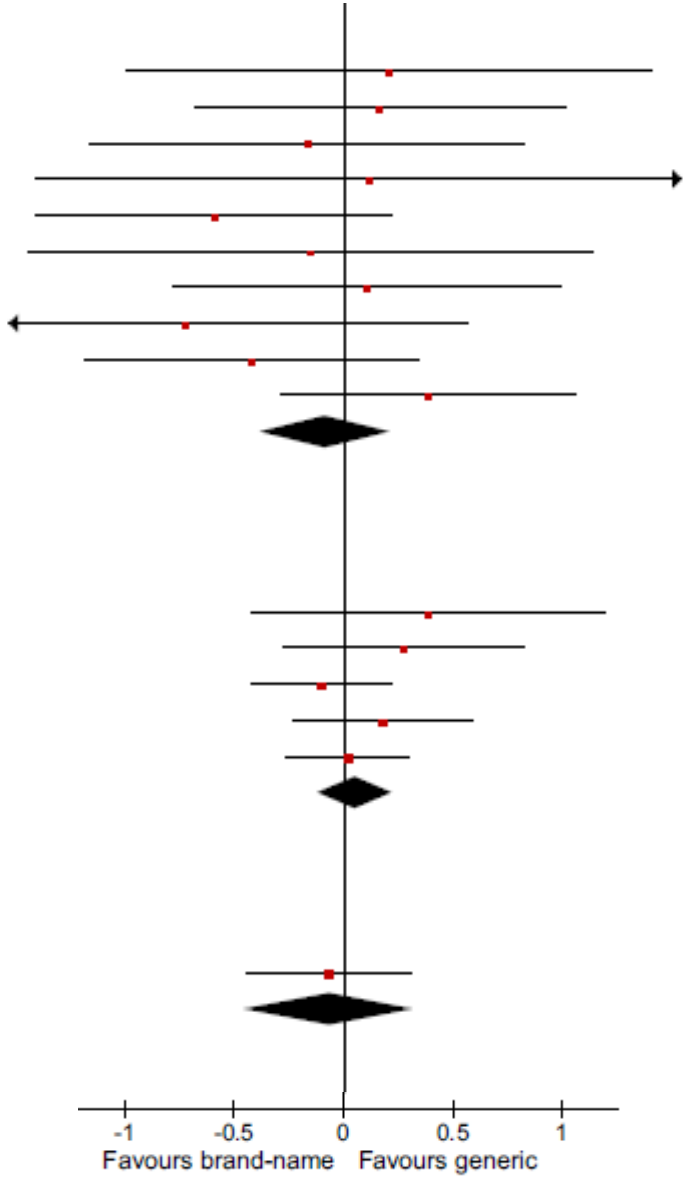
Wiwanitkit 2002	0.31 [-0.35, 0.97]	2002
Assawawitoontip 2002	0.22 [-0.23, 0.67]	2002
Kim 2010	-0.09 [-0.35, 0.17]	2010
Boh 2011	0.14 [-0.19, 0.47]	2011
Kim 2013	0.01 [-0.22, 0.24]	2013
Subtotal (95% CI)	**0.04 [-0.10, 0.18]**	

Heterogeneity: $Tau^2 = 0.00$; $Chi^2 = 2.63$, df = 4 (P = 0.62); $I^2 = 0\%$
Test for overall effect: Z = 0.54 (P = 0.59)

1.1.8 Others

Tsai 2007	-0.06 [-0.37, 0.25]	2007
Subtotal (95% CI)	**-0.06 [-0.37, 0.25]**	

Heterogeneity: Not applicable
Test for overall effect: Z = 0.38 (P = 0.70)



Lamberto Manzoli, Maria Elena Flacco, Stefania Boccia, Elvira D'Andrea, Nikola Panic, Carolina Marzuillo, Roberta Siliquini, Walter Ricciardi, Paolo Villari, John P. A. Ioannidis**Generic versus brand-name drugs used in cardiovascular diseases.** Eur J Epidem, Volume 31, 2016, p351-368

- Geeriline ravim on kliiniliselt ekvivalentne võrdlusravimiga

- Rohkem uuringuid kitsa terapeutilise vahemikuga ravimitega

Lamberto Manzoli, Maria Elena Flacco, Stefania Boccia, Elvira D'Andrea, Nikola Panic, Carolina Marzuillo, Roberta Siliquini, Walter Ricciardi, Paolo Villari, John P. A. Ioannidis**Generic versus brand-name drugs used in cardiovascular diseases.** Eur J Epidem, Volume 31, 2016, p351-368

Review

December 3, 2008

Clinical Equivalence of Generic and Brand-Name Drugs Used in Cardiovascular Disease

A Systematic Review and Meta-analysis

Aaron S. Kesselheim, MD, JD, MPH; Alexander S. Misono, BA; Joy L. Lee, BA; et al

JAMA. 2008;300(21):2514-2526. doi:10.1001/jama.2008.758

Abstract

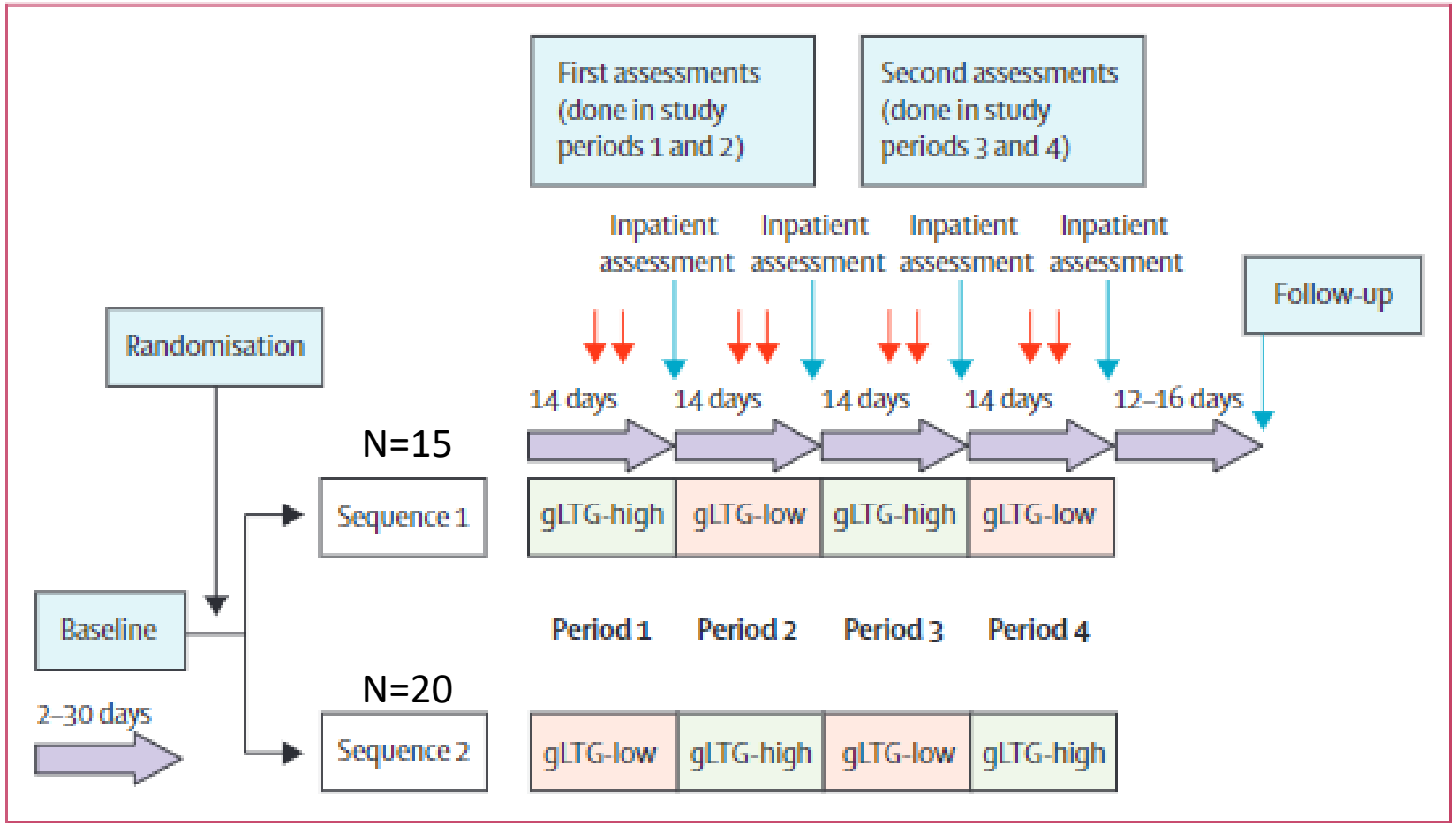
Context Use of generic drugs, which are bioequivalent to brand-name drugs, can help contain prescription drug spending. However, there is concern among patients and physicians that brand-name drugs may be clinically superior to generic drugs.

Objectives To summarize clinical evidence comparing generic and brand-name drugs used in cardiovascular disease and to assess the perspectives of editorialists on this issue.

Data Sources Systematic searches of peer-reviewed publications in MEDLINE, EMBASE, and International Pharmaceutical Abstracts from January 1984 to August 2008.

Study Selection Studies compared generic and brand-name cardiovascular drugs using clinical efficacy and safety end points. We separately identified editorials addressing generic substitution.

„EQUIGEN“ geneerik-geneeriku asendus



Michael D Privitera, Timothy E Welty, Barry E Gidal, Francisco J Diaz, Ron Krebill, Jerzy P Szafl arski, Barbara A Dworetzky, John R Pollard, Edmund J Elder Jr, Wenlei Jiang, Xiaohui Jiang, Michel Berg. Generic-to-generic lamotrigine switches in people with epilepsy: the randomised controlled EQUIGEN trial. Lancet Neurol, Volume 15, 2016 p365-72

„EQUIGEN“ geneerik-geneerik asendus

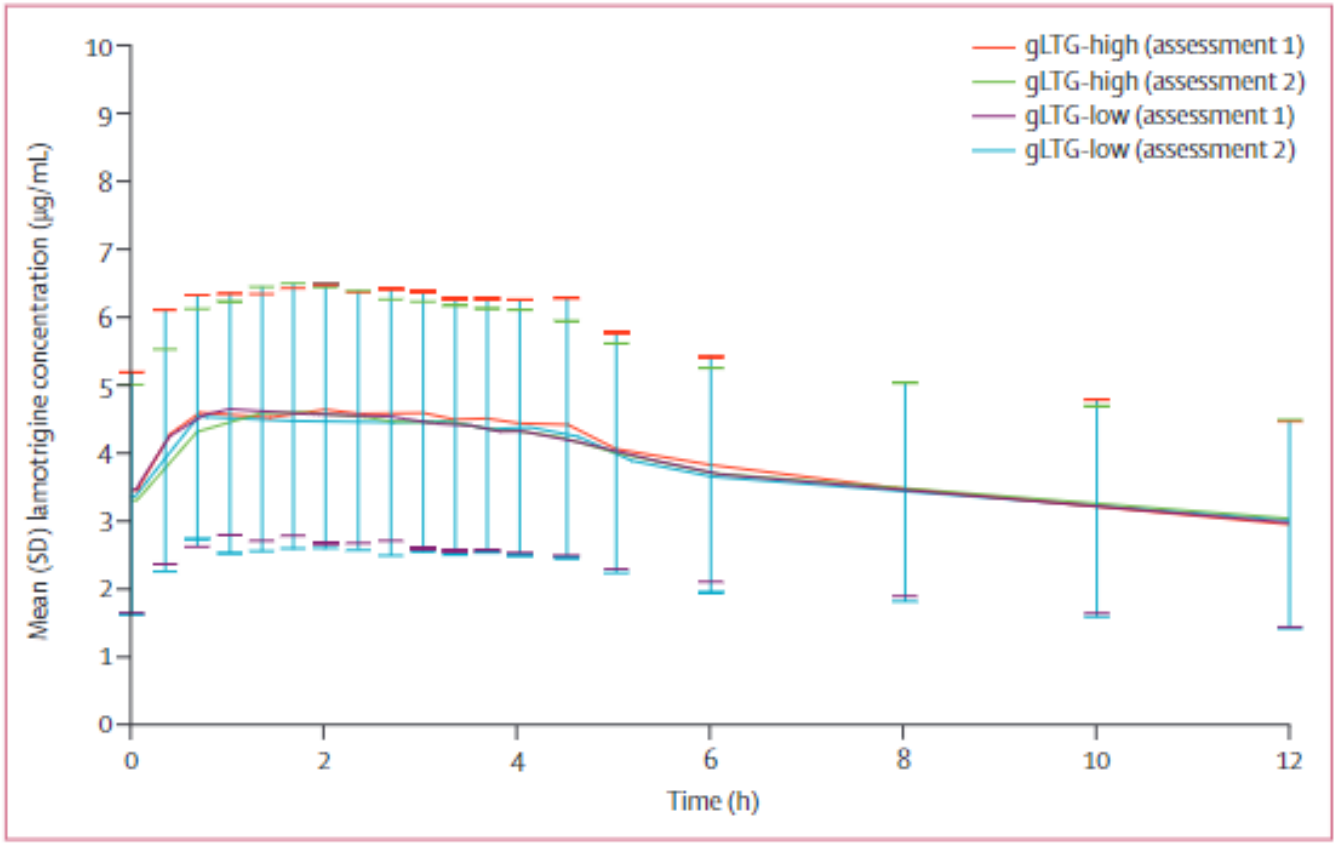
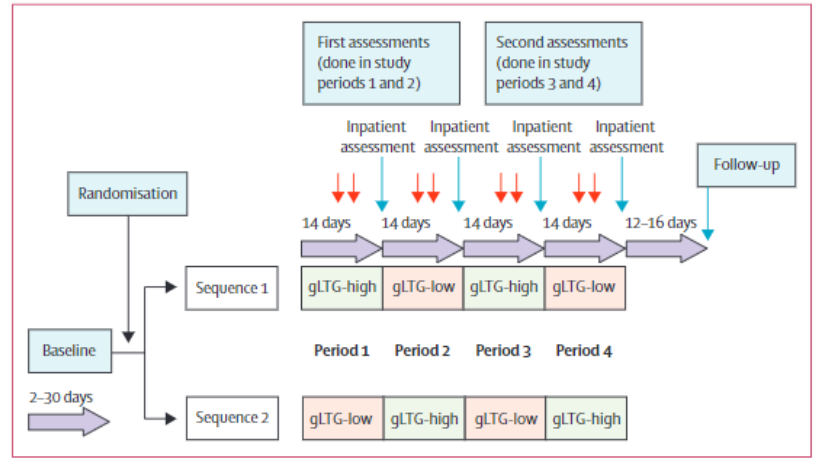


***Figure 3*: Lamotrigine plasma concentrations**
Dose normalised to 100 mg. Error bars are SDs. Assessment 1 was defined as pharmacokinetic assessment done during period 1 or 2. Assessment 2 was defined as pharmacokinetic assessment done during period 3 or 4. gLTG=generic lamotrigine.



Michael D Privitera, Timothy E Welty, Barry E Gidal, Francisco J Diaz, Ron Krebill, Jerzy P Szafl arski, Barbara A Dworetzky, John R Pollard, Edmund J Elder Jr, Wenlei Jiang, Xiaohui Jiang, Michel Berg. Generic-to-generic lamotrigine switches in people with epilepsy: the randomised controlled EQUIGEN trial. Lancet Neurol, Volume 15, 2016 p365-72

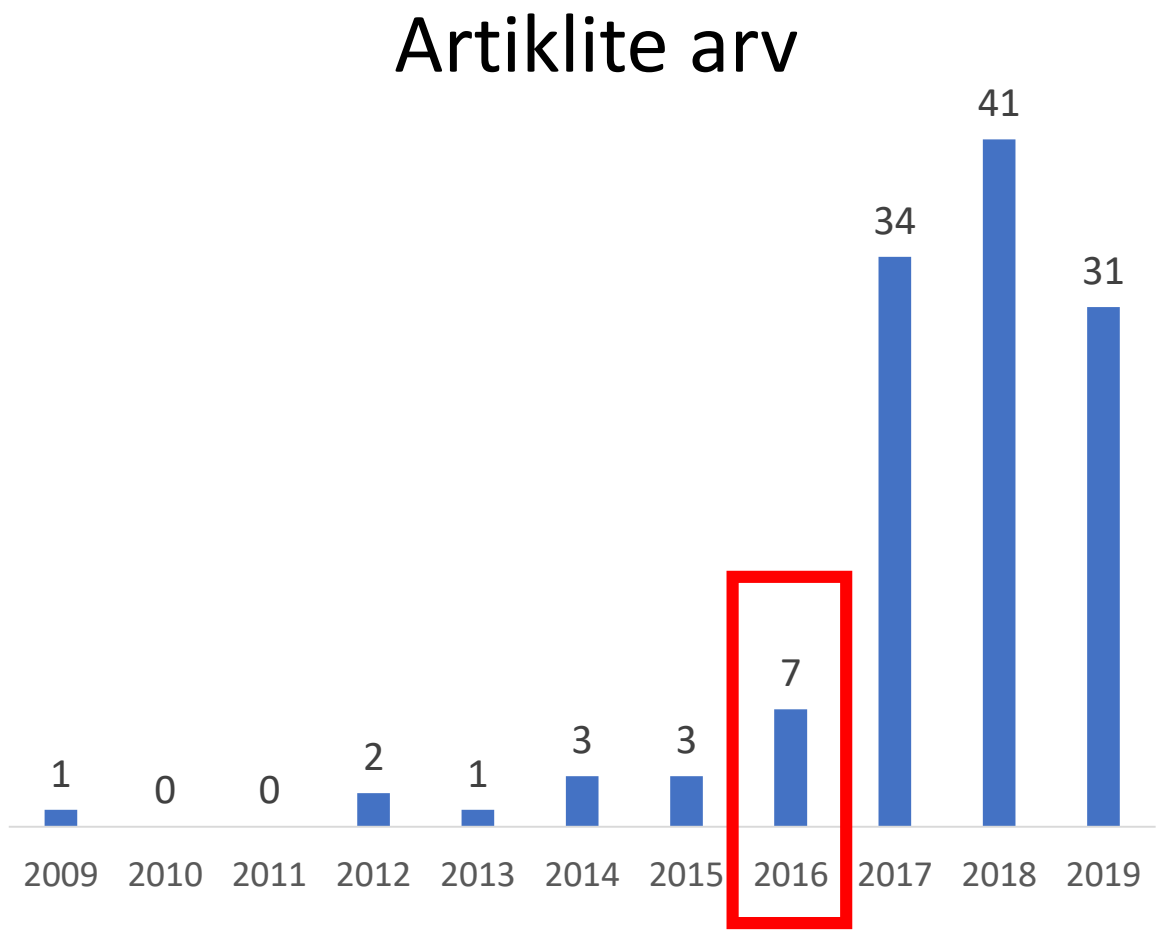
„EQUIGEN“ geneerik-geneerik asendus

- 3 patsienti said krambihoodu
  - Ühel jäi ravim võtmata
  - Teistel kahel erinevust AUC ja Cmax vahel ei esinenud
- Geneerikud olid bioekvivalentsed
- Arsti ja patsiendi eelarvamused geneeriku suhtes, hind?
- Geneeriline asendamine → trükk, kuju, suurus, värv

Michael D Privitera, Timothy E Welty, Barry E Gidal, Francisco J Diaz, Ron Krebill, Jerzy P Szafl arski, Barbara A Dworetzky, John R Pollard, Edmund J Elder Jr, Wenlei Jiang, Xiaohui Jiang, Michel Berg. Generic-to-generic lamotrigine switches in people with epilepsy: the randomised controlled EQUIGEN trial. Lancet Neurol, Volume 15, 2016 p365-72

EAFS
Eesti Akadeemiline Farmaatsia Selts

Pubmed 2009-2019 „biosimilar switch“



https://www.ncbi.nlm.nih.gov/pubmed

Skåne Ülikooli Kliinikum

Genotropin® (Somatropin)

Omnitrope® (Somatropin)

Vahetamine toimus raviarsti järelvalve all
Õde juhendas meditsiiniseadme kasutamist

https://www.omnitrope.com/about/about-omnitrope/

Table 1 Patient characteristics

Patients who agreed to switch (*n*)	98
Male/female (*n*)	52/46
Age range (years)	1–15
Primary growth disturbance (*n*)[a]	
GHD	40
Turner syndrome	9
Prader–Willi syndrome	6
Small for gestational age	11
Other	36

[a] Four patients had dual diagnosis

Carl-Erik Flodmark, Katarina Lilja, Heike Woehling, Kajsa Järvholm. **Switching From Originator to Biosimilar Human Growth Hormone Using Dialogue Teamwork: Single-Center Experience**

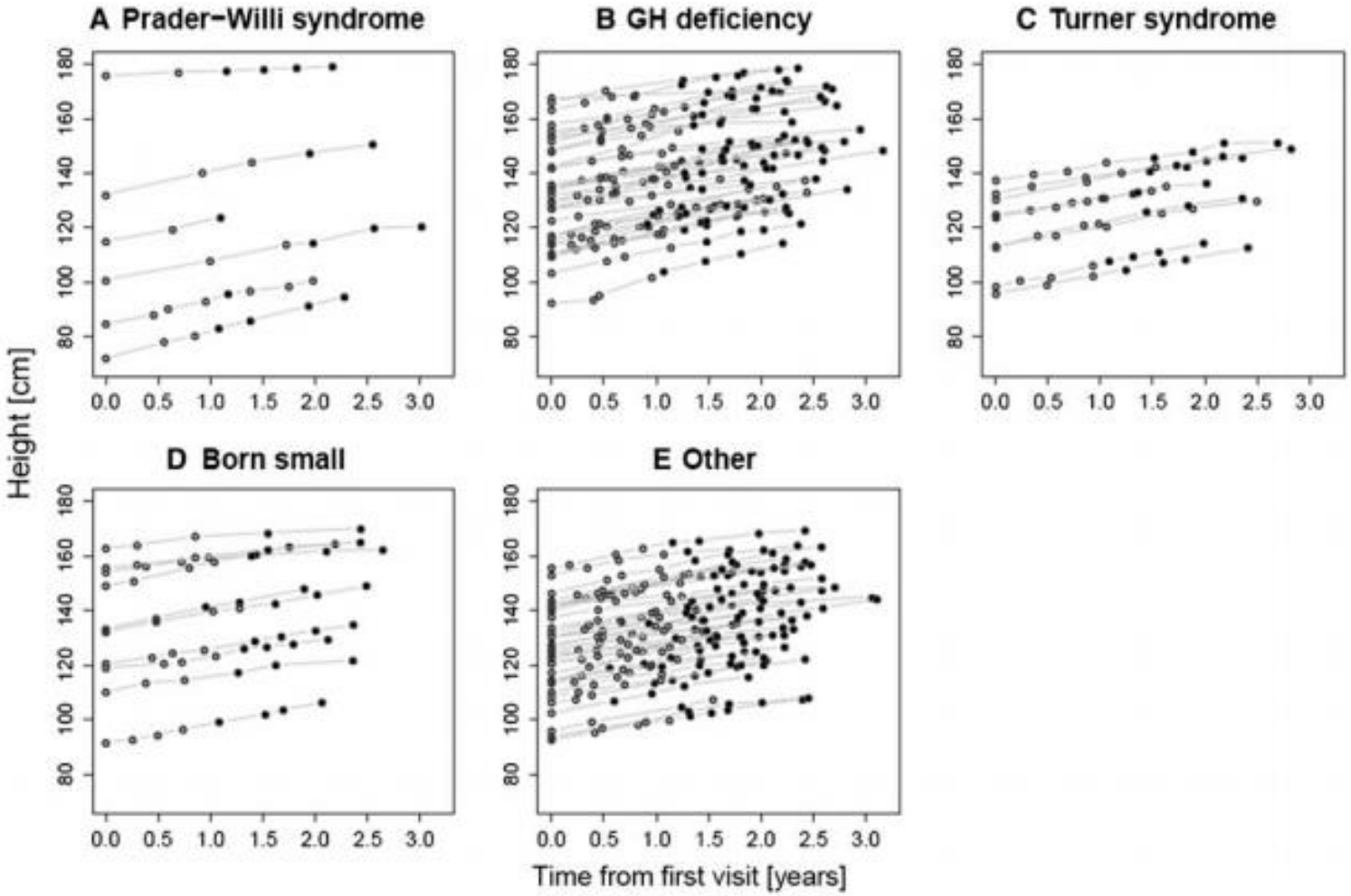


Fig. 2 Height data before and after switching to biosimilar recombinant human growth hormone in patients with different growth disturbances **a** Prader–Willi syndrome, **b** growth hormone deficiency, **c** Turner syndrome, **d** born small for gestational age, **e** other. *Open circle* originator rhGH, *filled circle* biosimilar rhGH

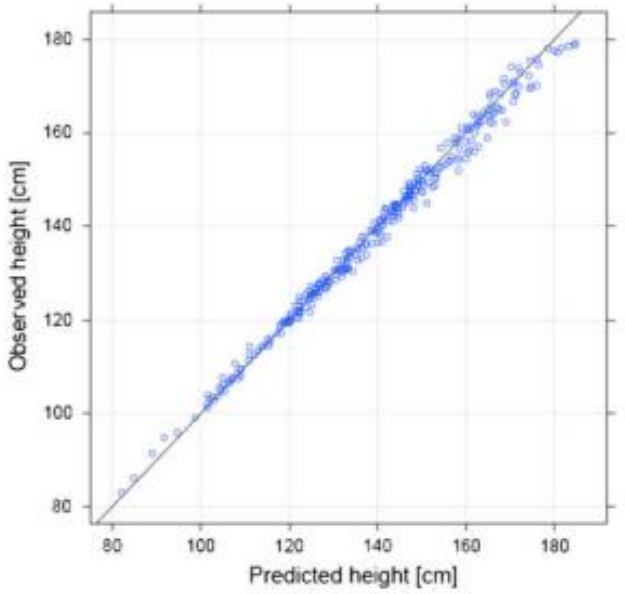


Fig. 4 Assessment of observed versus predicted height following the switch to recombinant human growth hormone. The *solid line* is the identity line (i.e., points lying on this line have the same predicted and observed values of height)

SARNANE KLIINILINE EFEKTIIVSUS

AASTANE MAJANDUSLIK KOKKUHOID €650 000

NOR-SWITCH (infliksimaab)

Remicade®
patent aegus 2015
n=202

CT-P13
turustamise luba 2013 EU
n=206

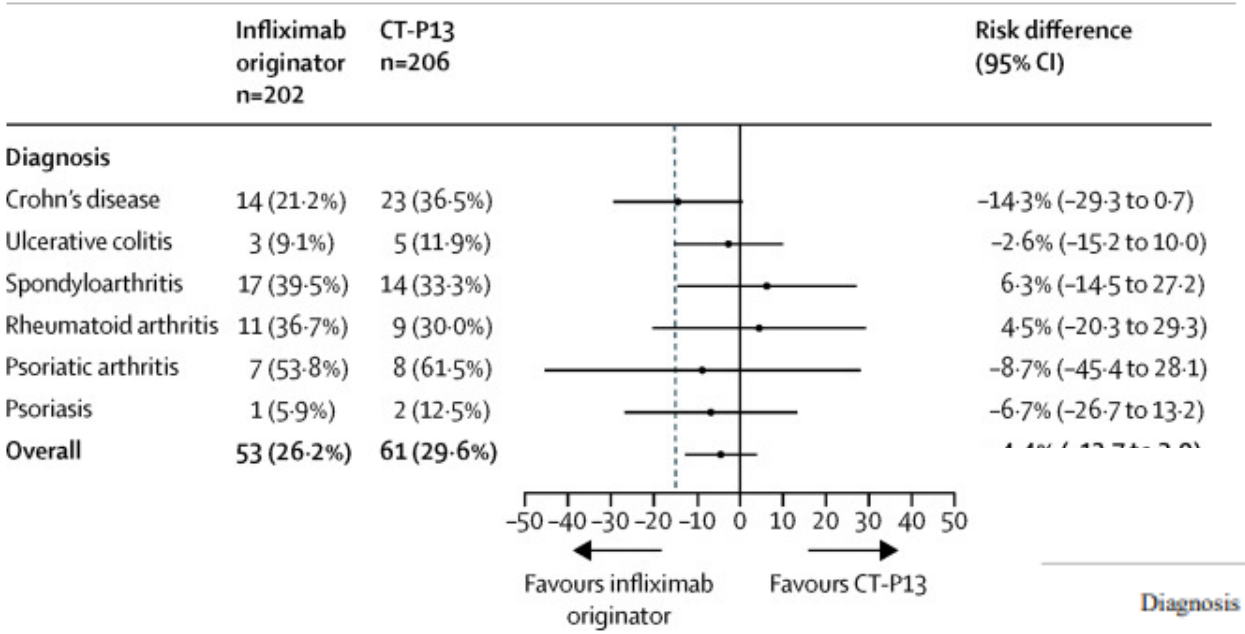
Randomiseeritud, topeltpime, samaväärsus uuring

autoimmuunhaigused (n=6)

jälgimisperiood kuni 52 nädalat

Kristin KJørgensen, Inge Colsen, Guro LGoll, Merete Lorentzen, Nils Bolstad, Prof Espen A Haavardsholm, Prof Knut E Alundin, Prof Cato Mørk, Prof Jørgen Jahnsen, Prof Tore K Kvien. Switching from originator infliximab to biosimilar CT-P13 compared with maintained treatment with originator infliximab (NOR-SWITCH): a 52-week, randomised, double-blind, non-inferiority trial. Lancet 389, 10086, 2017, p2304-2316

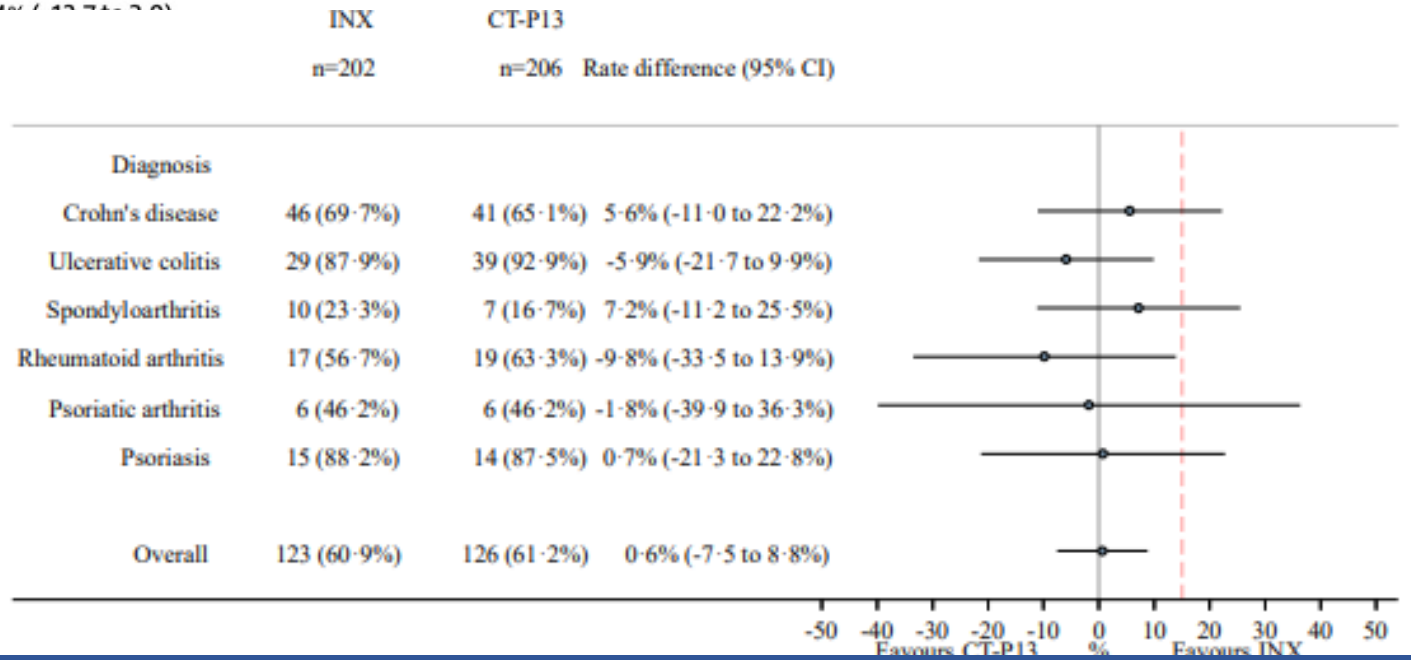
NOR-SWITCH



	Infliximab originator n=202	CT-P13 n=206	Risk difference (95% CI)
Diagnosis			
Crohn's disease	14 (21·2%)	23 (36·5%)	−14·3% (−29·3 to 0·7)
Ulcerative colitis	3 (9·1%)	5 (11·9%)	−2·6% (−15·2 to 10·0)
Spondyloarthritis	17 (39·5%)	14 (33·3%)	6·3% (−14·5 to 27·2)
Rheumatoid arthritis	11 (36·7%)	9 (30·0%)	4·5% (−20·3 to 29·3)
Psoriatic arthritis	7 (53·8%)	8 (61·5%)	−8·7% (−45·4 to 28·1)
Psoriasis	1 (5·9%)	2 (12·5%)	−6·7% (−26·7 to 13·2)
Overall	**53 (26·2%)**	**61 (29·6%)**	

Haigusseisundi halvenemine 26% patsientidest infliksimaab rühmas ja 30% patsientidest CT-P13 rühmas

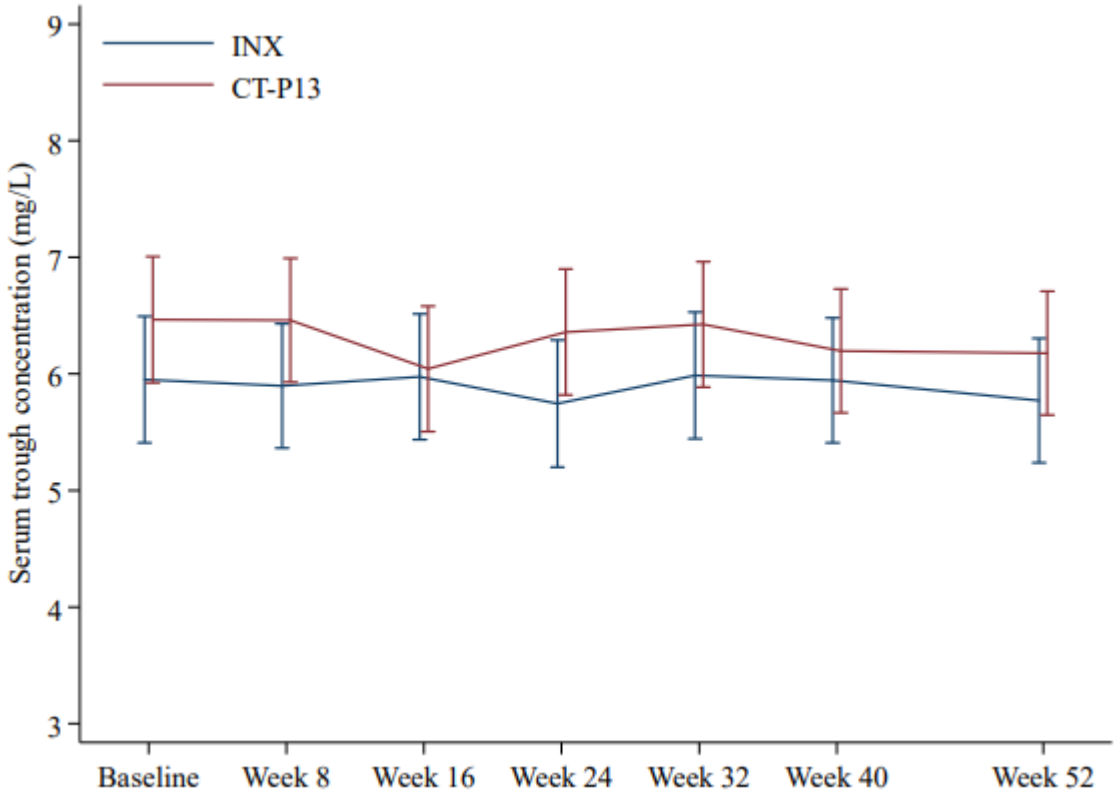
Remissioon 61% patsientidest infliksimaab rühmas ja 61% patsientidest CT-P13 rühmas



	INX n=202	CT-P13 n=206	Rate difference (95% CI)
Diagnosis			
Crohn's disease	46 (69·7%)	41 (65·1%)	5·6% (-11·0 to 22·2%)
Ulcerative colitis	29 (87·9%)	39 (92·9%)	-5·9% (-21·7 to 9·9%)
Spondyloarthritis	10 (23·3%)	7 (16·7%)	7·2% (-11·2 to 25·5%)
Rheumatoid arthritis	17 (56·7%)	19 (63·3%)	-9·8% (-33·5 to 13·9%)
Psoriatic arthritis	6 (46·2%)	6 (46·2%)	-1·8% (-39·9 to 36·3%)
Psoriasis	15 (88·2%)	14 (87·5%)	0·7% (-21·3 to 22·8%)
Overall	123 (60·9%)	126 (61·2%)	0·6% (-7·5 to 8·8%)

Kristin KJørgensen, Inge Colsen, Guro LGoll, Merete Lorentzen, Nils Bolstad, Prof Espen A Haavardsholm, Prof Knut E Alundin, Prof Cato Mørk, Prof Jørgen Jahnsen, Prof Tore K Kvien. Switching from originator infliximab to biosimilar CT-P13 compared with maintained treatment with originator infliximab (NOR-SWITCH): a 52-week, randomised, double-blind, non-inferiority trial. Lancet 389, 10086, 2017, p2304-2316

NOR-SWITCH



raviaine konsentratsioon oli mõlemas grupis sarnane

Biosimilar
↓
SAMAVÄÄRNE
↓
võrdlusravim

Kristin KJørgensen, Inge Colsen, Guro LGoll, Merete Lorentzen, Nils Bolstad, Prof Espen A Haavardsholm, Prof Knut E Alundin, Prof Cato Mørk, Prof Jørgen Jahnsen, Prof Tore K Kvien. Switching from originator infliximab to biosimilar CT-P13 compared with maintained treatment with originator infliximab (NOR-SWITCH): a 52-week, randomised, double-blind, non-inferiority trial. Lancet 389, 10086, 2017, p2304-2316

DANBIO (etanertsept)

- ETA võrdlusravim ja SB4 biosimilar
  - Reumatoidartriit, psoriaatiline artriit, aksiaalne spondüloartriit

- Uurida pt osakaal kes läheb üle SB4
- Haigusekulg kolm kuud enne/pärast vahetumist
- Ravist loobumise põhjused
- Pt karakteristikud, kes läksid ETA-le tagasi üle

- Riiklik nõue, üle minna SB4-le
- 3 uurimisgruppi: *switcher, non-switcher ja back-switcher*

Bente Glintborg, Anne Gitte Loft, Emina Omerovic, Oliver Hendricks, Asta Linauskas, Jakob Espesen, Kamilla Danebod, Dorte Vendelbo Jensen, Henrik Nordin, Emil Barner Dalgaard, Stavros Chrysidis, Salome Kristensen, Johnny Lillelund Raun, Hanne Lindegaard, Natalia Manilo, Susanne Højmark Jakobsen, Inger Marie Jensen HanseN, Dorte Dalsgaard Pedersen, Inge Juul Sørensen, Lis Smedegaard Andersen, Jolanta Grydehøj, Frank Mehnert, Niels Steen Krogh, Merete Lund Hetland. To switch or not to switch: results of a nationwide guideline of mandatory switching from originator to biosimilar etanercept. One-year treatment outcomes in 2061 patients with inflammatory arthritis from the DANBIO registryAnn Rheum Dist, 2019, 0, p1-9

	RA, N=1219		PsA, N=407		AxSpA, n=435	
	Switchers N=933 (77%)	Non-switchers N=286 (23%)	Switchers N=351 (86%)	Non-switchers N=56 (14%)	Switchers N=337 (77%)	Non-switchers N=98 (23%)
Baseline characteristics*						
Female, n (%)	689 (74%)	217 (76%)	160 (46%)	31 (55%)	115 (34%)	34 (35%)
Age, years	61 (49 to 70)	62 (48 to 70)	52 (43 to 61)	52 (43 to 58)	48 (39 to 57)	48 (40 to 57)
Concomitant MTX, n (%)	556 (60%)	140 (49%)	168 (48%)	17 (30%)	51 (15%)	18 (18%)
In remission, %†	65%	55%	70%	73%	28%	21%
PGS, mm	29 (13 to 55)	34 (16 to 64)	30 (12 to 54)	36 (19 to 63)	30 (12 to 53)	37 (17 to 70)
PGS <30 mm,%	52%	45%	51%	43%	51%	42%
DAS28	2.1 (1.6 to 3.0)	2.5 (1.8 to 3.3)	2.0 (1.6 to 2.8)	2.0 (1.8 to 2.8)	–	–
PASS yes, %	81%	67%	77%	68%	80%	77%
ASDAS	–	–	–	–	1.9 (1.2 to 2.6)	2.1 (1.4 to 3.1)
CRP, mg/L	3 (1 to 6)	3 (2 to 9)	2 (1 to 4)	3 (1 to 7)	3 (1 to 4)	3 (1 to 7)
HAQ	0.8 (0.3 to 1.3)	0.9 (0.4 to 1.5)	0.5 (0.0 to 1.0)	0.8 (0.6 to 1.3)	0.4 (0.0 to 0.8)	0.4 (0 to 0.9)
bDMARD treatment no, ETA, n (%)						
1	491 (53%)	116 (41%)	181 (52%)	23 (41%)	123 (36%)	42 (43%)
2	280 (30%)	104 (36%)	123 (35%)	18 (32%)	130 (39%)	33 (34%)
≥3	162 (17%)	66 (19%)	47 (13%)	15 (27%)	84 (25%)	23 (23%)
ETA dose, mg/dose, n (%)						
25	10 (1%)	124 (43%)	3 (1%)	10 (18%)	3 (1%)	35 (36%)
50	887 (95%)	142 (50%)	339 (96%)	39 (70%)	319 (95%)	52 (53%)
Other/unknown	36 (4%)	20 (7%)	9 (3%)	7 (13%)	15 (4%)	11 (11%)
ETA interval, days. n (%)						
3.5	7 (1%)	76 (27%)	4 (1%)	6 (11%)	4 (1%)	21 (21%)
7	751 (80%)	181 (63%)	303 (86%)	44 (79%)	273 (81%)	61 (62%)
Other/unknown	175 (19%)	29 (10%)	44 (13%)	6 (11%)	60 (18%)	16 (16%)
Prior ETA treatment duration, years	6.0 (3.6 to 8.6)	5.3 (2.4 to 8.6)	4.3 (2.9 to 7.3)	3.4 (1.6 to 6.0)	4.6 (2.8 to 6.8)	4.7 (2.9 to 9.0)
≥1 Comorbidities, %	29%	31%	26%	18%	22%	23%
ETA start year, n (%)						
1998–2004	72 (3%)	26 (9%)	16 (5%)	1 (2%)	9 (3%)	9 (9%)
2005–2009	344 (37%)	94 (33%)	92 (26%)	14 (25%)	84 (25%)	34 (35%)
2010–2016	517 (55%)	166 (58%)	243 (69%)	41 (73%)	244 (72%)	55 (56%)
1-year treatment retention‡						
Withdrawal during follow-up, n (%)	194 (21%)	96 (33%)	53 (15%)	25 (45%)	52 (15%)	24 (23%)
Prior ETA duration in withdrawers, years	5.6 (2.9 to 8.8)	4.4 (2.3 to 8.0)	3.6 (2.5 to 6.1)	3.3 (0.9 to 5.5)	3.4 (1.7 to 5.3)	3.7 (2.3 to 7.1)

Numbers are medians (interquartile ranges) unless otherwise stated.
*Baseline is according to first SB4 dose (–90 to +6 days) for switchers and according to 1 April 2016 (±180 days) for non-switchers.
†DAS28 <2.6 (RA, PsA), ASDAS <1.3 (AxSpA).
‡Median follow-up switchers: 383 (314–414) days, non-switchers: 483 (222–483) days.
ASDAS, the Ankylosing Spondylitis Disease Activity Score; AxSpA, axial spondyloarthritis; CRP, C reactive protein; DAS, Disease Activity Score; HAQ, Health Assessment

DANBIO

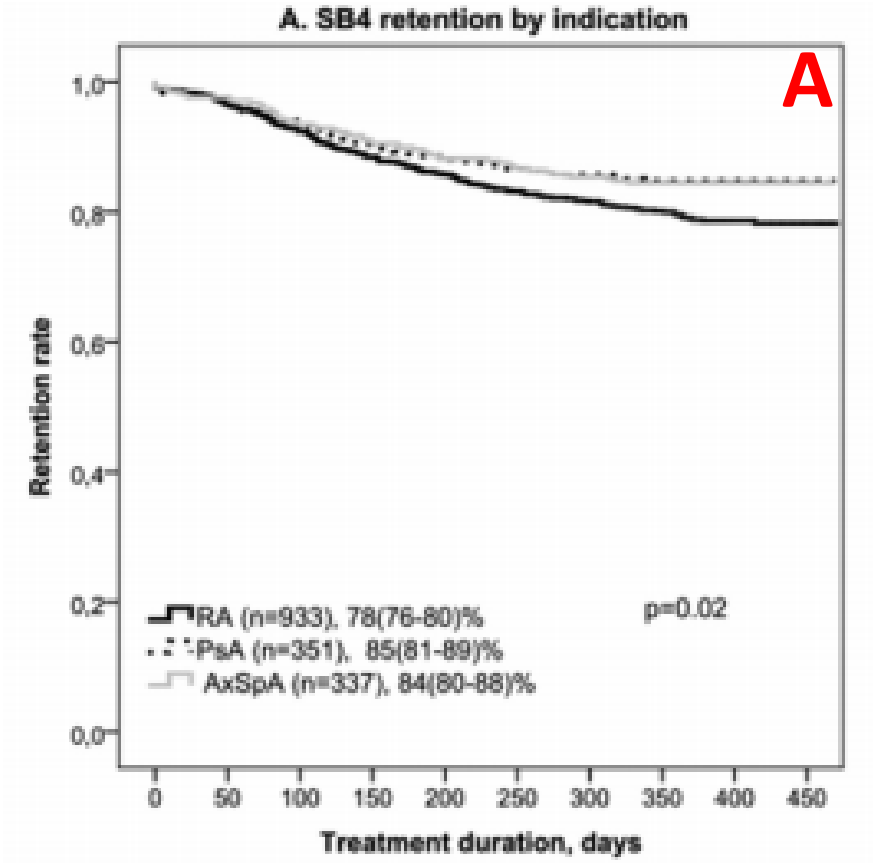
Table 3 Reason for withdrawal in switchers and non-switchers

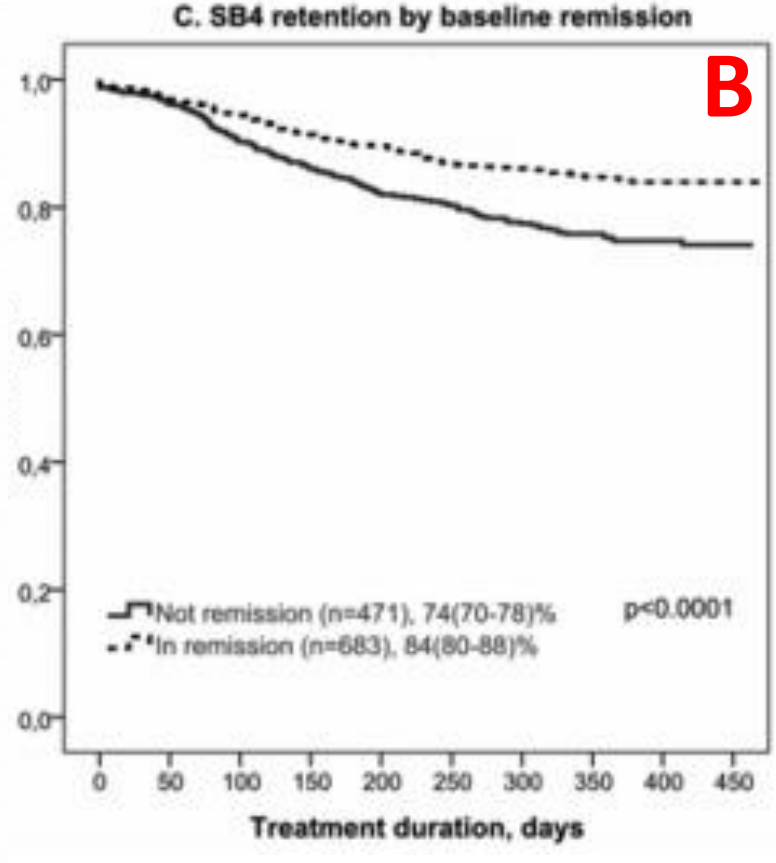
	Switchers N=1621	Non-switchers N=440
Reason, n (% of withdrawals)		
Lack of effect	137 (46)	48 (34)
Adverse events	77 (26)*	14 (10)
Several reasons	9 (3)	1 (1)
Cancer	6 (2)	11 (8)
Remission	8 (3)	10 (7)
Pregnancy	4 (1)	3 (2)
Death	9 (3)	15 (10)
Infection	3 (1)	8 (6)
Loss to follow-up	1 (2)	9 (6)
Surgery	2 (1)	1 (1)
Other	14 (5)	18 (13)
Not stated	29 (10)	7 (5)
Withdrawals, total, n (%)	299 (100)	145 (100)

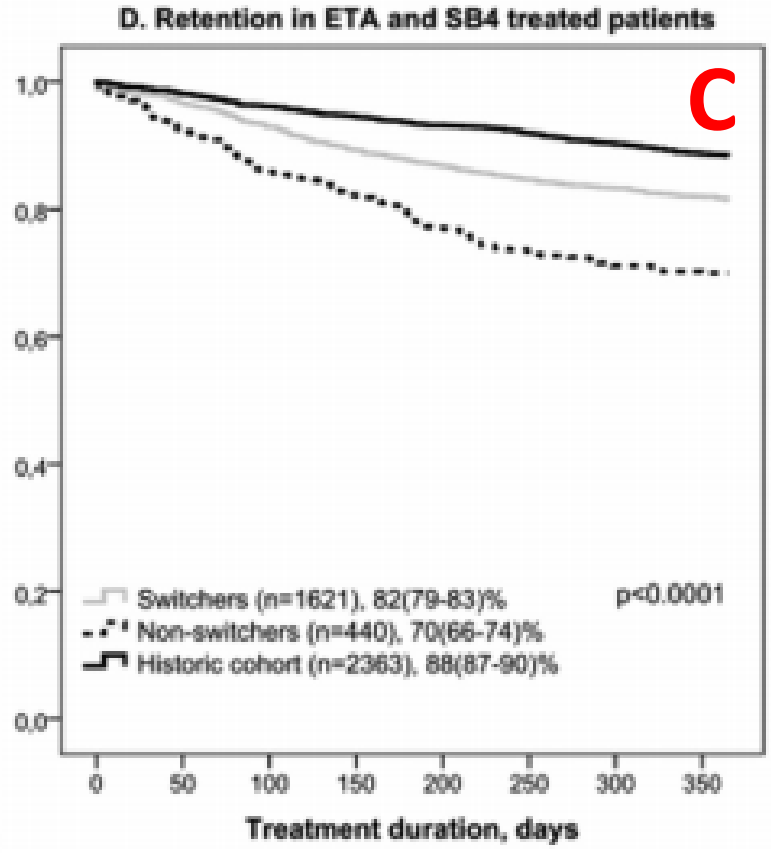
*Adverse events during biosimilar etanercept (SB4) treatment in switchers (77 patients): anxiety 1 patient, arthralgia 1, bladder dysfunction 1, blurred vision 1, chest pain 2, diarrhoea 4, dizziness 2, dyspnoea 2, erectile dysfunction 1, fatigue 1, fever 2, hair loss 1, headache/migraine 9, hyperhidrosis 2, hypertension 1, hypotension 1, infections 2, leg cramps 2, leucopenia 3, local injection problems 3, myalgia 2, nausea 4, neuropathies 1, psoriasis worsening or pustulosis 2, rash/itching 11, not stated 39 (total=101 events).

Bente Glintborg, Anne Gitte Loft, Emina Omerovic, Oliver Hendricks, Asta Linauskas, Jakob Espesen, Kamilla Danebod, Dorte Vendelbo Jensen, Henrik Nordin, Emil Barner Dalgaard, Stavros Chrysidis, Salome Kristensen, Johnny Lillelund Raun, Hanne Lindegaard, Natalia Manilo, Susanne Højmark Jakobsen, Inger Marie Jensen HanseN, Dorte Dalsgaard Pedersen, Inge Juul Sørensen, Lis Smedegaard Andersen, Jolanta Grydehøj, Frank Mehnert, Niels Steen Krogh, Merete Lund Hetland. To switch or not to switch: results of a nationwide guideline of mandatory switching from originator to biosimilar etanercept. One-year treatment outcomes in 2061 patients with inflammatory arthritis from the DANBIO registry. Ann Rheum Dist, 2019, 0, p1-9

DANBIO


A. SB4 retention by indication
A
Retention rate
1,0
0,8
0,6
0,4
0,2
0,0
RA (n=933), 78(76-80)%
PsA (n=351), 85(81-89)%
AxSpA (n=337), 84(80-88)%
p=0.02
0
50
100
150
200
250
300
350
400
450
Treatment duration, days


C. SB4 retention by baseline remission
B
1,0
0,8
0,6
0,4
0,2
0,0
Not remission (n=471), 74(70-78)%
In remission (n=683), 84(80-88)%
p<0.0001
0
50
100
150
200
250
300
350
400
450
Treatment duration, days


D. Retention in ETA and SB4 treated patients
C
1,0
0,8
0,6
0,4
0,2
0,0
Switchers (n=1621), 82(79-83)%
Non-switchers (n=440), 70(66-74)%
Historic cohort (n=2363), 88(87-90)%
p<0.0001
0
50
100
150
200
250
300
350
Treatment duration, days

DANBIO

- 79% pt läksid üle biosimilarile
- 21% pt jätkasid võrdlusravimiga
- 7% läksid tagasi võrdlusravimile
- Üleminek biosimilarile ei mõjutanud haiguse aktiivsust (3kuud)
- Peamiseks loobumise põhjuseks oli raviefekti puudumine

EAFS
Eesti Akadeemiline Farmaatsia Selts

Järeldused

- Vähene arstide/patsientide huvi võrdlusuuringute vastu
- Selge informatsioon geneerikust/biosilimarist ja põhjused üleminekuks
- Usaldus patsiendi ja tervishoiu töötajate vahel
- Ülemineku perioodil personaalne tugi
- Rohkem uuringuid kitsa terapeutilise vahemikuga ravimitega

EAFS
Eesti Akadeemiline Farmaatsia Selts

Tänan tähelepanu eest!