Statens legemiddelverk
Norwegian Medicines Agency

2018-02-08:

Regulation of biosimilars and success factors for uptake in clinical practice

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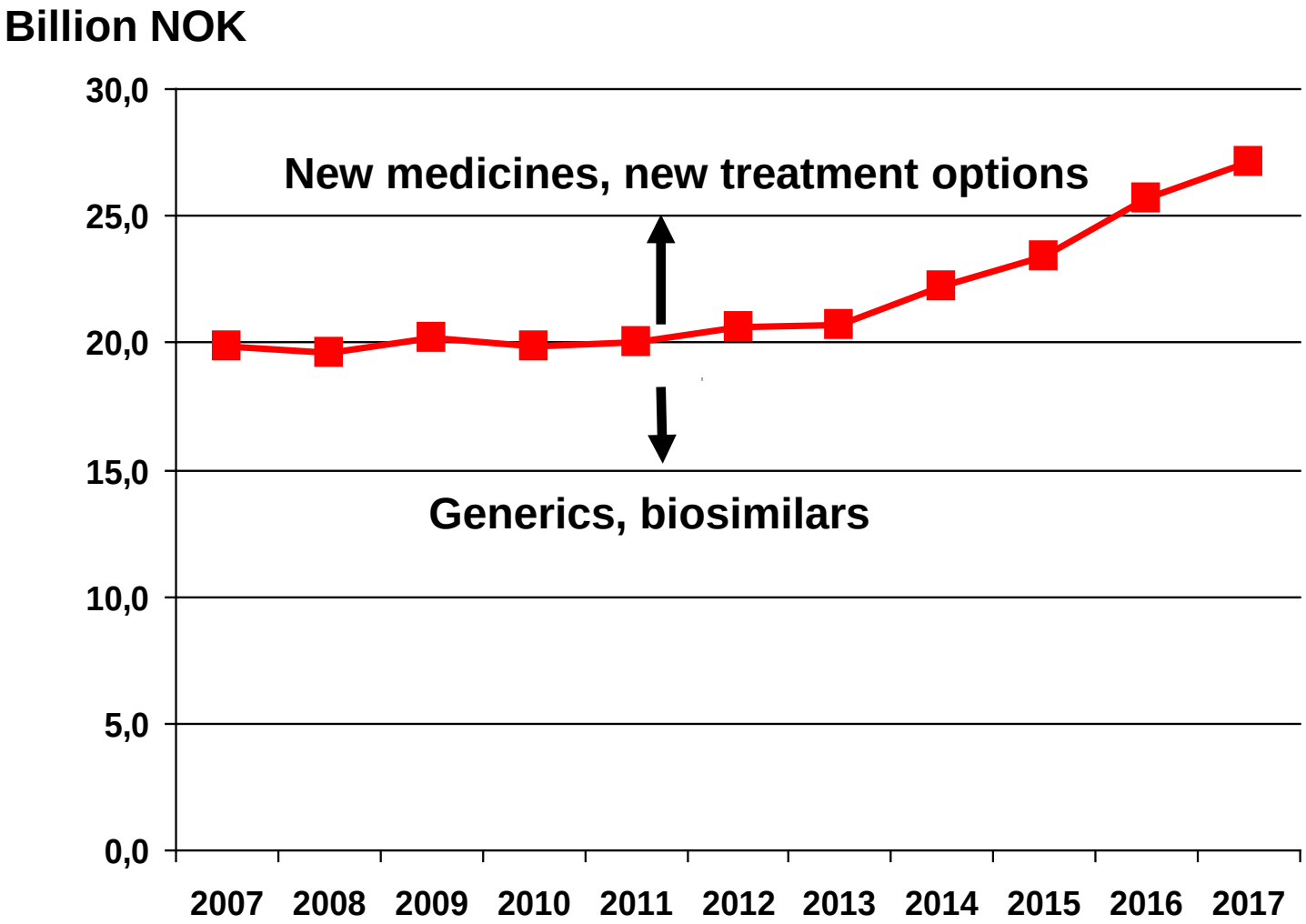
Drug costs in Norway



Constant 2015 NOK, LMI

Access to biological treatment in Europe

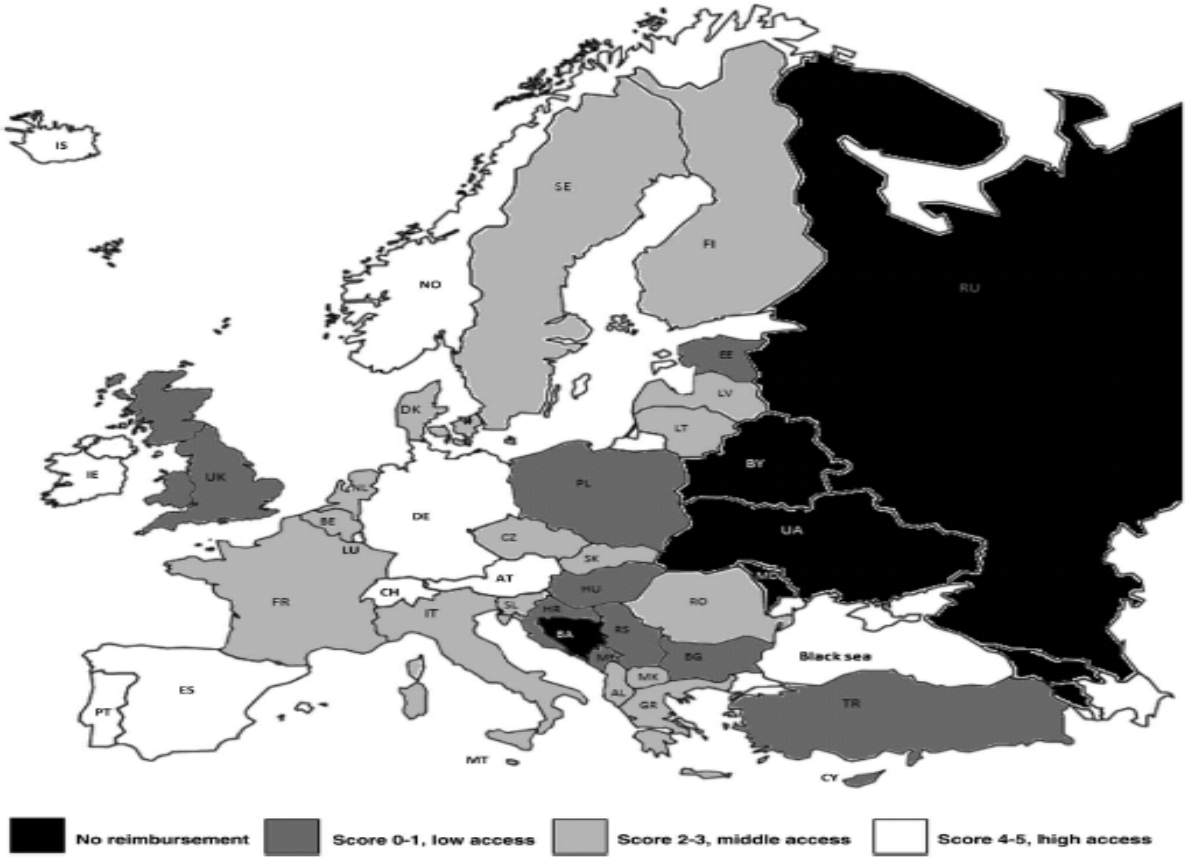
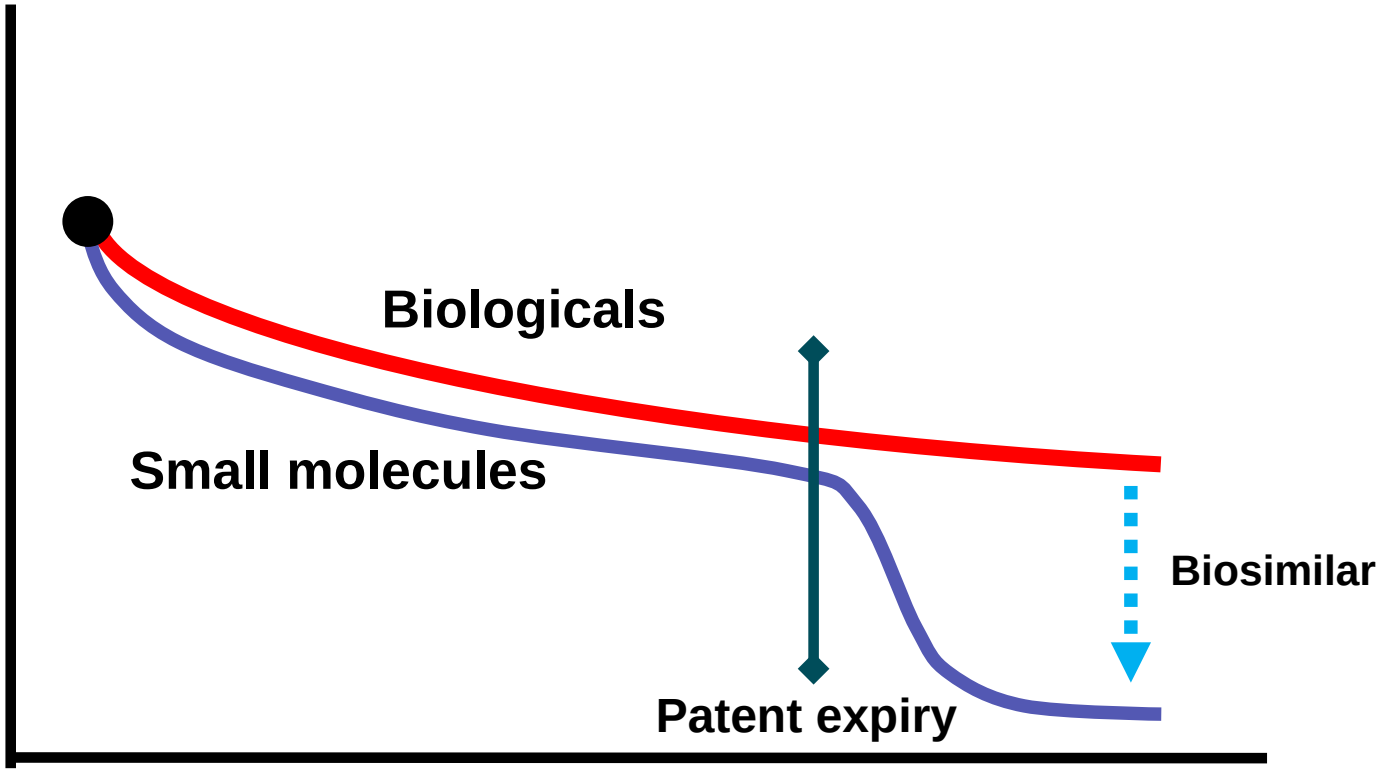


Figure 1 Composite score for restrictiveness of clinical criteria for initiation of a first reimbursed biologic (0–5) in the European Region (score is composed of (1) minimum required disease duration, (2) number of sDMARDs that have to be failed and (3) the level of DAS28). DAS28, disease activity score with 28-joint assessment; sDMARDs, synthetic disease-modifying antirheumatic drugs.
AL, Albania; AT, Austria; BE, Belgium; BG, Bulgaria; HR, Croatia; CY, Cyprus; CZ, Czech Republic; EE, Estonia; FI, Finland; FR, France; DE, Germany; DK, Denmark; GR, Greece; HU, Hungary; IS, Iceland; IE, Ireland; IT, Italy; LV, Latvia; LT, Lithuania; LU, Luxemburg; MK, Macedonia; MT, Malta; ME, Montenegro; NL, the Netherlands; NO, Norway; PL, Poland; PT, Portugal; RO, Romania; RS, Serbia; SK, Slovakia; SL, Slovenia; ES, Spain; SE, Sweden; CH, Switzerland; TR, Turkey; UK, United Kingdom.

Polina P et al. Ann Rheum Dis 2013

Biologicals – it all about costs



Biosimilars approved in Europa

Active ingredient (originator)	Main indication	Name, approved biosimilars
Somatropin (Genotropin)	Growth hormone	Omnitrope
Epoetion alfa (Eprex)	Anemia	Abseamed, Binocrit, Epotetin Alfa Hexal
Epoetin zeta (Erypo)	Anemia	Retacrit, Silapo
Filgrastim (Neupogen)	Granulocytopenia	Accofil, Filgrastim Hexal, Grastofil, Nivestim, Ratiograstim, Tevagrastim, Zarzio
Inflixsimab (Remicade)	TNF-inhibitor	Flixabi, Inflectra, Remsima
Follitropin alfa (Gonal–F)	Ovarial stimulation	Bemfola, Ovaleap
Insulin glargine (Lantus)	Diabetes	Abasaglar, Lusduna
Etanercept (Enbrel)	TNF-inhibitor	Benepali, Erelzi
Enoxaparine (Klexane)	Anticoagulant	Inhixa, Thorinane
Teriparatide (Forsteo)	Osteoporosis	Terrosa, Movymia
Adalimumab (Humira)	TNF-inhibitor	Amgevita, Solymbic, Imraldi, Cyltezo
Rituximab (MabThera)	B-cell inhibitor	Truxima, Rixathon, Blitzima, Rituzena, Riximyo
Insulin lispro (Humalog)	Diabetes	Insulin lispro Sanofi
Trastuzumab (Herceptin)	HER2, cancer	Ontruzant
Bevecizumab (Avastin)	VEGF-inhibitor, cancer	Mvasi

EMA 2018-02-01

Biosimilar applications in Europe

Active ingredient (originator)	Main indication	Name/ number	Status
Trastuzumab (Herceptin)	Breast cancer	3 drugs	Applications
Adalimumab (Humira)	TNF-inhibitor	5 drugs	Applications
Insulin glargine (Lantus)	Diabetes	Semglee	Avaiting commission decision
Pegfilgrastim (Neulasta)	Granulocytopenia	6 drugs	Applications
Infliximab (Remicade)	TNF-inhibitor	1 drug	Application

EMA 2018-02-01

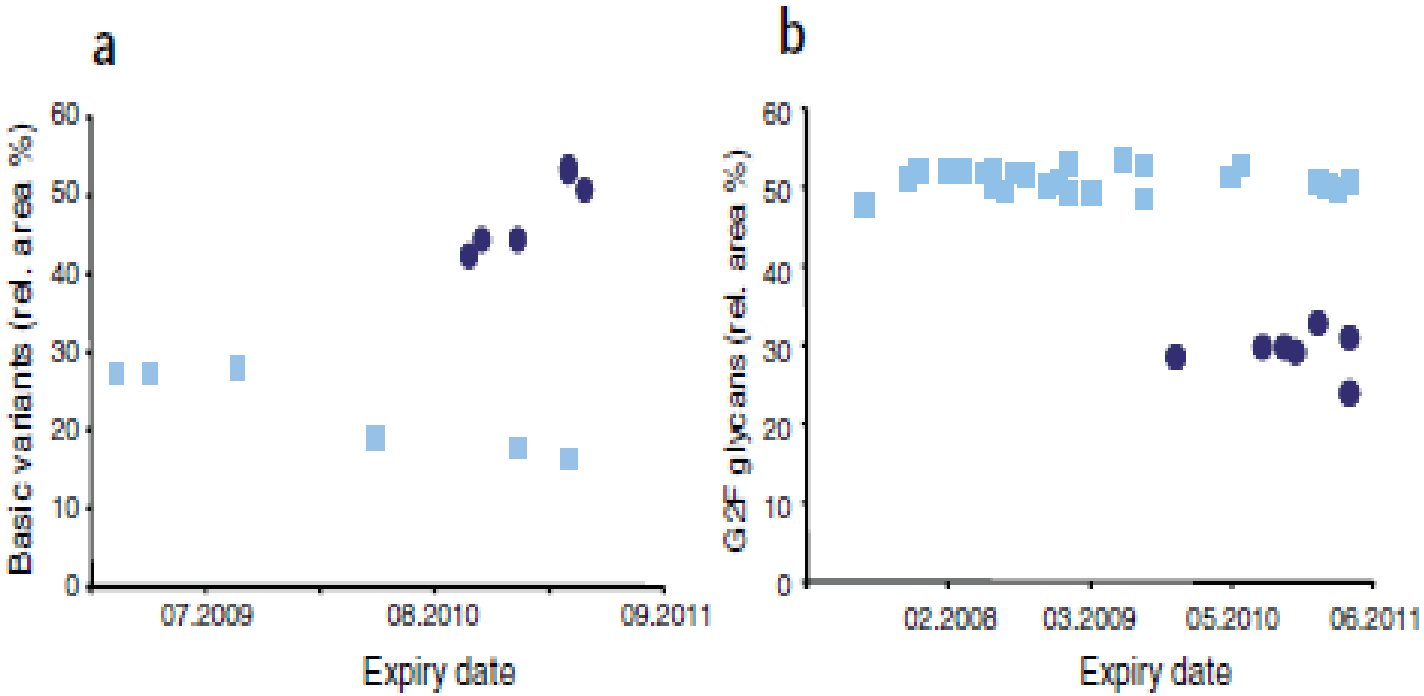
Biosimilars in USA

Status	Active ingredient
Approved	Filgrastim Infliximab (3) Etanercept Adalimumab (2) Bevacizumab Trastuzumab
Applications, unofficial	Etanercept Pegfilgrastim Epoetin Filgrastim Adalimumab
Declined	Pegfilgrastim (2)

Mythbusting

- ”The reference product is the gold standard”
  - There are no «gold standards»
  - All biologicals vary
    - From batch to batch
    - From manufacture site to manufacture site
    - After productions changes

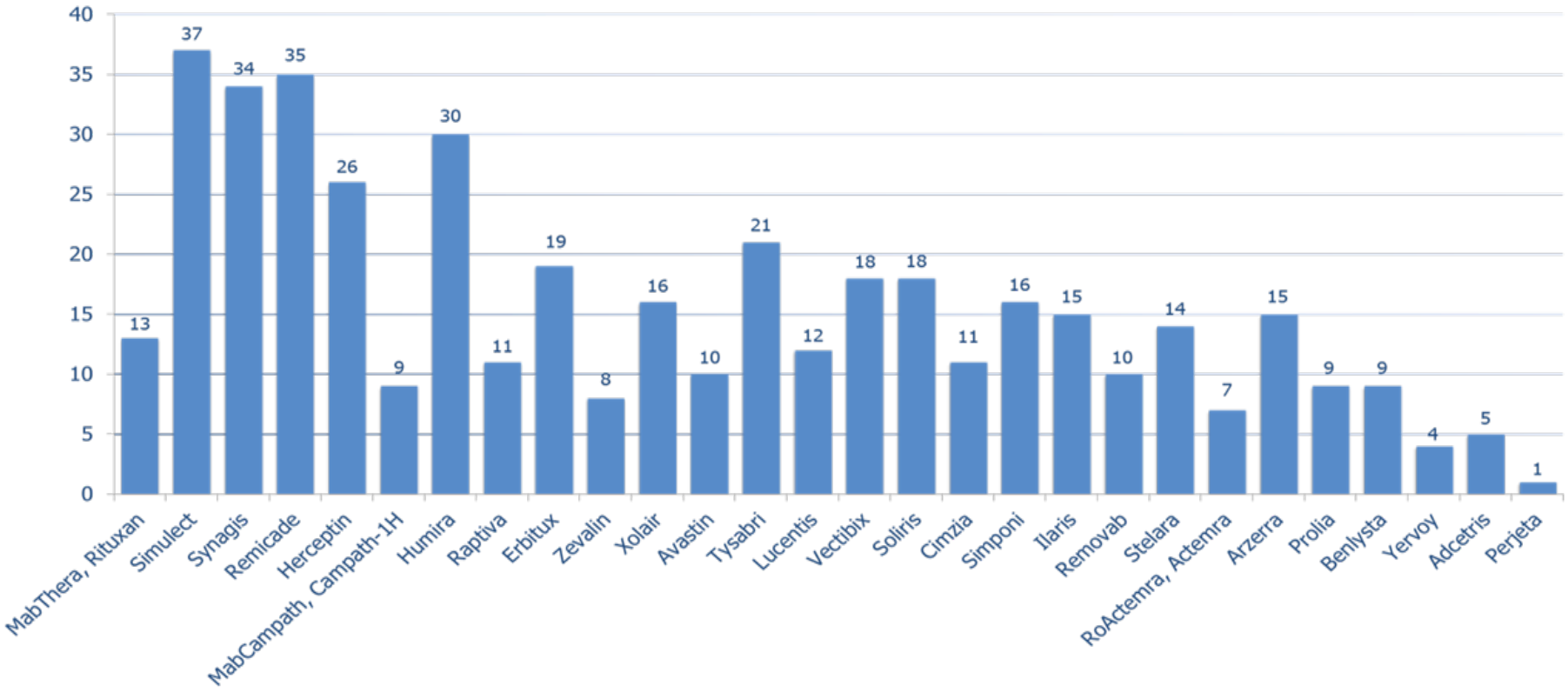
«All biologicals are biosimilars»



Differet versions of etanercept after production changes

Nature Biotechnology 2011; 29: 310-2

Most biologicals undergo production changes



Number of production changes reported in EPAR documents by Sep 2014
www.ema.europa.eu

Trastuzumab

The CHMP debated the apparent difference in terms of pathological complete response rate observed in the clinical efficacy trial between Ontruzant and Herceptin. Based on additional analysis, this observation was found to be likely the result of a temporary shift in some quality parameters of Herceptin impacting a number of batches used in the clinical efficacy/safety trial. Despite this apparent difference between Ontruzant and some batches of Herceptin used in this clinical study, the CHMP concluded that Ontruzant can be considered similar to the reference product Herceptin based on additional analyses conducted, pharmacodynamic knowledge of the product and considering all the evidence available from the comparative exercise.

CHMP minutes Sept. 2017

Views on biosimilars

- **Physicians are more positive than previously**
  - **Recognize that more patients can have treatment**
  - **Considerably influenced by the anti-biosimilar campaign**
    - **«Problems», «challenge», «uncertainty», «danger of switching»**
- **Patients and patients organizations are less sceptical**
  - **Use of biosimilars accepted**
  - **Sceptical to switch**
    - **”Never change a winning team”**

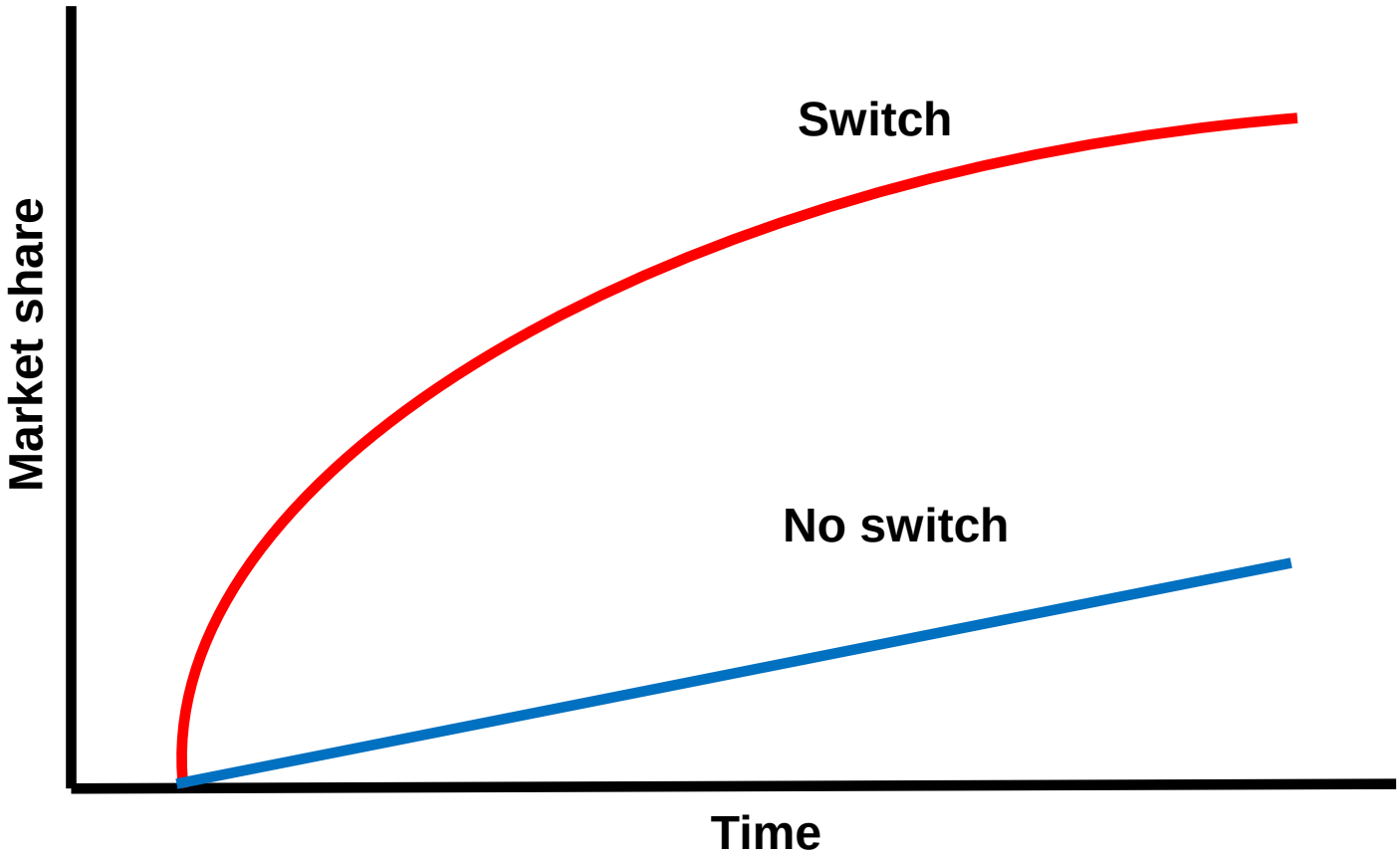
Experience with biosimilars in Europe

- **After 11 years, no unexpected problems have been discovered**
- **European approval ensures efficacy and saftey**
  - **For reference drug and biosimilar drug**
- **Mostly, the same drugs will be approved in Europe and the US**

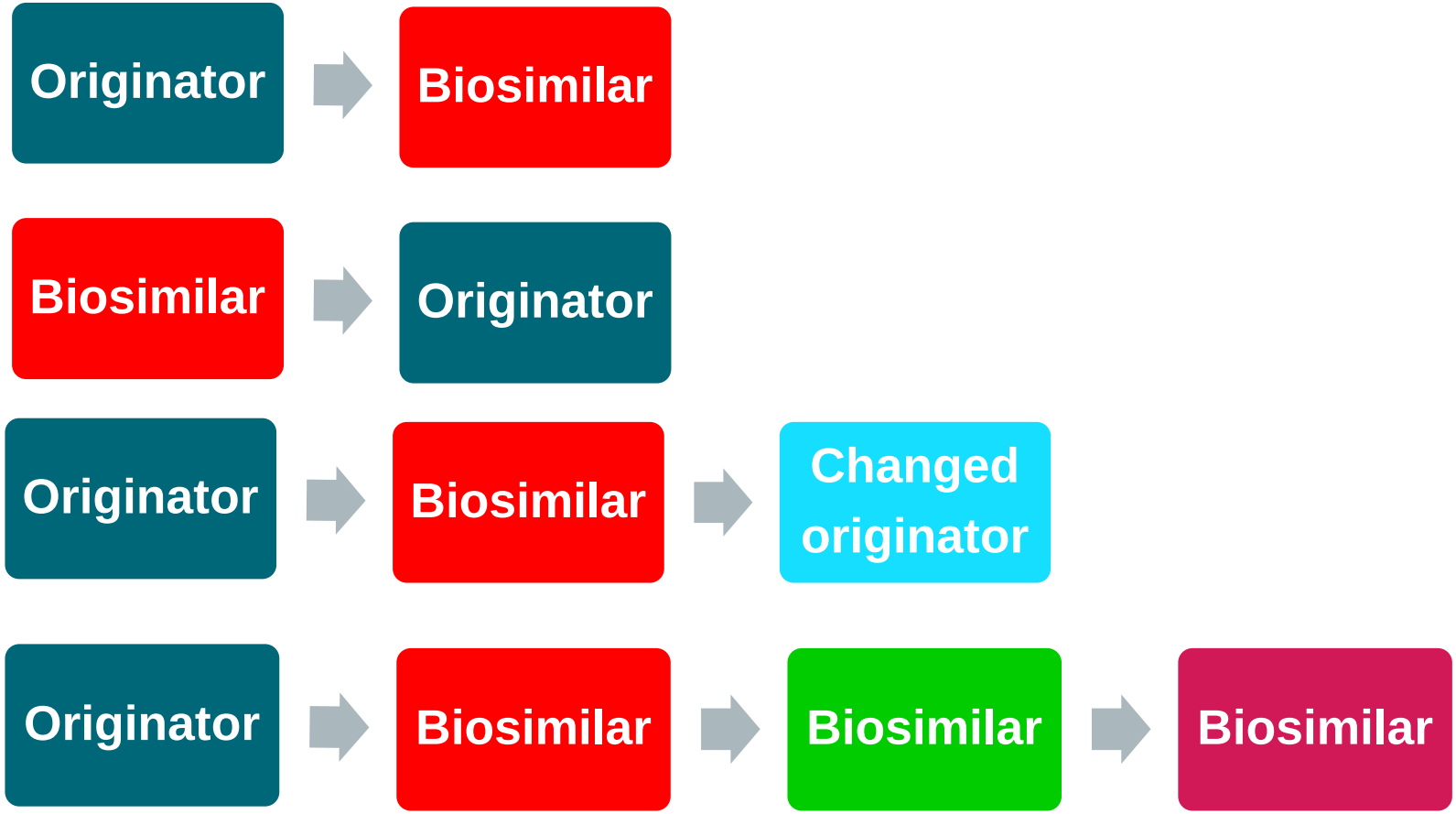
Treatment duration and impact of switching

Drugs/drug class	Treatment duration	Market share dependence on switching
TNF-inhibitors and similar drugs	Long term	High dependence
Growt hormones	Long term	High dependence
Filgrastim	Short term	No dependence
Oncology	Mostly short term	Low dependence
Enzymes	Long term	High dependence
Coagulation factors	Long term	High dependence
Multiple sclerosis	Long term	High dependence
Diabetes	Long term	High dependence

Market uptake – switch or no switch (To be or not to be)



Many different situations



Is the legal tide switching?

- Norwgian Agency adds filgrastim to substitution list (2010), updates position (2017)
- Swiching will be allowed in pharmacies (France, 2014)
- Dutch agency positive to physician directed switching, reverses 2010 negative recommendation (2015)
  - «No relevant differences»
- Finnish agency recommends physician directed switching (2015)
- Australian body recommends pharmacy switching (2015)
- FDA guidelines on interchangeable biosimilars (2017)

Norwegian Medicines Agency

- **Switching between reference products and biosimilars during ongoing treatment, is safe. It can apply to the following situations:**
  - **Switching from reference drug to biosimilar**
  - **Switching from biosimilar to reference drug**
  - **Switching from a biosimilar to another biosimilar based on the same reference drug**
- **Further clinical studies confirming safety of switching are considered unnecessary**

NOR-SWITCH study

- **Patent for infliximab expired one year early in Norway compared to rest of Europe**
  - **End of 2013 versus February 2015**
- **We were unsure on how biosimilar infliximab would be received in clinical practice in Norway (and Europe)**
- **Independent data could be important to increase confidence in biosimilars**

Primary endpoint

	INX (n= 202)	CT-P13 (n=206)	Rate difference (95% CI)
Disease worsening*	53 (26.2%)	61 (29.6%)	-4.4 (-12.7 – 3.9)

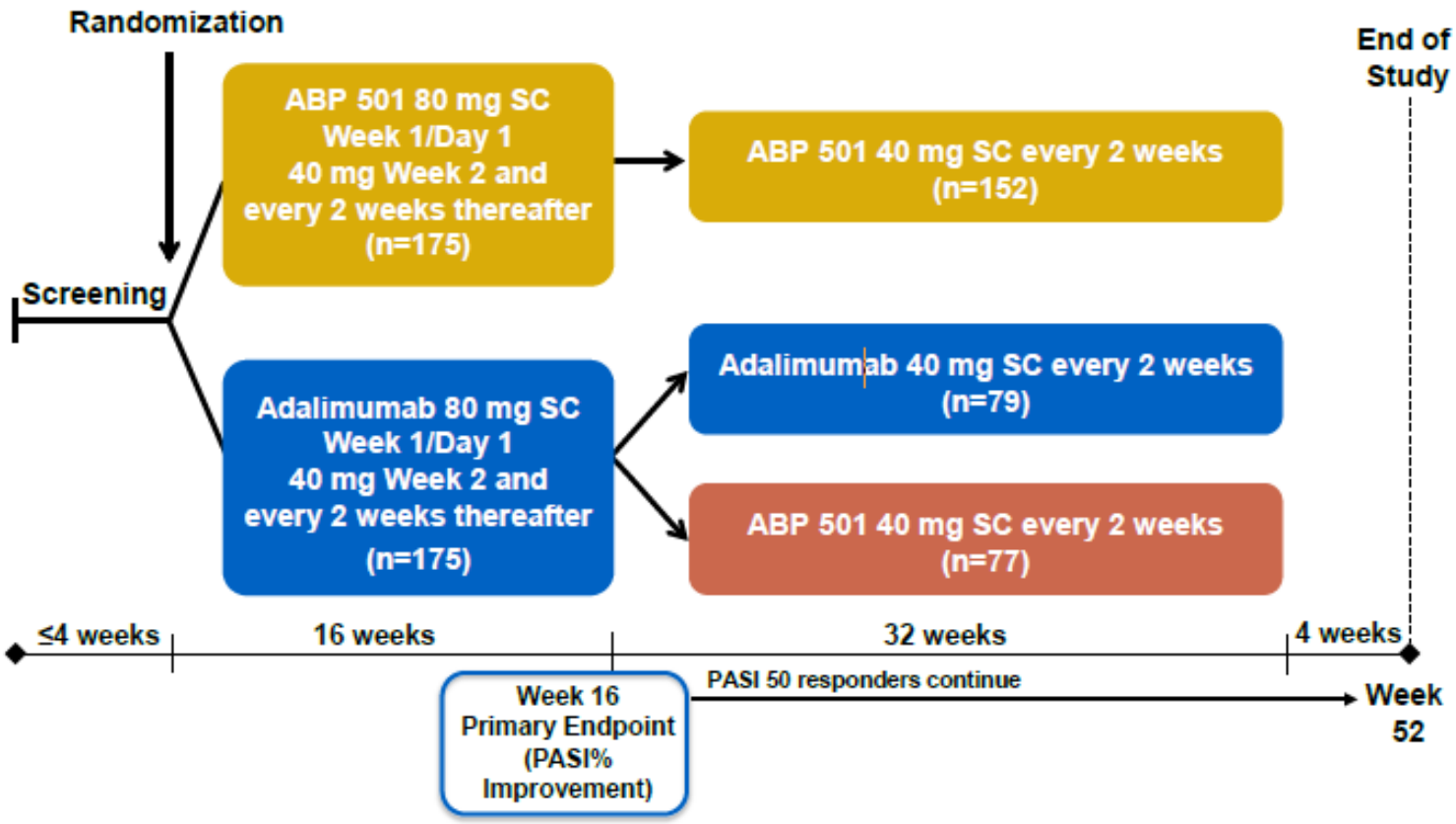
* UC: increase in p-Mayo score of ≥ 3 points and a p-Mayo score of ≥ 5 points,
CD: increase in HBI of ≥ 4 points and a HBI score of ≥7 points
RA/PsA: increase in DAS28 of ≥ 1.2 from randomization and a DAS score of ≥ 3.2
AS/SpA: increase in ASDAS of ≥1.1 and ASDAS of ≥ 2.1
Psoriasis: increase in PASI of ≥ 3 points from randomization and a minimum PASI score of ≥ 5

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 this should be considered as a disease worsening but recorded separately in the CRF

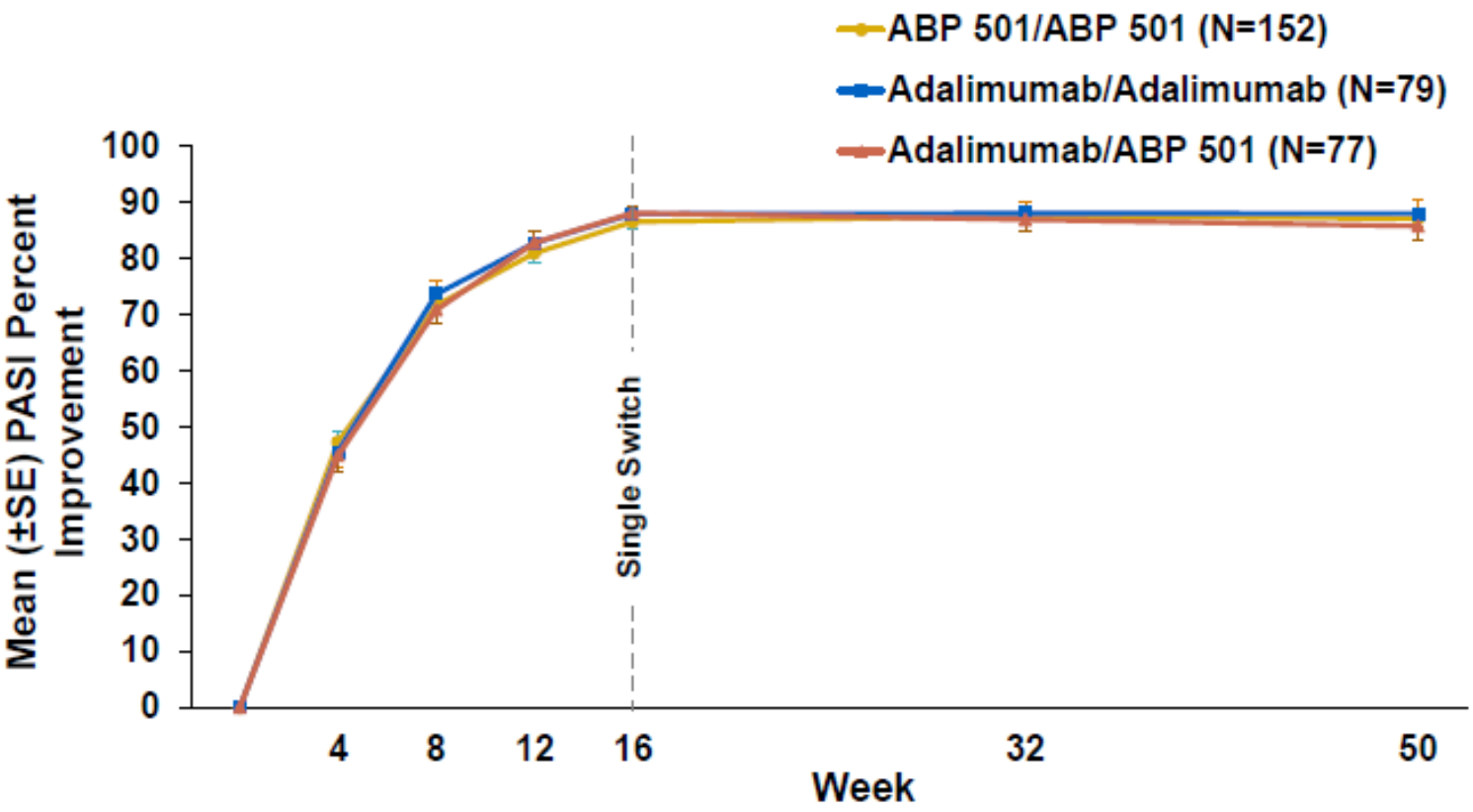
Disease worsening

Diagnosis	INX (n= 202)	CT-P13 (n=206)	Rate difference (95% CI)
Crohns 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%)
Rhematoid 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%)

Example: Switching study

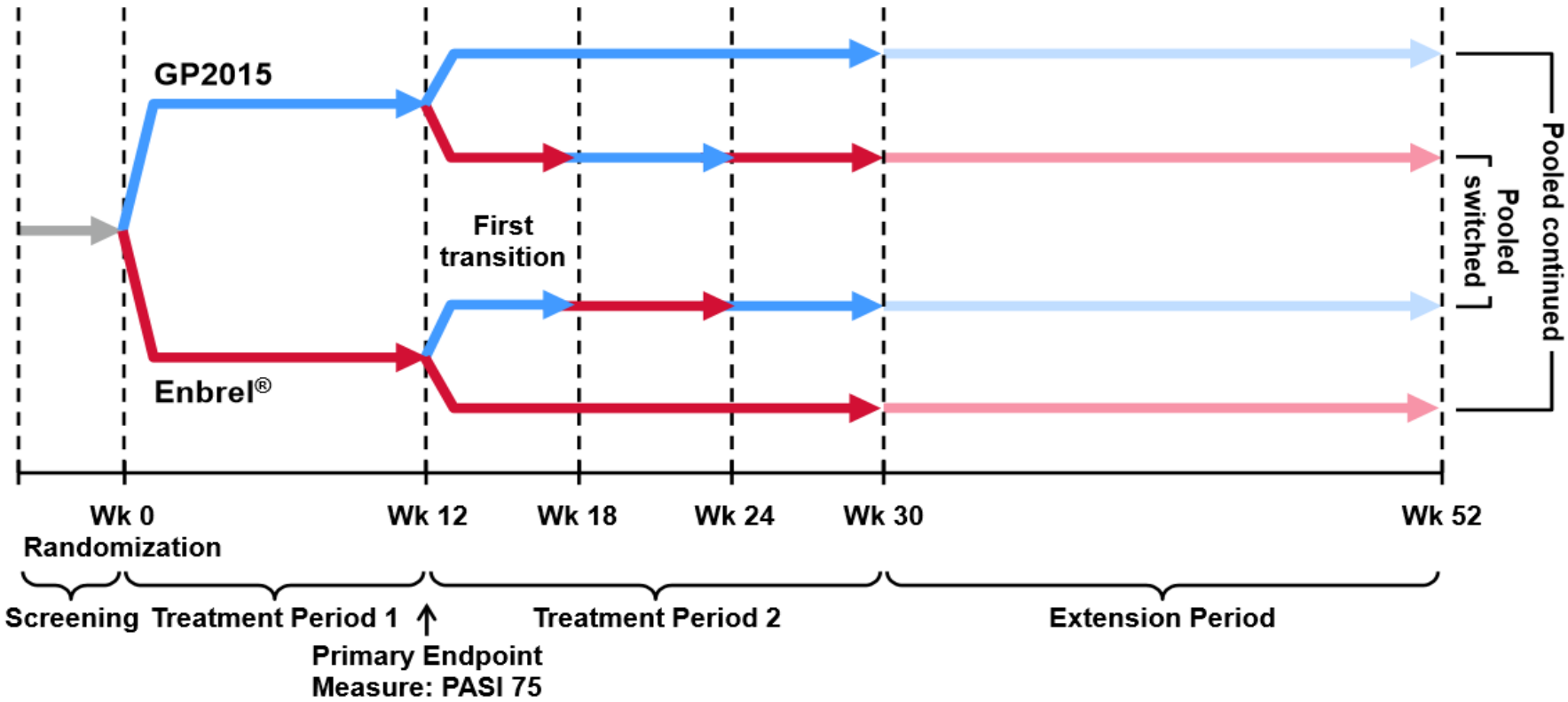


Clinical results



Amgen

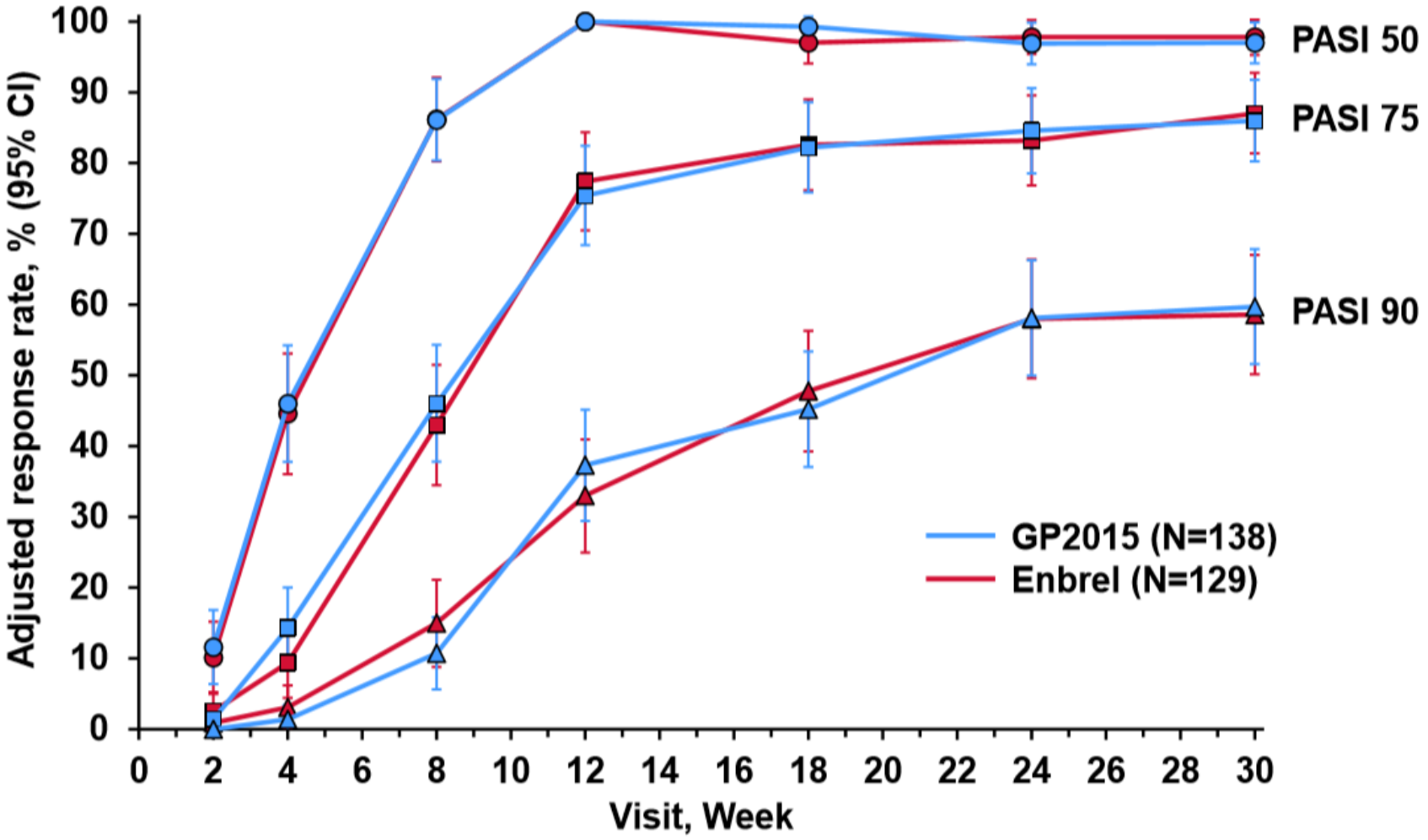
Exampele: Multiple switches



Study GP15-302 (etanercept biosimilar)

Sandoz

Clinical results



Treatment period 2

Sandoz

National tenders with biosimilar infliximab in Norway

Patient	Year	Remicade (original)	Remsima (biosimilar)	Inflectra (biosimilar)	Flixabi (biosimilar)	Zessly (biosimilar)	Discount
Rheuma-toid arthritis, 75 kg, one year treatment	2014	Lost bid	Won bid	Lost bid	-	-	39
	2015	Lost bid	Won bid	Lost bid	-	-	69
	2016	Lost bid	Lost bid	Won bid	-	-	61
	2017	Lost bid	Won bid	Lost bid	-	-	Large
	2018	Lost bid	Lost bid	Lost bid	Lost bid	Won bid	Large

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National tenders with biosimilar etanercept in Norway

Patient	Year	Enbrel (original)	Benepali (biosimilar)	Discount
Rheuma-toid arthritis, 75 kg, one year treatment	2016	83 000 NOK 8 700 EUR 9 800 USD	73 500 NOK 7 700 EUR 8 600 USD	Enbrel: 41% from maximum price Benepali: 47% from maximum price
	2017	Lost	Won	Large
	2018	Lost	Won	Large

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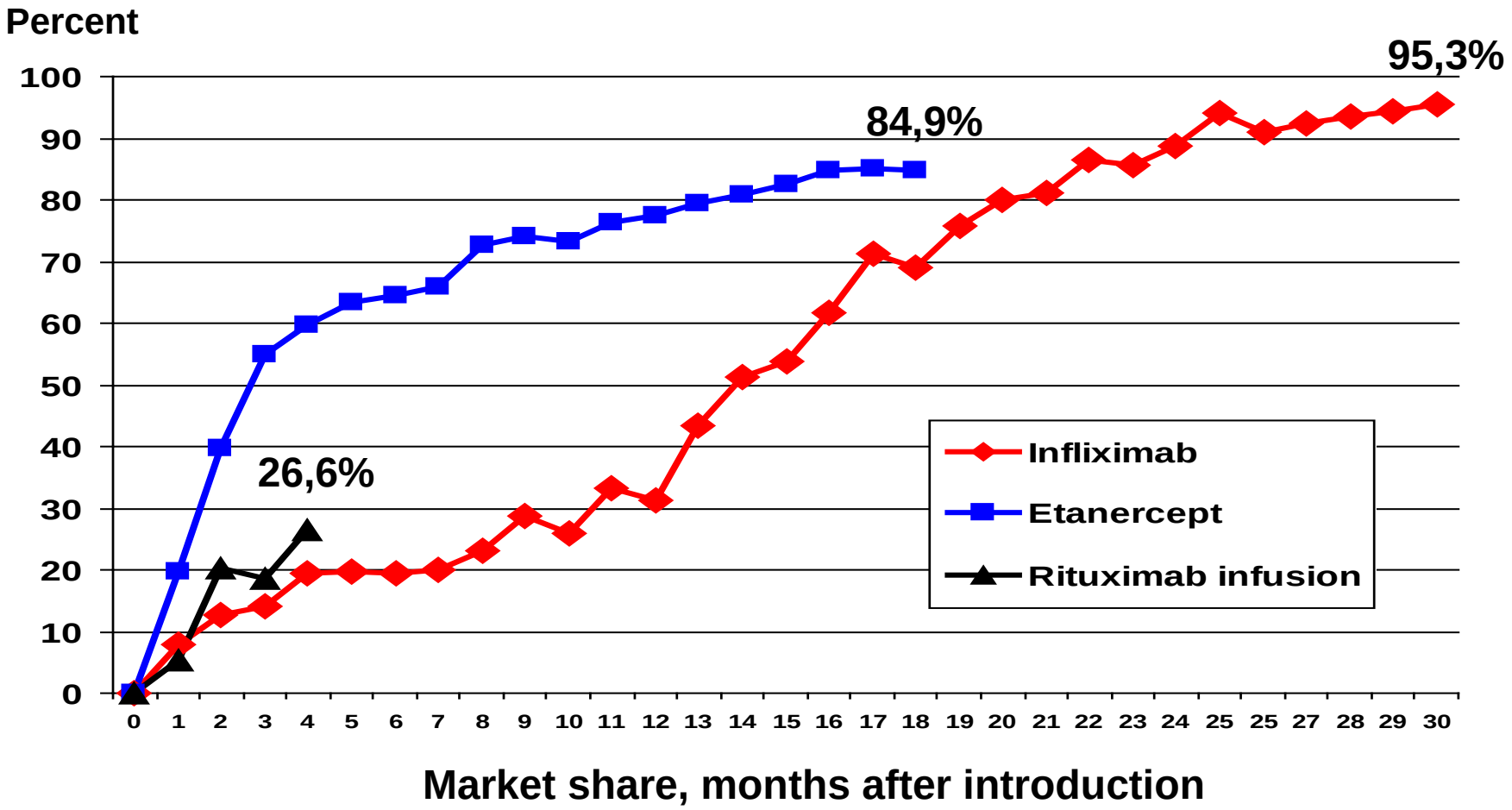
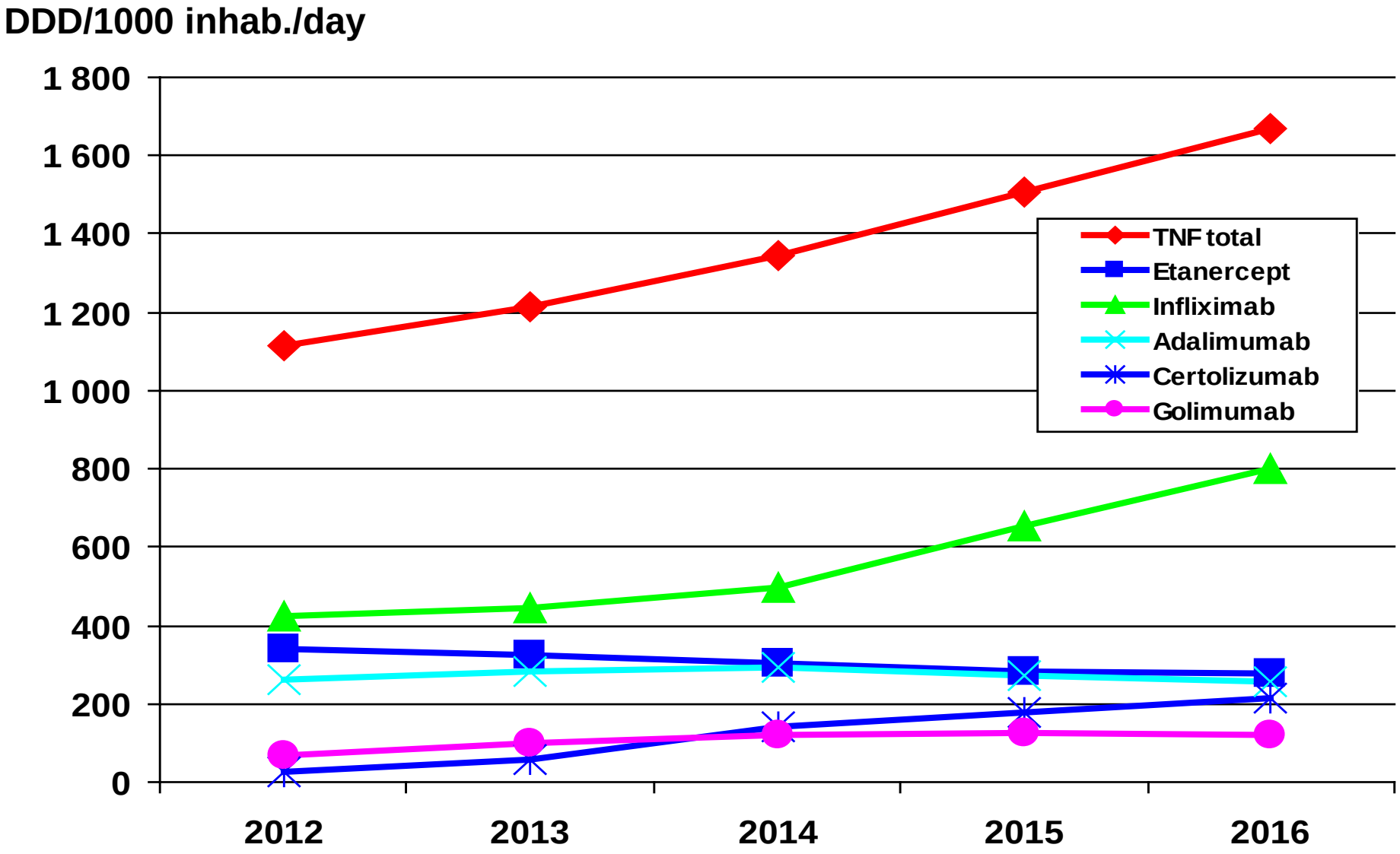
Market share, biosimilar infliximab, etanercept and rituximab, Norway*



*Units sold

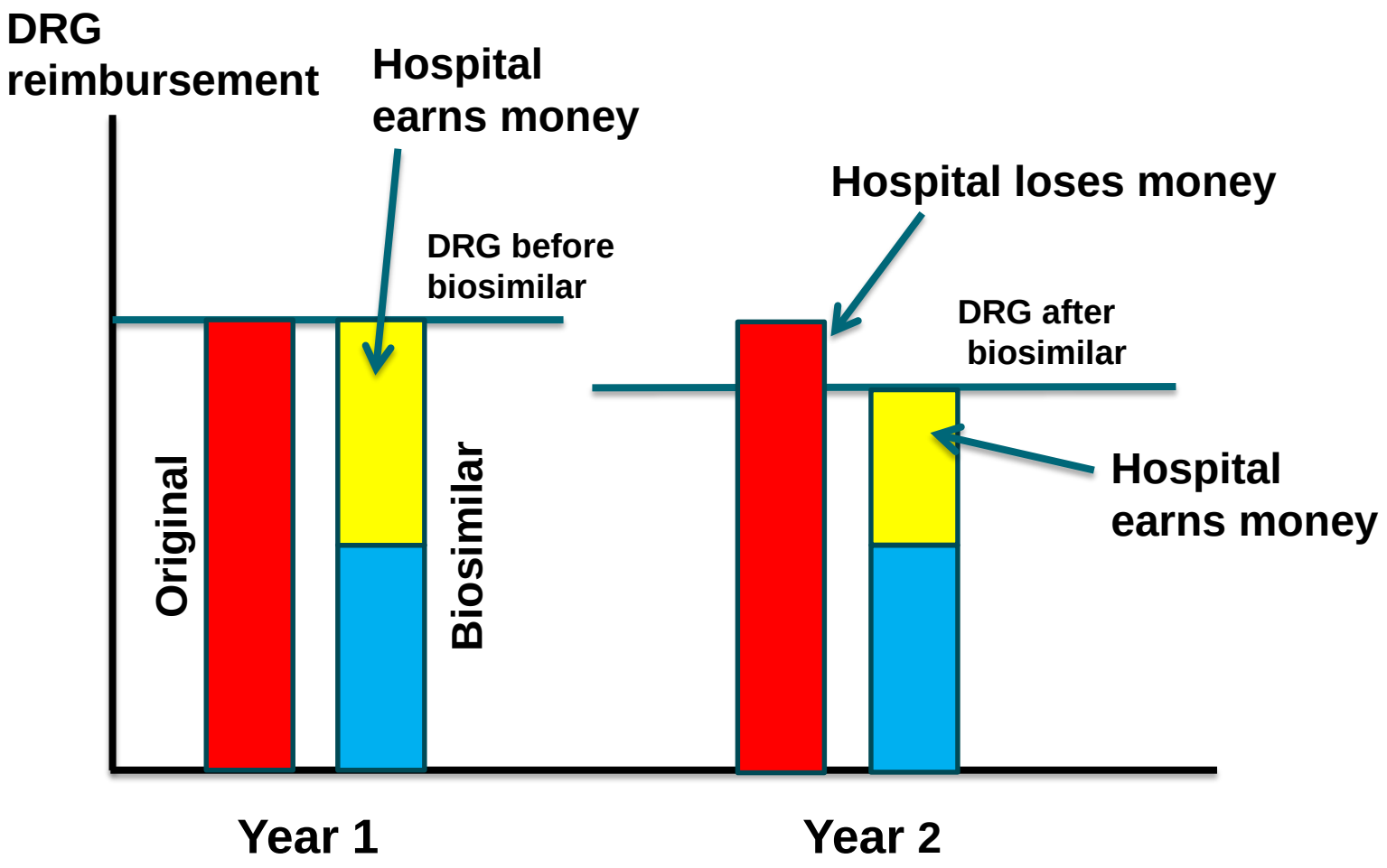
Farmastat

More treatment with TNF inhibitors

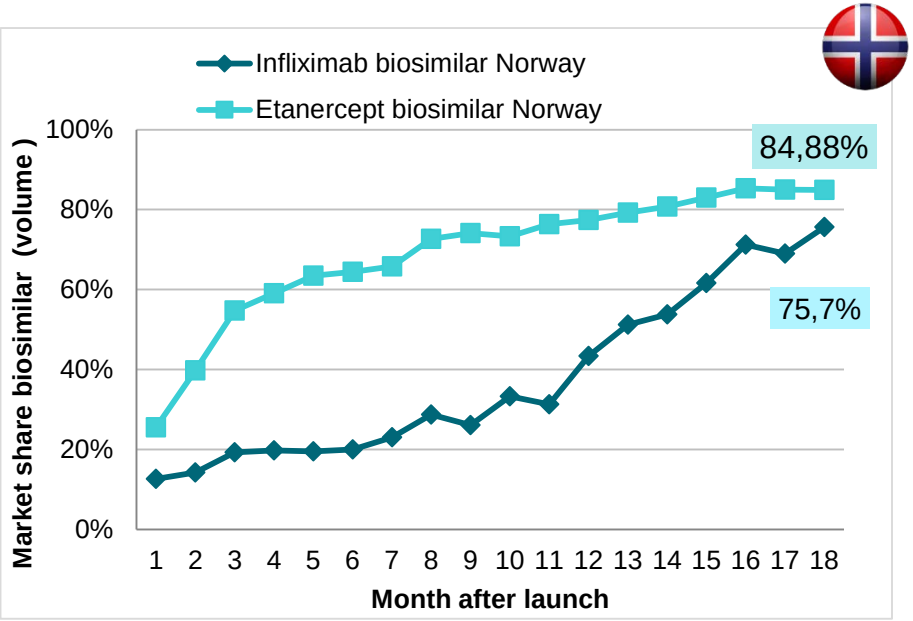


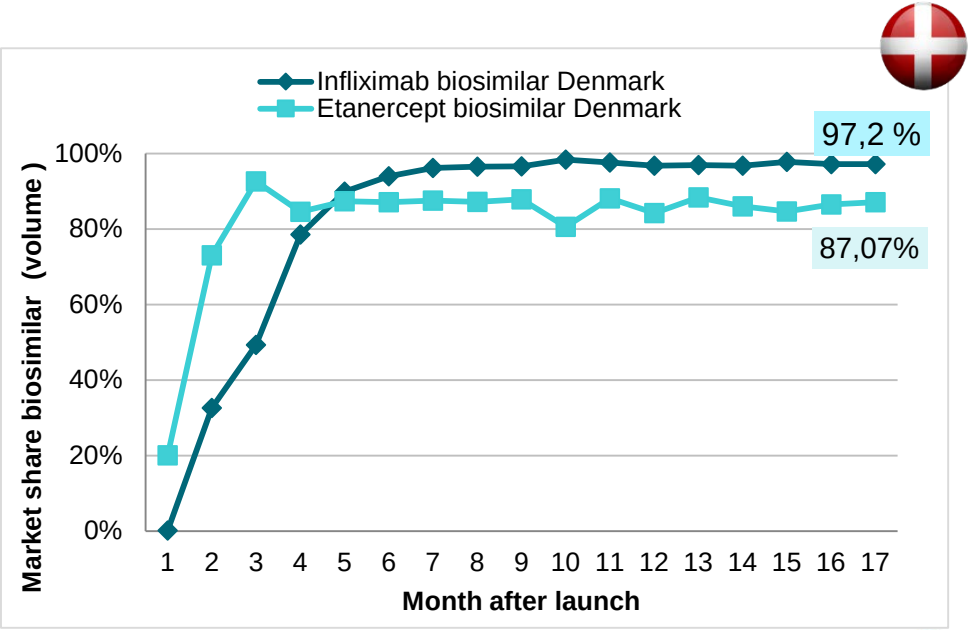
FHI

Principles of incentives in Norway

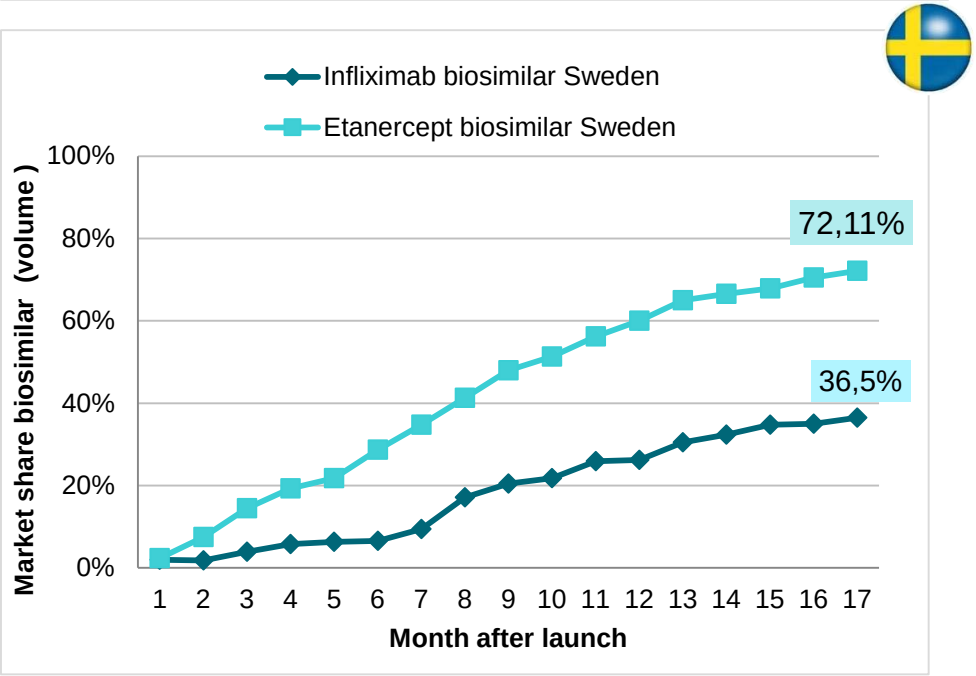


Market share - TNF biosimilars





Etanercept biosimilar not launched yet

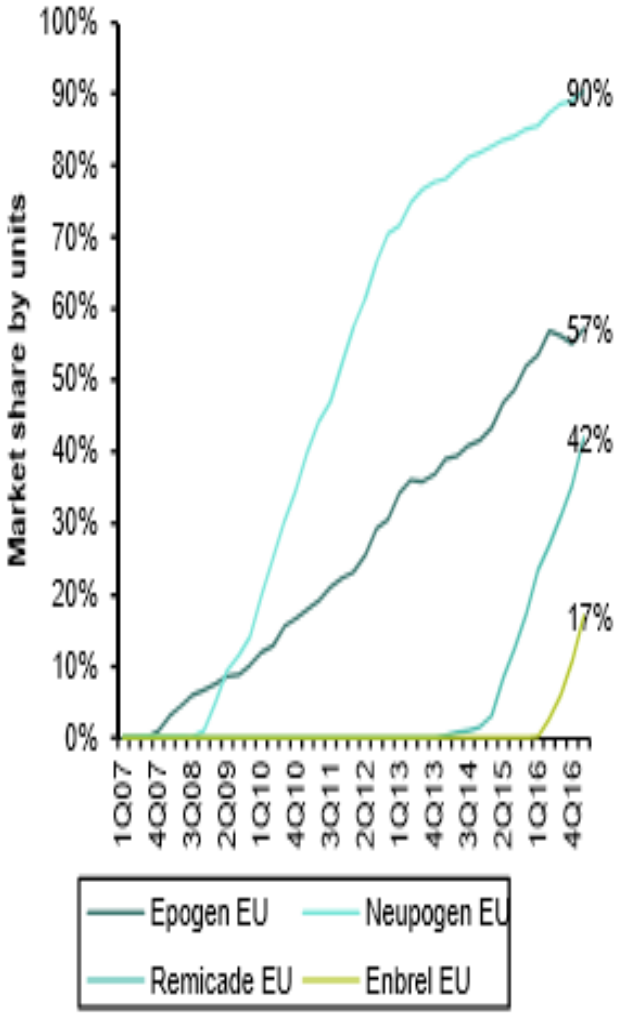


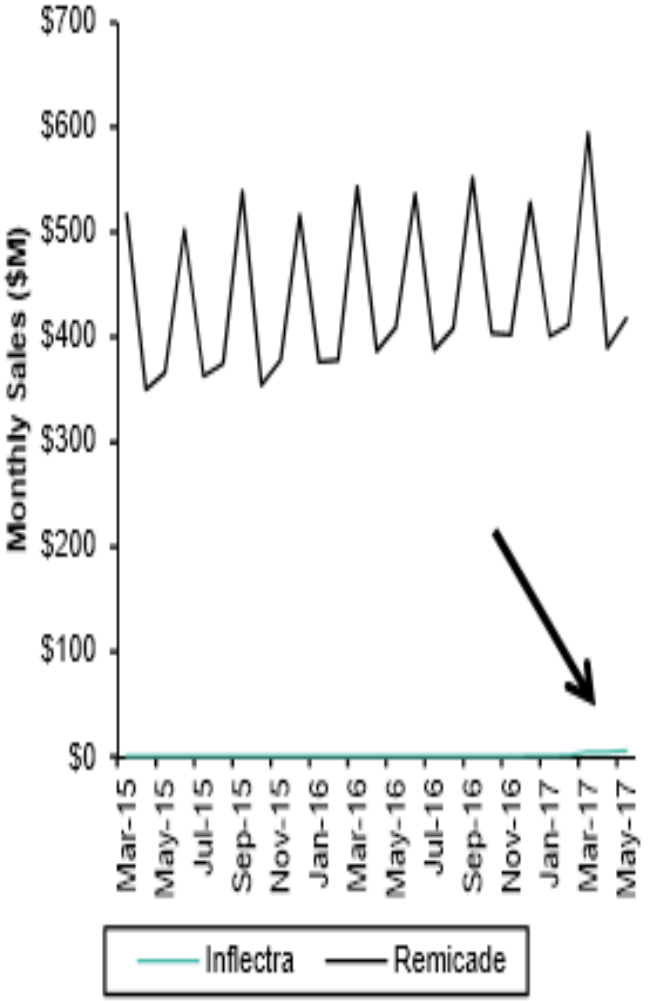
References:
Month 1: NO (March 2014). DK (March 2015). SWE (March 2015)
Sales data by volume. Norway: Farmastat AS https://farmastat.no/ ; Denmark: DLIMI AS https://www.dli-mi.dk/Pages/default.aspx; Sweden: Reveal AB http://www.reveal.se/lakemedelsstatistik/

Experiences in Nordic countries

- **Denmark:**
  - **Switching recommended**
  - **Strong financial incentives, one national tender**
  - **Strong mangement involvement**
  - **Drug authority now positive to switch, active**
- **Norway:**
  - **Switching recommended**
  - **Strong financial incentives, one national tender**
  - **Medium mangement involvement, but improving**
  - **Drug authority positive to switch**
- **Sweden:**
  - **Switching not recommended, but takes place**
  - **Strong financial incentives, complex tender structure**
  - **Low mangement involvement, but improving**
  - **Drug authority initially negative to switch, now positive**

European success – and an American tragedy





Panel A

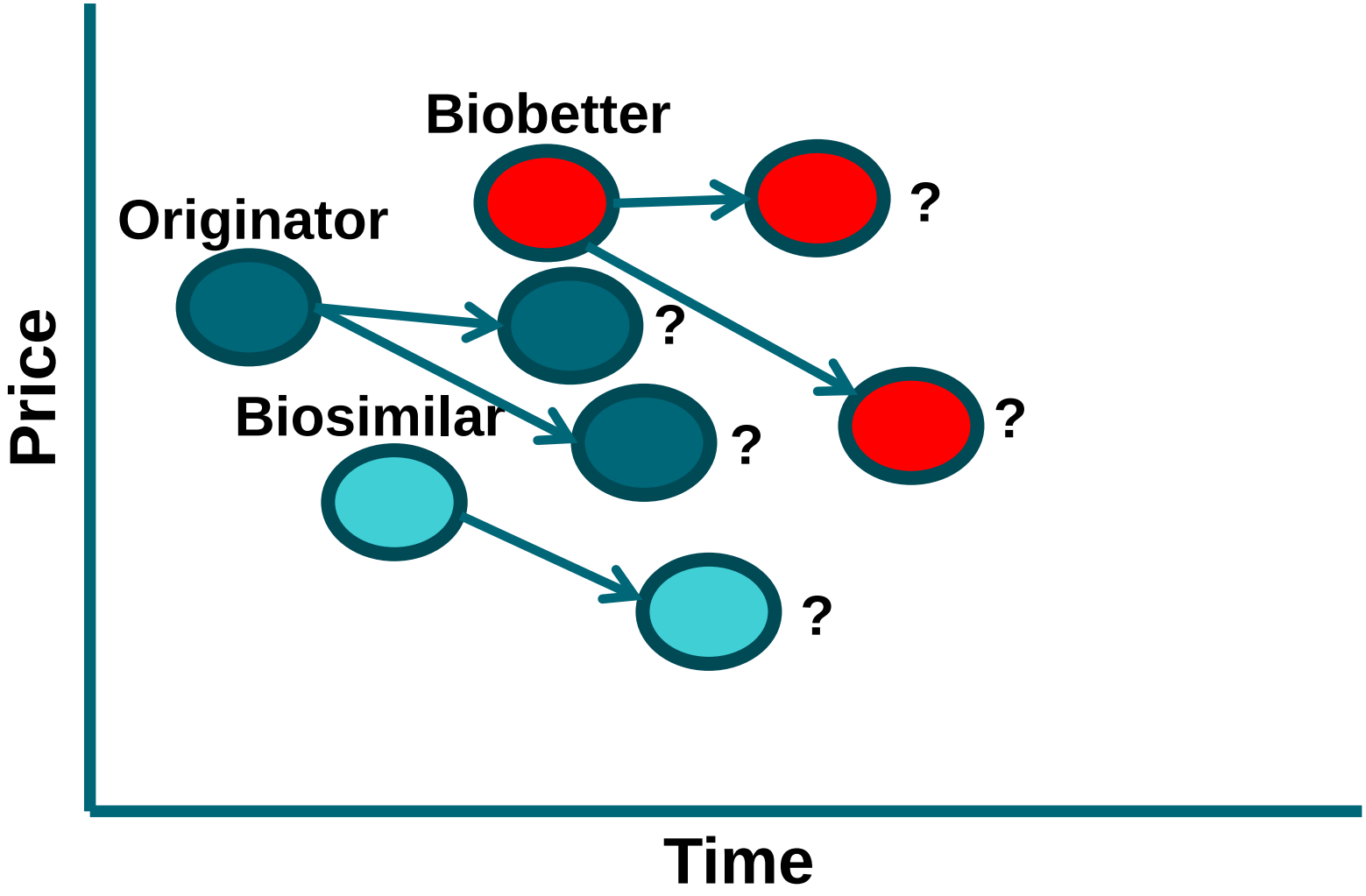
	Healthcare Access and Quality Index	Tuberculosis	Diarrhoeal diseases	Lower respiratory infections	Upper respiratory infections	Diptheria	Whooping cough	Tetanus	Measles	Maternal disorders
Andorra	95	98	99	85	100	100	98	99	100	100
Iceland	94	95	97	72	99	100	100	100	100	100
Switzerland	92	99	91	87	99	100	100	100	100	97
Sweden	90	98	96	80	99	100	100	100	100	98
Norway	90	95	92	78	99	100	100	100	100	95
Australia	90	100	94	82	99	100	100	100	99	98
Finland	90	93	99	89	99	100	100	100	100	95
Spain	90	97	96	80	99	100	98	100	100	95
Netherlands	90	99	94	71	99	100	100	100	100	98
Luxembourg	89	99	87	85	99	100	98	100	100	92
Japan	89	89	94	61	99	100	100	100	99	98
Italy	89	95	96	90	99	100	99	99	100	100
Ireland	88	91	94	71	99	100	100	100	100	98
Austria	88	95	97	95	99	100	100	100	99	95
France	88	92	92	76	99	100	99	100	99	95
Belgium	88	94	97	68	99	100	99	100	100	95
Canada	88	98	93	73	99	100	99	100	100	96
Slovenia	87	92	99	80	98	100	100	100	99	97
Greece	87	90	100	84	98	100	100	99	100	95
Germany	86	98	95	73	99	100	100	100	100	96
Singapore	86	79	96	39	99	100	100	100	100	95
New Zealand	86	96	90	87	99	100	100	100	99	89
South Korea	86	67	97	79	98	100	99	99	98	94
Denmark	86	96	90	74	98	100	100	100	100	95
Israel	86	95	91	69	99	100	99	100	100	92
Cyprus	85	96	84	84	99	100	97	98	99	100
Qatar	85	83	94	77	99	100	97	98	94	85
Malta	85	100	86	79	99	100	100	99	100	98
Czech Republic	85	96	96	70	98	100	100	100	99	97
UK	85	94	93	64	99	100	99	100	100	92
Portugal	85	81	97	60	98	100	99	100	99	97
Kuwait	82	77	91	60	99	100	100	100	95	96
Croatia	82	85	96	87	97	100	100	100	97	94
Estonia	81	75	98	72	97	100	99	100	100	98
USA	81	97	89	60	98	100	99	100	100	82
Montenegro	81	88	96	90	96	100	91	99	97	94
Lebanon	80	81	88	94	97	100	95	98	97	88
Hungary	80	91	93	89	96	100	100	100	100	95
Poland	80	80	97	68	97	100	100	100	100	95
Saudi Arabia	79	64	81	59	98	100	97	97	93	89
Bermuda	79	96	94	61	99	100	100	100	96	100
Bahrain	79	75	83	67	98	100	98	98	95	86
Slovakia	79	91	92	60	97	100	97	99	100	94
Latvia	78	72	97	65	96	100	100	100	100	93
Taiwan	78	78	95	64	98	100	94	98	80	95
Puerto Rico	77	90	87	49	98	100	99	99	95	89
Lithuania	77	61	97	62	96	100	100	100	100	94
Macedonia	76	74	80	89	95	100	89	98	99	94
Chile	76	72	92	66	97	100	97	99	100	89
Serbia	75	79	93	84	95	100	91	98	100	93

IMS, Lancet

Lessons learned

- **Biosimilar companies must have an aggressive price policy**
- **Purchasing system should be based on competition – not regulation**
  - **Winner takes (almost) all, guarantee volume, loyalty to agreements**
  - **Large or national tenders**
  - **Using biosimilars to increase price pressure on originators is a shortsighted strategy**
- **Restrictions on price matching and bundling should be in place**

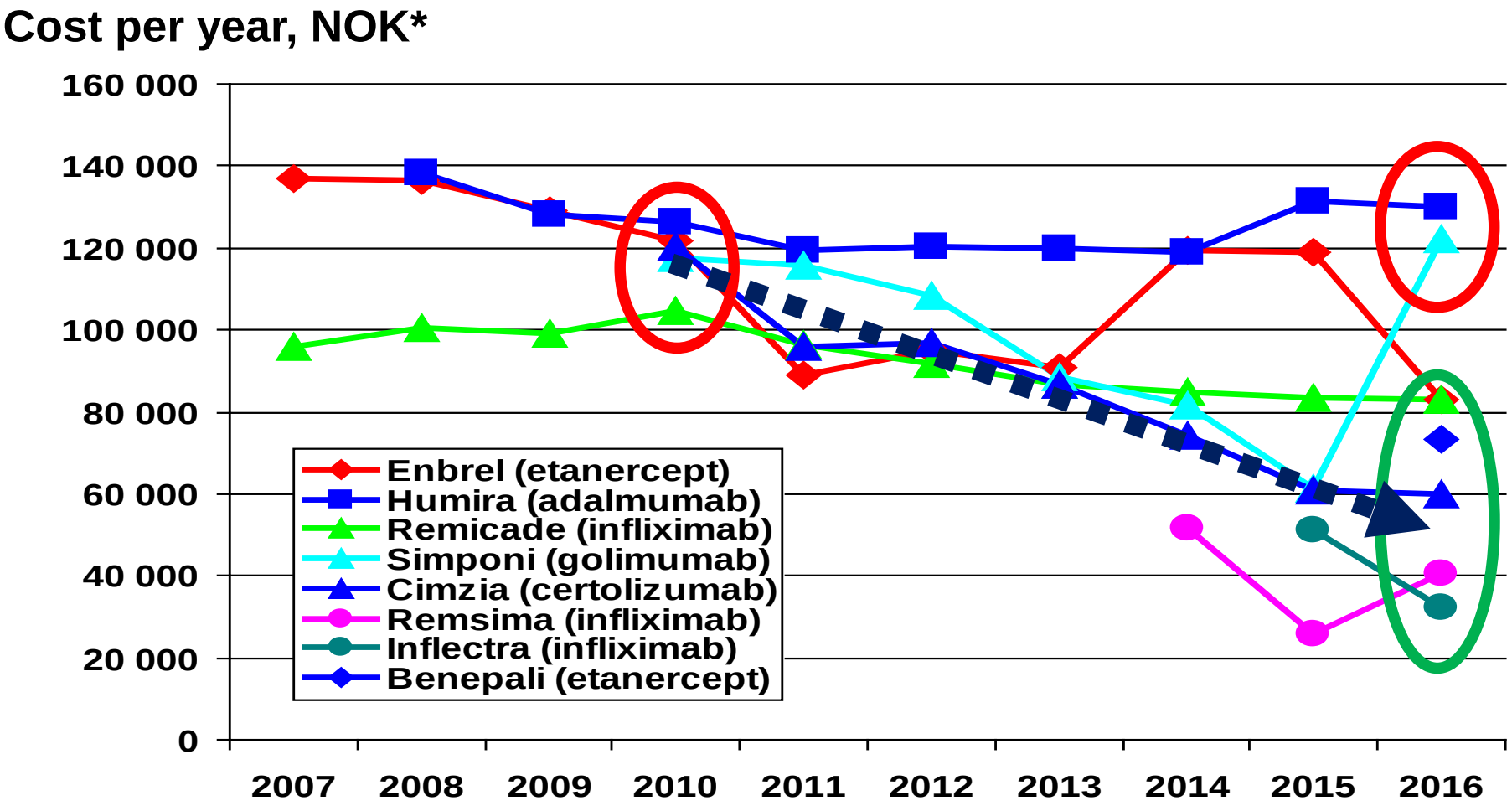
What will happen?



Why do we need biosimilars?

- **Biosimilars are more affordable**
  - **More treatment for more patients for less money**
  - **Makes room for new and expensive drugs**
- **Biosimilars will probably have a «chilling» effect on the prices of some new drugs**
  - **Important to mechanism to reduce prices**

A «chill» effect in Norway?



*Rheumatoid arthritis, 75 kg

LIS

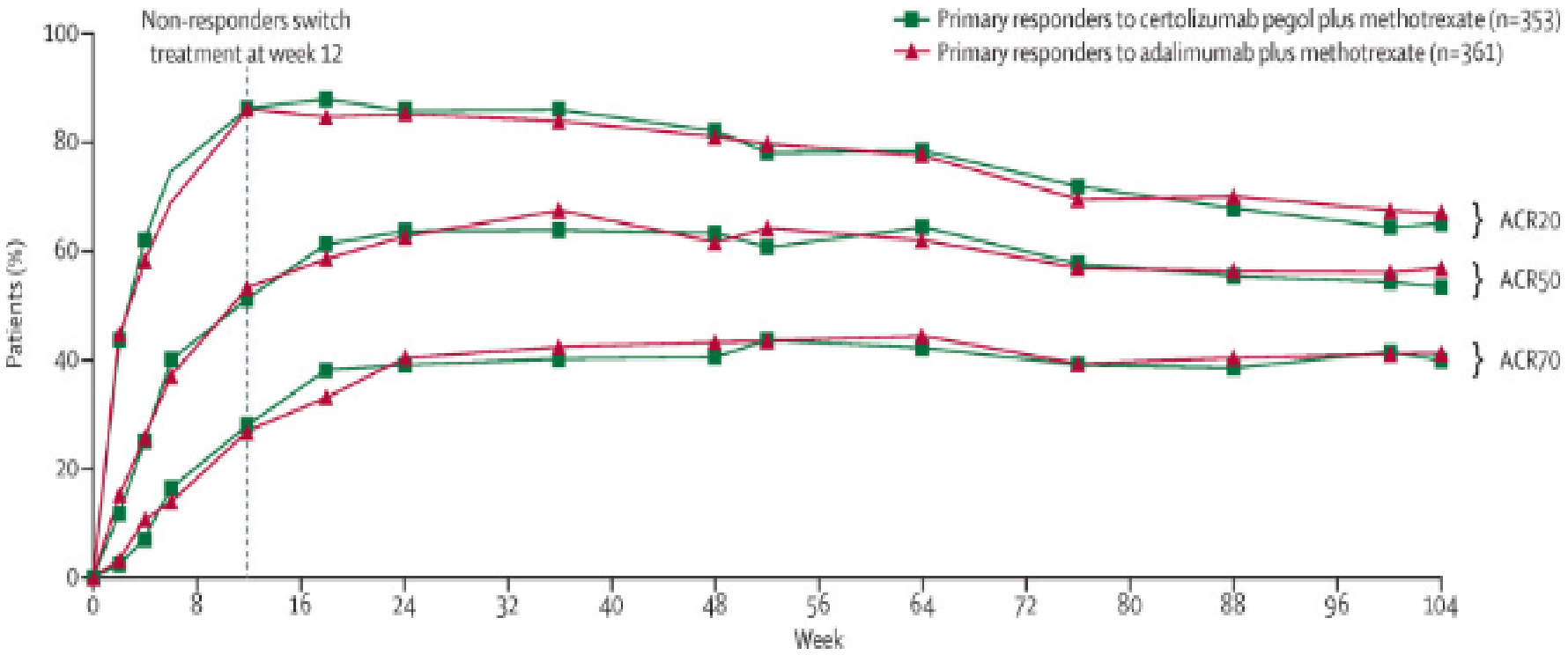
Effective competition

- **Effective switching to the lowest priced drug**
- **Effective economic mechanisms**
  - **«Something to gain for everybody»**
  - **«The winner takes (almost) all»**
  - **«Reasonable prices»**
- **Effective price pressure on other drug**
  - **Non-medical switch to lower priced drugs in same class where appropriate**

From biosimilars to biogenerics

- **So far – largely a one way ticket from orginator to biosimilar**
  - **Shuts out the second entrant**
  - **Not a sustainable model**
- **Biosimilar sustainability depends on biogeneric thinking paired with appropriate economic models**

Head to head – why not switch?



EXXELERATE study. Lancet, http://dx.doi.org/10.1016/S0140-6736(16)31651-8

Thank you!