Role of Biosimilars in the Treatment Paradigm of Inflammatory Bowel Disease

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Biosimilars: Key Points

- Not ‘generics’ or identical, rather *similar* to originator
- Relevant because immunogenicity matters
- Consequences of intermittent exposure to biological agent – tolerization vs sensitization
- Interchangeability is a good test of sensitization
- Caution with non-medical switch or substitution

Biosimilar or Biosimilarity

The biologic product that is **highly similar** to the reference product notwithstanding **minor differences** in clinically inactive components, and has **no clinically meaningful differences** in terms of safety, purity and potency from the reference product.

Food and Drug Administration

Section 7002(b)(2) of ACA, Amending Section 351(i) of PHS Act

Small Molecules

=

Generics

Biologicals

- Originator
- Reference
- Innovator

=

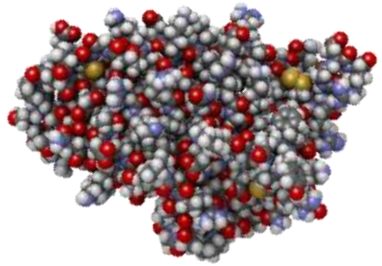
Biosimilar

Monoclonal Antibodies

Aspirin

MW = 180 daltons

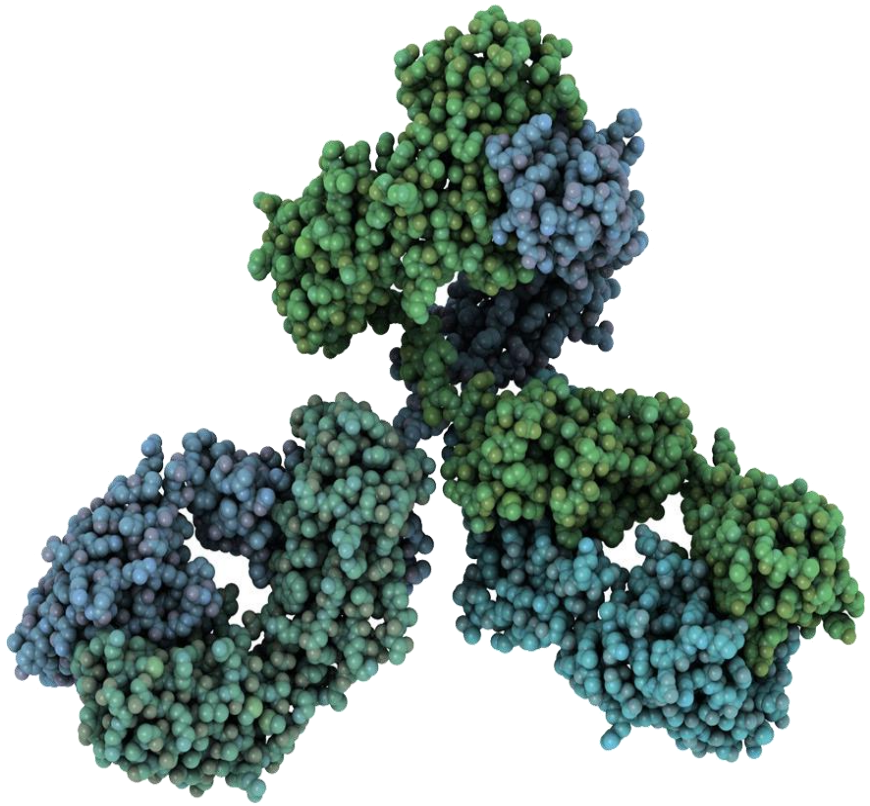
0 amino acids



Erythropoietin

MW = 30,000 daltons

166 amino acids

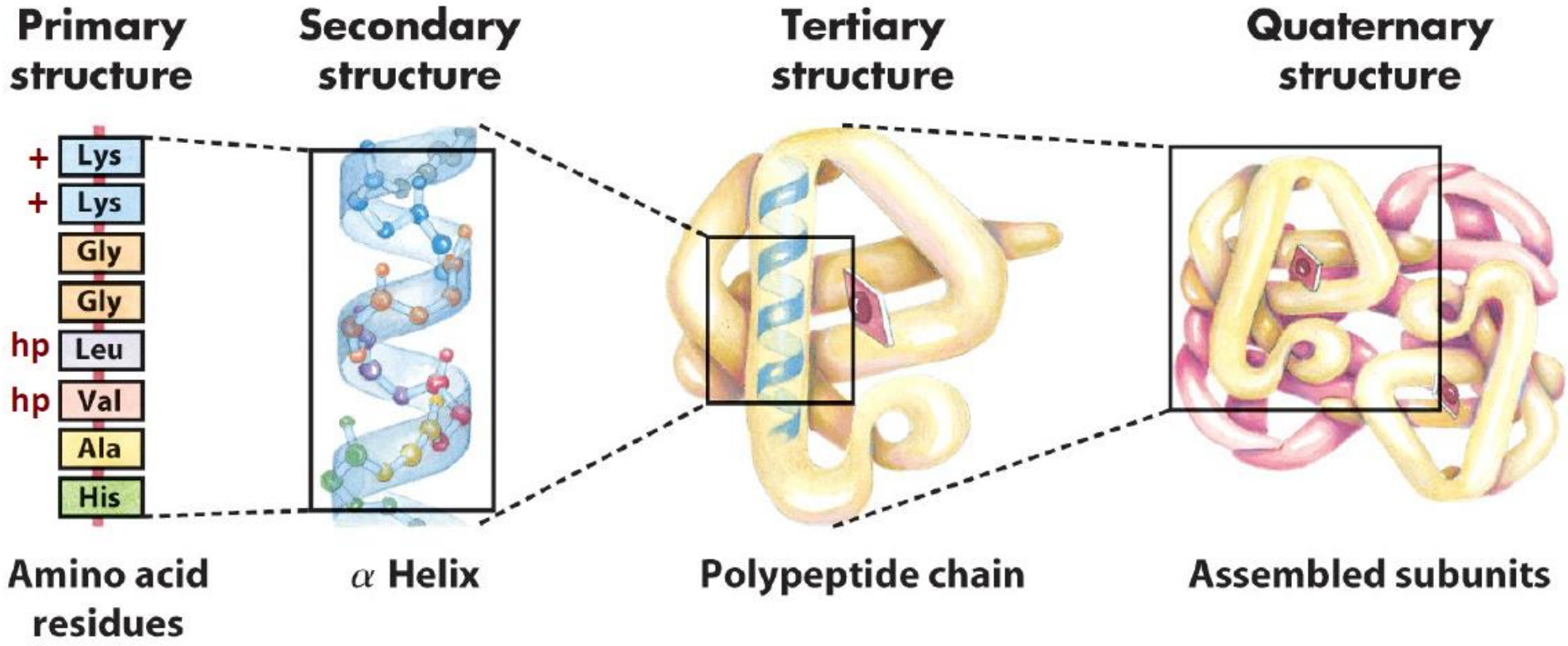


Antibody (IgG)

MW = 150,000 daltons

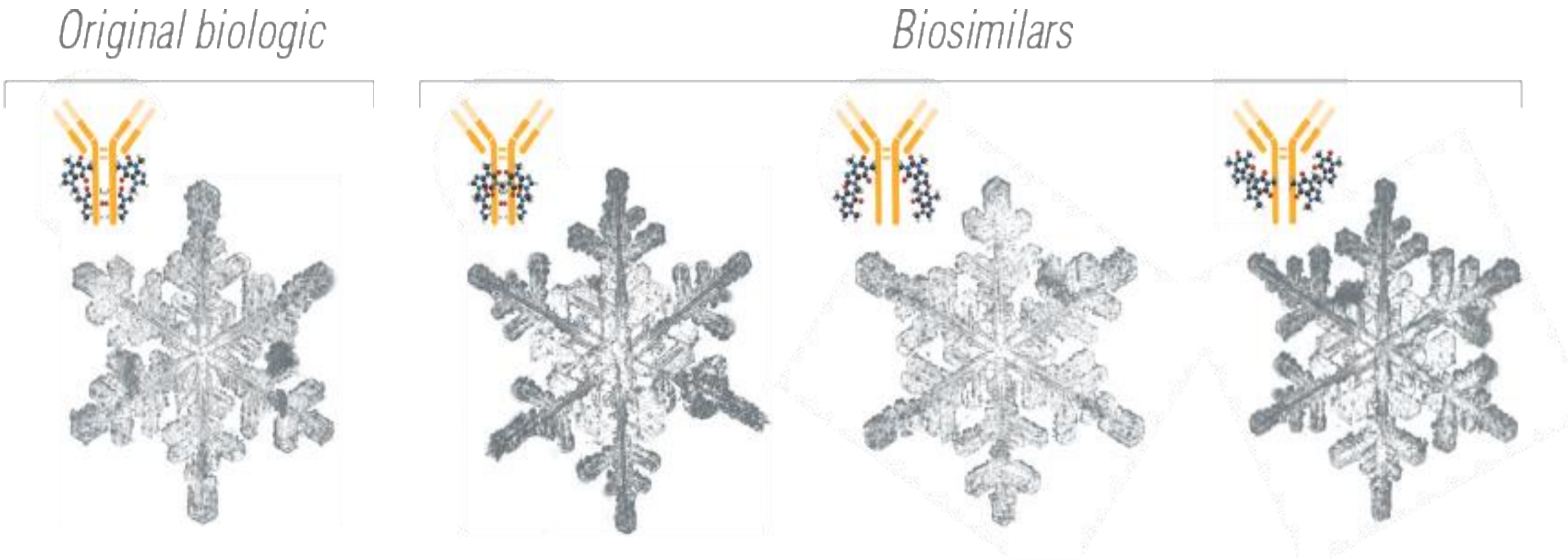
~1,300 amino acids

Protein Structure



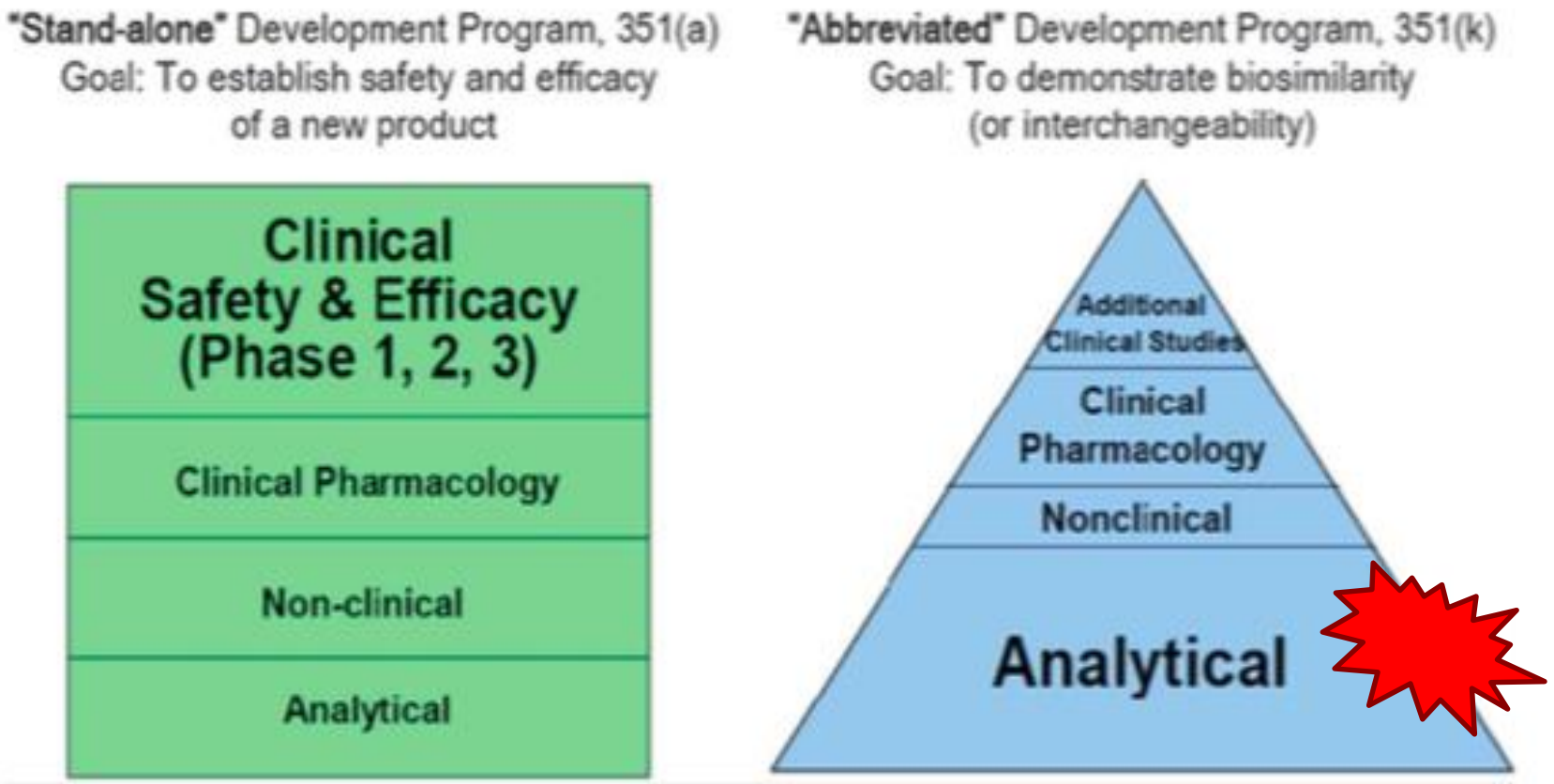
Kozlowski S. U.S. FDA. August 2012

Snowflake Effect



Taken from Amgenbiosimilars.com

Abbreviated Approval Process for Biosimilars



Taken from Ha C and Kornbluth A. Inflamm Bowel Dis 2016

Other Requirements for Biosimilars

- Same MOA to the originator product
- No new indications
- Same route of administration and dosage
- Must comply with good manufacturing practices (GMPs)

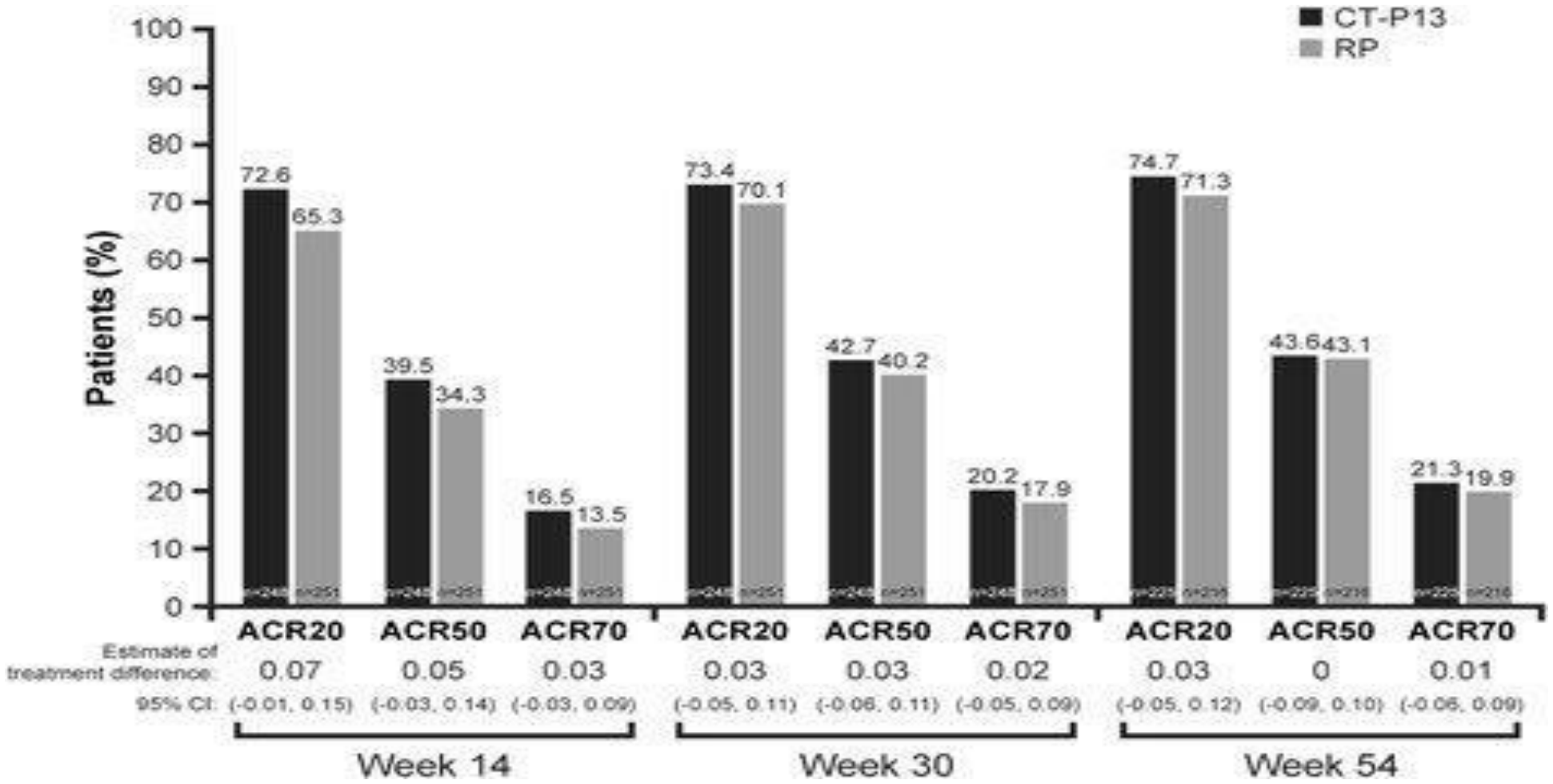
Other Requirements for Biosimilars

- Biosimilars can seek licensure for fewer indications than originator (patent)
- FDA must accept some differences
  - Formulation
  - Delivery packages
- No change can result in clinically meaningful differences
  - Biosuperiority is not allowed

Extrapolation

- Biosimilars may be extrapolated
- Supporting biosimilarity in one condition of use to support licensure in other conditions
- Choice of indication to study must be adequately sensitive to detect clinically meaningful differences
  - RA vs IBD?

PLANETRA: Results to 54 weeks



Yoo DH et al. Arthritis Res Ther 2016

Interchangeability

- Interchangeable: substituted for the originator without the intervention of the prescriber
- No FDA-approved interchangeables – YET.
- Recent FDA draft guidance – released January 2017
  - Case-by-case basis
  - Across all indications of use
  - At least *three* switches between reference and biosimilar
  - Sufficiently long to allow for washout of reference product

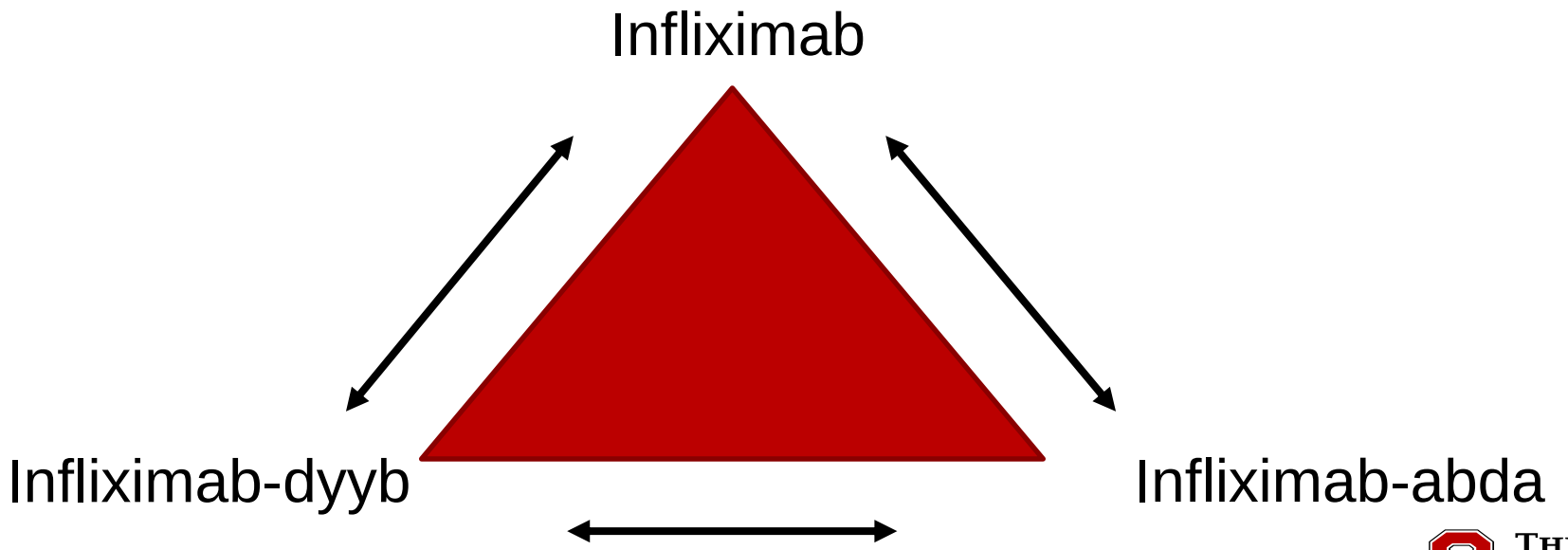
U.S. Dept of Health and Human Services. FDA Draft Guidance 2017

State Substitution Laws

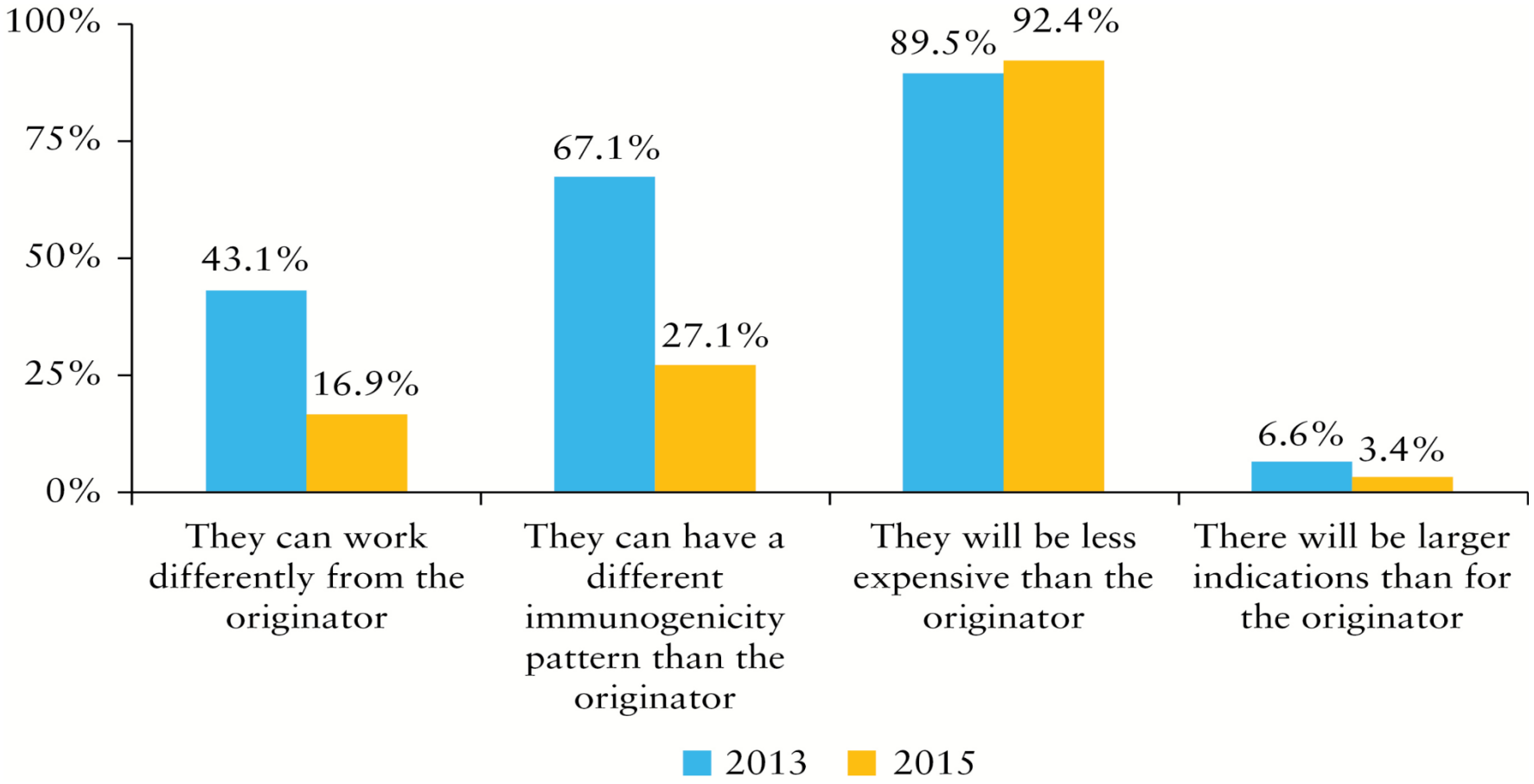
- Under many state laws: only interchangeable biosimilars are automatically substitutable for the prescribed originator
  - Biosimilars not interchangeable yet in IBD
- Some states: require prescriber notification with substitute
- Remains an evolving topic

Payers' Approach to Interchangeability

- None of the biosimilars approved for interchangeability
- Still may be confronted with this in clinical practice
- Negotiation between payers/insurance and pharma

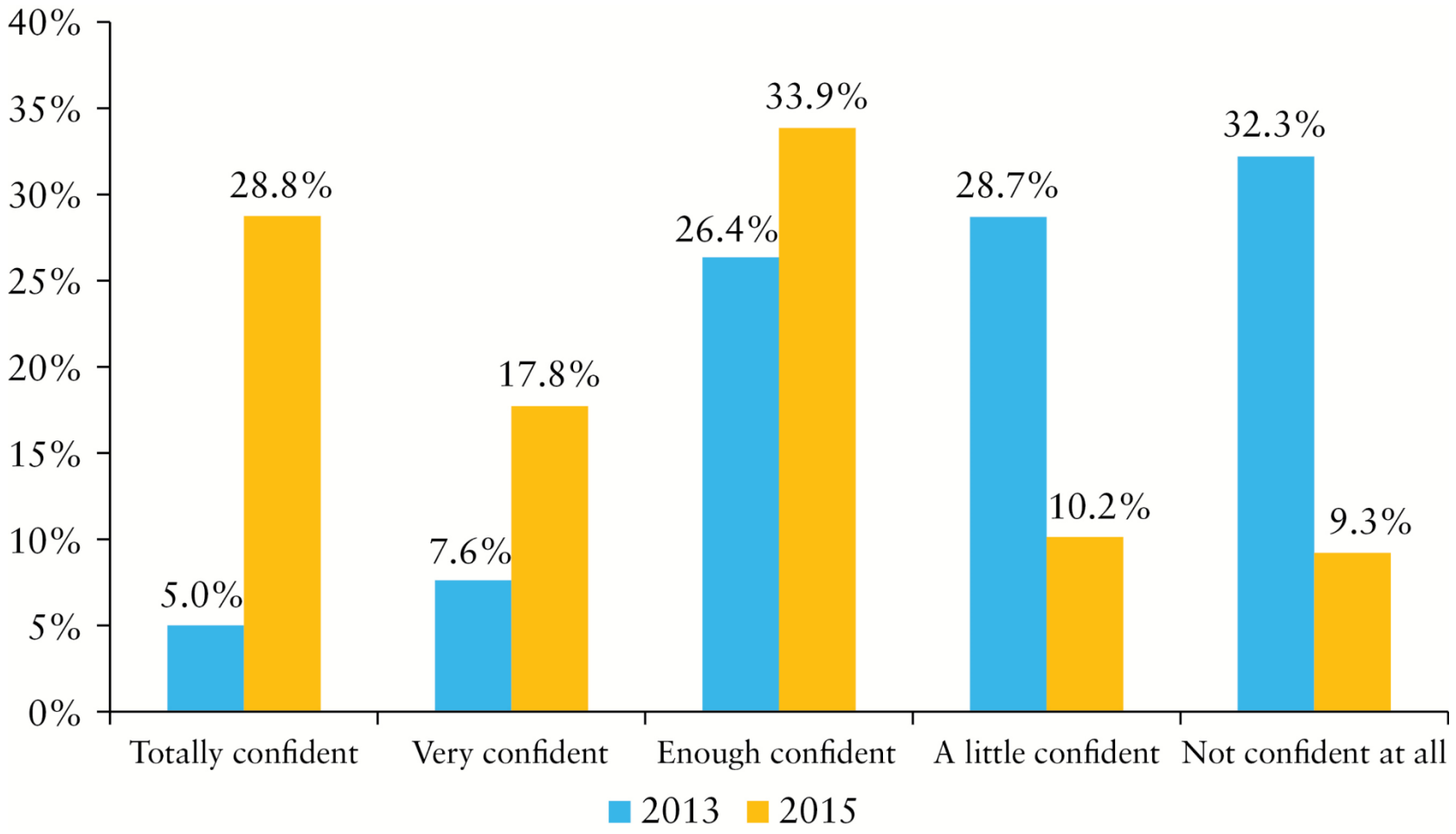


‘Extrapolating’ from European Experience



Danese S et al. J Crohns Colitis 2016

‘Extrapolating’ from European Experience



Danese S et al. J Crohns Colitis 2016

Status of Biosimilars in U.S.

- Inflectra (CT-P13): infliximab-dyyb
  - FDA approved April 2016; available since Nov 2016
- Renflexis: infliximab-abda
  - FDA approved April 2017; available fall 2017
- Amjevita (ABP 501)
  - FDA approved Sept 2016; not yet marketed
  - Legal issues - patent

Originator vs Biosimilars: Meta-analysis

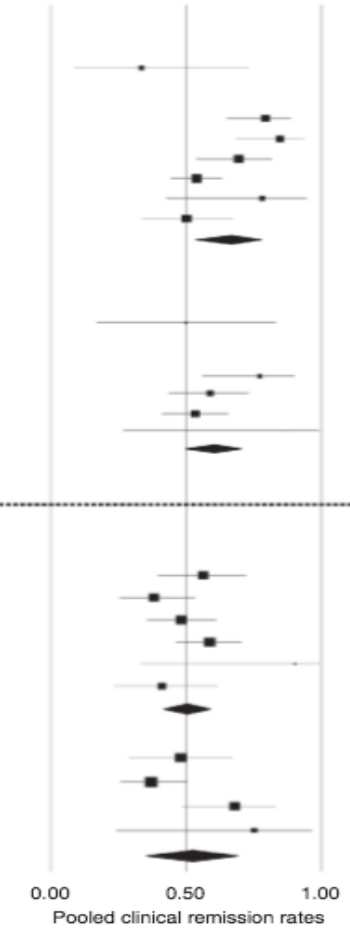
- 19 studies: 8 phase I, 5 phase III, 6 observational
- pK equivalence 80-125%
- No consistent adverse events
- “Preliminary evidence supports biosimilarity and interchangeability of biosimilar and reference TNFa-inhibitors”

Chingcuanco F et al. Annal Int Med 2016

Meta-Analysis: Remission Rates CTP-13

(b) Forest plot of pooled clinical remission rates at 8-14 weeks, 24-30 weeks

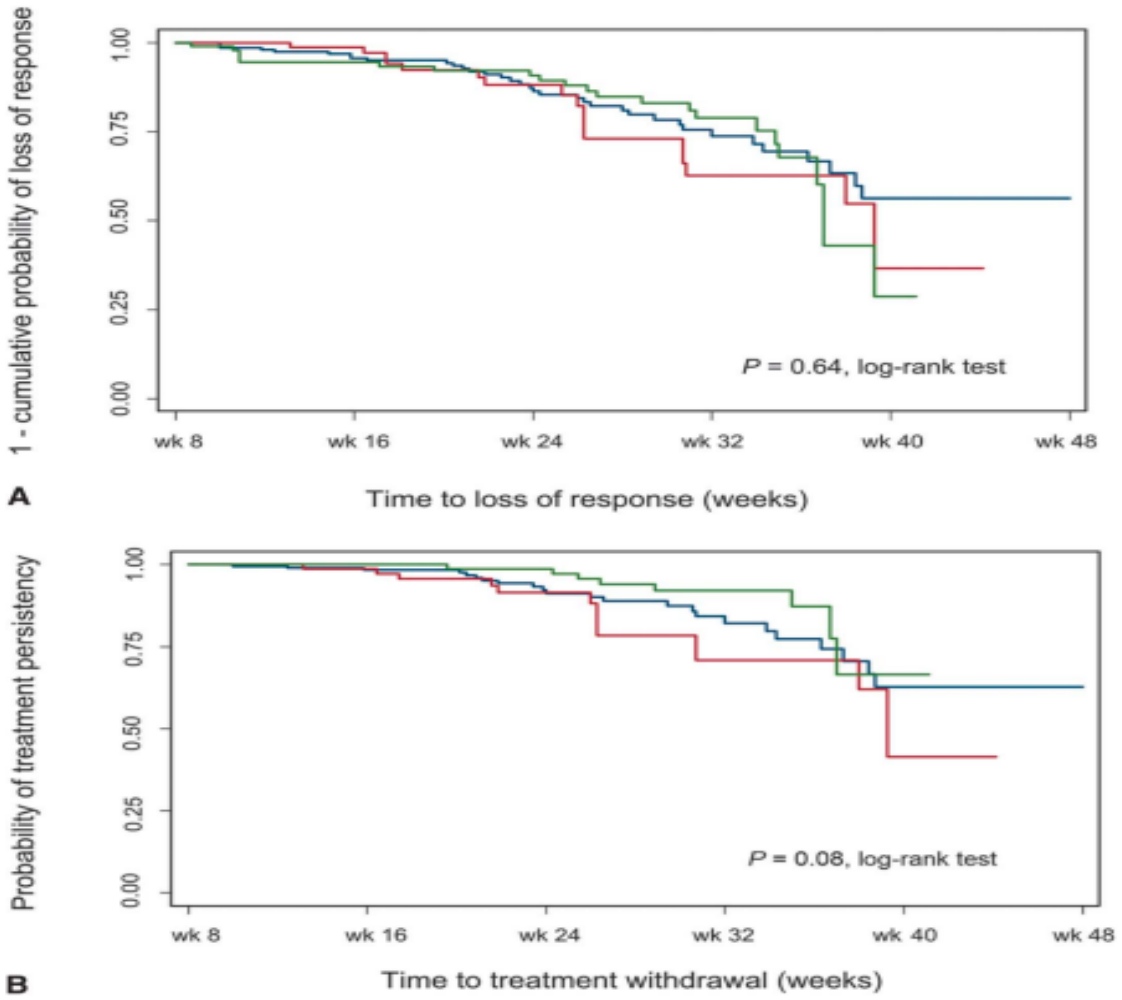
Study name	Event rate	Lower limit	Upper limit	Event /total (n)	Relative weight
Crohn's disease					
8-14 weeks					
Fistulizing CD					
Park et al.	0.33	0.08	0.73	2/6	7.21
Luminal CD					
Jahnsen et al.	0.79	0.64	0.89	34/43	16.45
Jung et al.	0.84	0.68	0.93	27/32	13.68
Park et al.	0.69	0.53	0.82	27/39	17.18
Gesce et al.	0.54	0.44	0.63	52/97	20.78
Hlavty et al.	0.78	0.42	0.94	7/9	8.00
Keli et al.	0.50	0.33	0.67	15/30	16.70
Total	0.66	0.53	0.77	164/256	
24-30 weeks					
Fistulizing CD					
Park et al.	0.50	0.17	0.83	3/6	6.90
Luminal CD					
Jung et al.	0.77	0.56	0.90	17/22	16.13
Park et al.	0.59	0.43	0.73	23/39	32.31
Gesce et al.	0.53	0.41	0.66	31/58	42.55
Hlavty et al.	0.88	0.27	0.99	3/3	2.11
Total	0.60	0.49	0.70	77/128	
Ulcerative colitis					
8-14 weeks					
Jahnsen et al.	0.56	0.39	0.72	18/32	17.23
Jung et al.	0.38	0.25	0.53	16/42	19.97
Park et al.	0.48	0.35	0.61	26/54	23.89
Gesce et al.	0.59	0.46	0.70	34/58	24.44
Hlavty et al.	0.90	0.33	0.99	4/4	1.43
Keli et al.	0.41	0.23	0.62	9/22	13.04
Total	0.50	0.41	0.59	107/212	
24-30 weeks					
Jung et al.	0.48	0.29	0.68	11/23	28.38
Park et al.	0.37	0.25	0.51	20/54	35.81
Gesce et al.	0.68	0.48	0.83	17/25	27.79
Hlavty et al.	0.75	0.24	0.97	3/4	8.02
Total	0.52	0.35	0.69	51/106	



PROSIT: Safety & Efficacy

- Multi-center *prospective* study in Italy
- 547 consecutive pts (CD 313, UC 234)
  - 311 pts TNF-naïve; 139 pts TNF-exposed
- 97 pts switched after mean 18 ± 14 infusions infliximab; mean follow up 4.3 ± 2.8 mo
- Infusion reactions more frequent in patients pre-exposed to infliximab (IRR 2.82, 95% CI: 1.05-7.9)

PROSIT: Efficacy



- Tx Naïve – BLUE
- Previously exposed – RED
- Switched – GREEN

A. Loss of Response
B. Treatment persistency

Fiorino G. Inflamm Bowel Dis 2017

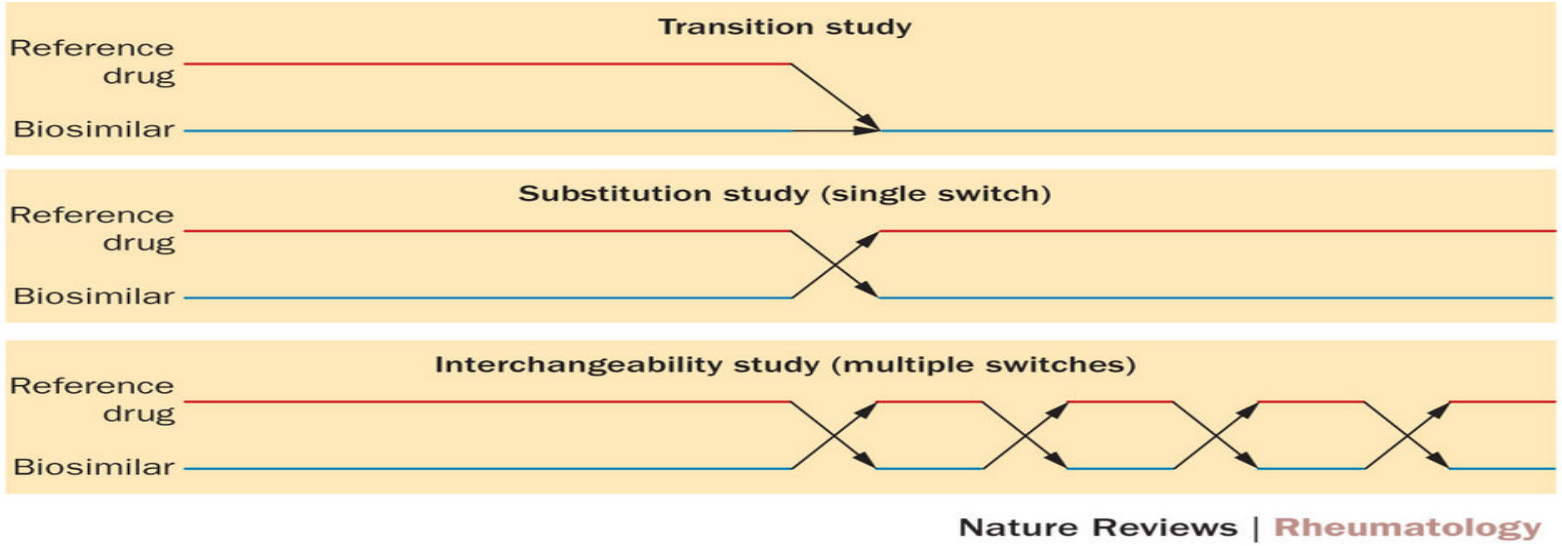
Non-Medical Switching: Risk of Immunogenicity

Clinical Consequences of Interchangeability

- Lack of evidence to support critical concepts of allowable switching and substitution
- Substitution policies: highly variable, difficult to monitor, hard to predict across different patient populations
- In stable patients, immune systems tolerized to originator may now become sensitized to biosimilar antibodies and develop drug-neutralizing antibodies
  - Immunogenicity
  - Loss of response

How to Assess Risk?

- Well designed switch studies
- Multiple switches
- Evaluate pK and immunogenicity for at least 18 months

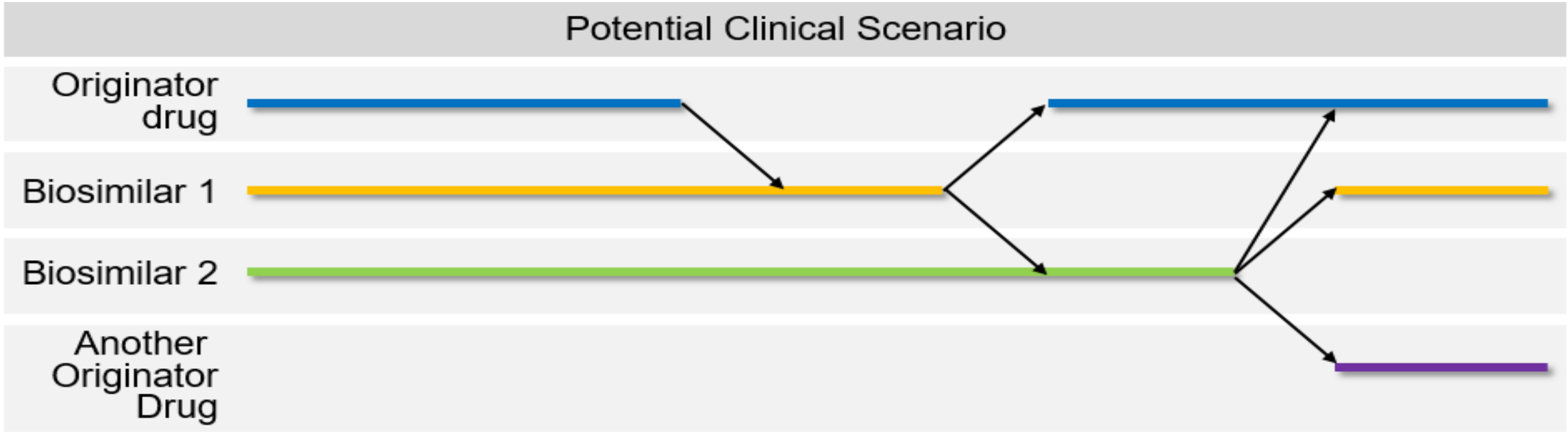


Dörner, T. & Kay, J. Nat. Rev. Rheumatol. 2015

Reality of Switching

Immune responses may affect safety and effectiveness:

- Alter pK, induce anaphylaxis, develop neutralizing antibodies

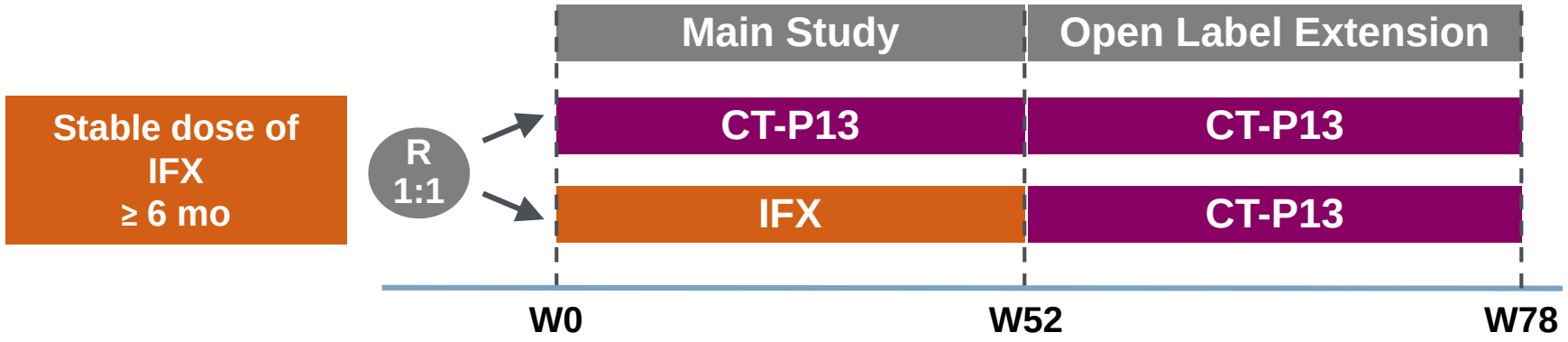


Clinical Evidence of RCTs to Support Substitution

- NOR-SWITCH – recently published
- NCT020096861 – preliminary results

- Both non-inferiority studies (15-20% margin)

NOR-SWITCH: Study Design

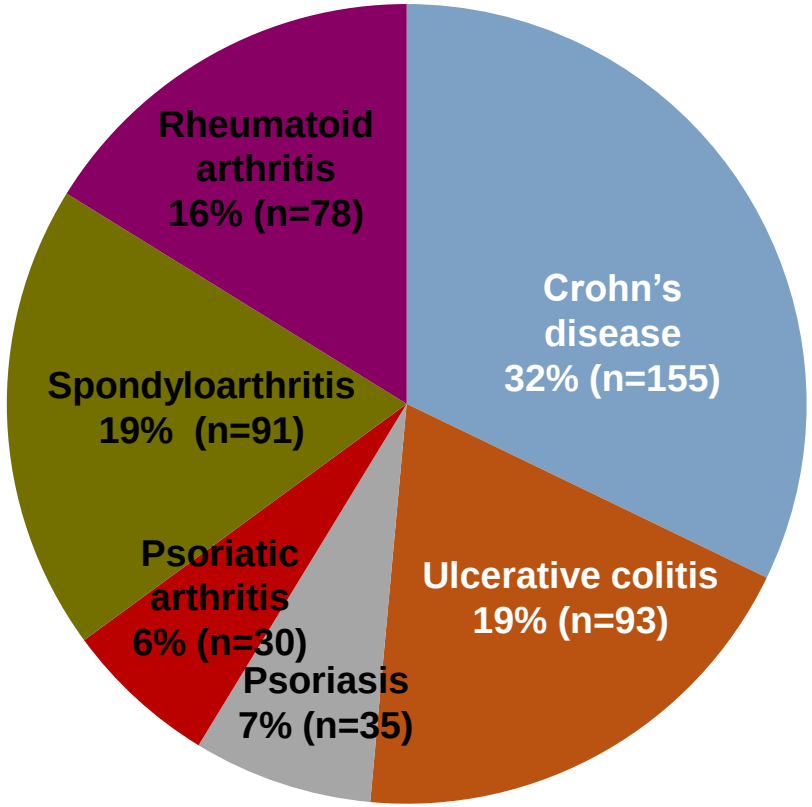


- Double-blind, non-inferiority study (15% margin)
- Primary endpoint: Occurrence of disease worsening 52wks
  - Defined differently for disease state (5)

Jørgensen KK et al. Lancet 2017

Nor-Switch: Disease Indication

Multicenter study, 40 sites across Norway

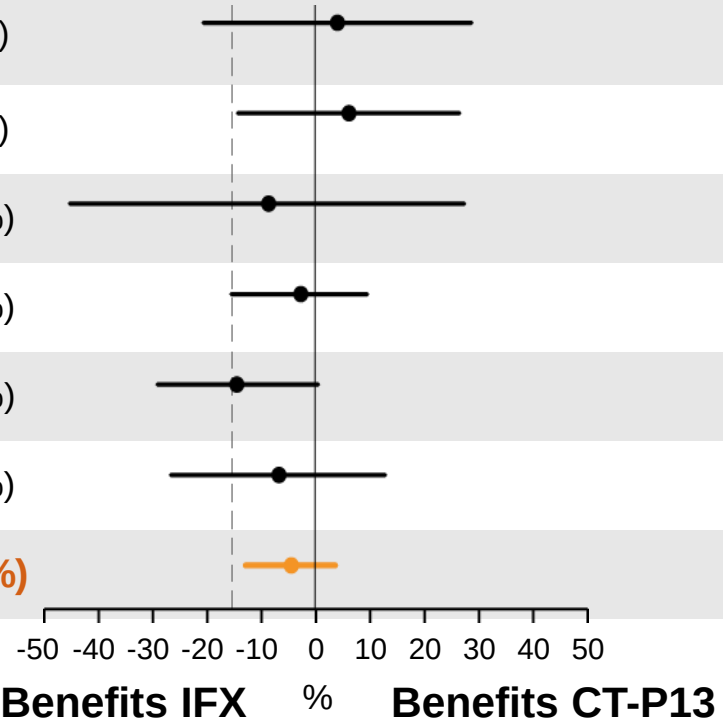


N=482

Jørgensen KK et al. Lancet 2017

Nor-Switch: Results

Diagnosis	IFX (n=202)	CT-P13 (n=206)	Adjusted Rate Difference (95% CI)
Rheumatoid arthritis	11 (36.7%)	9 (30.0%)	4.5% (-20.3-29.3%)
Spondyloarthritis	17 (39.5%)	14 (33.3%)	6.3% (-14.5-27.2%)
Psoriatic arthritis	7 (53.8%)	8 (61.5%)	-8.7% (-45.5-28.1%)
Ulcerative colitis	3 (9.1%)	5 (11.9%)	-2.6% (-15.2-10.0%)
Crohn's disease	14 (21.2%)	23 (36.5%)	-14.3% (-29.3-0.7%)
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%)**



Response:

IFX 53/202, 26.2%

CTP-13 61/206, 29.6%

ADA:

IFX: 7.1%, CTP-13: 7.9%

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Jørgensen KK et al. Lancet 2017

Long-Term Efficacy and Safety of CT-P13 after Switching from Originator IFX: Exploratory subgroup analyses in IBD in the NOR-Switch extension trial

- **Background:** Risk difference in CD was close to non-inferiority margin, though not powered for demonstrating non-inferiority for individual diagnoses
- **Methods:** 26-week open label extension trial from switch at week 52
  - Primary endpoint: overall disease worsening during follow up
- **Results:** 380 of 438 pts from main trial entered extension phase
  - Disease worsening occurred in 16.8% in maintenance group, 11.6% switch
  - Incidence of AE, ADAb, PROs comparable in both groups

NOR-Switch Extension Trial

- **Conclusions:**
  - No difference seen between CT-P13 vs switch from IFX to CT-P13
  - Exploratory subgroup CD and UC analysis showed similarity in efficacy, safety, immunogenicity

Diagnosis	Maintenance (n=190)	Switch (n=173)	Risk difference (95% CI)
Crohn's disease	13/63 (20.6%)	8/61 (13.1%)	7.9% (-5.2 to 21)
Ulcerative colitis	6/39 (15.4%)	1/35 (2.9%)	12.4% (-0.1 to 25)
Spondyloarthritis	3/38 (7.9%)	2/28 (7.1%)	0.6% (-12.2 to 13.5)
Rheumatoid arthritis	9/26 (34.6%)	6/27 (22.2%)	10.5% (-13.6 to 34.6)
Psoriatic arthritis	1/8 (12.5%)	3/9 (33.3%)	-20.8% (-59.1 to 17.6)

Suggests “switching for non-medical reasons” – we are not there yet…

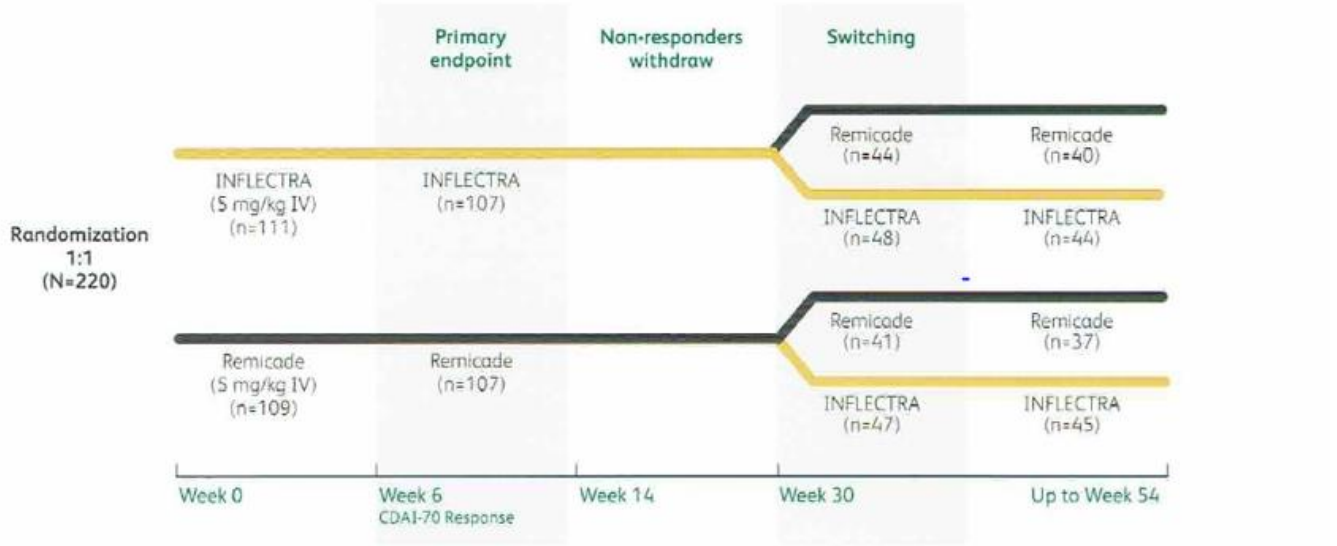
NCT02096861

- Muticenter trial to evaluate effects of multiple switching CT-P13 and originator
- 220 patients with active CD
- All naïve to prior TNF
- Primary endpoint: rate of >70-pt worsening CDAI week 6
- Secondary: remission rates, QOL, safety, ADA titers up to week 54

Kim YH et al. Gastroenterology 2017; 152:S65

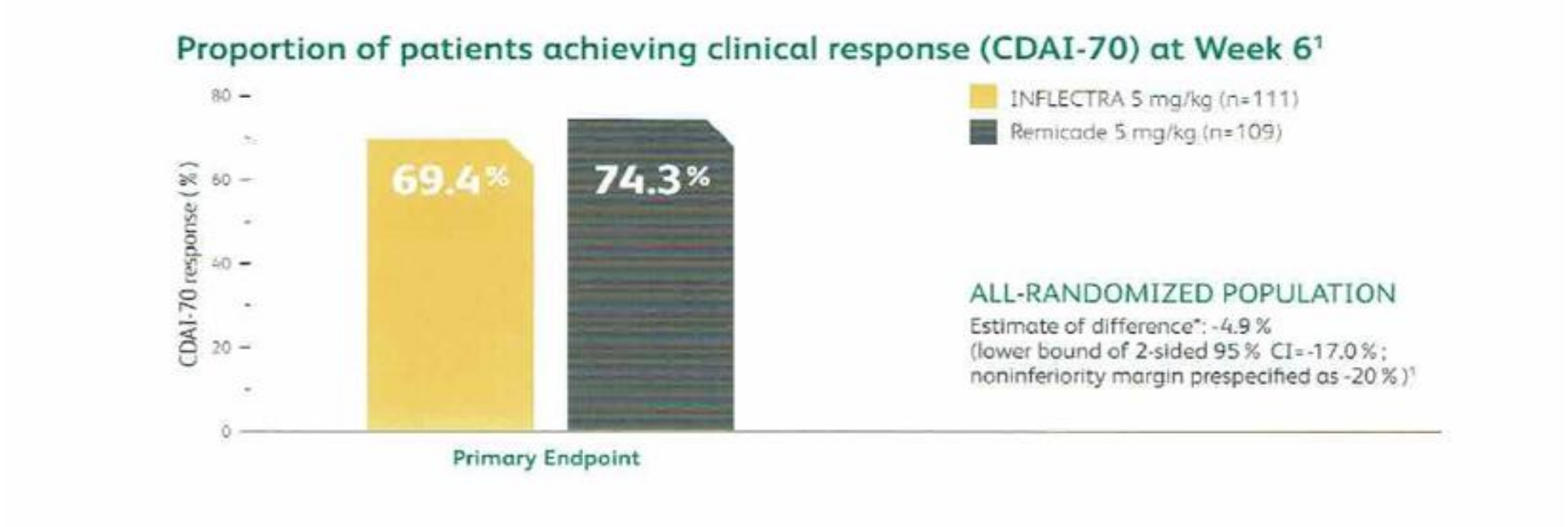
NCT02096861: Study Design

- Four-arm design:
  - Two arms randomized to originator; Two arms biosimilar
  - One originator and one biosimilar arm switched



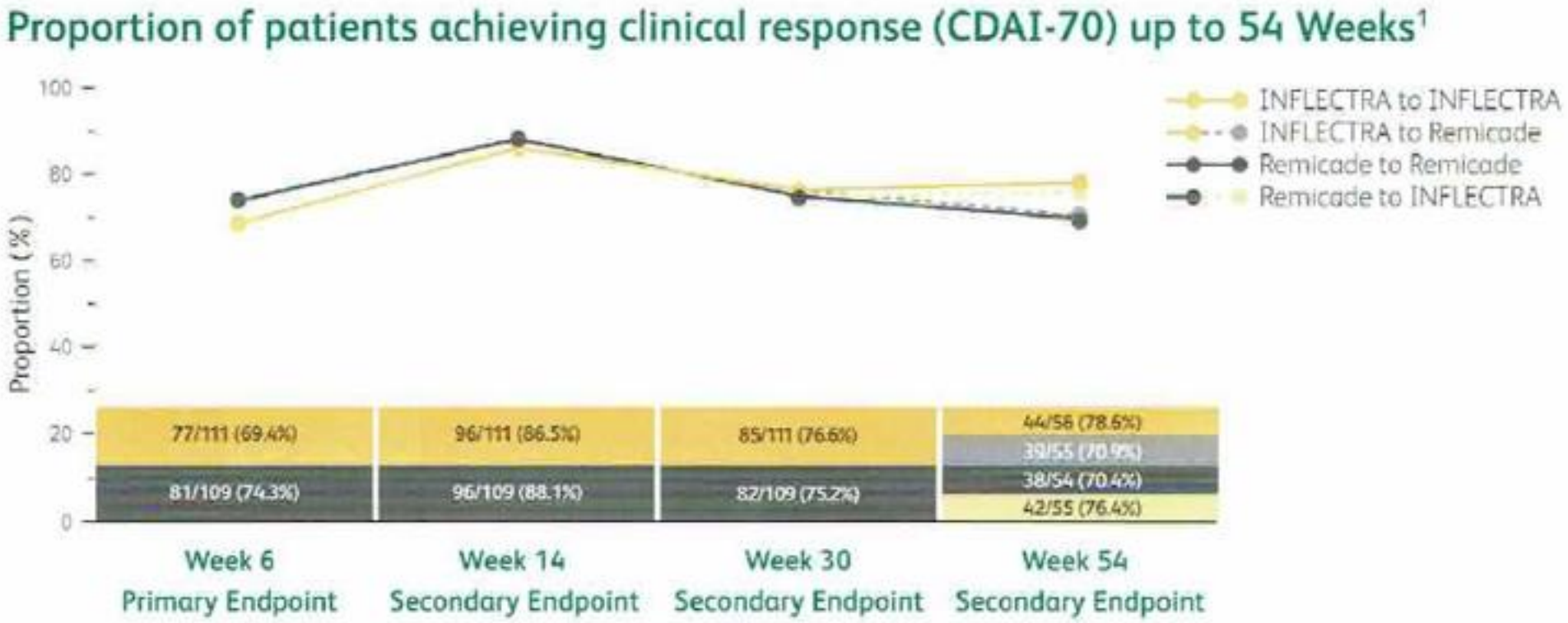
Kim YH et al. Gastroenterology 2017; 152:S65

NCT02096861: Primary Endpoint Results



Non-inferiority margin of -20%

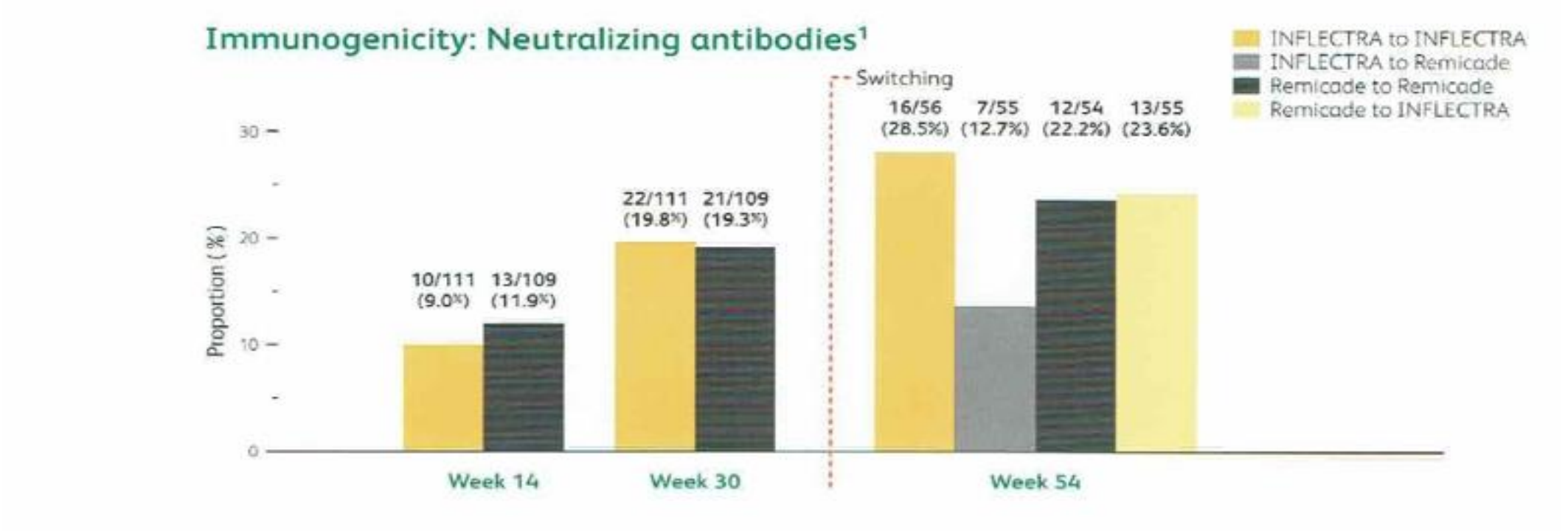
NCT02096861: Results, 54 weeks



Comparable clinical response among all groups

NCT02096861: Immunogenicity

Risk for immunogenicity after 1 switch



NCT02096861: Infusion Rxn, SAE

- No new or unexpected safety findings observed including:
  - Similar infusion-related reactions
  - Higher % treatment-emergent serious adverse events at 1 yr switch

Limitations of RCTs

- Non-inferiority study (15-20% margin)
  - 12% was clinically meaningful in superiority trial to support IMM
- Chronic sequential exposure, multiple switches
  - Higher rates sensitization, ADA formation, reduced rates of response
- NOR-SWITCH:
  - Point-estimates aggregation of 5 different disease populations
  - Not powered for individual diseases
- NCT02096861:
  - TNF-naïve different than substitution TNF-exposed

Economic Considerations of Biosimilars

- Generic medications: $1 - 4 million to develop
- New biologics: $1.9 billion to develop, with < 10% introduced successfully into market
- Biosimilars: $100 – 250 million to develop, takes 7-8 years before available for clinical use
- Over 650 biosimilars in development - >50% preclinical

Ha C and Kornbluth A. Inflamm Bowel Dis 2016

Economic Considerations of Biosimilars

- Biosimilars *may* have:
  - Potential for cost savings
  - Increase patient access for biologics
- Payers: price discount
- Patient: reduced out-of-pocket? Increased tx access?
- Psychological component for care providers, patients:
  - Perceive less expensive care as less effective

Ha C and Kornbluth A. Inflamm Bowel Dis 2016

Biosimilar Policy Options: Payers

- Watchful waiting
- Use product listing agreements to manage uncertainty
  - Downward pressure on price
- Provide access for one-time *informed* substitution with biosimilar to any patient
- Mandate manufacturers to provide evidence of interchangeability

Conclusions

- No clinically meaningful differences between originator and biosimilar
- Extrapolation data & recent IBD studies: OK
- Interchangeability: Remains a big concern
  - NOT currently approved by FDA
- Non-medical switching, substitution: NO
- Careful with payers – what they approve today may not be tomorrow

THANK YOU

Email: anita.afzali@osumc.edu