L'esperienza del gastroenterologo con i biosimilari di anticorpi monoclonali

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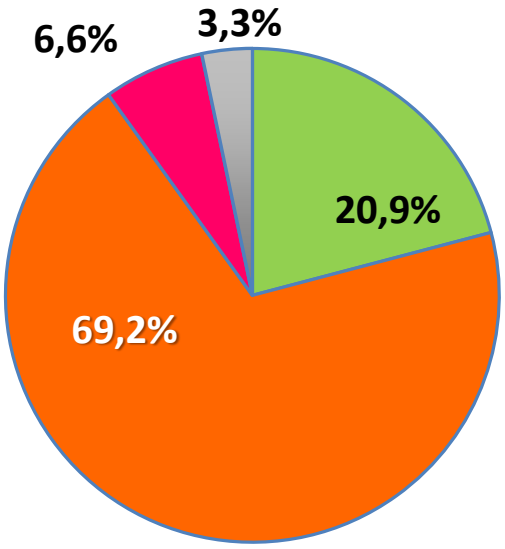
Evolution of expert opinion

Survey on the knowledge of biosimilars in immune-mediated diseases

- Web-based questionnaire of ECCO members – 307 responders[1]
- 68% worked in a university hospital[2]
- 87% autonomously prescribe mAb for >2 years[1]

Knowledge of biosimilars

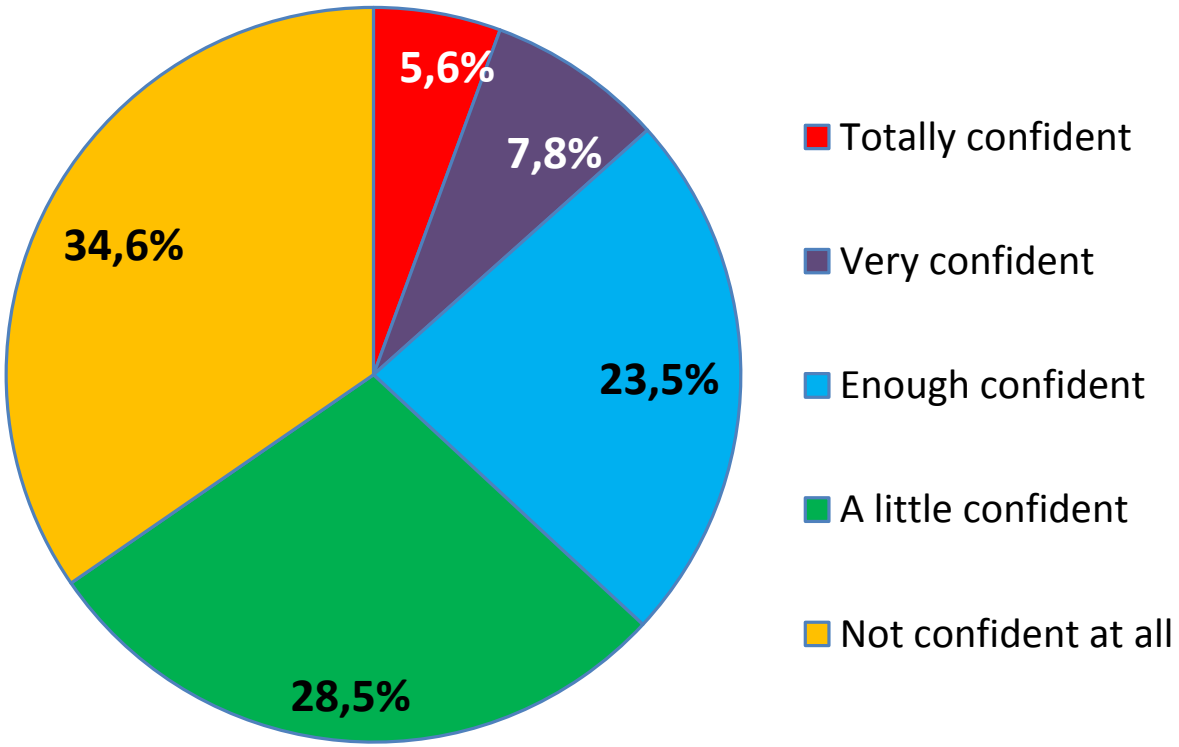
How would you best define a monoclonal antibody (mAb) biosimilar? This is…



- A copy of a biological agent, whose patent is expired, which is identical to the originator *(a generic of a biological)*
- A copy of a biological agent, whose patent is expired, which closely resembles but is not equal to the originator
- A copy of a biological agent, whose patent is expired, which is based on the originator and is as similar to it as adalimumab is similar to infliximab *(like a new member of the anti-TNF class)*
- I do not know

Confidence in biosimilars

Do you feel confident in using biosimilars in your everyday clinical practice?

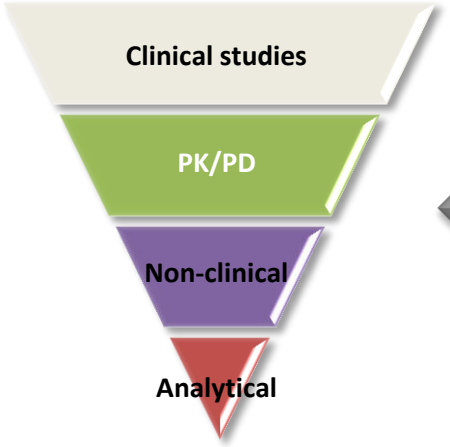


How can we explain this state of mind?

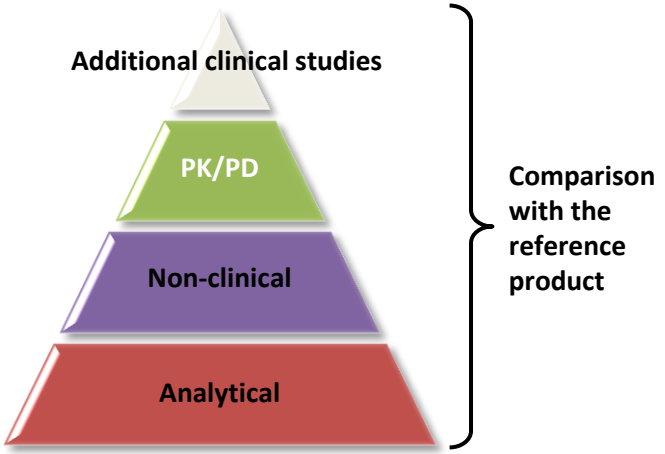
- GI community was not ready
- Gaps in knowledge

First brick of the evolution:
the developmental approach for biosimilars

Originator development



Biosimilar development



- Several trials >1000 pts, replication needed
- Primary endpoint: ACR20 - 6 months min
- Secondary: ACR 50, ACR70, DAS28, remission, HAQ
- Structural damage (6–12 months with 12 month F/U)

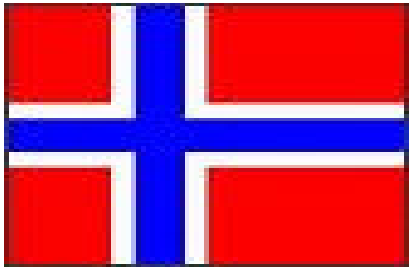
- One study 200–600 pts
- Primary endpoint at 3–6 months: DAS28
- Secondary: averaged score over time, ACR20, 50, etc.
- Immunogenicity as a key parameter

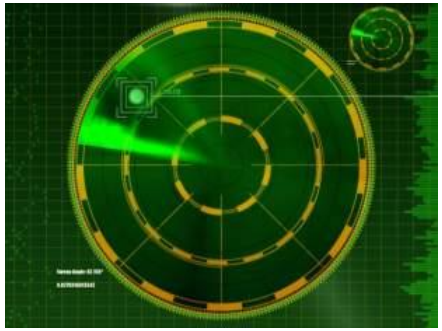
Second brick of the evolution:
the science of extrapolation

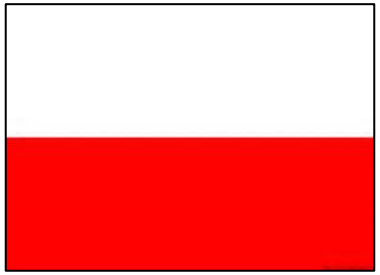
Extrapolation for biosimilars travels along a path long traveled by originator biologics

- *Approval of indications based on extrapolation of data is neither a "bonus" granted by regulators to biosimilar developers, nor is it driven by economic considerations to decrease the cost of biosimilars; rather,* ***extrapolation is a logical consequence of the biosimilar concept that has been successfully implemented in the EU.***
- ***Extrapolation has already been exercised for many years with changes in the manufacturing process for biologicals****, where often more than minor changes were observed, and virtually all mAbs have been subject to several changes after authorisation –* ***a fact that is not well known by clinicians and that is rarely explicitly communicated****.*

Extensive real-life experience in other European countries in naive patients





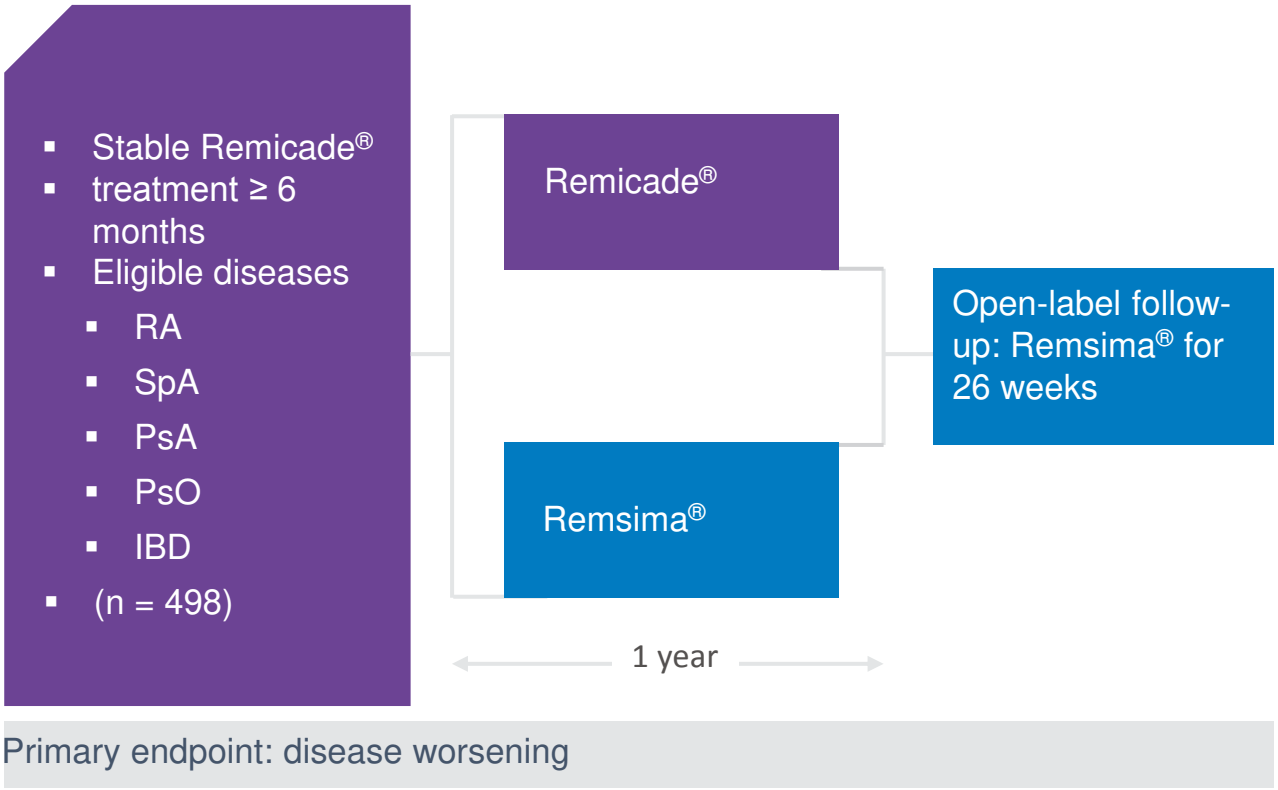


Summary of clinical experience with CT-P13 in IBD: naïve patients

Country, first author	Patient numbers	Efficacy	Safety
South Korea, Park	173 (CD=95, UC=78)	Response: 79.5 and 72.2% in CD and UC at week 30 Remission: 59.0 and 37.0% in CD and UC at week 30	No unexpected AEs, well tolerated
South Korea, Jung	110 (CD=59, UC=51)	Naïve: response 95.5 and 91.3% in CD and UC at week 30; remission 77.3 and 47.8% in CD and UC at week 30	AEs related to CT-P13 occurred in 11.8% of UC pts
South Korea, Kang	17 (CD=8, UC=9)	Response: Mayo/CDAI: ~87.5% at week 8 in switch and naïve	Arthralgia in 1 UC patient
Hungary, Gecse	90 (CD=57, UC=33)	Significant decrease in CDAI and partial Mayo score	Four allergic reactions
Hungary, Molnar	12 (UC)	Mucosal healing: 78% after induction therapy	Not reported
Hungary, Farkas	39 (CD=18, UC=21)	Response: 37.5% and 20% in CD and UC at week 8 Remission: 50% and 66.7% in CD and UC at week 8	Not reported
Norway, Jahnsen	78 (CD=46, UC=32)	Remission: 79 and 56% in CD and UC at week 14	No unexpected AEs
Poland, Sieczkowska	12 (paediatric CD)	Paediatric CDAI: 52.5 →5 after induction dose	AEs observed in 2/12 (17%)
Poland, Jarzebicka	6 (paediatric UC)	Paediatric UCAI: 47.5 at initiation→28.3 at week 10	Not reported
Ireland, Murphy	36 (14 for CT-P13, 22 for RMP)	Clinical efficacy results were not reported Surgery: 4 and 0 in CT-P13 and RMP-treated patients, respectively (in two cases, surgery was performed within 2 weeks and the remainder within 6 weeks of initiating CT-P13)	

NOR-SWITCH Study Design: the final answer?

NOR-SWITCH Study*: A Phase 4 Noninferiority Single-Arm Switch Study to Assess Safety and Efficacy of Switching From Remicade® to Remsima®



Primary endpoint: disease worsening

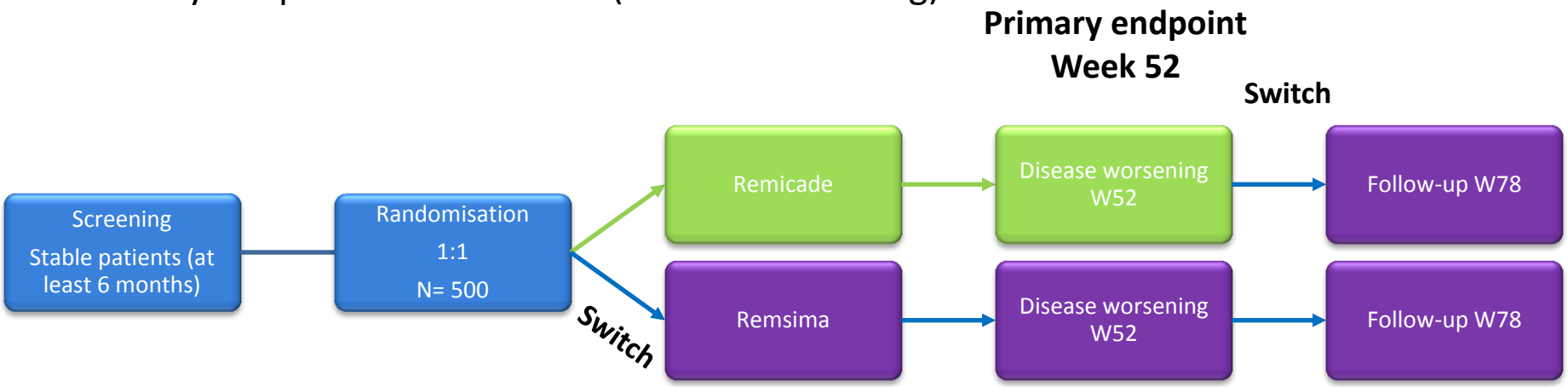
*Primary data is expected to be presented at UEG Week 2016.

SPA = spondyloarthritis; PsA = psoriatic arthritis; IBD = inflammatory bowel disease.

1. US National Institutes of Health. ClinicalTrials.gov. www.clinicaltrials.gov. Accessed May 19, 2016. 2. Dörner T, et al. Ann Rheum Dis. 2016;0:1-9.

NOR- SWITCH Study design

- Exploring switching for non-medical reasons
- Primary endpoint: Effectiveness (disease worsening)



A randomized, double-blind, parallel-group study to evaluate the safety and efficacy of switching from innovator infliximab to biosimilar infliximab compared with continued treatment with innovator infliximab in patients with rheumatoid arthritis, spondylarthritis, psoriatic arthritis, ulcerative colitis, Crohn's disease and chronic plaque psoriasis

Assumption : 30% worsening in 52 weeks
Non-inferiority margin:15%

Open Label Follow-up

NOR SWITCH

Courtesy of Prof. J. Jahnsen

Primary endpoint: 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%)

Non-inferiority margin: 15%

NOR SWITCH

Courtesy of Prof. J. Jahnsen

PRospective Observational cohort Study on patients with Inflammatory bowel disease receiving Therapy with BIOsimilars (PROSIT-BIO)

Multicenter real-life study across referral centers in Italy

All consecutive patients undergoing therapy with CT-P13 were prospectively included since March 2015

Study population

1. Naïve to infliximab (never exposed)
2. Previously exposed to anti-TNF
3. Switched from originator

Methods

Study Objectives

- To evaluate the safety of IFX biosimilars in IBD patients
- To assess the efficacy of IFX biosimilars
- Endpoints:
  - Safety at 12 months → **primary endpoint**
  - Efficacy of biosimilars at 12 months and at last observation
  - Immunogenicity (infusion reactions, anti-drug antibodies)
  - Predictive factors for efficacy and safety

Methods

Study definitions

Safety

Number of patients with adverse events
(any AE; infusion reactions; and AEs leading to discontinuation)

Efficacy

UC

Response: >30% AND 3 points reduction in MCS
Remission: MCS <2 with no partial scores >1

CD

Response: 3-point in HBI OR 100-point reduction in CDAI
Remission: HBI ≤ 4 or CDAI <150

Immunogenicity

Dosage of TL and ADA (to be determined by further analyses, still ongoing)

Methods

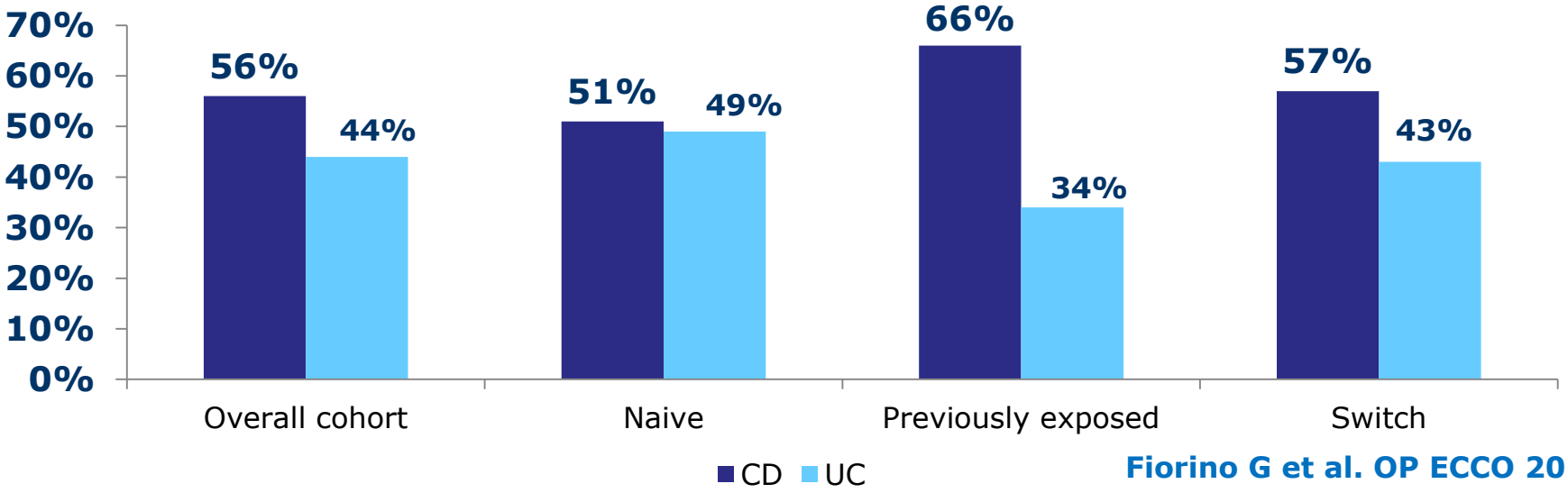
Statistical plan

- Descriptive analysis
- Comparison between the 3 study groups
- **For safety**: Incidence Rate Ratios were calculated (person-time of follow-up).
- **For efficacy:** primary failures, treatment persistency

Results

Study population

- **801 patients** enrolled in 33 referral Centers
- **462 patients** were **naïve to anti-TNFα**
- **193 patients** had a **previous exposure to one o more biologics (43** exposed to IFX originator**)**
- **146 patients** switched from IFX originator to CT-P13



Fiorino G et al. OP ECCO 2017

Results

Baseline characteristics

	Total Cohort (n=801)	Naïve (n=62)	Previously exposed (n=193)	Switch (n=146)	P value
Sex (females, %)	357 (45%)	212 (46%)	89 (46%)	56 (38%)	p=0.25
Age at diagnosis (yrs)	31.8 ± 13.8; 29 (22–41)	32.5 ± 13.6; 30.5 (22–41)	31.6 ± 14.2; 28 (21–43)	29.6 ± 13.8; 27.5 (19–38)	p=0.06
Duration of disease (yrs)	8.6 ± 8.5; 6 (2–13)	7.7 ± 7.8; 5 (2–11)	9.9 ± 10.6; 8 (4–16)	9.6 ± 6.9; 7 (5–13)	p<0.001
Active smokers	17%	18%	18%	12%	p=0.13
Combination with AZA/6-MP	21%	16%	24%	32%	p=<0.001
Follow-up time (months)	9.6 ± 6	9.6 ± 6	9.6 ± 6	10.8 ± 7.2	p<0.002

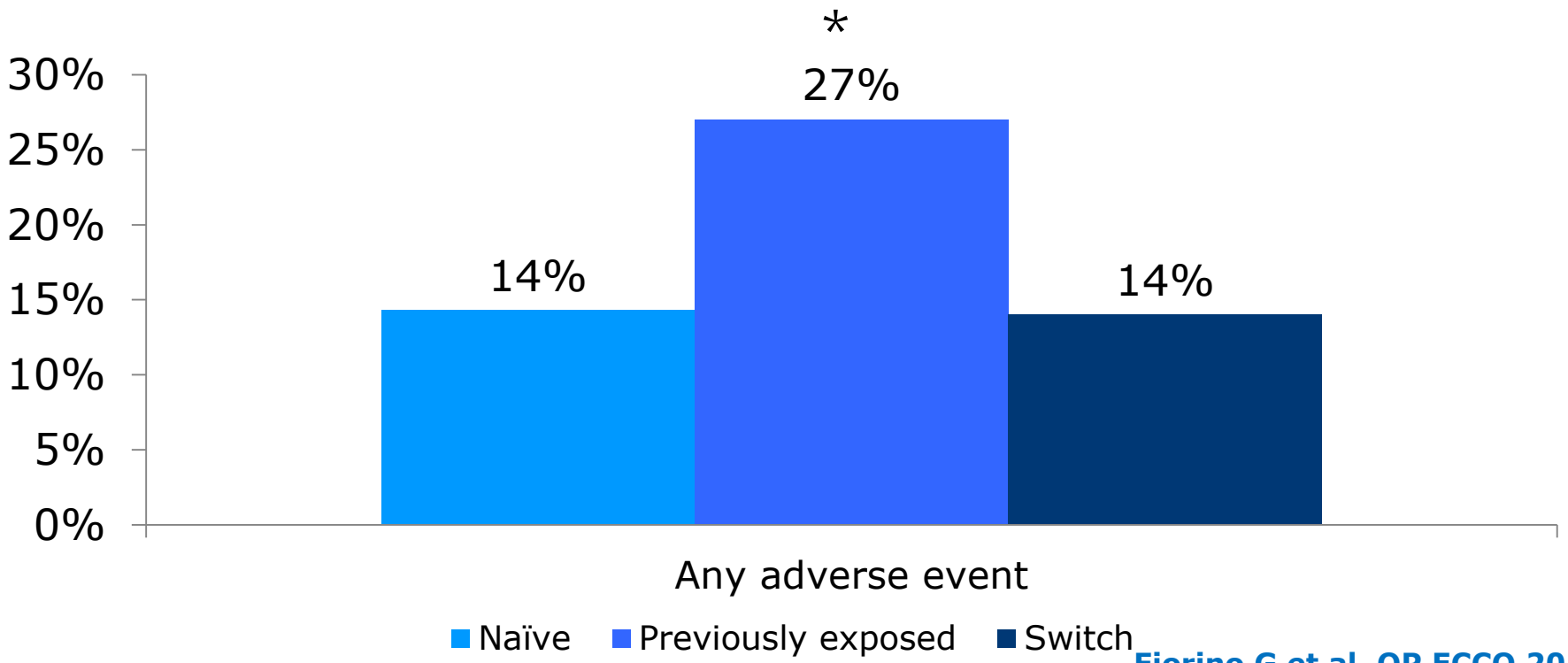
Data are presented as means ± SD, or percentages when appropriate.
The Chi-squared test, and the Kruskal-Wallis (equality-of-populations) rank test, were used for the statistical evaluations.

Results

Safety (any adverse events)

Incidence Rate Ratios

Naïve vs. Switched	**1.26** (0.76–2.20), p = NS
Naïve vs. Previously exposed	**0.51** (0.35–0.75), p < 0.001
Previously exposed vs. Switched	**2.48** (1.46–4.37), p < 0.001



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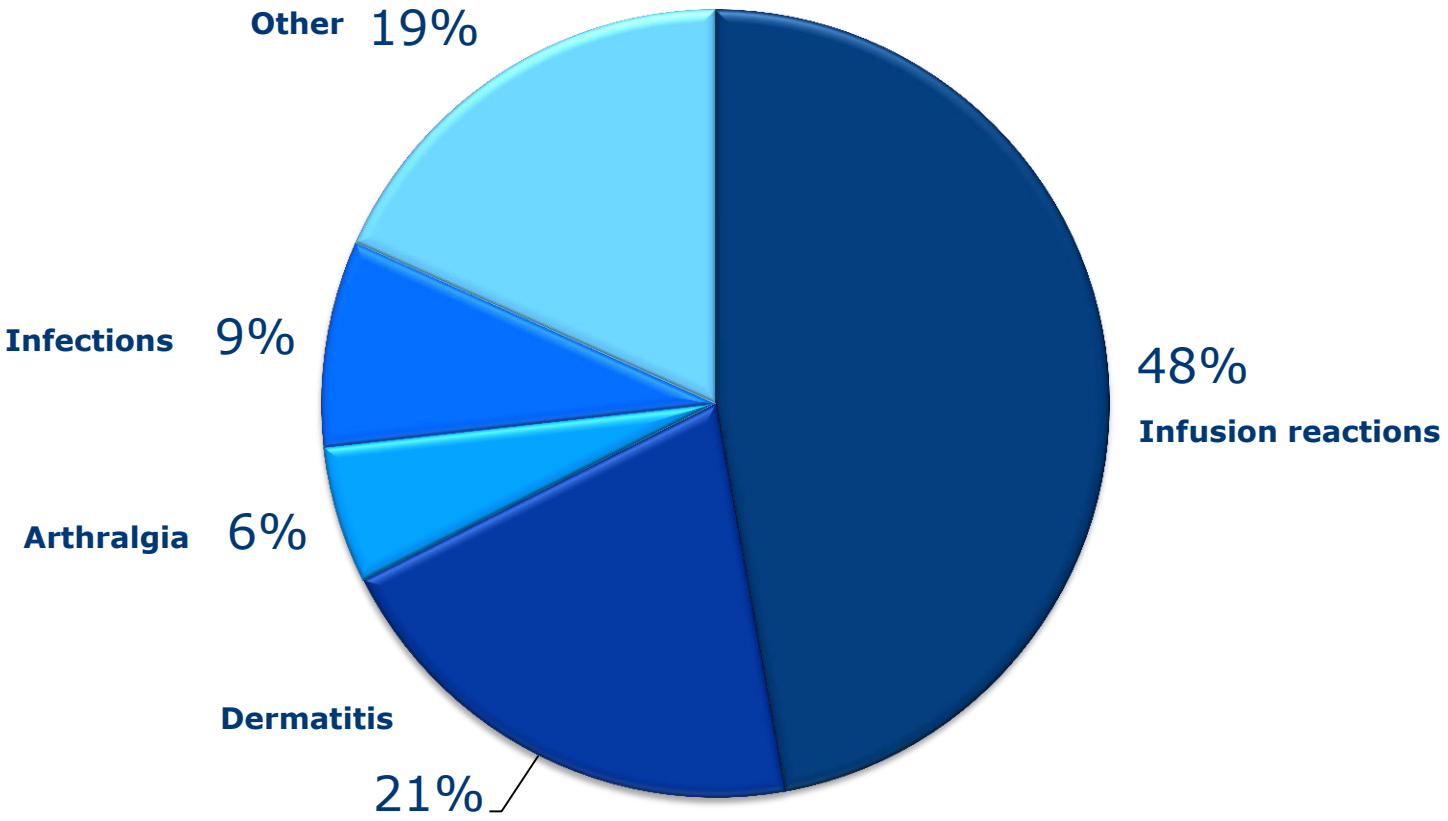
Results

Adverse events (n=139)



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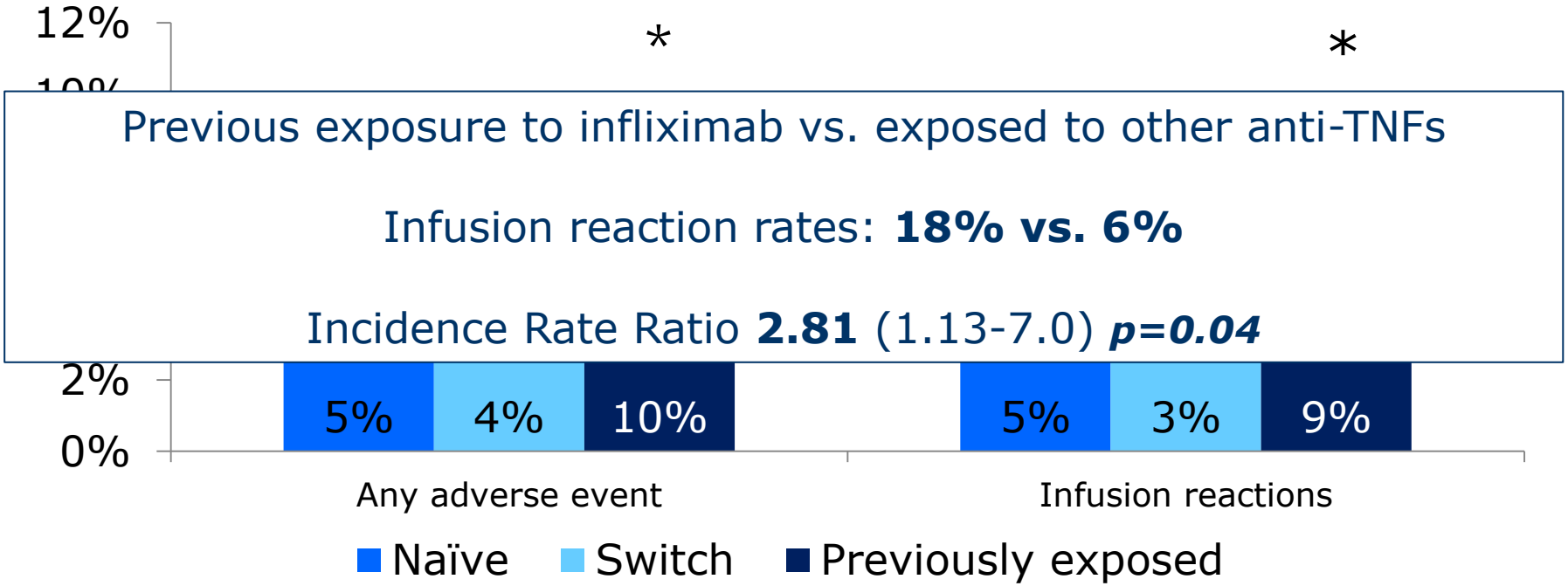
Adverse events leading to discontinuation

	Other AEs	P value	Infusion reactions	P value
Naive vs. previously exposed	IRR: **0.45** (0.23–1.89)	*0.015*	IRR: **0.58** (0.30–1.15)	*NS*
Naive vs. switch	IRR: **1.34** (0.52–4.06)	*NS*	IRR: **1.83** (0.69–6.17)	*NS*
Previously exposed vs. switch	IRR: **2.98** (1.14–9.05)	*0.015*	IRR: **3.17** (1.12–11.0)	*0.016*



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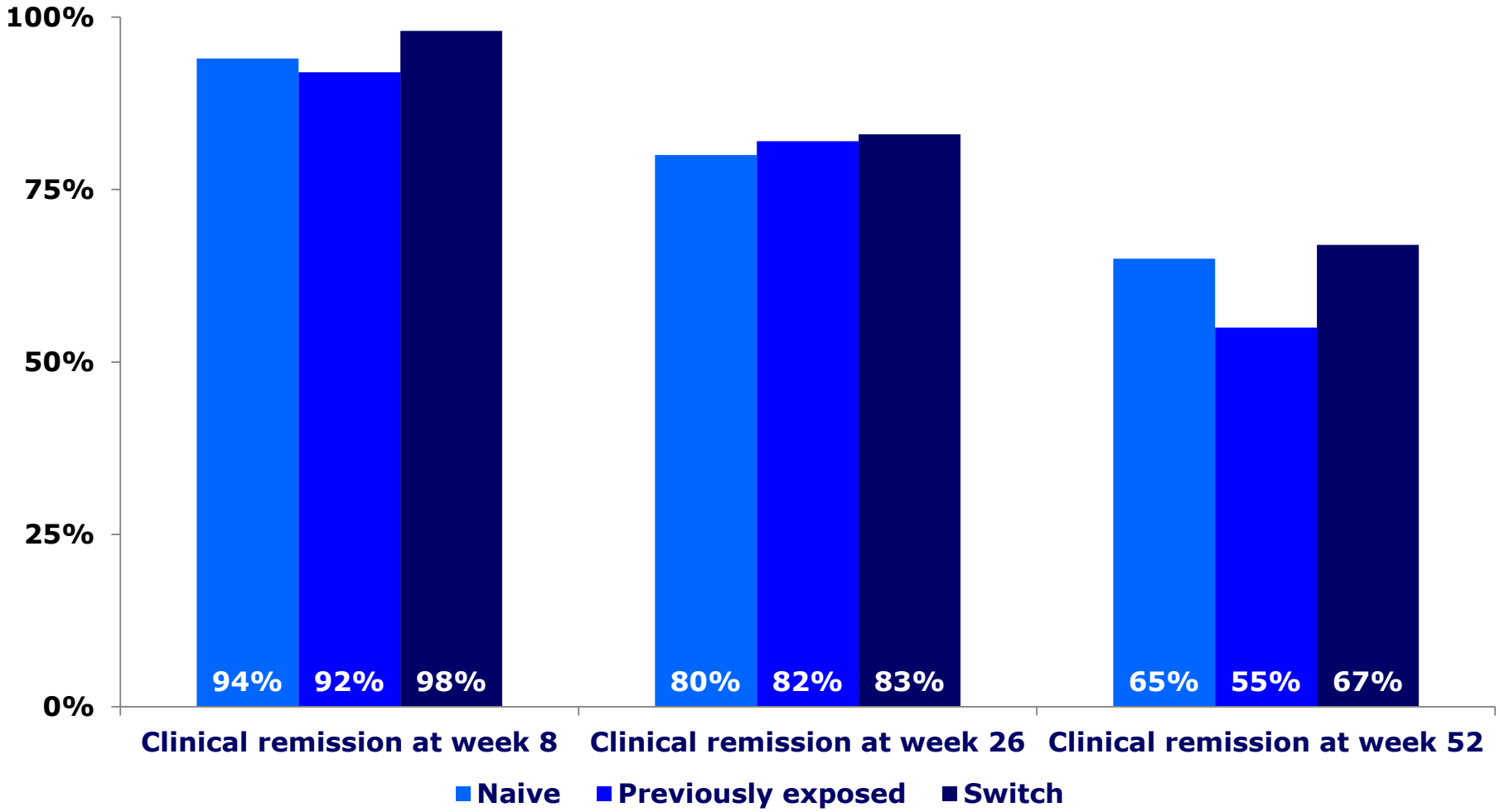
Results

Treatment persistency (n=633*)



*Patients with treatment duration > 8 weeks

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Clinical activity and Biomarkers

Crohn's disease (n=222)

Marker	Baseline	Week 52	p value
HBI	7.1 ± 3.4	3.2 ± 2	<0.01
SES-CD	10.1 ± 42	3 ± 2.6	<0.01
CRP (mg/L)	1.9 ± 1.7	0.9 ± 0.8	<0.01
Fecal calprotectin (mg/kg)	565 ± 485	126 ± 133	<0.01

Ulcerative colitis (n=89)

Marker	Baseline	Week 52	p value
Partial Mayo Score	6.1 ± 2.3	1.9 ± 1.8	<0.01
Mayo endoscopic subscore	2.1 ± 0.6	1.3 ± 0.8	<0.01
CRP (mg/L)	3 ± 2	0.9 ± 0.7	<0.01
Fecal calprotectin (mg/kg)	759 ± 516	72 ± 65	<0.01

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Predictors of loss of response

	Univariable Cox PH model		
Baseline parameter	**HR**	**(95% CI)**	**p-value**
Diagnosis (CD or UC)	0.71	(0.45–1.11)	0.14
Age*	1.00	(0.99–1.02)	0.84
Disease duration*	0.99	(0.96–1.02)	0.59
Current smoking	0.94	(0.51–1.71)	0.83
Combination therapy	0.79	(0.46–1.34)	0.38

PH, proportional hazards; HR, hazard ratio; CI, confidence interval; CD, Crohn's disease; UC, ulcerative colitis.
Symbol: *per 1-year increase.

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Conclusions

- **This is currently the largest cohort enrolling IBD patients treated by CT-P13**
- **No significant issues in terms of safety raised from the study population**
- **The infusion reaction rates observed in patients previously exposed to anti-TNF is in line with the literature data on the originator**
- **Efficacy profile seems to be in line with IFX originator**
- **The safety and efficacy profile of CT-P13 is not different from the originator in a real-life setting**

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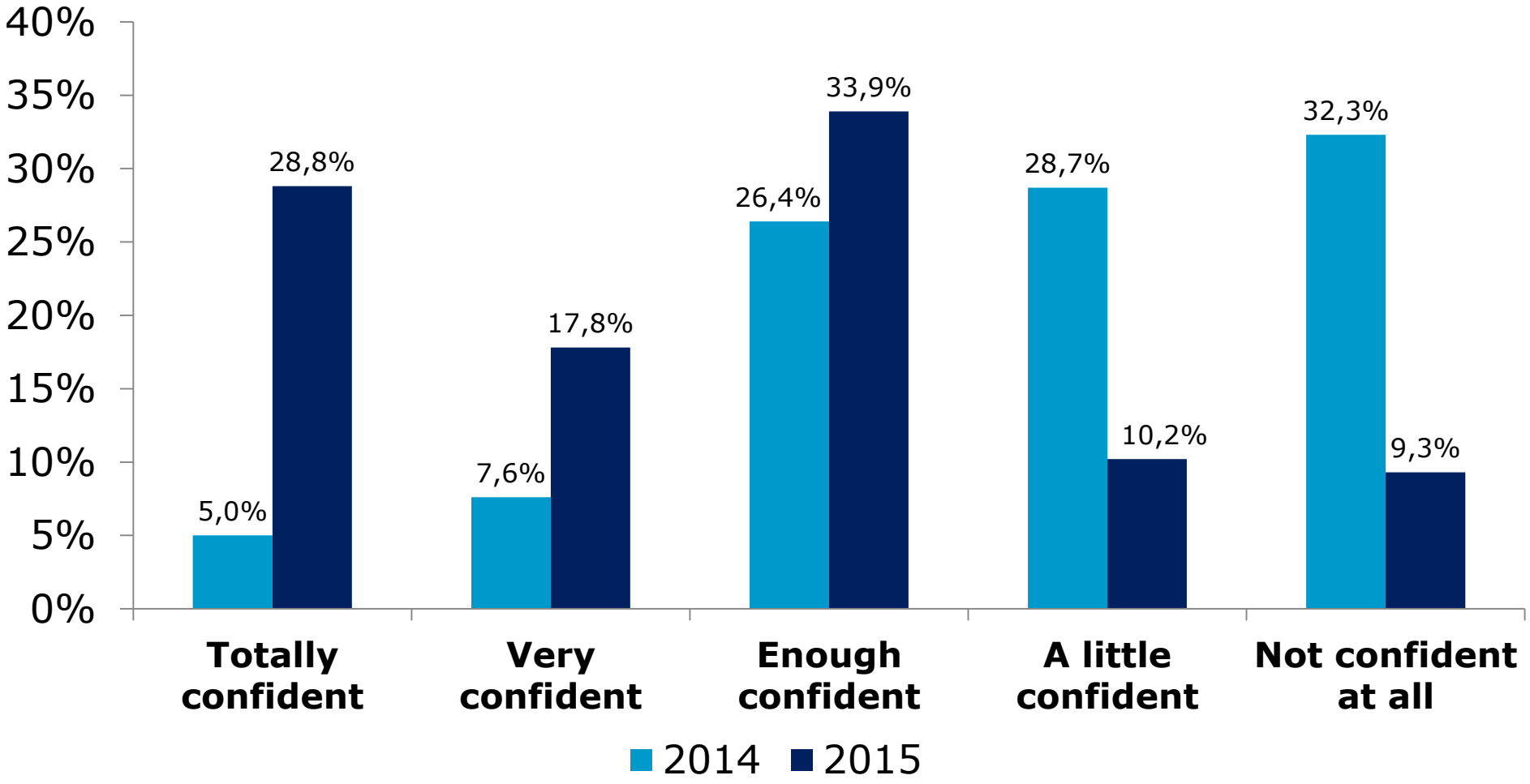
Do you feel confident in using biosimilars in your everyday clinical practice?



ECCO statements

1. Biosimilarity is more sensitively characterised by performing suitable ***in vitro* assays than clinical studies**.

2. Clinical studies of equivalence in **the most sensitive indication** can provide the **basis for extrapolation**. Therefore data for the usage of ***biosimilars in IBD can be extrapolated from another sensitive indication.***

3 . When a biosimilar product is registered in the EU, **it is considered to be as efficacious as the reference product** when used in accordance with the information provided in the Summary of Product Characteristics.

4. Demonstration of **safety of biosimilars** requires large observational studies with long-term follow-up in IBD patients. This should be supplemented by **registries** supported by all involved stakeholders [manufacturer, healthcare professionals and patients' associations].

ECCO statements (2)

15. **Adverse events and loss of response due to immunogenicity** to a biologic drug **cannot be expected to be overcome with a biosimilar** of the same molecule.

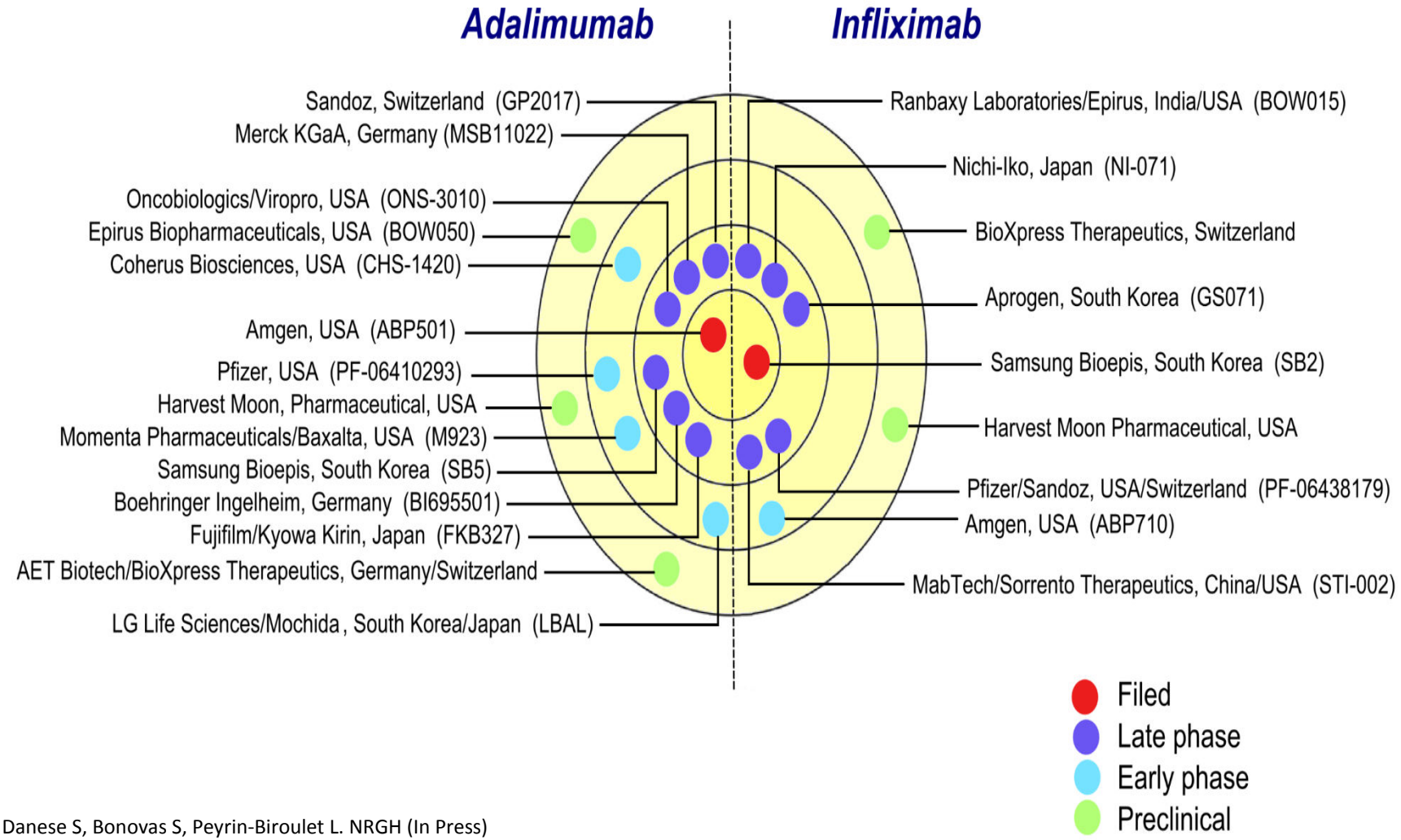
6. **As for all biologics, traceability** should be based on a robust pharmacovigilance system and the manufacturing risk management plan.

7. **Switching from the originator to a biosimilar in patients with IBD is acceptable**. Studies of switching can provide valuable evidence for safety and efficacy. Scientific and clinical evidence **is lacking regarding reverse switching, multiple switching, and cross-switching** among biosimilars in IBD patients.

8. Switching from originator to a biosimilar should be performed following appropriate discussion between physicians, nurses, pharmacists, and patients, and according to national recommendation. The IBD nurse can play a key role in communicating the importance and equivalence of biosimilar therapy.

Only the beginning of the story?

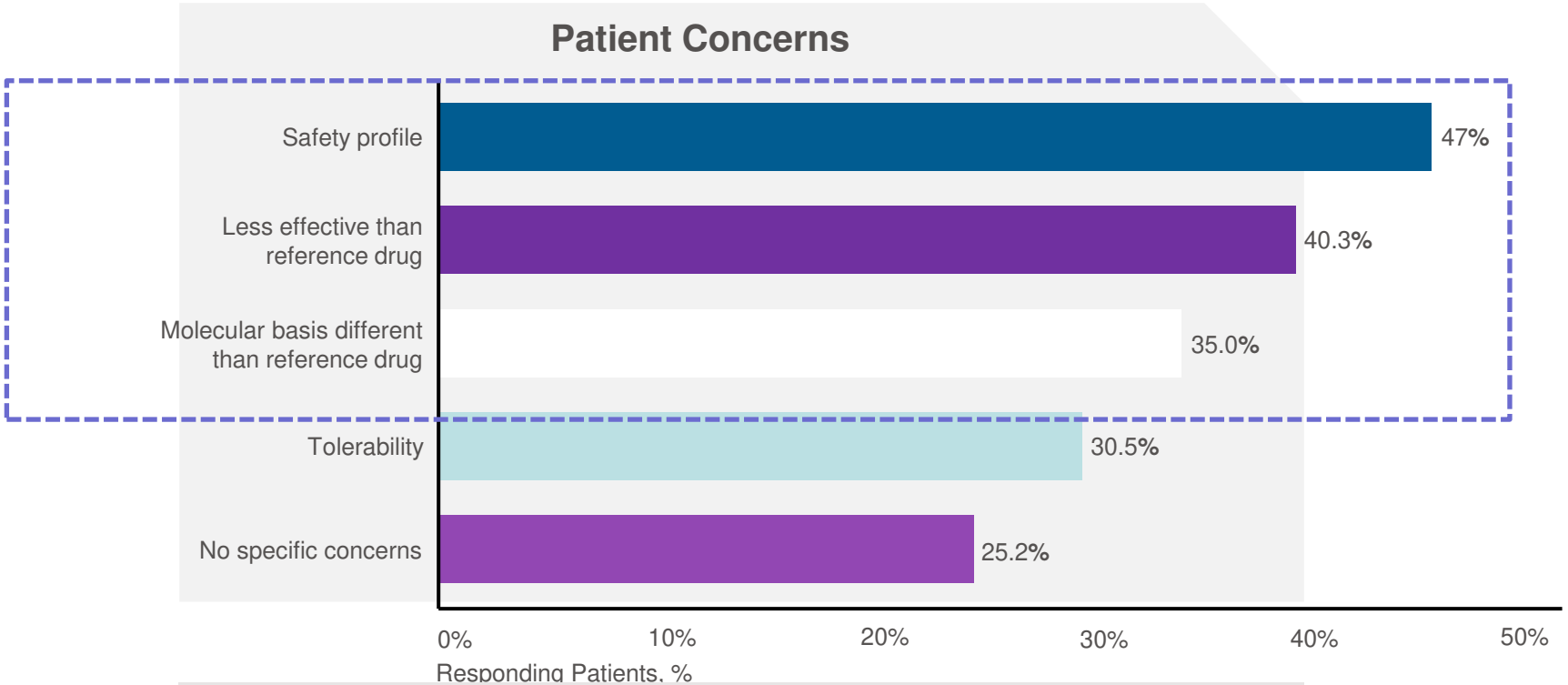
Biosimilars for adalimumab and infliximab in the pipeline, March 2016.



Danese S, Bonovas S, Peyrin-Biroulet L. NRGH (In Press)

Based on a 2015 Survey, Opportunity Exists for Patient Education About Biosimilars

The majority of patients (62%) had never heard of biosimilars



- Patients wished to be informed and involved in decision making:
  - 39.9% felt that patients should be systematically informed
  - 26.7% felt that patient associations should be informed

*Respondents could choose more than 1 response. 14 question anonymous web-based survey developed and translated into nine languages and conducted November 2014 through October 2015 on the website of EFCCA; N=1181.
EFCCA, European Federation of Crohn's and Ulcerative Colitis Associations.
Peyrin-Biroulet L, et al. ECCO 2016, P432.

Biosimilars of adalimumab: next challenge

Author	Adalimumab biosimilar	Disease	Number of patients	Primary outcome measure	Results (biosimilar vs. RP)
Papp et al.	ABP 501	Plaque psoriasis	350	PASI % improvement	80.9% vs. 83.1% at week 16
Papp et al.	ABP 501	Plaque psoriasis	350	PASI % improvement	87.2% (ABP 501/ABP 501), 88.1% (RP/RP) 85.8% (RP/ABP 501) at week 50
Cohen et al.	ABP 501	RA	526	RR of ACR20 at week 24	74.6% (ABP 501) 72.4% (RP)
Cohen et al.	BI 695501	RA	645	ACR 20 response at week 12 and 24	67.0% and 61.1% at week 12 69.0% and 64.5% at week 24
Blauvelt et al.	GP2017	Psoriasis	465	PASI improvement	66.8% and 65.0% at week 16
Weinblatt et al.	SB5	RA	542	ACR20 improvement at week 24	72.4% vs. 72.2%
Jani et al	ZRC-3197 (India)	RA	210	ACR20 response at week 12.	Week 12 ACR20 12: 82% vs. 79.2% ACR50: 46%, vs. 43.4% ACR70: 14% vs. 15.1%
Jamshidi et al	CinnoRA®, (CinnaGen, Iran)	RA	136	DAS28-ESR/EULAR response at weeks12 and 24	Week 12 DAS28-ESR: 2.95 ±1.30 vs 2.96 ±1.41 EULAR: 97% vs 89% Week 24 DAS28-ESR: 2.58 ±1.06 vs 2.55 ±1.14 EULAR: 98% vs 98%

Abbreviations: RCT=Randomized controlled trial; RA= rheumatoid arthritis; PASI=Psoriasis Area Severity Index; ACR=American College of Rheumatology; RP= reference product

Challenges in using biosimilars

- Is there an ideal patient for biosimilars?
- Is cross-switching applicable?
- How to choose a biosimilar vs. another?

Conclusions

- Biosimilars are as effective and safe as the originator in IBD patients
- Real-life data have confirmed the preclinical data on bioequivalence of biosimilars
- Cross-switching among biosimilars still needs some evidence to be supported
- Patients (and also doctors) need to be educated on the opportunities given by biosimilars in the next future