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Preliminary data from the prospective ABIRISK IBD cohort
Clinical response and anti-drug antibodies

The research leading to these results has received support from the Innovative Medicines Initiative Joint Undertaking under grant agreement n° [115303], resources of which are composed of financial contribution from the European Union's Seventh Framework Programme (FP7/2007-2013) and EFPIA companies' in kind contribution.
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The classical objectives of IBD management

- ✓ **To induce and maintain remission**
  - Resulting in decreased hospitalizations and surgery
- ✓ **To prevent complications**
  - Including treatment adverse events
- ✓ **Resulting in improved quality of life**

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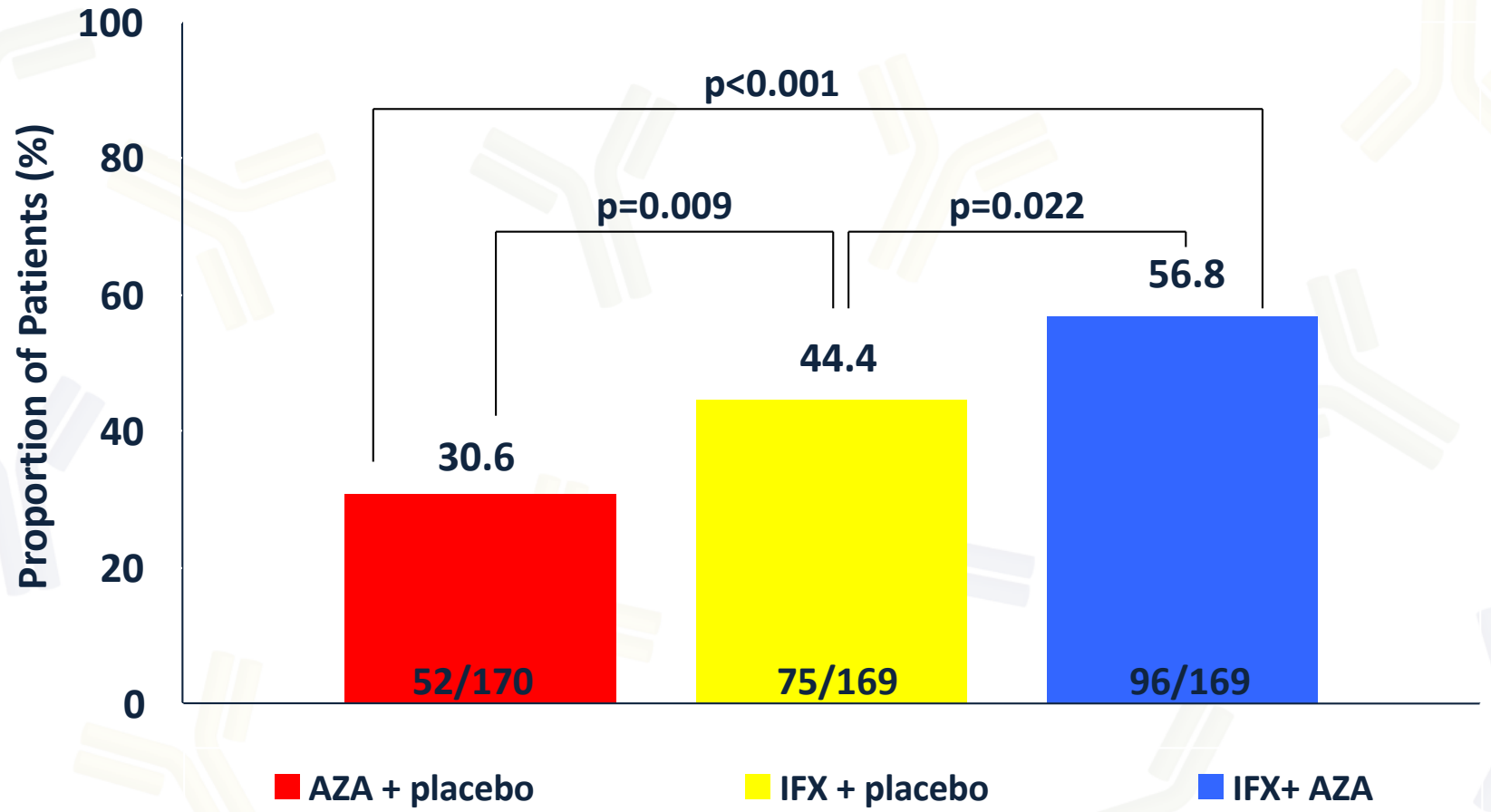
The SONIC Study

Primary Endpoint: remission without steroid at 26 weeks



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Am J Gastroenterol. 2008;103(Suppl1):Abstract 1117

Anti-TNF failures in IBD

- Approximately 1/3 of patients do not show primary response and 2/3 do not show remission
- In placebo-controlled trials, about 50% of patients lost response over 1 year
- Treatment optimization with increased dose or shortened interval allowed to recover response in 50-90% of the patients
- In literature reviews, yearly loss of response despite optimization was 13% for IFX and 20% for ADA

Allez M, et al. JCC 2010
Gisbert JP, Panes J. Am J Gastroenterol. 2009
Billioud V, et al. Am J Gastroenterol 2011

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Immunogenicity

Presence of antibodies against anti-TNF mAbs confers a risk of discontinuation of treatment and a risk of development of hypersensitivity reactions in all immune-mediated inflammatory diseases

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Factors affecting the pharmacokinetics of anti-TNF mAbs

	Impact on pharmacokinetics
Presence of ADAs	Decreases serum (mAbs) Threefold-increased clearance Worse clinical outcomes
Concomitant use of IS	Reduces ADA formation Increases serum (mAbs) Decreases mAbs clearance Better clinical outcomes
High baseline (TNF-α)	May decrease (mAbs) by increasing clearance
Low albumin	Increases clearance Worse clinical outcomes
High baseline CRP	Increases clearance
Body size	High body mass index may increase clearance
Gender	Males have higher clearance

Ordas I et al, Clin Pharm Ther 2012

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IBD prospective cohort

➢ Primary objective

- To find early bio-markers able to predict immunization against the biopharmaceuticals within the first year of treatment.

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IBD prospective cohort

➢ Secondary objectives

- To find bio-markers able to predict long-term immunization against the biopharmaceuticals
- To analyze the correlation between immunization to biopharmaceuticals with hypersensitivity reactions, loss of response and biopharmaceuticals levels
- To identify molecular and cellular biomarkers associated with the development of anti-drug-antibodies (ADA)
- To be able to associate an immunological signature to patients with anti-drug-antibodies

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IBD prospective cohort

- **Study design**
  - Multicenter, prospective, **non interventional study** for collection of biological samples (blood) to be used for in vitro biomarker assay(s)

- **Main selection criteria**
  - **Patients in the first line of anti-TNF therapy** including adalimumab or infliximab

- **Total expected number of patients :**
  - 200 patients are to be enrolled to have at least 50 ADA+ patients for the final evaluation in 17 centers (France, Belgium and Israel)

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IBD prospective cohort

Judgment criteria

- **Immunization against the BP is defined by the presence of ADA within the first 12 months**
- Quantification of ADA at W0, W6, W12 and W52
- Clinical response and remission at W6, W12, W52 and at withdrawal if the drug is discontinued
- ADA-associated adverse clinical events at any time points

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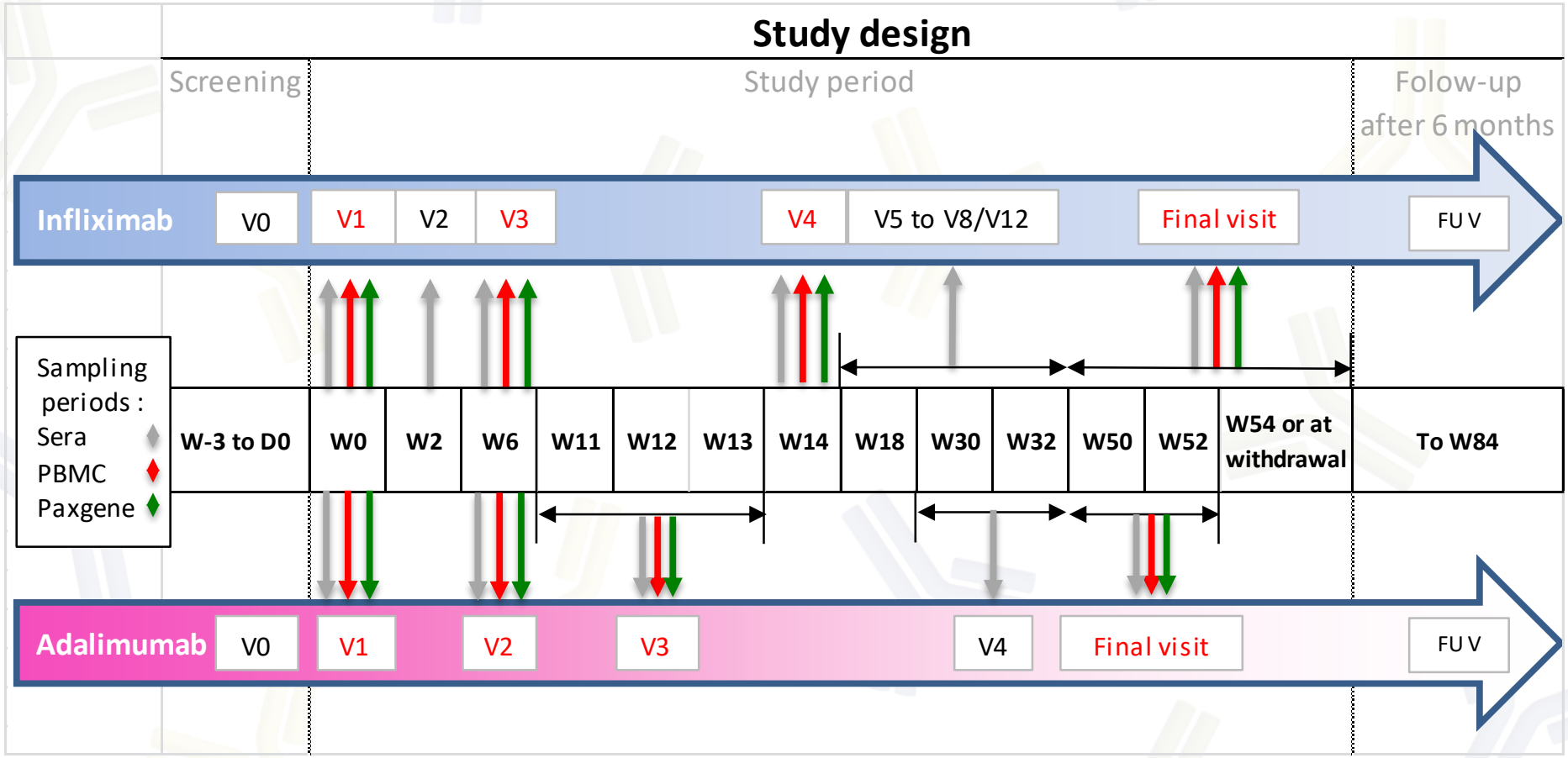
IBD prospective cohort



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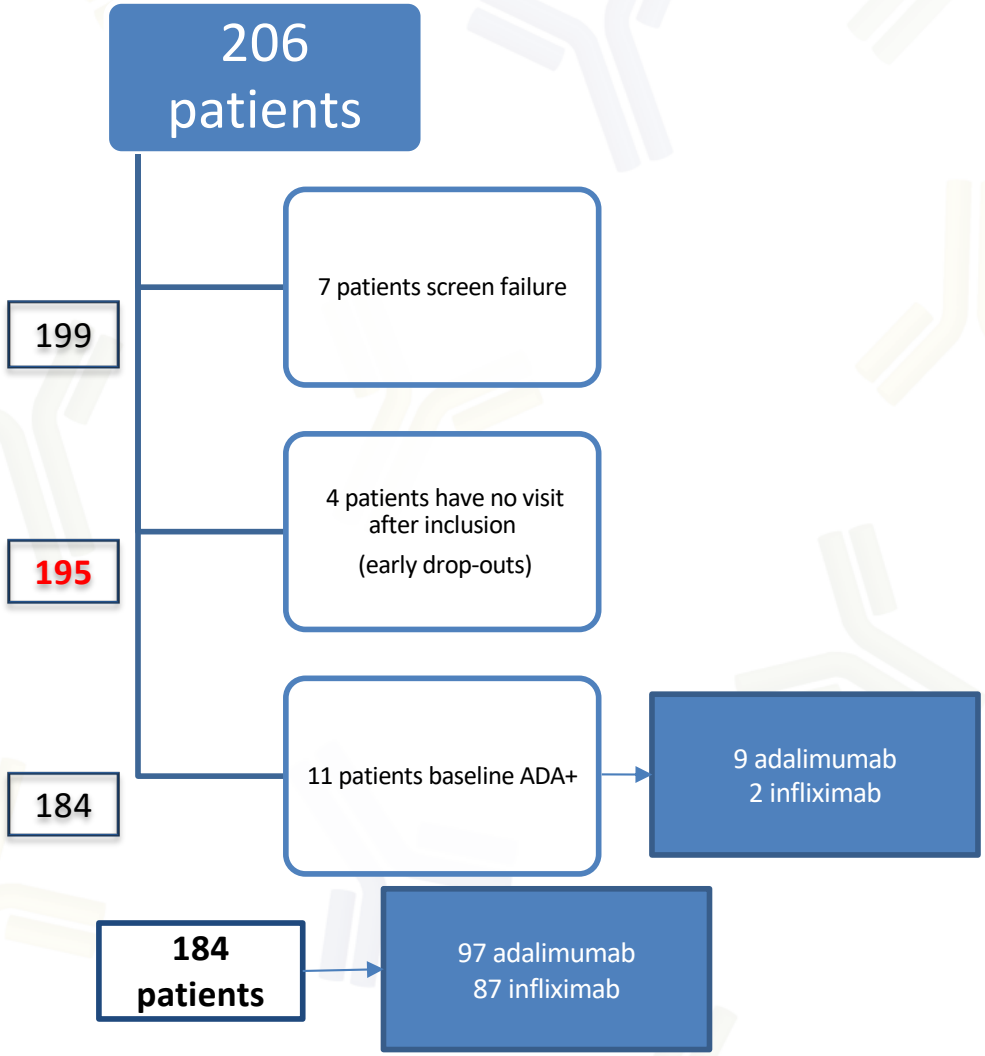
Flow chart



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Definitions of remission and response

- Crohn's disease (Harvey-Bradshaw index)
  - Response : $HBI_i - HBI_0 \geq 3$ or $HBI \leq 4$
  - Remission : $HBI \leq 4$

- Ulcerative Colitis (Mayo score)
  - Response : $Mayo_i - Mayo_0 \geq 3$ or $Mayo \leq 2$
  - Remission : $Mayo \leq 2$

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Rates of clinical remission

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  - Remission : $Mayo \leq 2$

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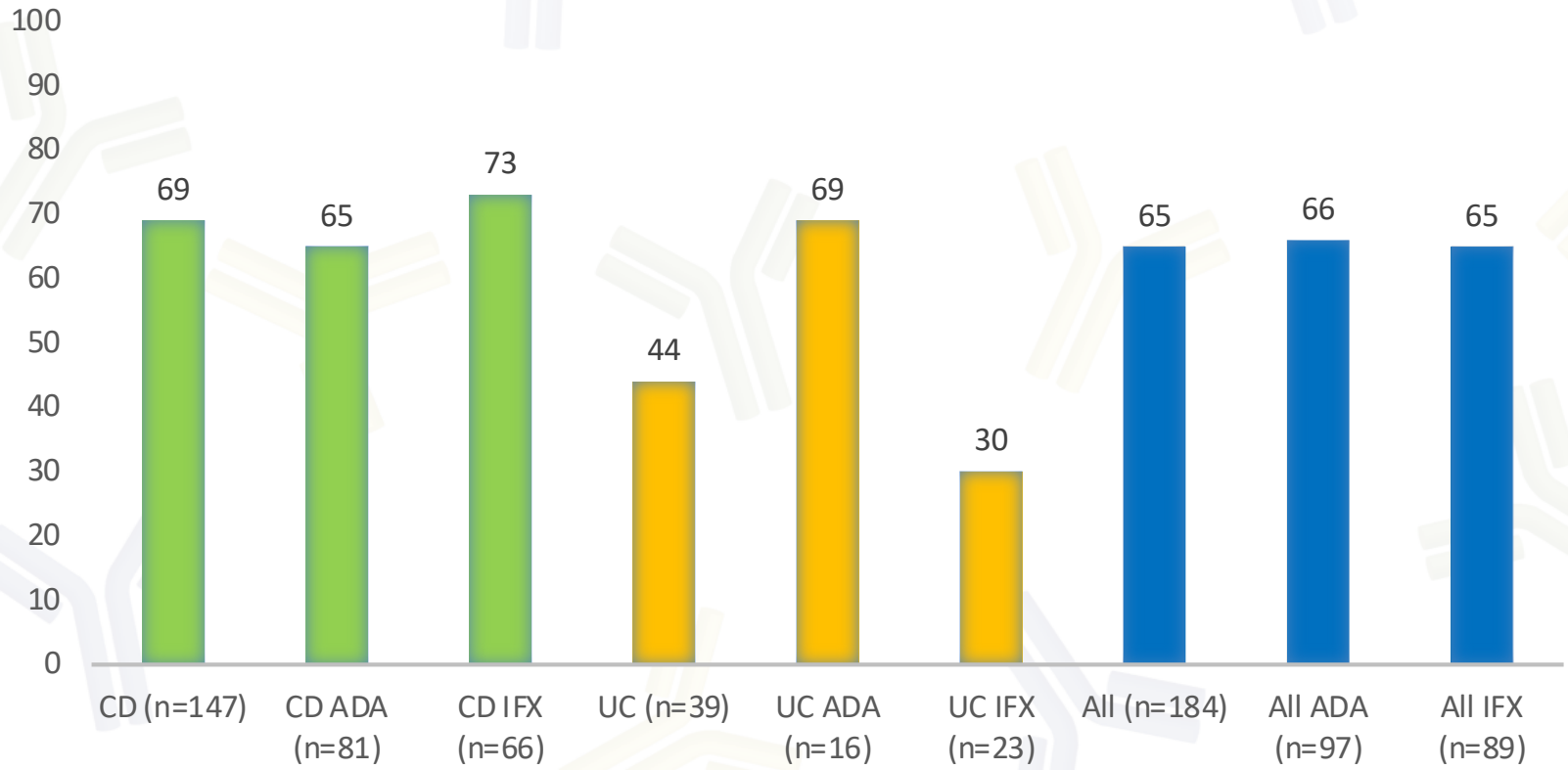
CLINICAL REMISSION AT W12-14



CD Remission : HBI≤4

UC remission : Mayo ≤2

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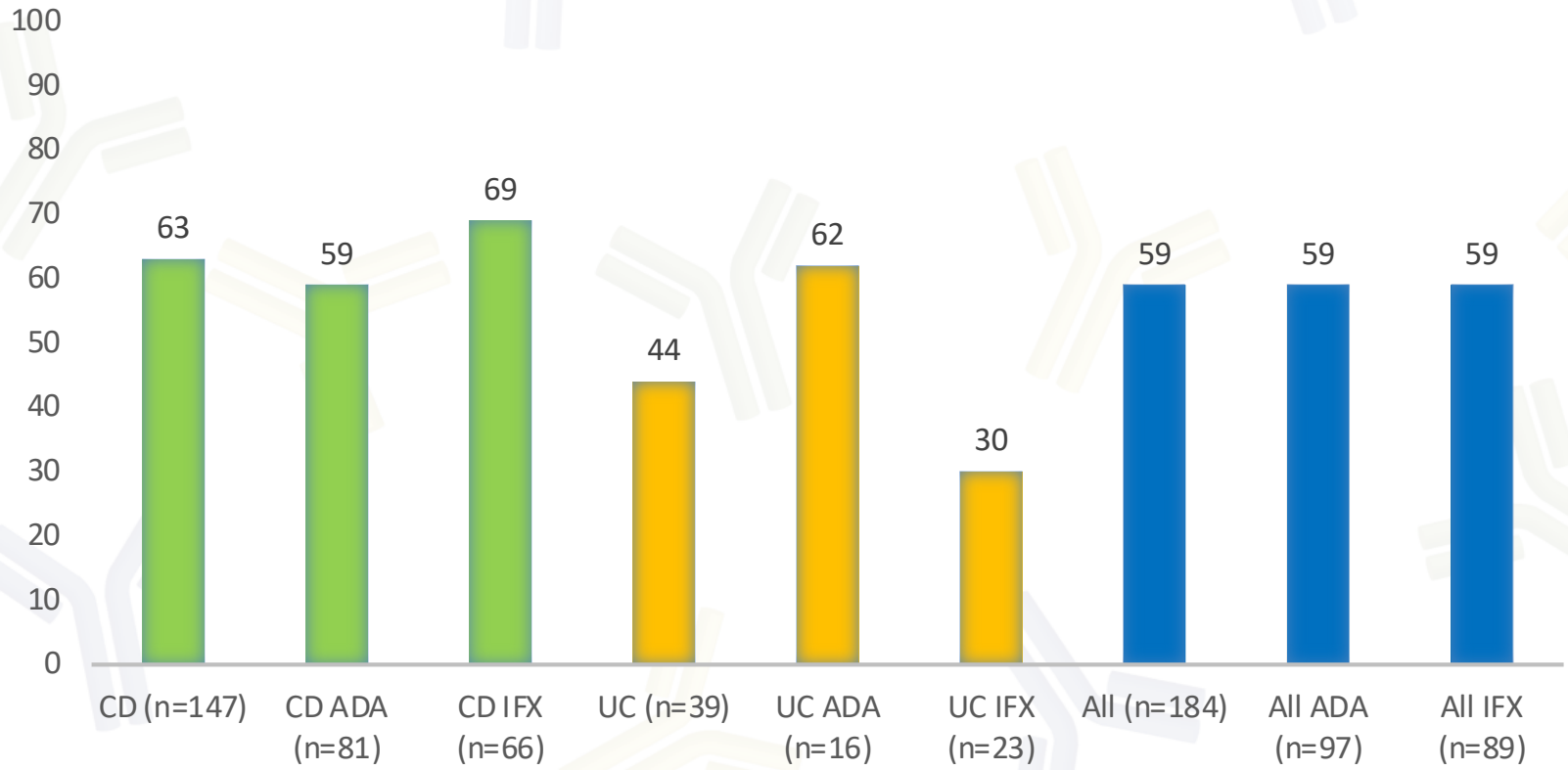
CLINICAL REMISSION AT W52



CD Remission : HBI≤4

UC remission : Mayo ≤2

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Influence of anti-drug antibodies on clinical outcome ?

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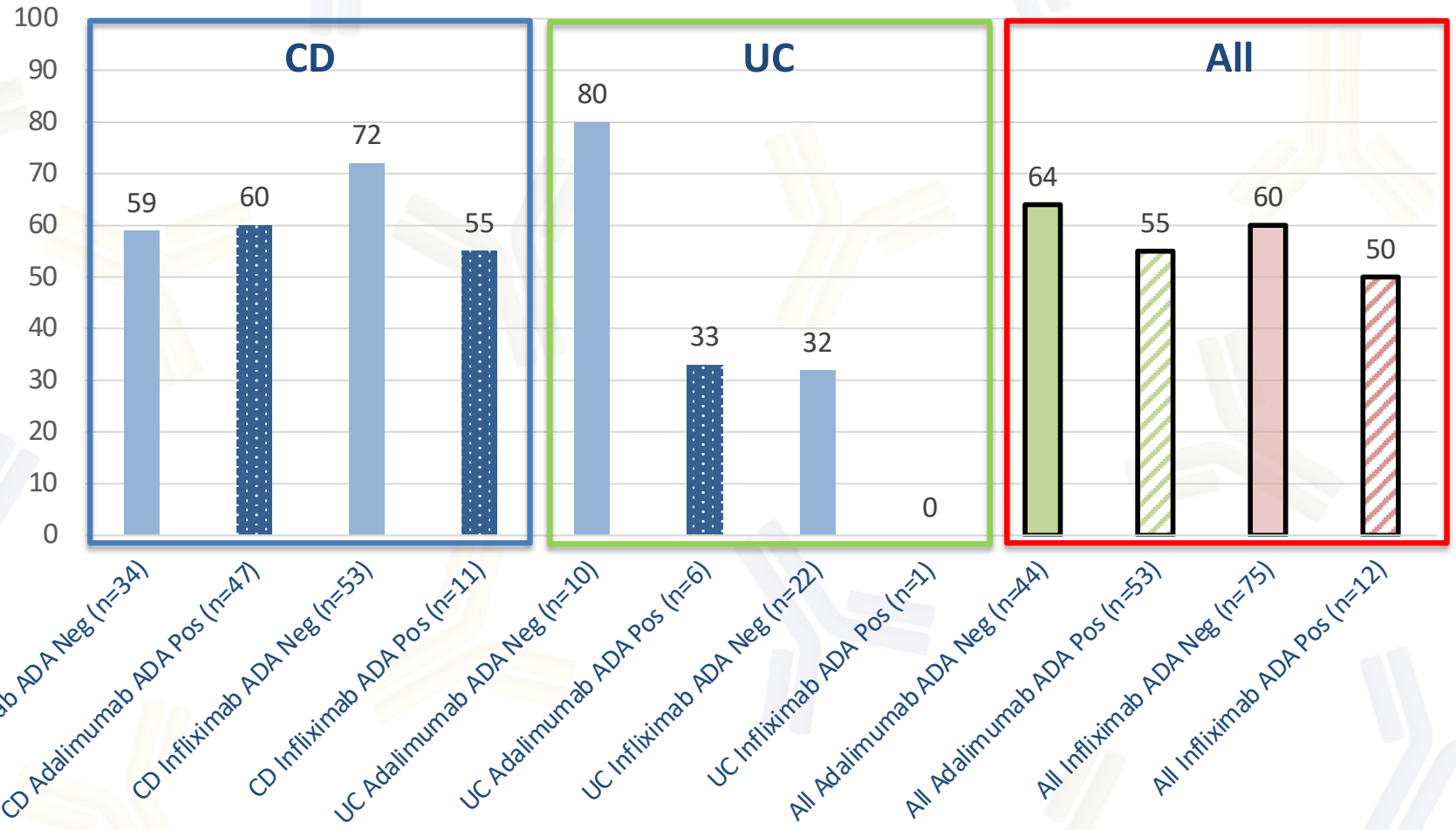
Remission W52, according to ADA status (Theradiag)



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	ADAb status (theradiag) * Pos as at anytime	REM W12-14 (V3)	REM W52 (V13)
ADA CD	ADAb Neg (n=34)	24/34 (70%)	**20/34 (59%)**
	ADA Pos* (n=47)	29/47 (62%)	**28/47 (60%)**
ADA UC	ADAb Neg (n=10)	9/10 (90%)	8/10 (80%)
	ADA Pos (n=6)	2/6 (33%)	2/6 (33%)
ADA All	**ADAb Neg (n=44)**	33/44 (75%)	**28/44 (64%)**
	ADAb Pos (n=53)	31/53 (58%)	**29/53 (55%)**
IFX CD	ADAb Neg (n=53)	39/53 (74%)	**38/53 (72%)**
	ADA Pos (n=11)	9/11 (81%)	**6/11 (54%)**
IFX UC	ADAb Neg (n=22)	7/22 (32%)	7/22 (32%)
	ADA Pos (n=1)	0/1	0/1
IFX All	**ADAb Neg (n=75)**	46/75 (61%)	**45/75 (60%)**
	ADAb Pos (n=12)	9/12 (75%)	**6/12 (50%)**

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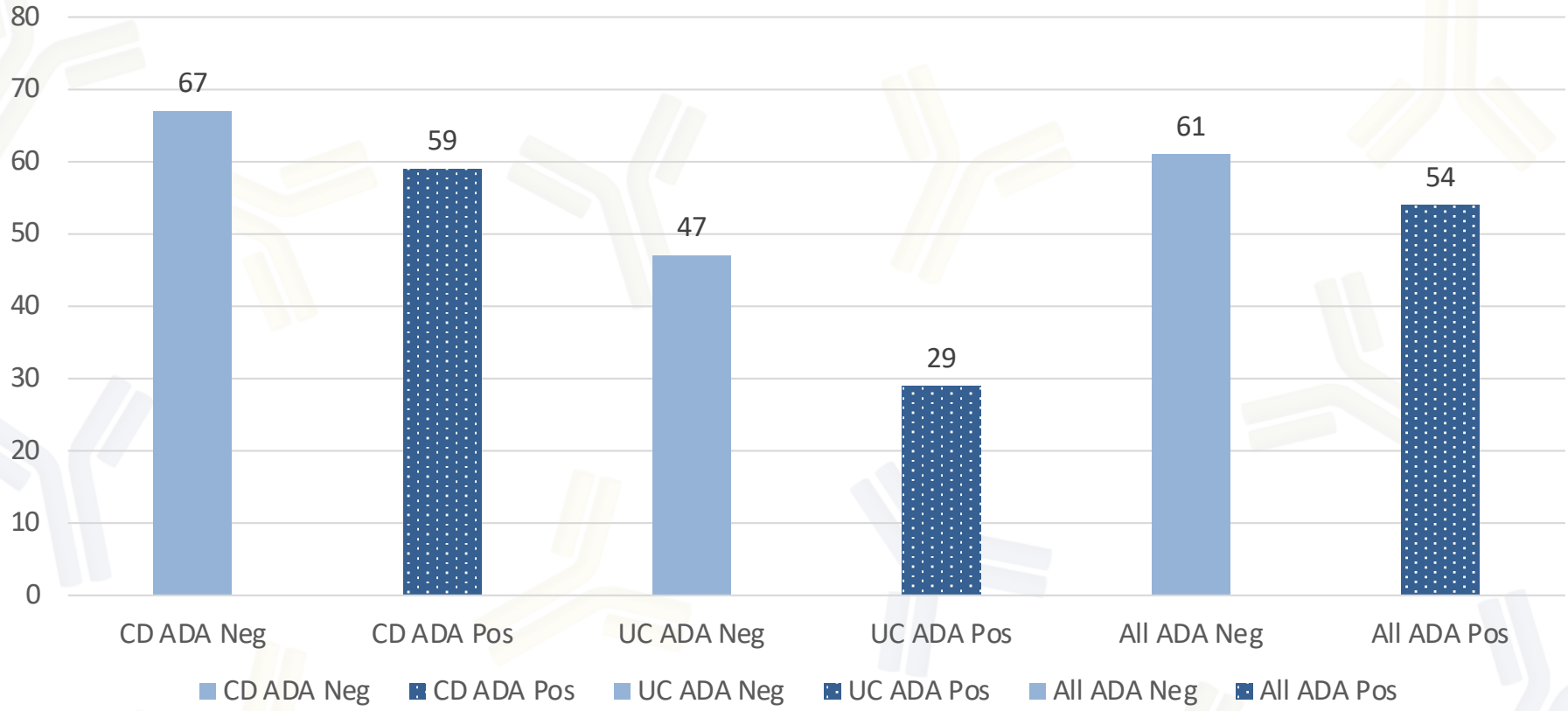
Remission W52, according to ADA status (Theradiag)
Pooling infliximab and adalimumab data



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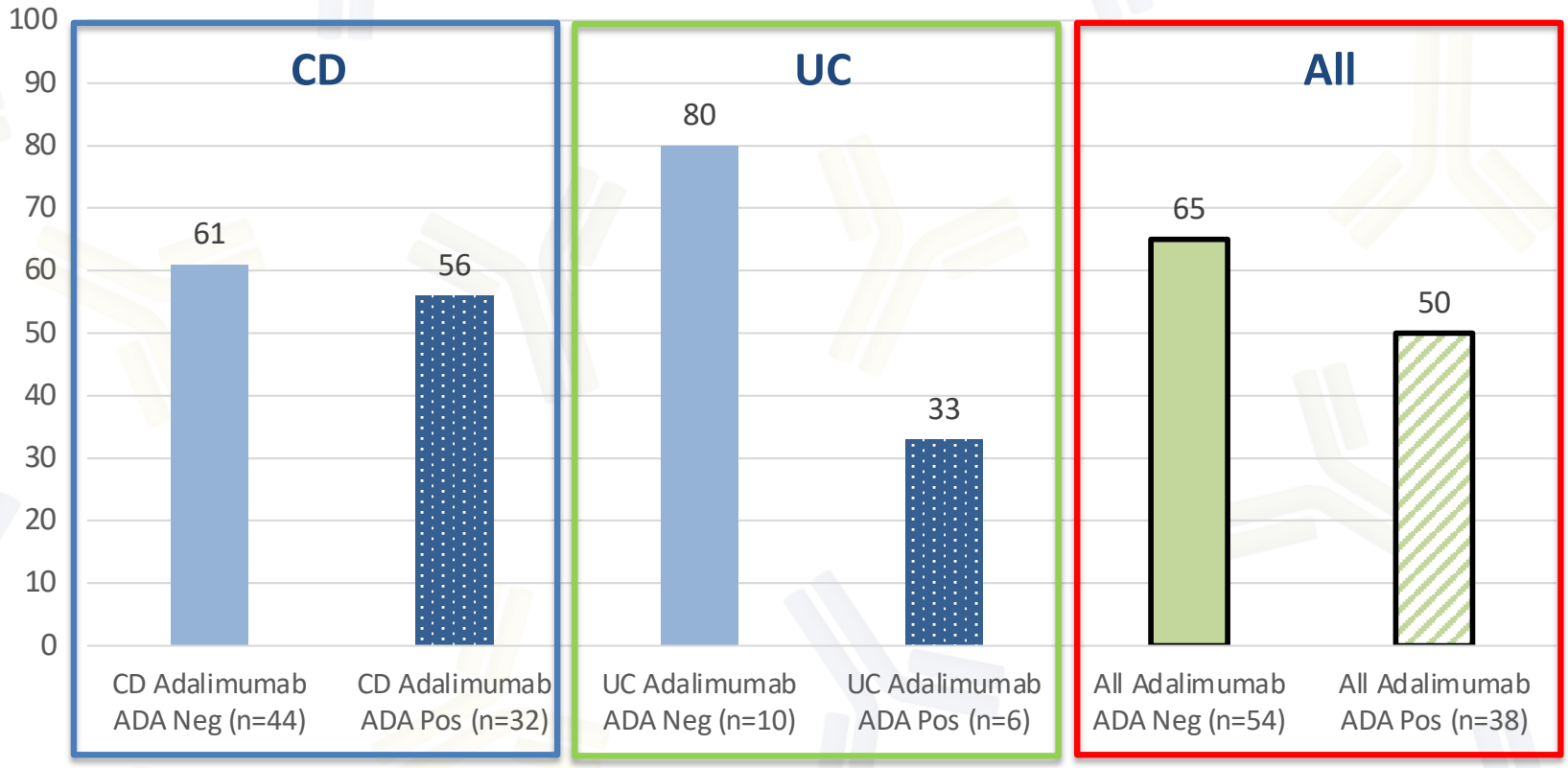
Remission W52, according to ADA status (MSD)



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ADAb / MSD

		REM W12-14 (V3)	REM W52 (V13)
ADA CD	ADAb Neg (n=44)	31/44 (70%)	27/44 (61%)
	ADA Pos* (n=32)	20/32 (62%)	18/32 (56%)
ADA UC	ADAb Neg (n=10)	8/10 (80%)	8/10 (80%)
	ADA Pos (n=6)	3/6 (50%)	2/6 (33%)
ADA All	ADAb Neg (n=54)	39/54(72%)	35/54 (65%)
	ADAb Pos (n=38)	23/38 (61%)	19/38 (50%)

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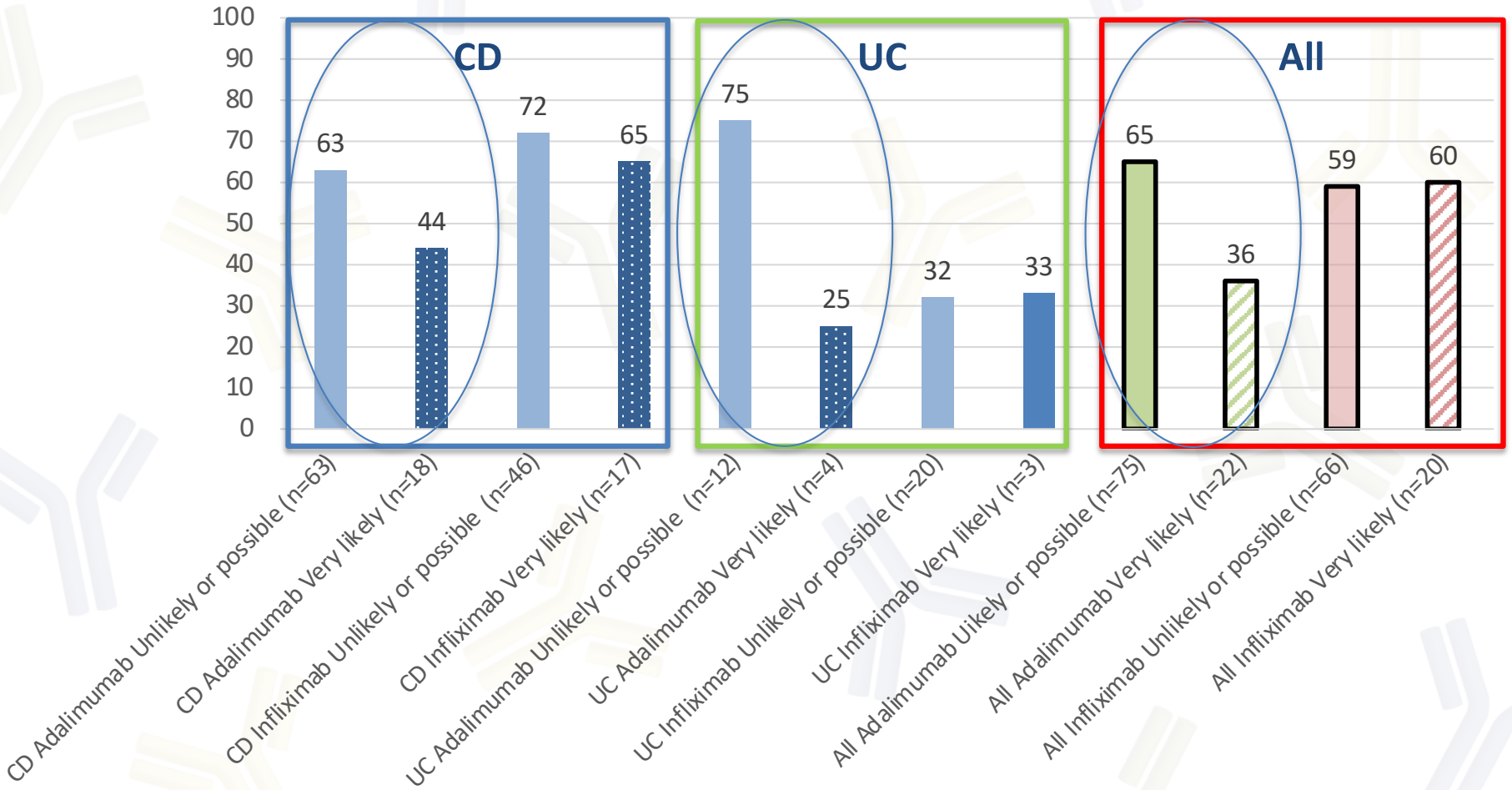
Remission W52, according to PK measurement



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PK

	ADAb status (theradiag) * Pos as at anytime	REM W12-14 (V3)	REM W52 (V13)
ADA CD	Unlikely or possible (n=63)	42/63 (65%)	40/63 (63%)
	Very likely (n=18)	12/18 (67%)	8/18 (44%)
ADA UC	Unlikely or possible (n=12)	10/12 (83%)	9/12 (75%)
	Very likely (n=4)	1/4 (25%)	1/4 (25%)
ADA All	Unlikely or possible (n=75)	39/75(72%)	49/75 (65%)
	Very likely (n=22)	13/22 (59%)	8/22 (36%)
IFX CD	Unlikely or possible (n=46)	35/46 (76%)	33/46 (72%)
	Very likely (n=17)	9/12 (75%)	11/17 (65%)
IFX UC	Unlikely or possible (n=20)	7/20 (35%)	7/22 (32%)
	Very likely (n=3)	0/3	1/3 (33%)
IFX All	Unlikely or possible (n=66)	42/66 (64%)	39/66 (59%)
	Very likely (n=20)	13/20 (65%)	12/20 (60%)

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Conclusion - 1

- These are preliminary results (full monitoring of the prospective cohort finished last week)
  - Statistical analysis …

- High rates of clinical remission in this prospective cohort
  - The lower rates of remission with infliximab in UC may be related to a higher proportion of acute severe colitis
  - Analysis to be done: Clinical remission without steroid, Clinical remission and CRP normalization, statistics, predictors?

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Conclusion - 2

- Assessment of immunogenicity
  - Different assays …
  - Significant correlation between clinical outcome and ATI in CD (to be confirmed)
  - Immunogenicity was defined by the presence of ADAb at any anytime
- These are preliminary results which must be completed:
  - Primary Vs. secondary failures, Impact on the early detection of ADAb on clinical outcome? Exclusion of transient ADAb? Impact of the optimization on the detection of ADAb,
  - Comparison of MSD and Theradiag assays, Correlation with PK
  - Analysis pooled with RA and JIA

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- Co-investigators

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  Yehuda Chowers

- GETAID

  Sabrina Williams, all co-investigators

- ABIRISK

  Marc Pallardy, Sebastian Spindeldreher, Philippe Broet, Delphine Bachelet, Signe Hassler, Agnes Hincelin-Mery, Vincent Mikol, Sophie Tourdot, Pierre Doennes, Anna Fogdell-Hahn, Florian Deisenhammer, Xavier Mariette

  Denis Mulleman, Gilles Paintaud, David Ternant, Salima Hacein-Bey, Niek de Vries, Bernard Maillere, Claudia Mauri

- All partners

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