STRATÉGIES DE TRAITEMENT EN MALADIE DE CROHN: COMMENT POSITIONNER NOS OPTIONS?

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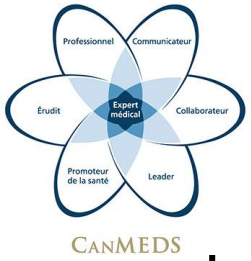
13 avril 2024

Conflits d'intérêts potentiels

- ❑ **Je n'ai pas établi de relation avec une organisation à but lucratif ou sans but lucratif**
- ☒ **J'ai établi des relations avec une organisation à but lucratif ou sans butcratif**

Nature des relations	Nom de l'organisation à but lucratif ou sans but lucratif
Les paiements directs incluant les honoraires	Abbvie, Janssen, Pfizer, Takeda Ferring, Sandoz, Eli Lilly
La participation à des comités consultatifs ou des bureaux de conférenciers	Abbvie, Janssen, Pfizer, Takeda Ferring, Sandoz, Eli Lilly
Le financement de subventions ou d'essais cliniques	Abbvie, Janssen
Les brevets sur un médicament, un produit ou un appareil	N/A
Tout autre investissement ou toute autre relation qu'un participant raisonnable et bien informé pourrait considérer comme un facteur d'influence sur le contenu de l'activité éducative	N/A

COMPÉTENCES CANMEDS

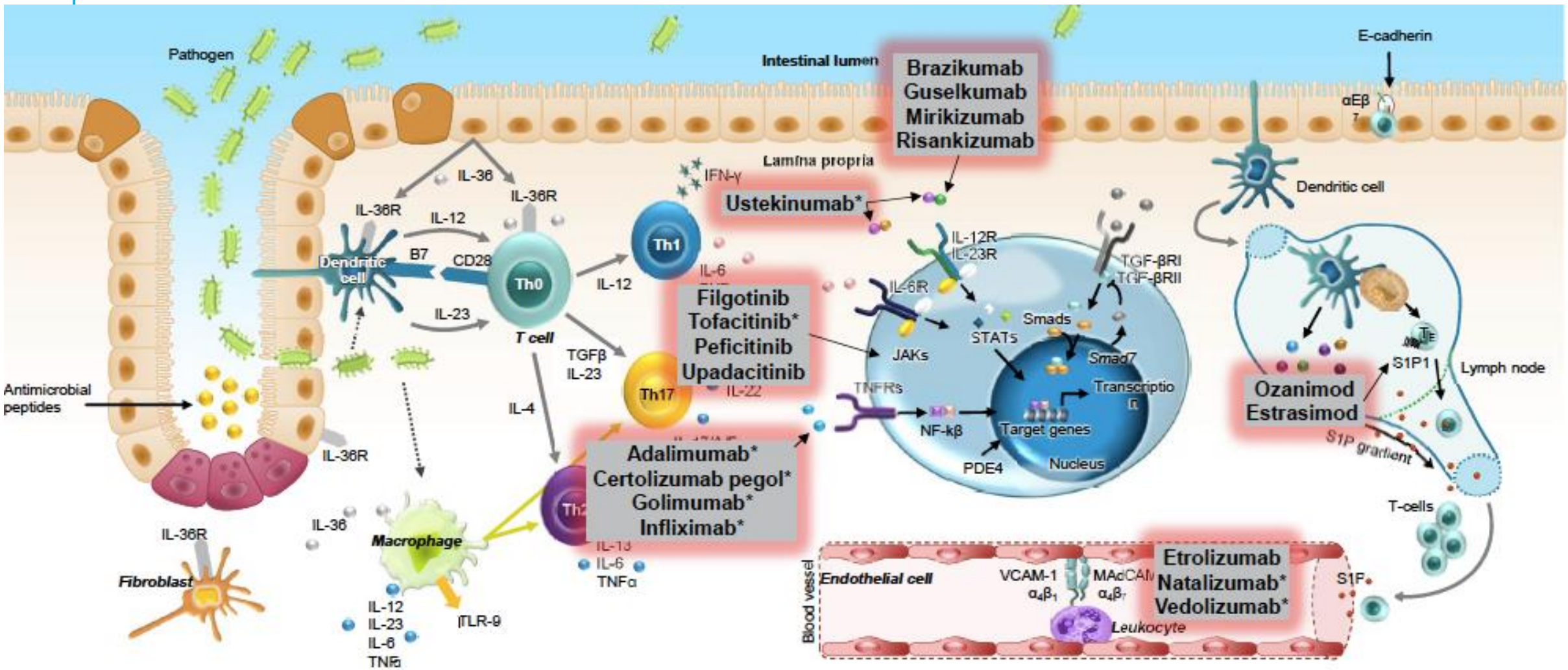


X	**Expert médical** (En tant qu'experts médicaux, les médecins assument tous les rôles CanMEDS et s'appuient sur leur savoir médical, leurs compétences cliniques et leurs attitudes professionnelles pour dispenser des soins de grande qualité et sécuritaires centrés sur les besoins du patient. Pivot du référentiel CanMEDS, le rôle d'expert médical définit le champ de pratique clinique des médecins .)
X	**Communicateur** (En tant que communicateurs, les médecins développent des relations professionnelles avec le patient et ses proches ce qui permet l'échange d'informations essentielles à la prestation de soins de qualité.)
X	**Collaborateur** (En tant que collaborateurs, les médecins travaillent efficacement avec d'autres professionnels de la santé pour prodiguer des soins sécuritaires et de grande qualité centrés sur les besoins du patient.)
X	**Leader** (En tant que leaders, les médecins veillent à assurer l'excellence des soins, à titre de cliniciens, d'administrateurs, d'érudits ou d'enseignants et contribuent ainsi, avec d'autres intervenants, à l'évolution d'un système de santé de grande qualité.)
X	**Promoteur de santé** (En tant que promoteurs de la santé, les médecins mettent à profit leur expertise et leur influence en oeuvrant avec des collectivités ou des populations de patients en vue d'améliorer la santé. Ils collaborent avec ceux qu'ils servent afin d'établir et de comprendre leurs besoins, d'être si nécessaire leur porte-parole, et de soutenir l'allocation des ressources permettant de procéder à un changement.)
X	**Érudit** (En tant qu'érudits, les médecins font preuve d'un engagement constant envers l'excellence dans la pratique médicale par un processus de formation continue, en enseignant à des tiers, en évaluant les données probantes et en contribuant à l'avancement de la science.)
X	**Professionnel** (En tant que professionnels, les médecins ont le devoir de promouvoir et de protéger la santé et le bien-être d'autrui, tant sur le plan individuel que collectif. Ils doivent exercer leur profession selon les normes médicales actuelles, en respectant les codes de conduite quant aux comportements qui sont exigés d'eux, tout en étant responsables envers la profession et la société. De plus, les médecins contribuent à l'autoréglementation de la profession et voient au maintien de leur santé.)

THÉRAPIES MÉDICALES DISPONIBLES ET STRATÉGIES SÉQUENTIELLES
OBJECTIFS

À la fin de cette présentation, le participant sera en mesure de:

- ❖Planifier une stratification de traitements avancés en maladie de Crohn
- ❖Synthétiser les principales avenues de traitement disponibles et leurs risques et bénéfices
- ❖Discuter d'une stratégie de traitement personnalisée pour leurs patients



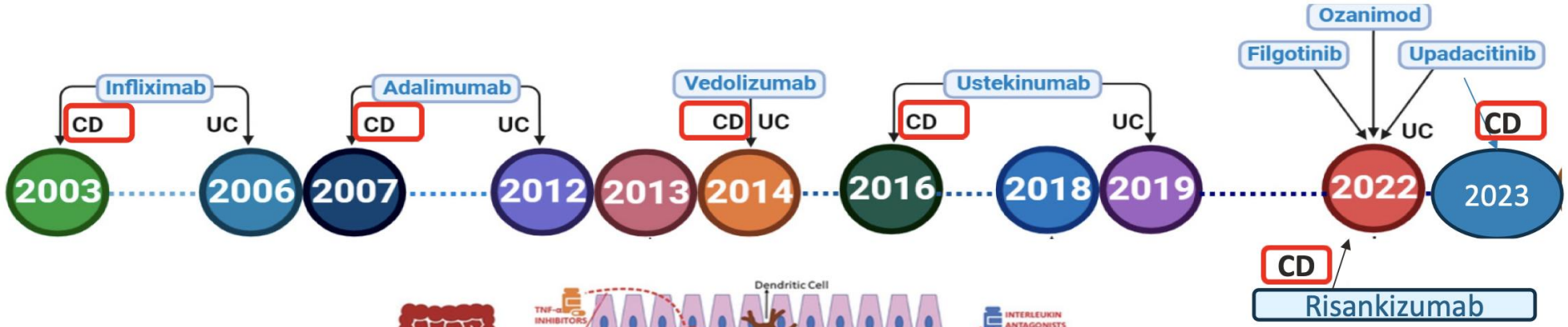
Adapted from Coskún M, et al. Tr*ends Pharm Sci* 2017;38:127–42; and Nielsen OH, et al. *Expert Opin Investig Drugs* 2016;25:709–18.

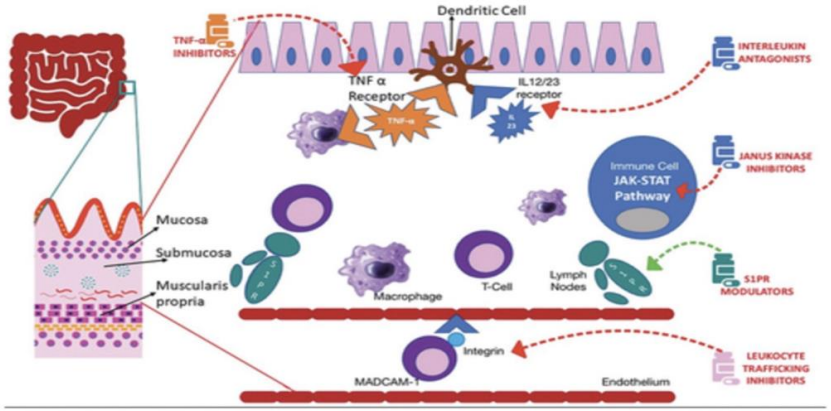
QUELLES SONT LES OPTIONS ACTUELLEMENT DISPONIBLES ?

OPTIONS DISPONIBLES

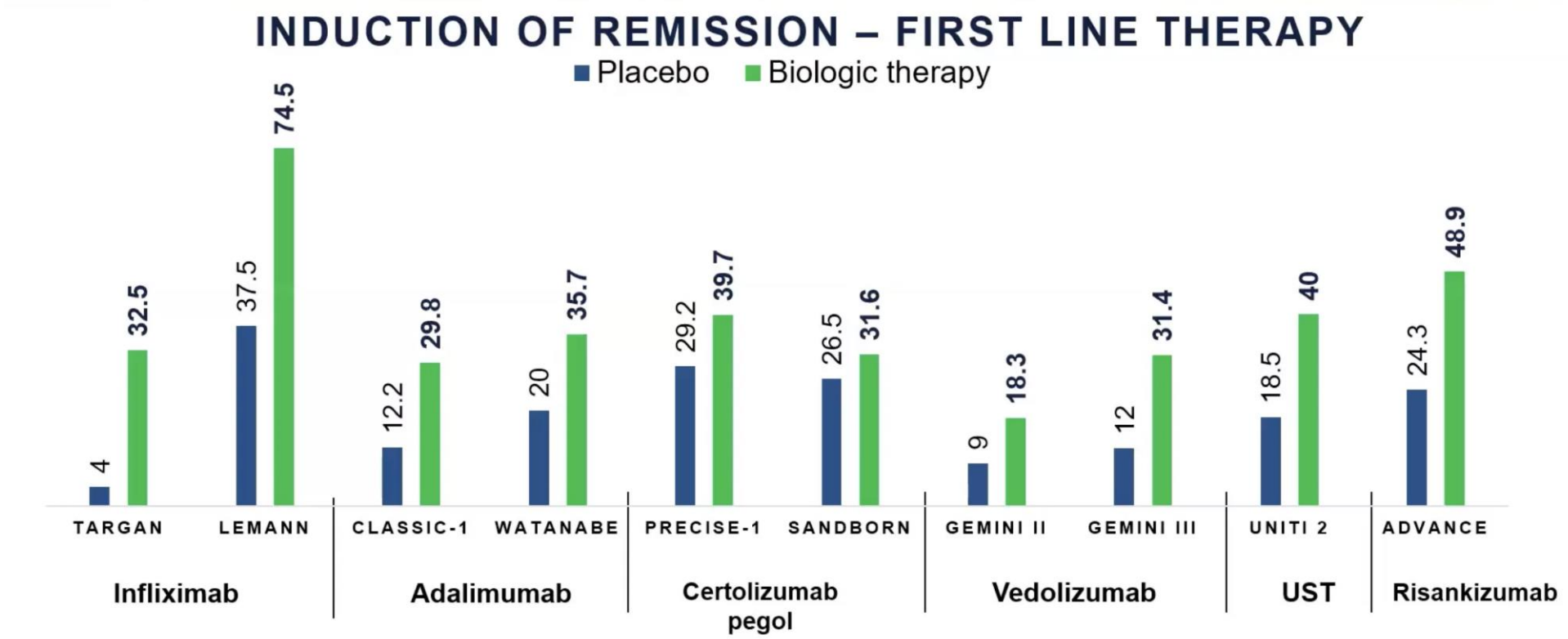
- Crohn
  - Anti-TNFs
  - Vedolizumab
  - Ustekinumab
  - Risankizumab
  - Upadacitinib
- Colite ulcéreuse
  - Anti-TNF
  - Vedolizumab
  - Tofacitinib
  - Upadacitinib
  - Ustekinumab
  - Mirikizumab
  - Ozanimod

DERNIÈRE DÉCENNIE TRÈS ACTIVE!





EFFICACITÉ DES BIOLOGIQUES EN CROHN



!!

- Après induction avec chacune de ces thérapies, moins que 20% des patients sont en rémission clinique
- Ce pourcentage augmente à seulement 50% de tous les patients après le traitement de maintien
- Culmine en un faible taux de persistance au fil du temps avec une même molécule
- Environ 1/3 des patients vont changer de biologique après un an, et 20% à un 3e.
- QUESTION: Pouvons-nous tenter d'éviter les conséquences de multiples années d'efficacité thérapeutique sous-optimale via une meilleure stratégie de séquence thérapeutique?

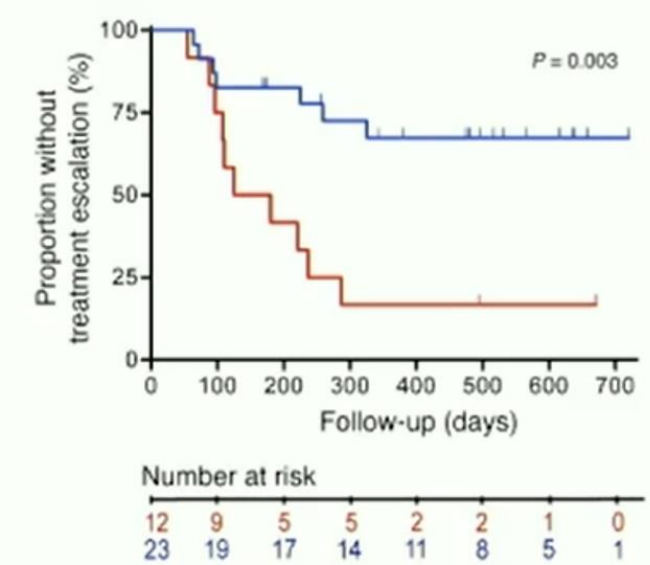
Zhao M et al. Aliment Pharmacol Ther 2022

COMMENT AMÉLIORER NOTRE PERFORMANCE?

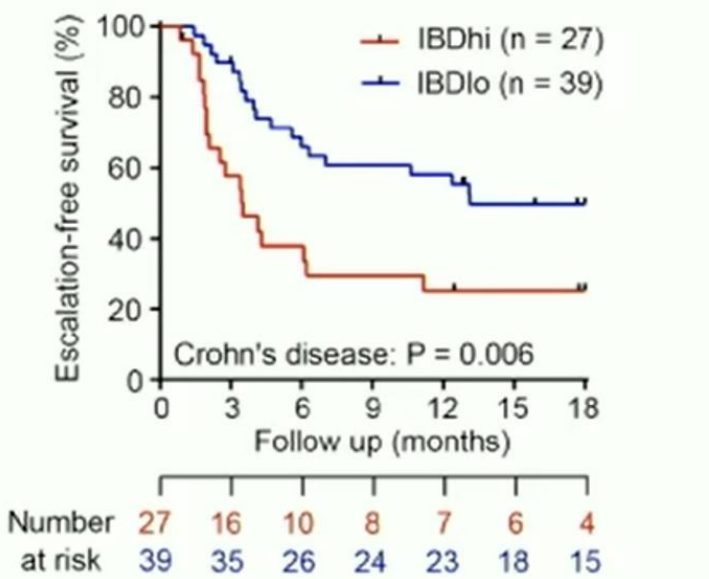
- Stratégie de thérapie séquentielle
- Recherche
- Médecine personnalisée
- Proactivité ! **Top down dès le dx en Crohn actif modéré à sévère et ce pour TOUS**

BIOMARQUEUR PRONOSTIC VALIDÉ – COHORTES OBSERVATIONNELLES PROSPECTIVES

- Identifier les patients à haut risque de récidive récurrentes

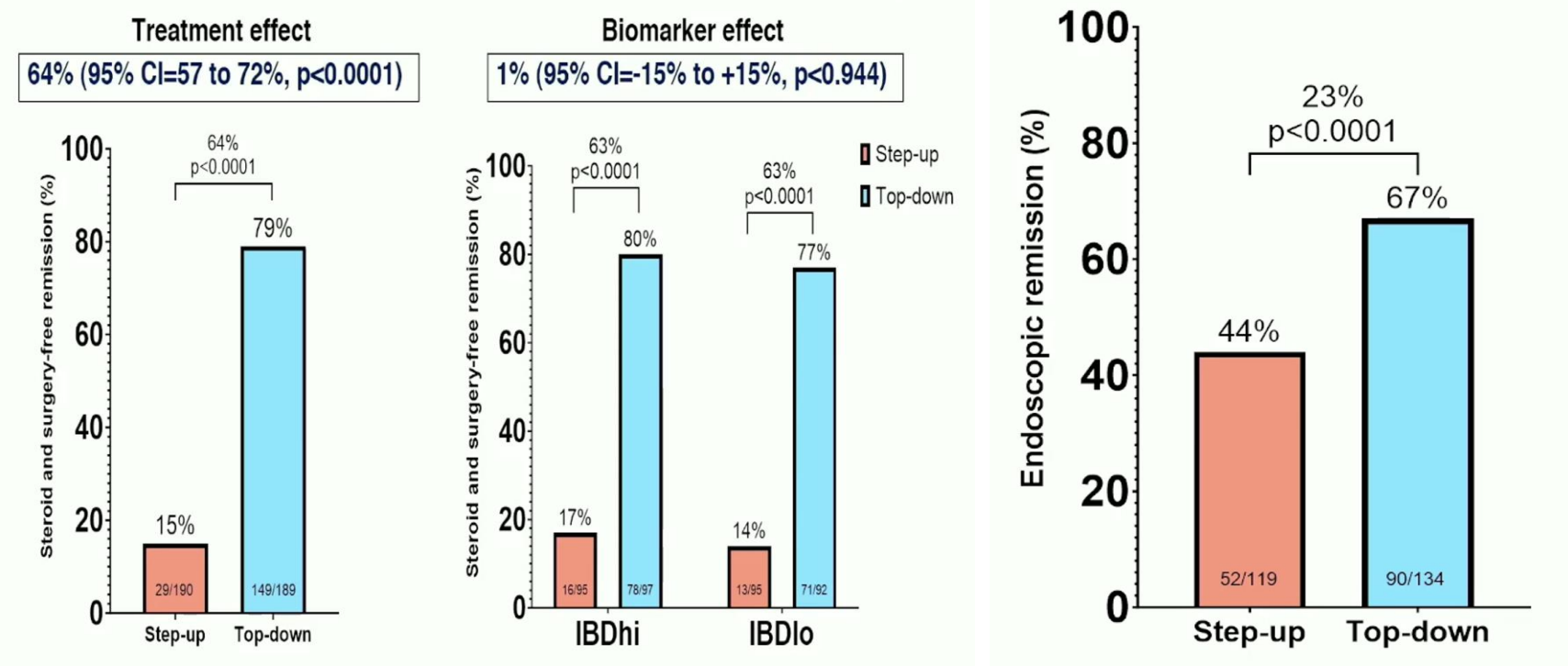


Lee JC et al. JCI 2011



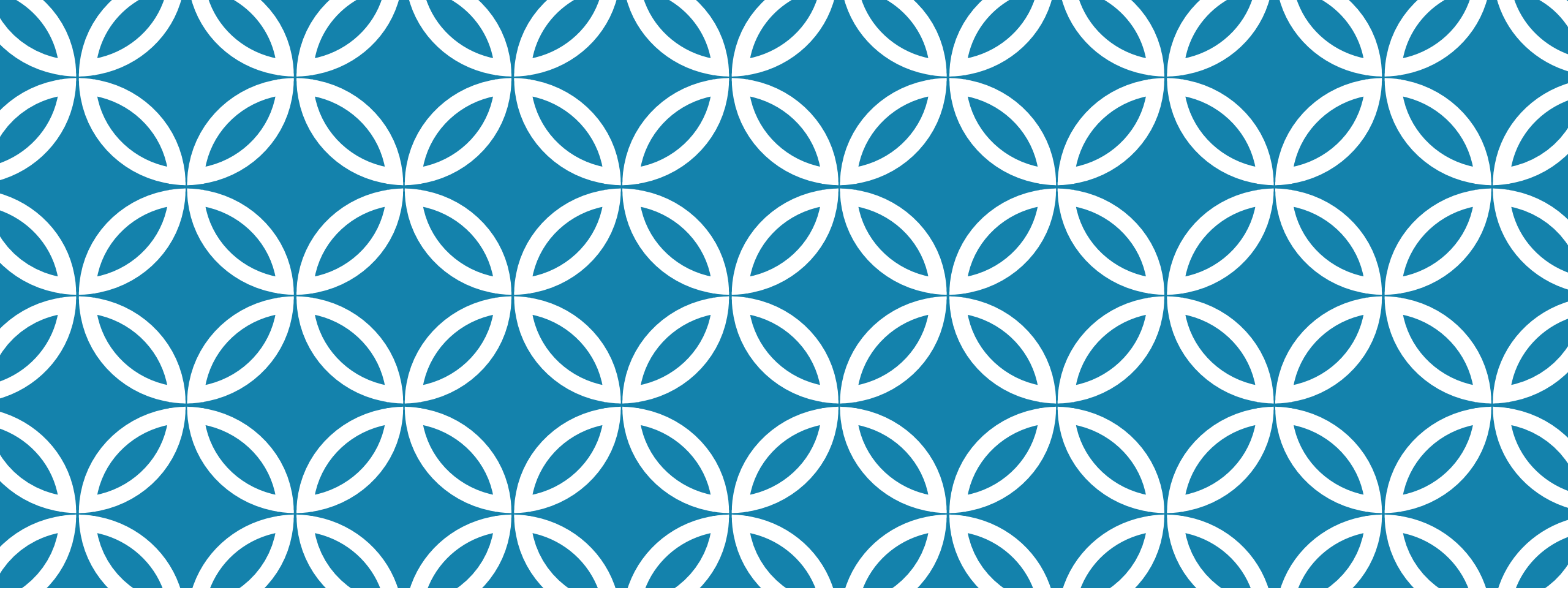
Biasci D et al. Gut 2019

ISSUE PRIMAIRE : RÉMISSION SOUTENUE SANS CHX ET SANS CS JUSQU'À LA SEMAINE 48



- Plus grand nombre d'événements indésirables dans le groupe step up accéléré, d'événements indésirables sérieux et de chx abdominales urgentes
- Pas d'augmentation du risque d'infections sérieuses avec le top-down

Noor N ECCO 2024



EFFICACITÉ OU INNOCUITÉ?

EFFICACITÉ VS INNOCUITÉ

- Efficacité vs innocuité de la molécule
  - Immunosuppression systémique d'un tx spécifique (R infectieux long terme)
- Risque inhérent d'une maladie de Crohn active et non contrôlée (R infectieux à court terme)

➢ **L'innocuité d'une stratégie thérapeutique devrait être prioritaire vs l'innocuité d'un traitement spécifique!**

➢ Objectifs : Rémission soutenue, absence de chx ou complication, absence de complications ou infections liées au traitement, absence d'invalidité

RISQUE INFECTIEUX

Clinical Gastroenterology and Hepatology 2021;

Comparative Risk of Serious Infections With Tumor Necrosis Factor α Antagonists vs Vedolizumab in Patients With Inflammatory Bowel Diseases

Siddharth Singh,[*,‡] Herbert C. Heien,[§] Jeph Herrin,[||] Parambir S. Dulai,[*] Lindsey Sangaralingham,[§] Nilay D. Shah,[§,¶] and William J. Sandborn[*]

Vedolizumab vs. TNFα antagonists (reference), adjusted HR (95% CI)	All serious infections	Extra-intestinal serious infections	Gastrointestinal serious infections
All patients with IBD	0.79 (0.56-1.13)	0.81 (0.45-1.43)	**1.82 (1.08-3.07)**
IBD phenotype • Crohn's disease • Ulcerative colitis	1.30 (0.80-2.11) **0.54 (0.35-0.83)**	1.43 (0.73-2.79) 0.41 (0.15-1.12)	**2.90 (1.21-6.94)** 1.20 (0.57-2.53)

RISQUE D'INFECTIONS AVEC LES THÉRAPIES AVANCÉES MÉTA-ANALYSE

Ustekinumab vs. TNFα antagonists
(5 cohorts; 23,232 patients)

- **CD**: **51% lower risk** of serious infections with ustekinumab
- **UC**: Knowledge gap

Vedolizumab vs. TNFα antagonists
(17 cohorts; 51,596 patients)

- **CD**: **No difference** in risk of serious infections (OR, 1.03)
- **UC**: **32% lower risk** of serious infections with vedolizumab

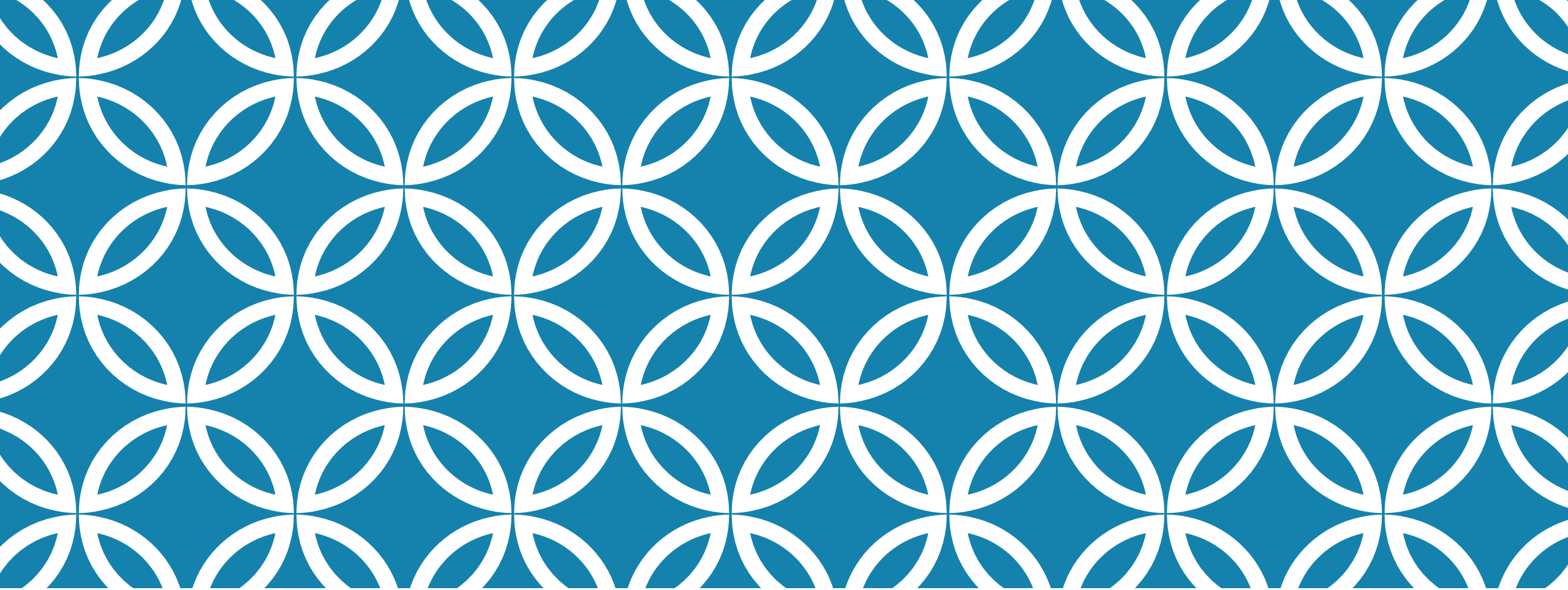
Ustekinumab vs. vedolizumab
(5 cohorts; 1,420 patients)

- **CD**: **60% lower risk** of serious infections with ustekinumab
- **UC**: Knowledge gap

Solitano et al. Clin Gastroenterol Hepatol 2022

CONSIDÉRATIONS

- Les taux d'événements indésirables demeurent faibles à travers toute la gamme de thérapies actuelles
- Le risque de la maladie elle-même si traitée de façon sous-optimale surpasse le risque inhérent à une thérapie prise individuellement
- Peu importe la séquence choisie ou adoptée, le monitoring et la détection précoce des signes de non réponse et le changement proactif de thérapie subséquent est d'une importance capitale dans la prise en charge de nos patients atteints de MII



QUELLE SÉQUENCE À ADOPTER?

QUELS OUTILS SONT DISPONIBLES POUR COMPARER L'EFFICACITÉ?

- Études cliniques randomisées H2H
  - SEAVUE : ustekinumab vs adalimumab bionaïfs
  - SEQUENCE : ustekinumab vs risankizumab échec antérieur avec anti-TNF
- Études cliniques randomisées avec bras comparateur actif
  - VIVID1: mirikizumab vs pbo avec comparateur actif : ustekinumab
- Méta-analyse en réseau de données issues d'études randomisées contrôlées
- Analyse avec score de propension
  - Études randomisées contrôlées
  - Données observationnelles (études de vraie vie)

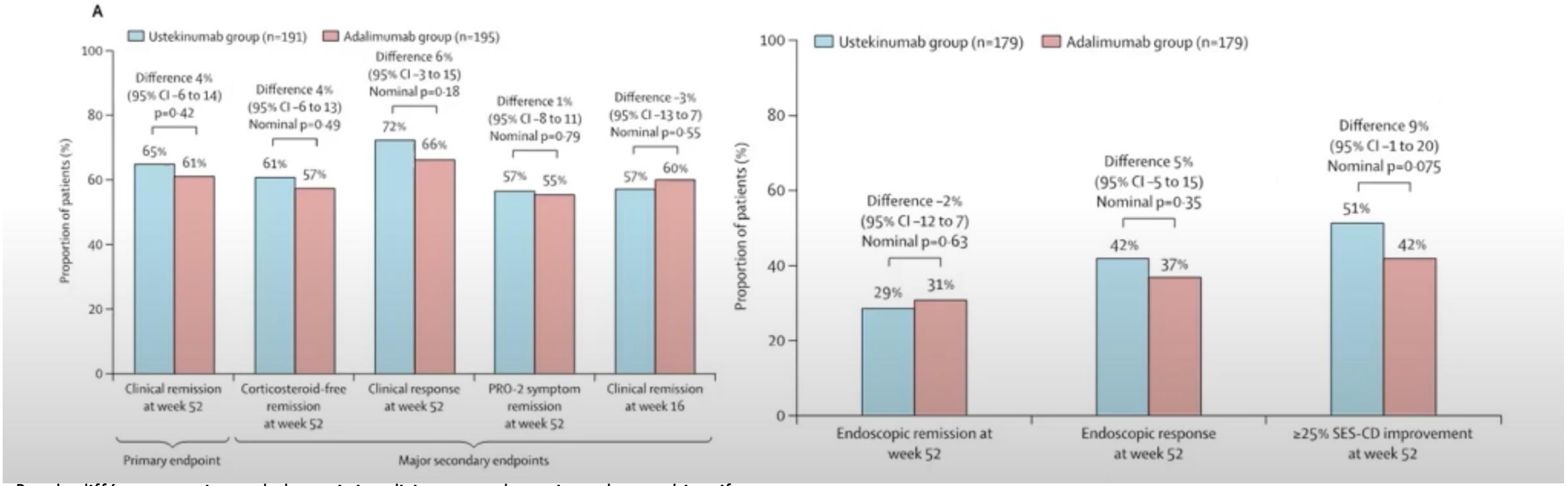
Y A-T-IL UNE « MEILLEURE » PREMIÈRE THÉRAPIE QU'UN ANTI-TNF EN CROHN?

Monothérapie et absence d'optimisation

ETUDE SEAVUE

Ustekinumab versus adalimumab for induction and maintenance therapy in biologic-naive patients with moderately to severely active Crohn's disease: a multicentre, randomised, double-blind, parallel-group, phase 3b trial

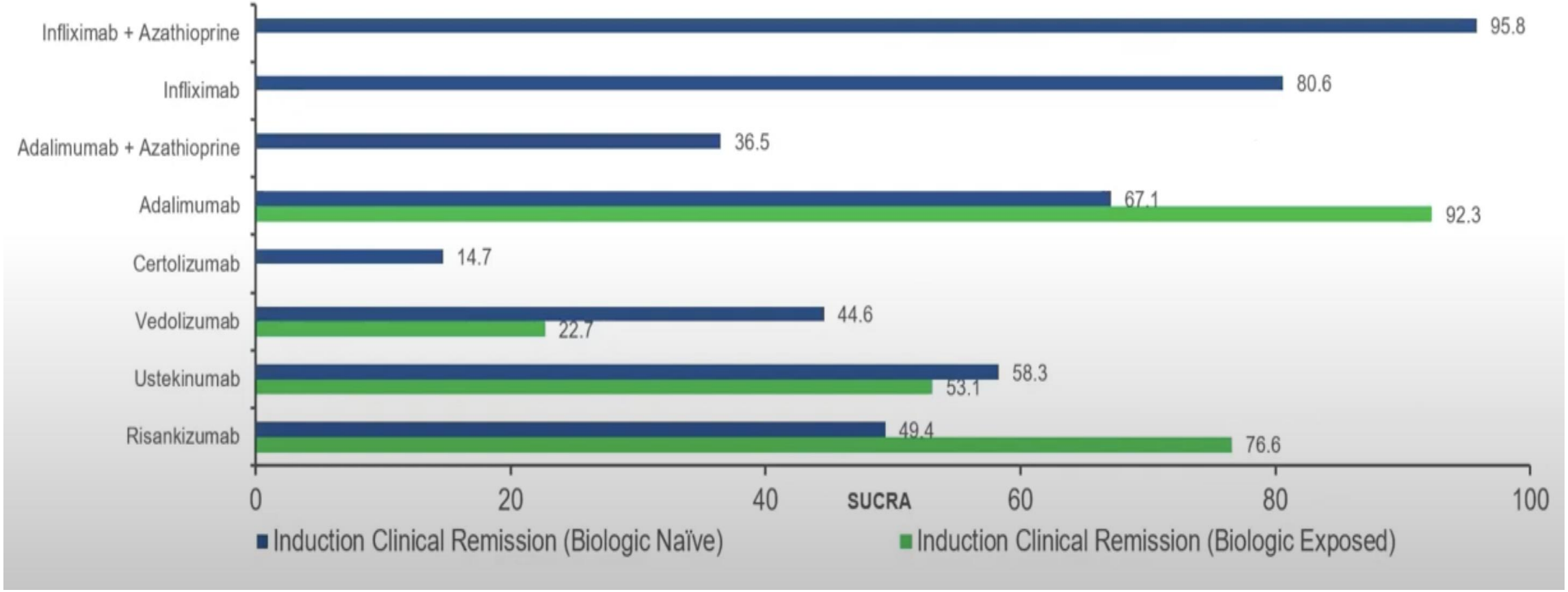
*Bruce E Sands, Peter M Irving, Timothy Hoops, James L Izanec, Long-Long Gao, Christopher Gasink, Andrew Greenspan, Matthieu Allez, Silvio Danese, Stephen B Hanauer, Vipul Jairath, Tanja Kuehbacher, James D Lewis, Edward V Loftus Jr, Emese Mihaly, Remo Panaccione, Ellen Scherl, Oksana B Shchukina, William J Sandborn, on behalf of the SEAVUE Study Group**



Pas de différence au niveau de la remission clinique et endoscopique chez pts bionaifs

Sands et al. Lancet 2022

REVUE SYSTÉMATIQUE & MÉTA-ANALYSE EN RÉSEAU



Singh et al. Lancet Gastroenterol Hepatol 2021

ÉTUDE EVOLVE EXPANSION (CROHN BIONAÏF)

- Taux cumulatifs sur 36 mois similaires entre les pts traités par VDZ vs UST pour la réponse clinique et la rémission clinique
- Taux de cicatrisation muqueuse plus élevés chez les pts traités par VDZ que chez ceux traités par UST
- Persistance du traitement plus élevée chez les pts traités par UST sur 36 mois (VDZ 70,6% UST 80,3%)
- Taux similaire entre les 2 molécules pendant 36 mois dans les sous-groupes de localisation de la maladie iléale, colique ou iléocolique pour la rép et rém clinique, la cicatrisation muqueuse et la persistance au tx

Ferrante et al P636 ECCO 2023
Scharl et al P627 ECCO 2024

GUÉRISON ENDOSCOPIQUE

Comparative Effectiveness of Biologics for Endoscopic Healing of the Ileum and Colon in Crohn's Disease

Neeraj Narula, MD, MPH, FRCPC[1], Emily C.L. Wong, BHSc[1], Parambir S. Dulai, MD[2], John K. Marshall, MD, MSc, FRCPC[1], Vipul Jairath, MD, PhD[3] and Walter Reinisch, MD, PhD[4]

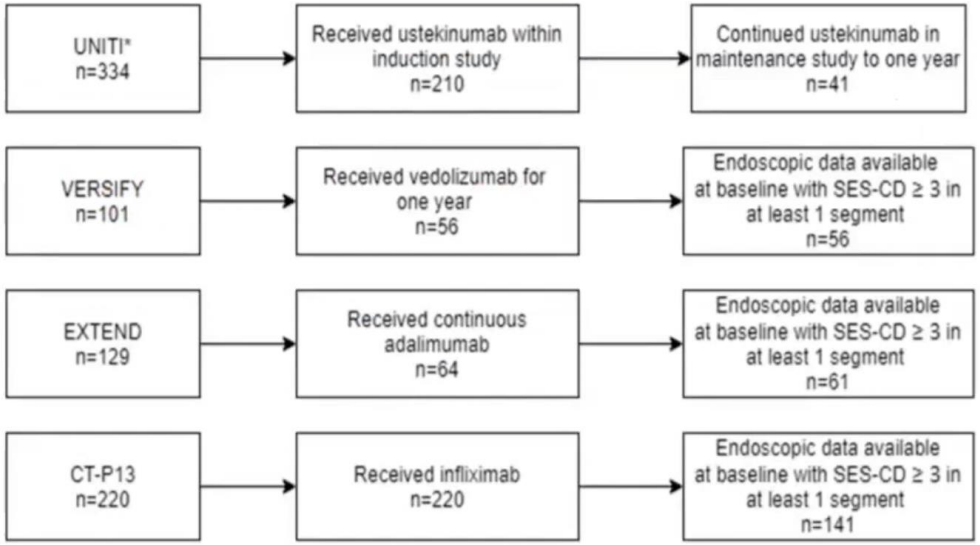


Table 2. Endoscopic outcomes at 1 year among all participants

		Endoscopic healing at 1 yr among participants (n = 299)		
Treatment	**N**	**Endoscopic healing at 1 yr, n (%)**	***P* (pairwise)[a]**	***P***
Adalimumab	61	17/61 (27.9)	0.004	0.009
Infliximab	141	39/141 (27.7)	0.002	
Ustekinumab	41	7/41 (17.1)	0.128	
Vedolizumab	56	4/56 (7.1)	N/A	

Narula et al. Am J Gastroenterol 2022

EFFICACITÉ ET RAPIDITÉ D'ACTION

Comparative Efficacy and Rapidity of Action for Infliximab vs Ustekinumab in Biologic Naïve Crohn's Disease

Neeraj Narula,* Emily C. L. Wong,* Parambir S. Dulai,‡ Neil K. Sengupta,* John K. Marshall,* Jean-Frederic Colombel,§ and Walter Reinisch‖

Clin Gastro Hepatol 2022: 20: 1579-1587

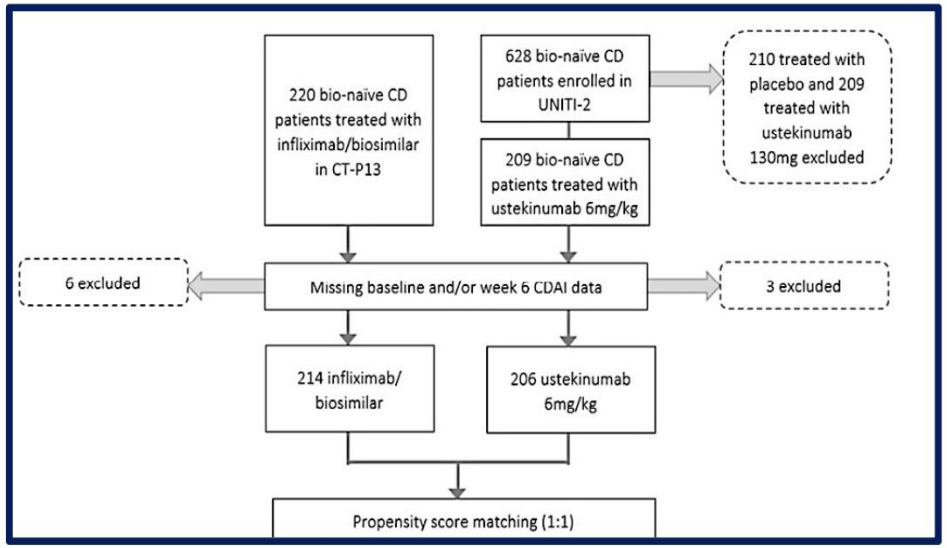


Table 3. Clinical Outcomes Achieved by Patients Treated With Ustekinumab and Infliximab

	Infliximab (n = 214)	Ustekinumab (n = 206)	P
Overall cohort			
Week 6 clinical response, n (%)	125 (58.4)	113 (54.9)	
Week 6 clinical remission, n (%)	96 (44.9)	78 (37.9)	
Baseline fecal calprotectin level >250 mcg/L and week 6 fecal calprotectin level <250 mcg/L, n (%)	55/130 (42.3)	43/124 (34.7)	
Baseline fecal calprotectin level >250 mcg/L and week 6 fecal calprotectin level <50 mcg/L, n (%)	19/130 (14.6)	9/124 (7.3)	
	Infliximab (n = 168)	**Ustekinumab (n = 168)**	
Propensity score matched cohort			
Week 6 clinical response, n (%)	101 (60.1)	94 (56.0)	
Week 6 clinical remission, n (%)	73 (43.5)	65 (38.7)	
Baseline fecal calprotectin level >250 mcg/L and week 6 fecal calprotectin level <250 mcg/L, n (%)	47/106 (44.3)	38/113 (33.6)	
Baseline fecal calprotectin level >250 mcg/L and week 6 fecal calprotectin level <50 mcg/L, n (%)	14/106 (13.2)	7/113 (6.2)	

ANTI-IL 12/23 OU 23 SPÉCIFIQUE?

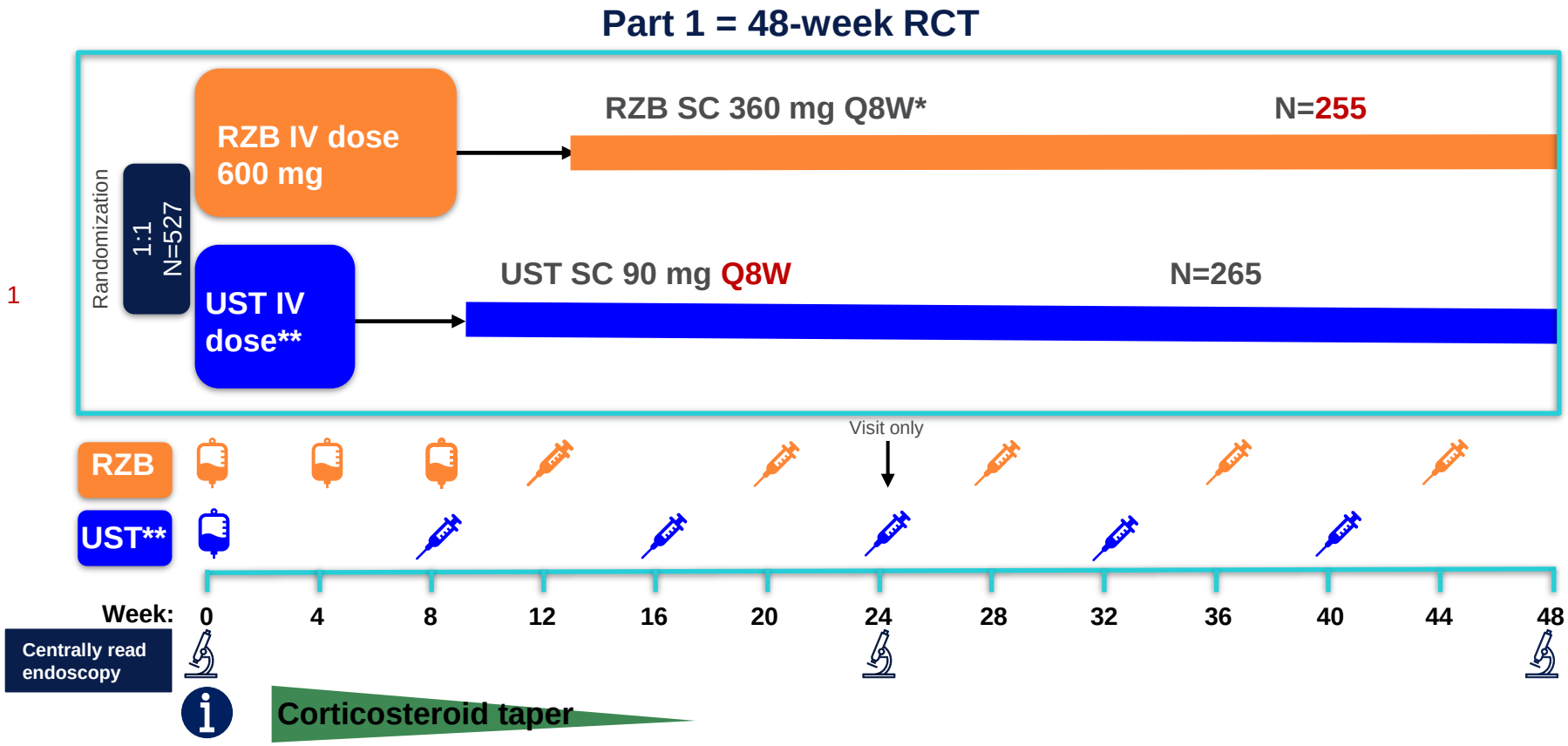
- SEQUENCE
- VIVID

ETUDE SEQUENCE PHASE 3B

Key eligibility
- CDAI 220-450
- SF ≥4 and/or APS ≥2
- SES-CD ≥6 or ≥4 for isolated ileal disease (excluding the narrowing component) as scored by blinded central review
- Subjects must have failed 1 or more anti-TNFs

Stratification factors
- Number of prior anti-TNF failures (1, >1)
- Corticosteroid use at baseline (yes or no)

The trial was OL for study drug, however, CDAI was blinded to the site and patient, central reader was blinded to study drug



***Risankizumab Wk 48 completers may enter extension study (SC 360 mg Q8W) up to Wk 220. ****UST baseline IV dose was weight-based**: ≤55 kg: 260 mg, >55 kg to 85 kg: 390 mg or >85 kg: 520 mg

RISA Dosing Regimens:
- Study initiated prior to RZB CD pivotal results and all subjects randomized to RZB initially received 1200mg IV induction followed by either 360mg or 180mg SC maintenance.
- After the CD pivotal results, this study was amended to the **selected RZB dosing regimen** (600mg IV induction and 360mg SC maintenance) (7 subjects received the **non-selected RZB dosing regimen** and were excluded from the primary efficacy analysis)

APS, abdominal pain score; CD, Crohn's disease; CDAI, Crohn's Disease Activity Index; IV, intravenous; Q8W, once every 8 weeks; OL, open label; RCT, randomized controlled trial; RZB, risankizumab; SC, subcutaneous; SES-CD, Simple Endoscopic Score for Crohn's Disease; SF, stool frequency; TNF, tumor necrosis factor; UST, ustekinumab

Caractéristiques démographiques et cliniques de la population à l'étude

Variable (ITT1)[1]	RZB 600/360 (N = 255)[2]	UST (N = 265)[2]
Female, n (%)	119 (46.7)	134 (50.6)
Race (white), n (%)	195 (77.4)	188 (71.5)
Age (years), Median (range)	36.0 (18, 75)	36.0 (18, 73)
Weight (kg), Mean (SD)	68.924 (17.9346)	71.280 (19.3971)
Disease duration (years), Mean (SD)	9.439 (7.7684)	9.413 (8.6514)
Baseline immunomodulator use, n (%)	34 (13.3)	47 (17.7)
Baseline steroid use, n (%)[3]	58 (22.7)	71 (26.8)
Number of prior anti-TNF failed[3] 1, n (%) >1, n (%)	 196 (76.9) 59 (23.1)	 204 (77.0) 61 (23.0)
Fecal calprotectin (mcg/g), Median (range)	1030.0 (30, 26823)	1515.0 (30, 26361)
hs-CRP (mg/L), Median (range)	8.20 (0.2, 287.1)	9.40 (0.2, 196.6)
Baseline CDAI, Mean (SD) ≤300, n (%) >300, n (%)	N=251 309.43 (61.727) 118 (47.0) 133 (53.0)	N=263 310.14 (62.632) 114 (43.3) 149 (56.7)
Baseline SES-CD, Mean (SD) ≤15, n (%) >15, n (%)	13.5 (7.06) 174 (68.2) 81 (31.8)	14.1 (7.39) 163 (61.5) 102 (38.5)
Baseline SF, Mean (SD)	N=251 5.538 (2.7071)	N=263 5.627 (2.5445)
Baseline AP, Mean (SD)	N=251 1.929 (0.5160)	N=263 1.907 (0.5781)

VIVID : 30%
VIVID : 30%

VIVID : 52% Bionaive
30% failed 1
18 failed ≥ 2

[1] ITT1: includes subjects who were randomized to the UST or the selected RZB dose regimen group (RZB 600 mg IV followed by RZB 360 mg SC) and received at least one dose of study drugs during Part 1 of the study.

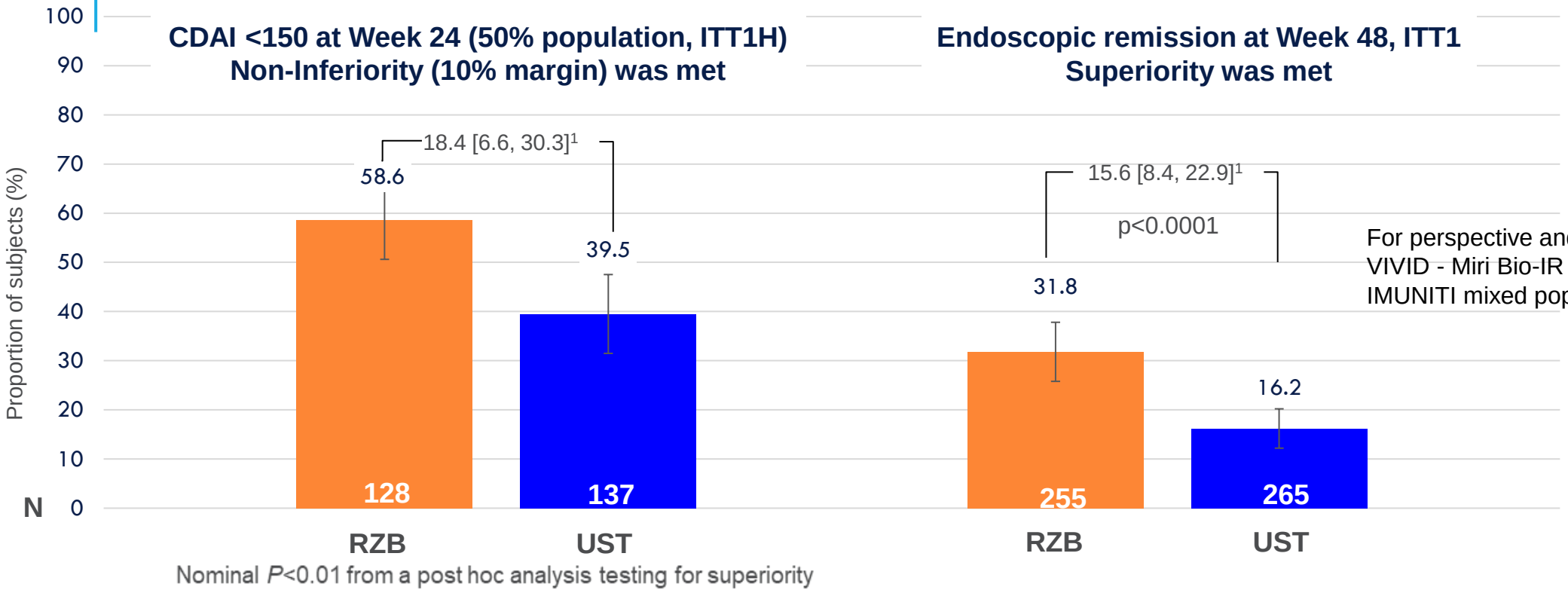
[2] The different sample size is presented below for variables where there are missing data at baseline. Percentage calculated on non-missing values.

[3] Stratification factors.

AP, abdominal pain; CDAI, Crohn's Disease Activity Index; hs-CRP, high-sensitivity C-reactive protein; ITT, intention to treat; IV, intravenous; RZB, risankizumab; SC, subcutaneous; SD, standard deviation; SES-CD, Simple Endoscopic Score for Crohn's Disease; SF, stool frequency; TNF, tumor necrosis factor; UST, ustekinumab; wk, week.

Issues primaires

- Disease duration : 8y
- Mean CDAI :310
- CDAI > 300 : 55%
- Mean SES-CD : 14
- **SES-CD > 15 : 35%**

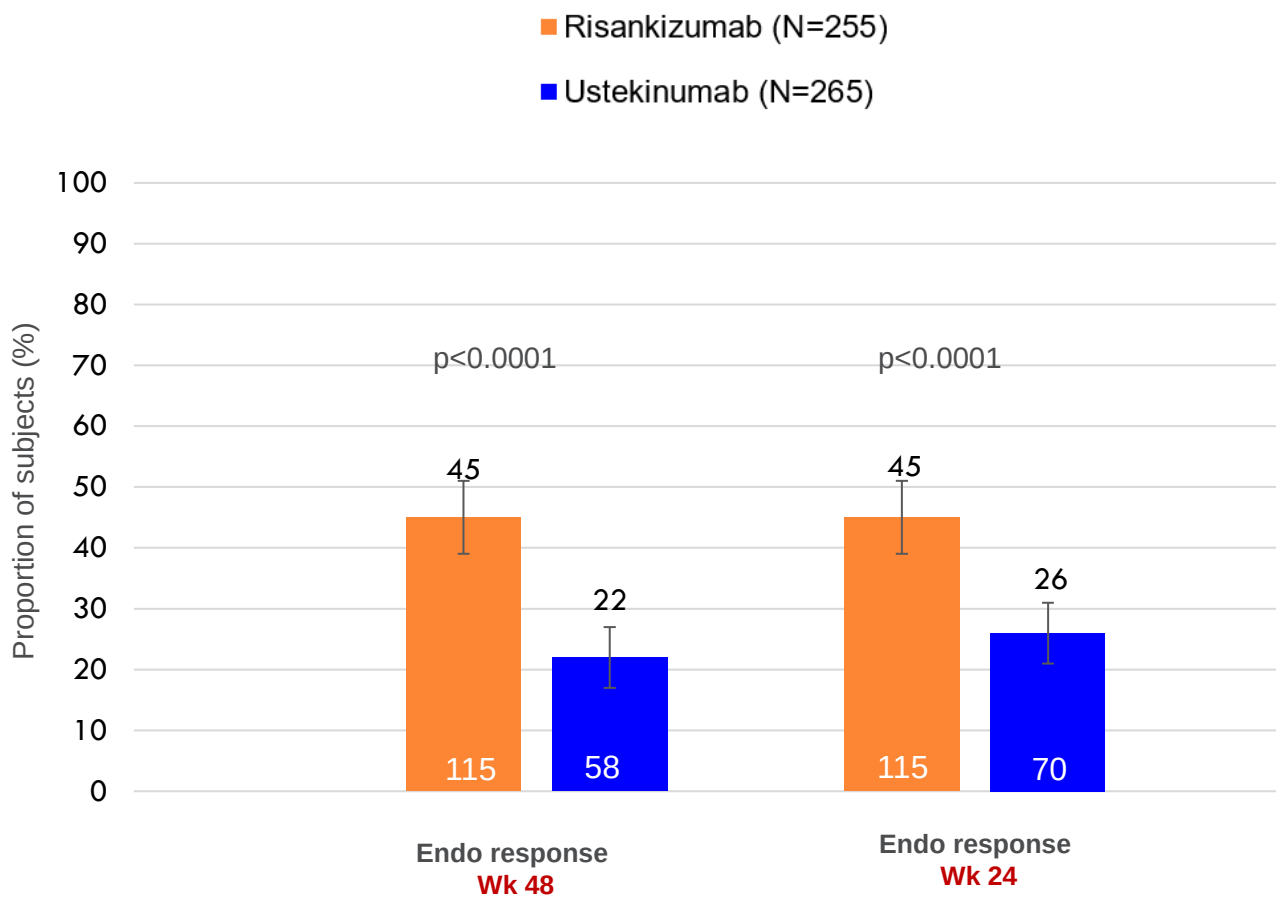


For perspective and not direct comparaison :
VIVID - Miri Bio-IR Wk 52 : 23% VS 18%
IMUNITI mixed pop Wk 44 : 10% (SES-CD ≤ 2)

Error bars: 95% CI. Endoscopic remission: SES-CD ≤4 and at least a 2-point reduction versus baseline and no subscore >1 in any individual variable, as scored by a central reviewer. ITT1: includes subjects who were randomized to the UST or the selected RZB dose regimen group (RZB 600 mg IV followed by RZB 360 mg SC) and received at least one dose of study drugs during Part 1 of the study. ITT1H: The ITT1H population is a subset of the ITT1 population (approximately 50%) who reached Week 24 and is the population for the primary efficacy endpoint of clinical remission (CDAI <150) at Week 24. [1]Stratum-adjusted treatment difference (%) [95% CI] RZT–US .

Réponse endoscopique – issue secondaire

- Disease duration : 8y
- Mean CDAI :310
- CDAI > 300 : 55%
- **Mean SES-CD : 14**
- **SES-CD > 15 : 35%**
- CS : 25% Max 20mg



For perspective and not direct comparaison :
VIVID - Miri Bio-IR Wk 52 : 45% VS 40%
IMUNITI mixed pop Wk 44 : 24%

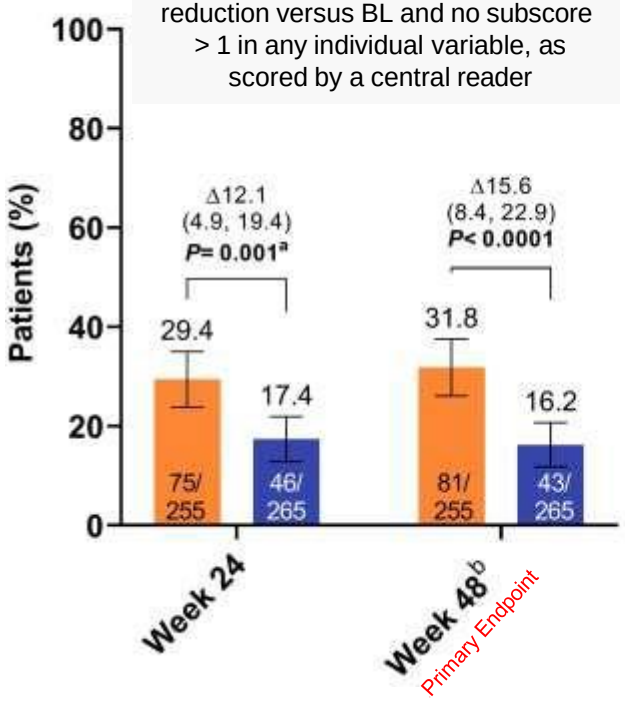
Error bars: 95% CI. Endoscopic response: Decrease in SES-CD >50% from baseline (or for subjects with isolated ileal disease and a baseline SES-CD of 4, at least a 2-point reduction from baseline), as scored by central reviewer. Endoscopic remission: SES-CD ≤4 and at least a 2-point reduction versus baseline and no subscore >1 in any individual variable, as scored by a central reviewer.ITT1: includes subjects who were randomized to the UST or the selected RZB dose regimen group (RZB 600 mg IV followed by RZB 360 mg SC) and received at least one dose of study drugs during Part 1 of the study. Steroid-free: subject not receiving steroids at the corresponding visit.

ISSUES ENDOSCOPIQUES - ANALYSE POST HOC

- Disease duration : 8y
- Mean CDAI :310
- CDAI > 300 : 55%
- **Mean SES-CD : 14**
- **SES-CD > 15 : 35%**
- CS : 25% Max 20mg

Endoscopic Remission

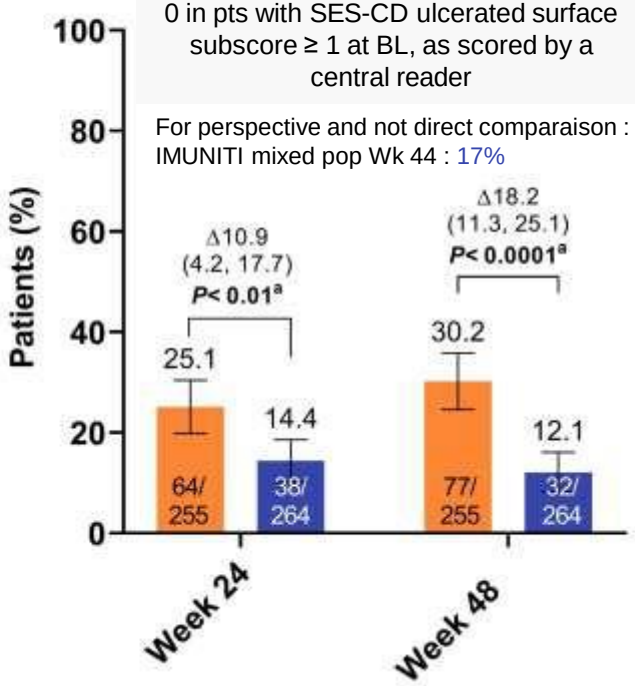
SES-CD ≤ 4 and at least a 2-point reduction versus BL and no subscore > 1 in any individual variable, as scored by a central reader



Mucosal Healing

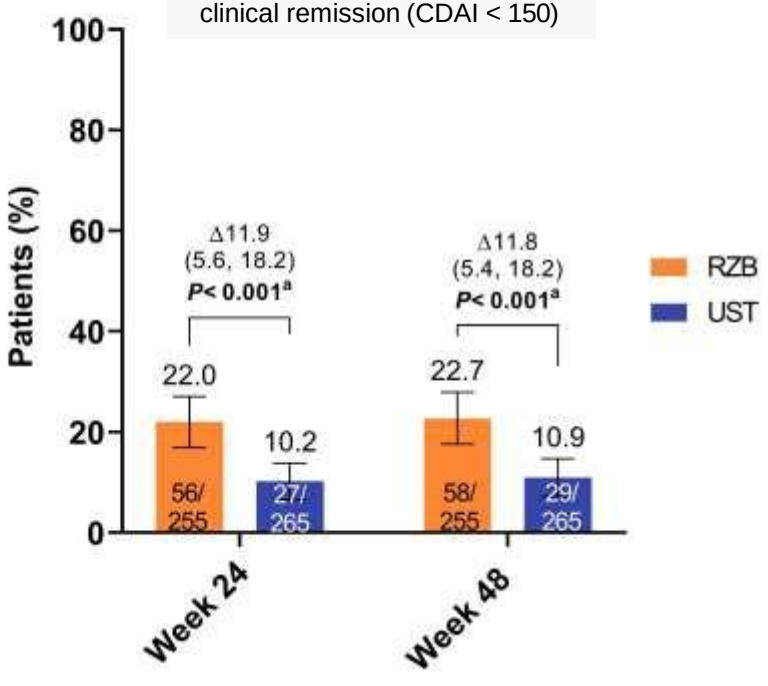
SES-CD ulcerated surface subscore of 0 in pts with SES-CD ulcerated surface subscore ≥ 1 at BL, as scored by a central reader

For perspective and not direct comparaison : IMUNITI mixed pop Wk 44 : 17%



Deep Remission

Endoscopic remission + clinical remission (CDAI < 150)



Δ, adjusted treatment difference; BL, baseline; CD, Crohn's disease; CI, confidence interval; RZB, risankizumab; SES-CD, simple endoscopic score for CD; UST, ustekinumab.

Adjusted treatment difference based on Cochran-Mantel-Haenszel test (NOT raw percentage difference); 95% CIs for Δ and *P* values calculated based on Cochran-Mantel-Haenszel test adjusted for strata.

Efficacy population includes patients randomised to UST or RZB (600 mg IV, 360 mg SC) and who received at least one dose of study drug; point estimates and 95% CIs for treatment difference (RZB group - UST group) were adjusted by the stratification factors.

The calculations are based on non-responder imputation incorporating multiple imputation to handle missing data due to COVID-19 and/or geopolitical conflict or non-responder imputation only if there are no missing data due to COVID-19 and/or geopolitical conflict.

[a]*P* value is nominal.

[b]Primary endpoint

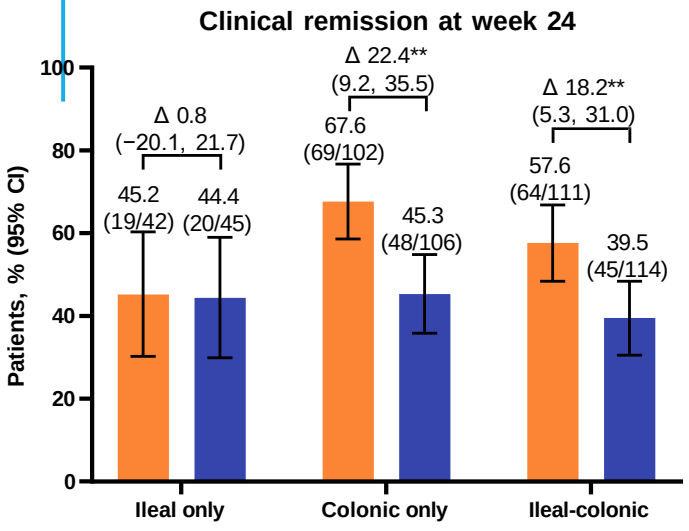
Caractéristiques démographiques et cliniques

Parameter	Ileal only		Colonic only		Ileal-colonic	
	RZB (n = 42)	UST (n = 45)	RZB (n = 102)	UST (n = 106)	RZB (n = 111)	UST (n = 114)
Female, n (%)	18 (42.9)	29 (64.4)	50 (49.0)	48 (45.3)	51 (45.9)	57 (50.0)
Age, years, mean (SD)	43.0 (13.7)	42.5 (15.2)	39.0 (13.2)	38.0 (13.5)	35.3 (12.3)	36.8 (13.3)
Immunomodulator use, n (%)	5 (11.9)	5 (11.1)	14 (13.7)	17 (16.0)	15 (13.5)	25 (21.9)
Corticosteroid use, n (%)	3 (7.1)	13 (28.9)	26 (25.5)	31 (29.2)	29 (26.1)	27 (23.7)
Prior failure of > 1 anti-TNF, n (%)	12 (28.6)	8 (17.8)	21 (20.6)	28 (26.4)	26 (23.4)	25 (21.9)
CD duration, mean (SD)	11.7 (10.1)	9.5 (9.6)	8.7 (7.4)	9.9 (7.9)	9.3 (6.9)	9.0 (9.0)
FCP, mg/kg, median (IQR)	350 (1096)	989 (1884)	1532 (2492)	2012 (3181)	1037 (2250)	1416 (2147)
hsCRP, mg/L, median (IQR)	3.7 (7.1)	7.0 (13.0)	10.2 (26.3)	11.7 (30.7)	10.0 (26.5)	9.3 (28.0)
CDAI, mean (SD)	**292.5 (52.6)**	**305.5 (63.1)**	**320.3 (63.3)**	**308.3 (64.1)**	**306.2 (62.2)**	**313.6 (61.4)**
SES-CD, mean (SD)	**6.5 (2.4)**	**7.1 (2.5)**	**15.0 (6.4)**	**14.6 (6.9)**	**14.9 (7.3)**	**16.5 (7.4)**
Average daily SF, mean (SD)	4.5 (2.0)	5.2 (2.2)	6.3 (2.9)	5.9 (2.7)	5.3 (2.6)	5.5 (2.5)
Average daily APS, mean (SD)	1.9 (0.5)	2.0 (0.6)	1.9 (0.5)	1.8 (0.6)	1.9 (0.5)	2.0 (0.6)

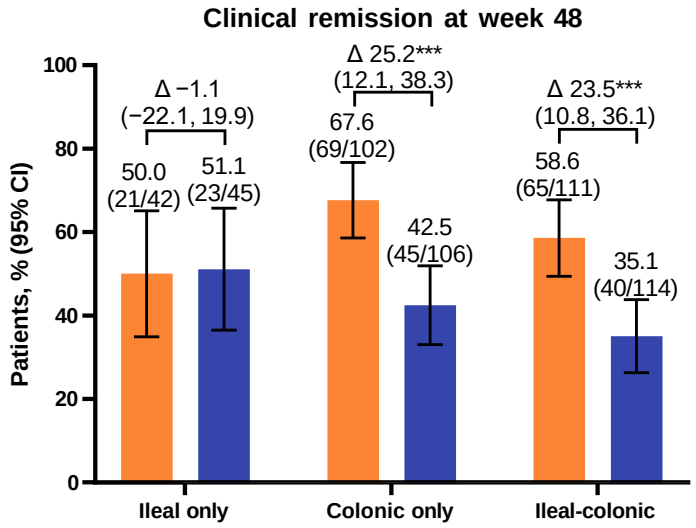
APS, abdominal pain score; CD, Crohn's disease; CDAI, Crohn's Disease Activity Index; FCP, faecal calprotectin; hsCRP, high-sensitivity C-reactive protein; IQR, interquartile range; RZB, risankizumab; SES-CD, Simple Endoscopic Score for Crohn's Disease; SF, stool frequency; TNF, tumour necrosis factor; UST, ustekinumab.

Issues cliniques selon la localisation de la maladie

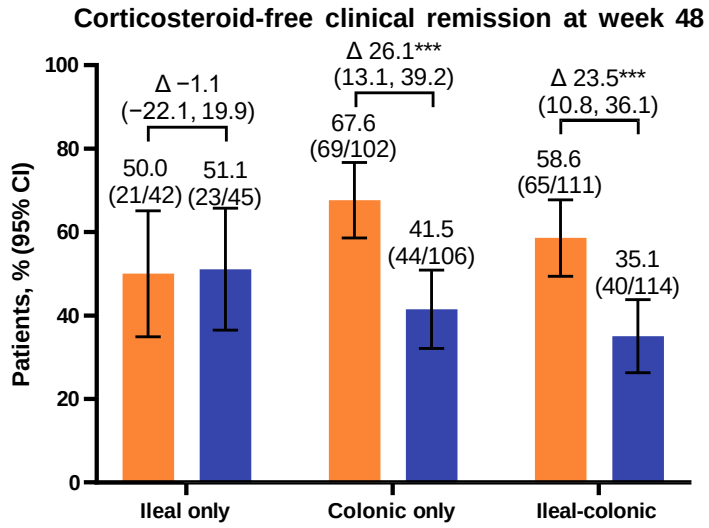
RZB UST



Main Cohort
60% VS 43%
(whole population)



Main Cohort
61% VS 41%

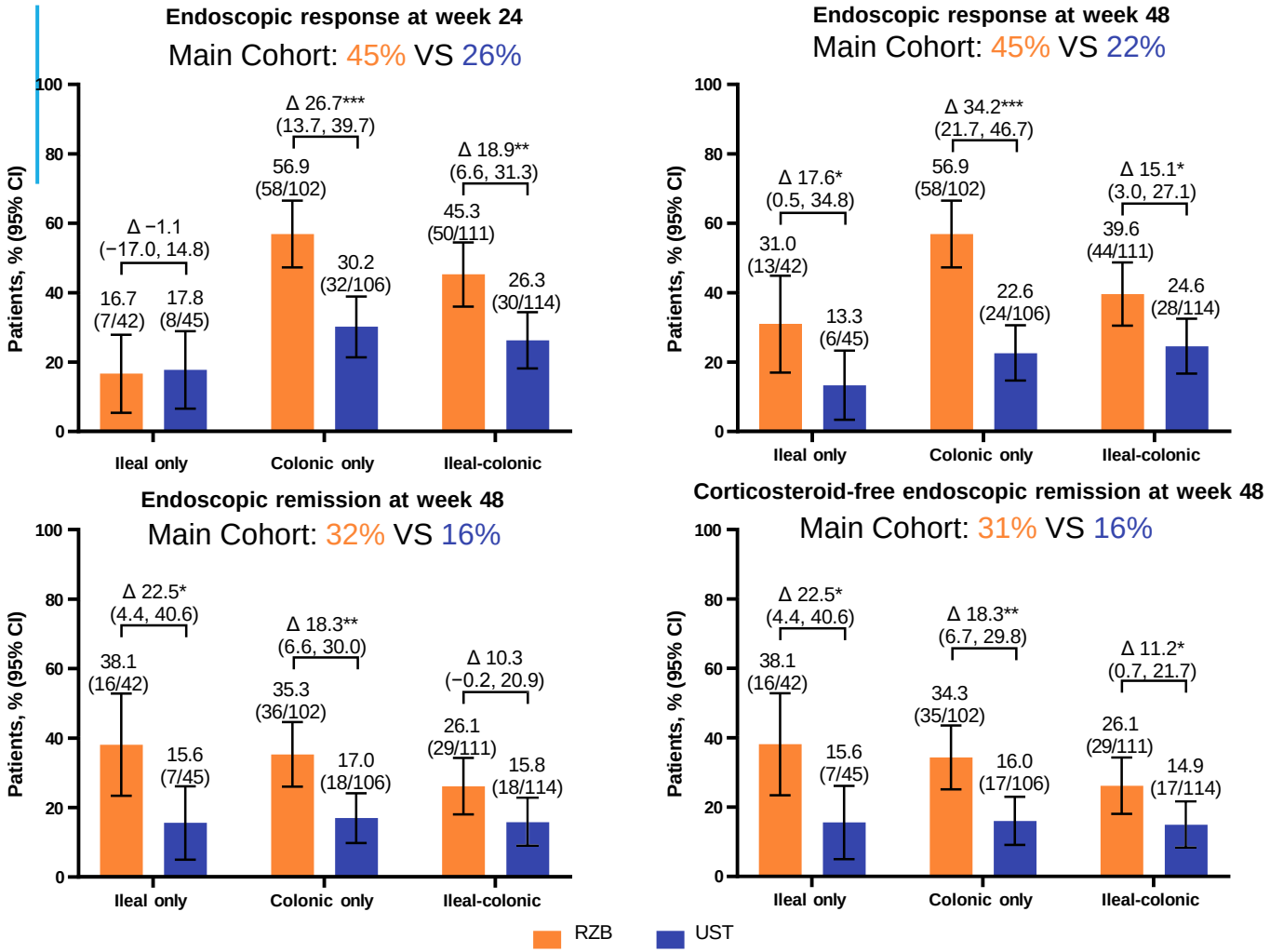


Main Cohort
61% VS 40%

- Plus haut taux de rémission clinique vs UST en maladie colique et iléocolique
- Taux de rémission clinique similaire entre RZB et UST en maladie iléale isolée

CD, Crohn's disease; RZB, risankizumab; UST, ustekinumab.
Nonresponder imputation incorporating multiple imputation to handle missing data due to COVID-19 and/or geopolitical conflict was used. Differences vs UST (Δ) were calculated as risankizumab − placebo.
95% CI for differences are calculated based on normal approximation to the binomial distribution for the comparison of 2 treatment groups. *P* values are based on Chi-square test or Fisher's exact test if more than 20% of the cells have expected counts of < 5 and there are no missing values due to COVID-19 and/or geopolitical conflict.
**Nominal $P \leq .01$; ***nominal $P \leq .001$ vs UST.

Issues endoscopiques selon la localisation de la maladie

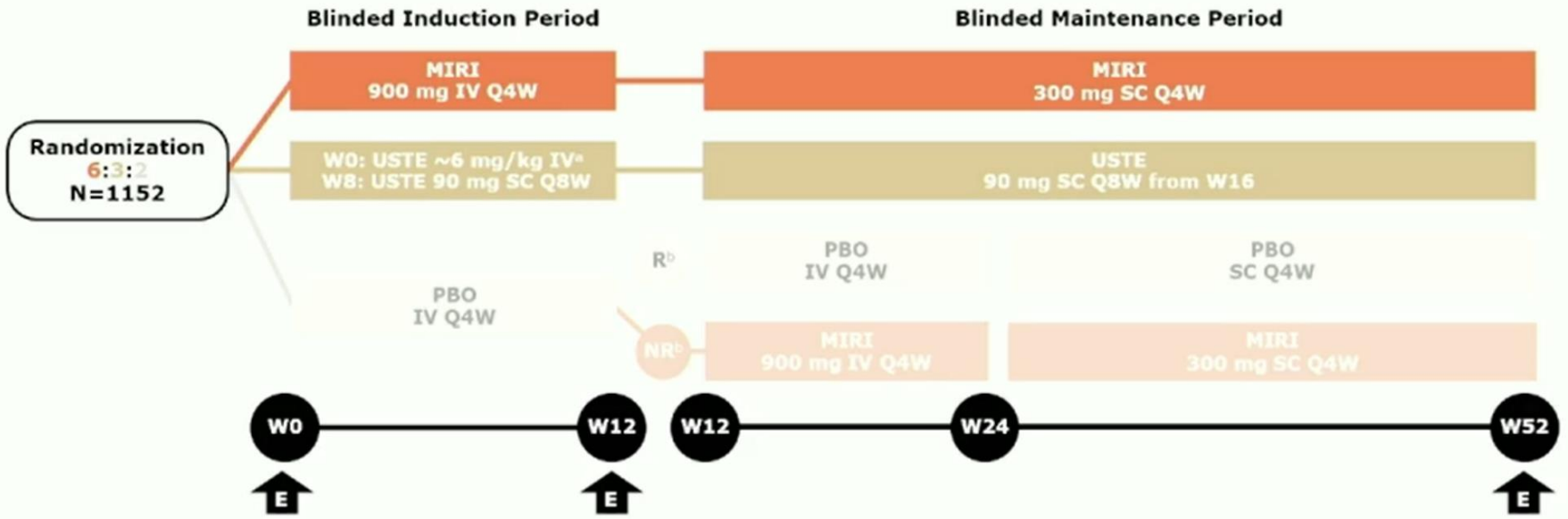


- Plus haut taux de réponse et de rémission endo à la S48 avec RZB vs UST peu importe la localisation de la maladie
- Plus haut taux de réponse et de rémission endo à la S48 avec RZB vs UST en maladie iléale isolée

CD, Crohn's disease; RZB, risankizumab; UST, ustekinumab.
Nonresponder imputation incorporating multiple imputation to handle missing data due to COVID-19 and/or geopolitical conflict was used. Differences vs UST (Δ) were calculated as risankizumab − placebo.
95% CI for differences are calculated based on normal approximation to the binomial distribution for the comparison of 2 treatment groups. *P* values are based on Chi-square test or Fisher's exact test if more than 20% of the cells have expected counts of < 5 and there are no missing values due to COVID-19 and/or geopolitical conflict.
*Nominal $P \leq .05$; **nominal $P \leq .01$; ***nominal $P \leq .001$ vs UST.

ÉTUDE VIVID-1

A Phase 3, Multicenter, Randomized, Double-Blind, Double-Dummy, Placebo- and Active-Controlled, Treat-Through Study



[a] Single dose; [b] Responders by PRO at Week 12 of VIVID-1, defined as having achieved ≥30% decrease in loose stool frequency and/or abdominal pain, with neither score higher than baseline. Notes: PBO was administered IV and SC from Weeks 8 to 20; otherwise administered IV at Weeks 0 and 4; from Week 24, PBO was administered SC only. Visits occurred every 2 weeks during induction except at W10 and every 4 weeks during maintenance

CDAI=Crohn's Disease Activity Index; E=endoscopy; IV=intravenous; MIRI=mirikizumab; NR=non-responder; PBO=placebo; PRO=Patient Reported Outcome (2 of the patient-reported items of the CDAI [stool frequency and abdominal pain]); Q4W=every 4 weeks; Q8W=every 8 weeks; R=responder; SC=subcutaneous; USTE=ustekinumab; W=Week

©Speaker: Prof. Vipul Jairath at ECCO'24 Congress

Key Entry Criteria

- Adults aged ≥18 and ≤80 years
- Diagnosis of CD or fistulizing CD for ≥3 months
- Average daily liquid/soft stool frequency (SF) ≥4 and/or average daily abdominal pain (AP) ≥2
- Simple Endoscopic Score for Crohn's Disease (SES-CD) ≥7 (or ≥4 for patients with isolated ileal disease)
- Inadequate response, loss of response, or intolerant to conventional or biologic therapy

Demographics and Baseline Characteristics

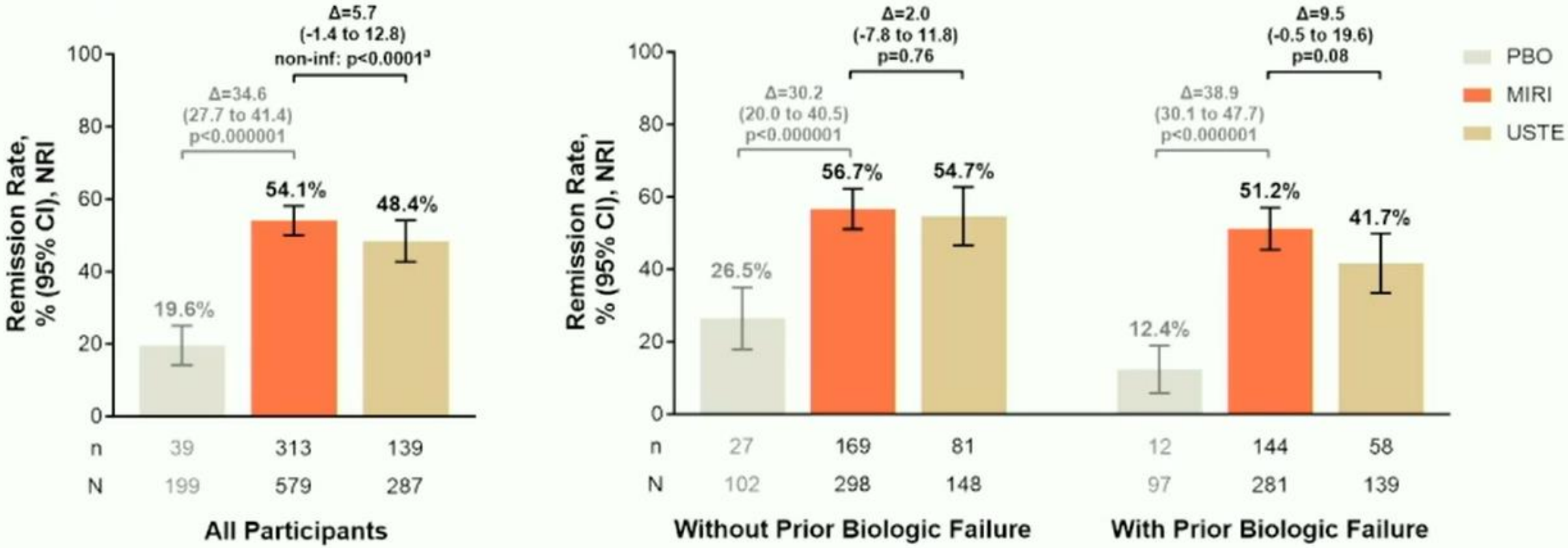
Characteristic	PBO (N=199)	MIRI (N=579)	USTE (N=287)
Age, years, mean (SD)	36.3 (12.7)	36.0 (13.2)	36.6 (12.7)
Male, n (%)	118 (59.3)	332 (57.3)	137 (47.7)
Weight, kg, mean (SD)	69.6 (19.0)	68.0 (18.3)	66.9 (17.6)
Duration of CD, years, median (IQR)	5.6 (2.0-10.4)	4.6 (1.7-9.3)	5.1 (2.2-9.0)
Baseline CDAI, median (IQR)	320.3 (259.6-374.7)	318.0 (268.0-374.9)	309.6 (247.0-379.0)
SF daily average	5.6 (4.1-7.1)	5.6 (4.1-6.7)	5.4 (4.1-7.0)
AP score daily average	2.0 (2.0-2.4)	2.0 (2.0-2.6)	2.0 (1.7-2.6)
SES-CD total score, median (IQR)	11.5 (8.7-17.0)	11.7 (8.5-17.5)	12.0 (8.5-18.0)
Disease location, n (%)			
Ileum only	19 (9.5)	65 (11.2)	29 (10.1)
Colon only	77 (38.7)	225 (38.9)	120 (41.8)
Ileum and colon	103 (51.8)	289 (49.9)	138 (48.1)
FCP, µg/g, median (IQR)	1161 (324-2170)	1315 (444-2676)	1489 (519-2814)
CRP, mg/L, median (IQR)	7.6 (2.9-18.8)	8.5 (2.9-25.0)	8.9 (3.4-24.8)

Note: Includes all randomized patients who received ≥1 dose of allocated treatment with baseline SES-CD ≥7 (or ≥4 for isolated ileal disease)

AP=abdominal pain; CD=Crohn's disease; CDAI=Crohn's Disease Activity Index; CRP=C-reactive protein; FCP=fecal calprotectin; IQR=interquartile range; MIRI=mirikizumab; PBO=placebo; SD=standard deviation; SES-CD=Simple Endoscopic Score for Crohn's disease; SF=stool frequency; USTE=ustekinumab

CDAI Clinical Remission at Week 52

Key Secondary Endpoint

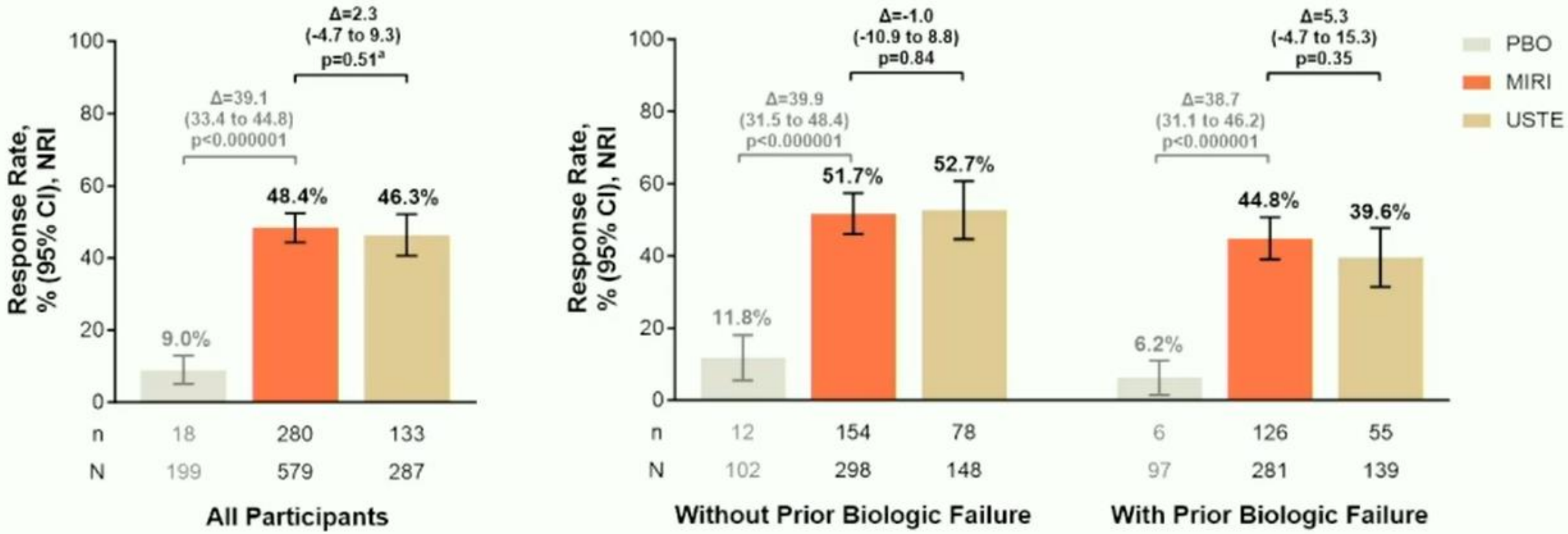


[a] Multiplicity-adjusted comparison using a **non-inferiority test with 10% margin.** The p-value for the corresponding superiority test is p=0.11

Notes: Unless otherwise specified, comparisons are superiority test and not multiplicity-adjusted. CDAI clinical remission was defined as CDAI total score <150. Δ is the risk difference between the groups indicated and is adjusted for covariates (biologic-failed status [yes or no], baseline SES-CD total score [<12 or ≥12], and either baseline SF ≥7 and/or baseline AP ≥2.5 [yes or unknown/no]) for the analysis of all patients and unadjusted for the subgroup analysis. For PBO, NRI is used for binary outcomes at Week 52 for patients who switched to MIRI at Week 12. *AP=abdominal pain; CDAI=Crohn's Disease Activity Index; CI=confidence interval; MIRI=mirikizumab; non-inf=non-inferior; NRI=non-responder imputation; PBO=placebo; SES-CD=Simple Endoscopic Score for Crohn's disease; SF=stool frequency; USTE=ustekinumab*

Endoscopic Response at Week 52

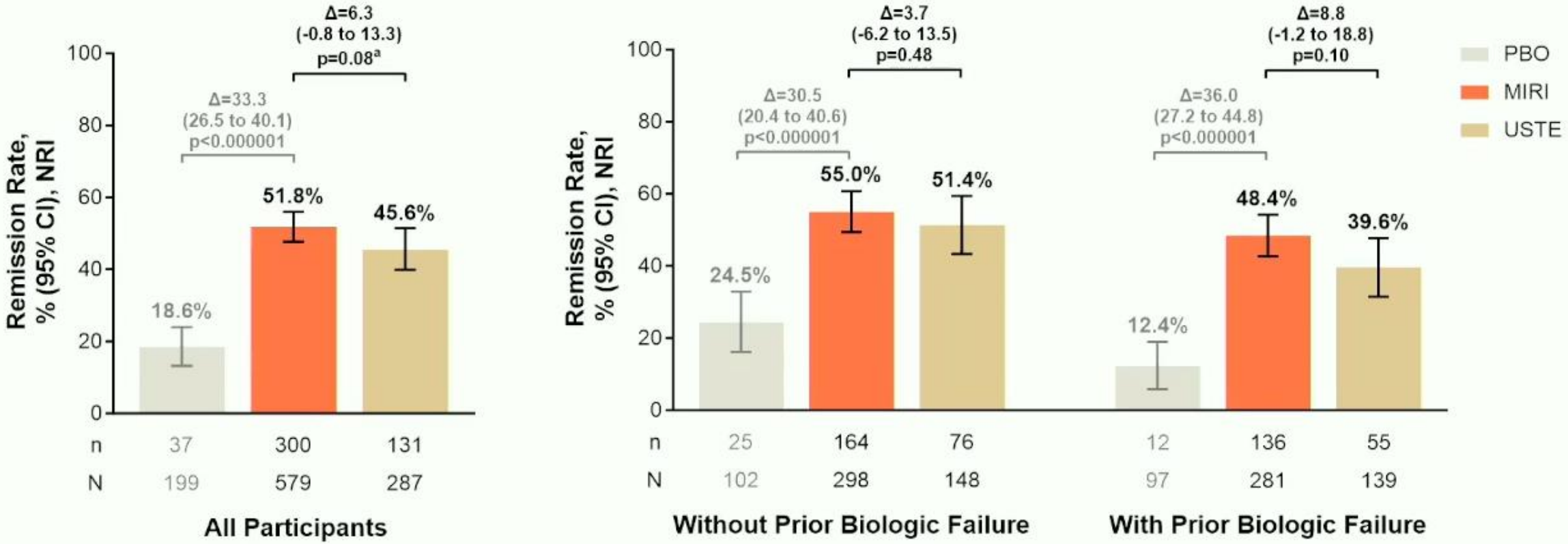
Key Secondary Endpoint



[a] Multiplicity-adjusted comparison using a **superiority test**

Notes: Unless otherwise specified, comparisons are superiority test and not multiplicity-adjusted. Endoscopic response was defined as ≥50% reduction from baseline in SES-CD. Δ is the risk difference between the groups indicated and is adjusted for covariates (biologic-failed status [yes or no], baseline SES-CD total score [<12 or ≥12], and either baseline SF ≥7 and/or baseline AP ≥2.5 [yes or unknown/no]) for the analysis of all patients and unadjusted for the subgroup analysis. For PBO, NRI is used for binary outcomes at Week 52 for patients who switched to MIRI at Week 12. *AP=abdominal pain; CI=confidence interval; MIRI=mirikizumab; NRI=non-responder imputation; PBO=placebo; SES-CD=Simple Endoscopic Score for Crohn's disease; SF=stool frequency; USTE=ustekinumab*

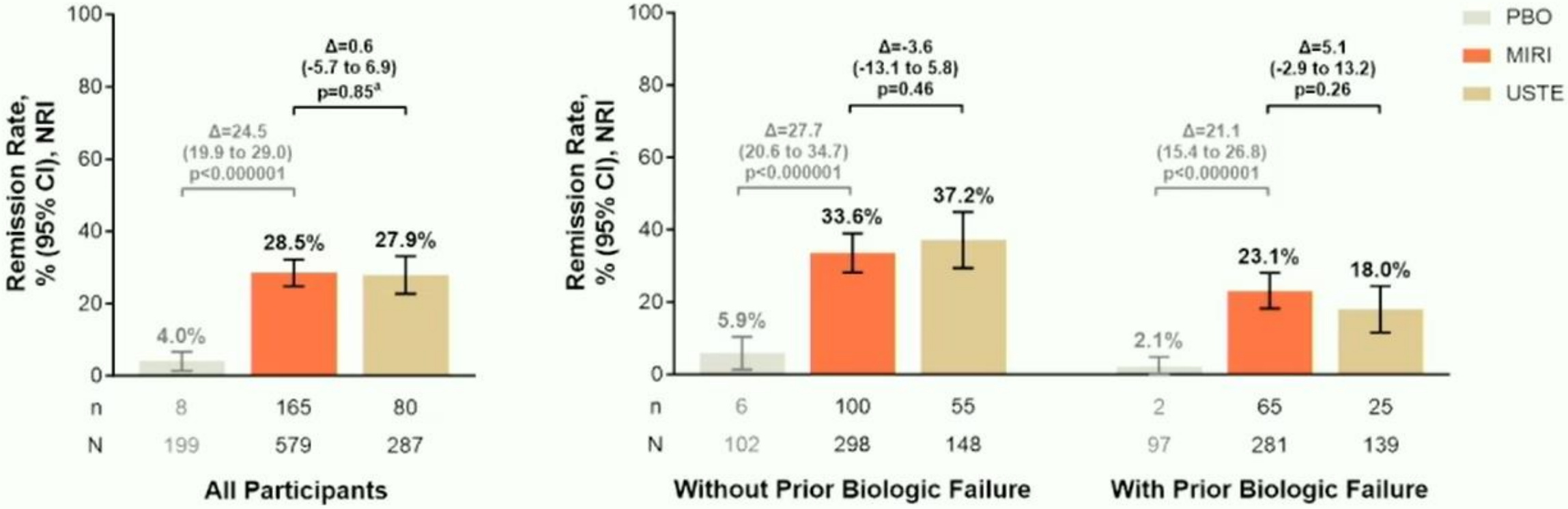
Corticosteroid-Free CDAI Remission at Week 52



[a] **Superiority test** not adjusted for multiplicity

Notes: Unless otherwise specified, comparisons are superiority test and not multiplicity-adjusted. CDAI clinical remission was defined as CDAI total score <150. Δ is the risk difference between the groups indicated and is adjusted for covariates (biologic-failed status [yes or no], baseline SES-CD total score [<12 or ≥12], and either baseline SF ≥7 and/or baseline AP ≥2.5 [yes or unknown/no]) for the analysis of all patients and unadjusted for the subgroup analysis. For PBO, NRI is used for binary outcomes at Week 52 for patients who switched to MIRI at Week 12. *AP=abdominal pain; CDAI=Crohn's Disease Activity Index; CI=confidence interval; MIRI=mirikizumab; NRI=non-responder imputation; PBO=placebo; SES-CD=Simple Endoscopic Score for Crohn's disease; SF=stool frequency; USTE=ustekinumab*

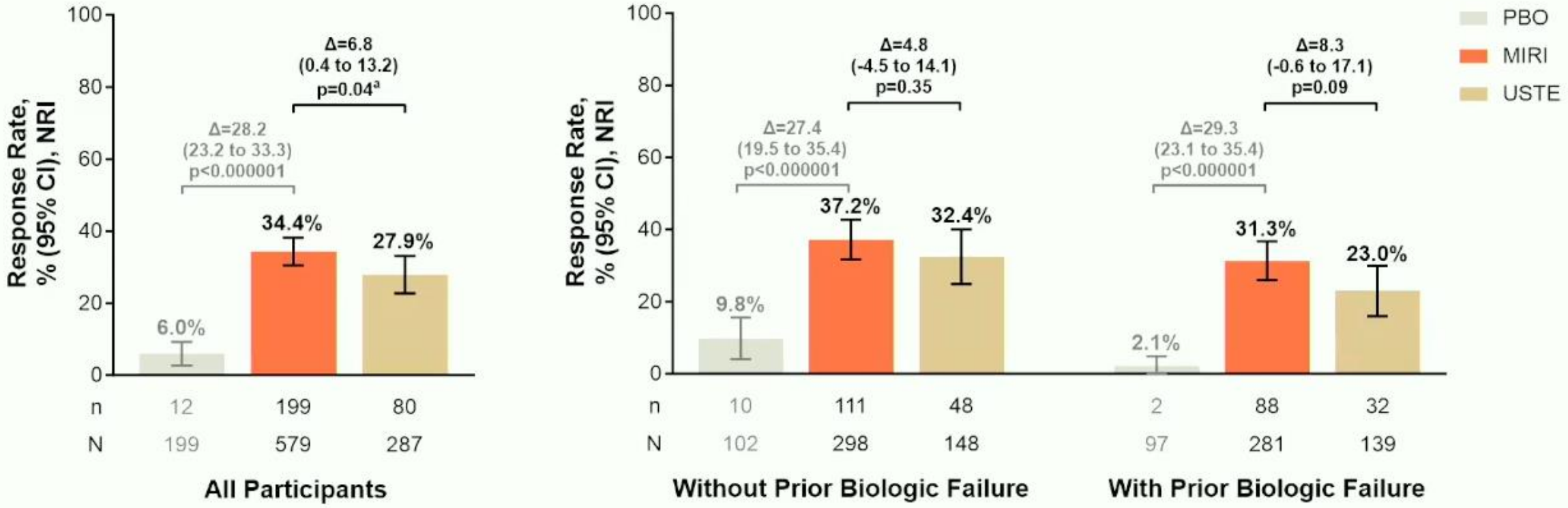
Endoscopic Remission at Week 52



[a] **Superiority test** not adjusted for multiplicity

Notes: Unless otherwise specified, comparisons are superiority test and not multiplicity-adjusted. Endoscopic remission was defined as SES-CD total score ≤4, a ≥2-point reduction from baseline, and no subscore >1 for any individual variable. Δ is the risk difference between the groups indicated and is adjusted for covariates (biologic-failed status [yes or no], baseline SES-CD total score [<12 or ≥12], and either baseline SF ≥7 and/or baseline AP ≥2.5 [yes or unknown/no]) for the analysis of all patients and unadjusted for the subgroup analysis. For PBO, NRI is used for binary outcomes at Week 52 for patients who switched to MIRI at Week 12. *AP=abdominal pain; CI=confidence interval; MIRI=mirikizumab; NRI=non-responder imputation; PBO=placebo; SES-CD=Simple Endoscopic Score for Crohn's disease; SF=stool frequency; USTE=ustekinumab*

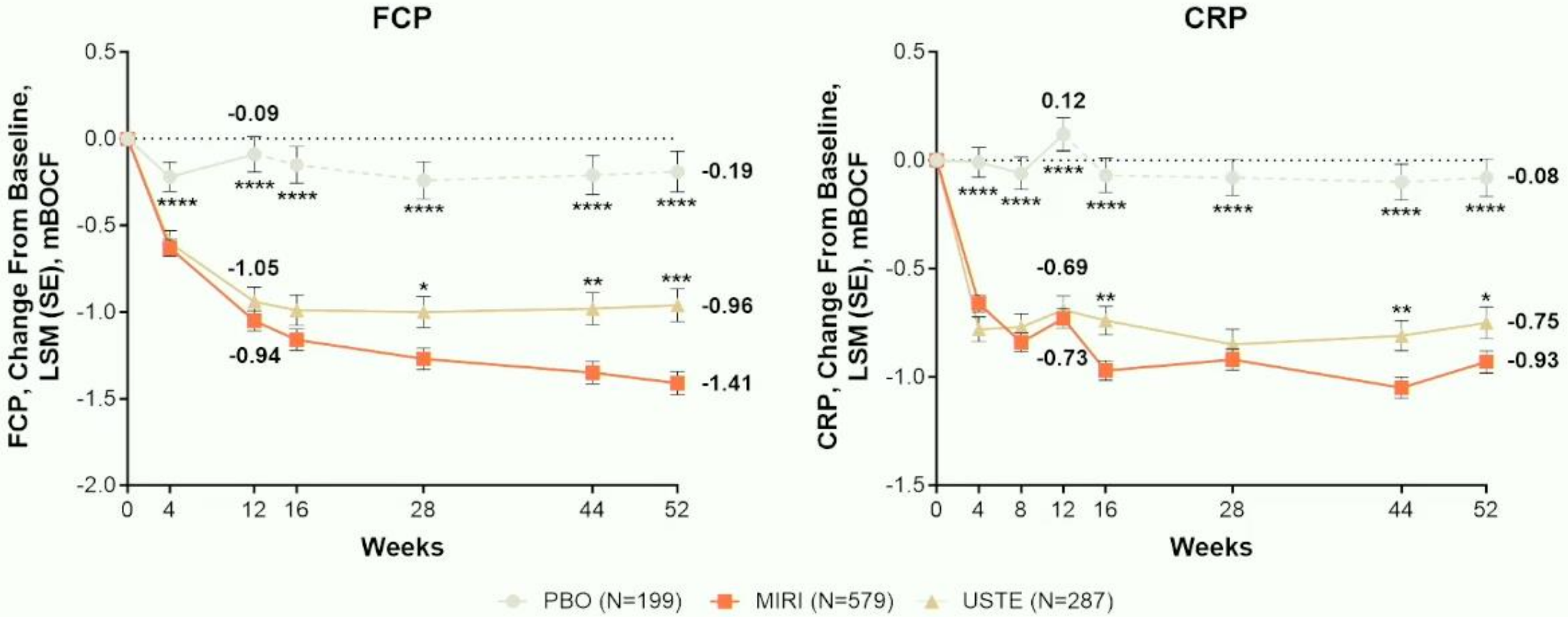
Combined CDAI Clinical Remission and Endoscopic Response at Week 52



[a] **Superiority test** not adjusted for multiplicity

Notes: Unless otherwise specified, comparisons are superiority test and not multiplicity-adjusted. CDAI clinical remission was as defined CDAI total score <150. Endoscopic response was defined as ≥50% reduction from baseline in SES-CD. Δ is the risk difference between the groups indicated and is adjusted for covariates (biologic-failed status [yes or no], baseline SES-CD total score [<12 or ≥12], and either baseline SF ≥7 and/or baseline AP ≥2.5 [yes or unknown/no]) for the analysis of all patients. For PBO, NRI is used for binary outcomes at Week 52 for patients who switched to MIRI at Week 12. *AP=abdominal pain; CDAI=Crohn's Disease Activity Index; CI=confidence interval; MIRI=mirikizumab; NRI=non-responder imputation; PBO=placebo; SES-CD=Simple Endoscopic Score for Crohn's disease; SF=stool frequency; USTE=ustekinumab*

FCP and CRP Change From Baseline



* p<0.05; ** p<0.01; *** p<0.001; **** p<0.0001 vs. MIRI

Notes: Data are LSM (SE) of log-transformed values. For participants in the PBO group who switched to MIRI at Week 12, baseline values were carried forward to derive the change from baseline at Week 52.

CRP=C-reactive protein; FCP=fecal calprotectin; LSM=least squares mean; mBOCF=modified baseline observation carried forward; MIRI=mirikizumab; PBO=placebo; SE=standard error; USTE=ustekinumab

EST-CE QUE TOUS LES INHIBITEURS DE L'IL23 SE MONTRERONT ÉGAUX EN CROHN?

Les paris sont ouverts!!

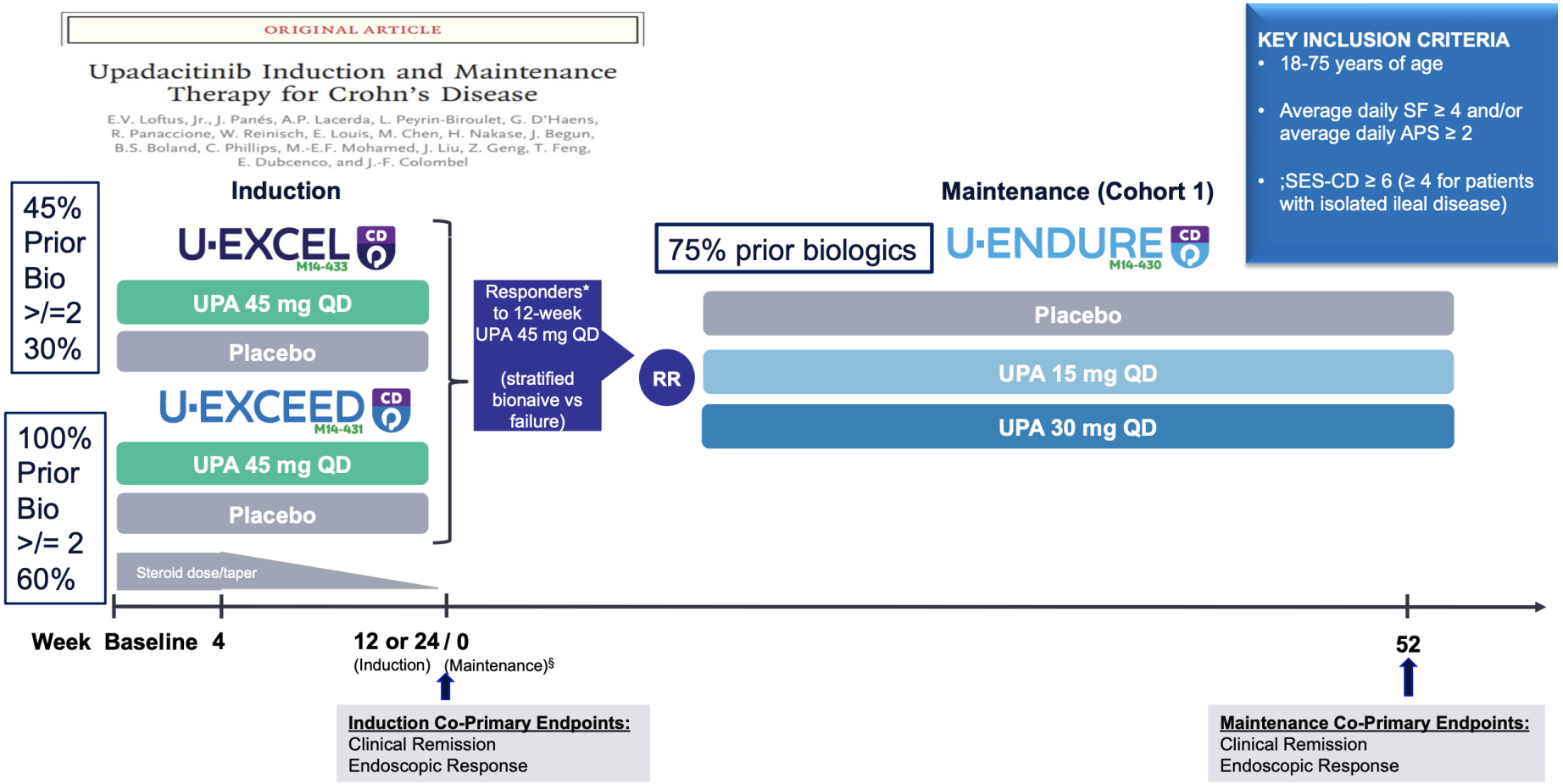
ANTI-TNF AVANT ANTI-IL OU VICE-VERSA?

ANTI-TNF AVANT ANTI-IL OU VICE-VERSA?

- Augmentation ds cellules T IL23 positives résistantes à l'apoptose lesquelles favorisent l'inflammation
- Régulation à la hausse de l'IL23 p19, IL23R, IL17A (résistant à l'apoptose) chez les patients exposés aux anti-TNFs
- Mais qu'en est-il de l'utilisation d'un anti-TNF après usage d'un anti-IL??

UPADACITINIB EN CROHN

UPADACITINIB

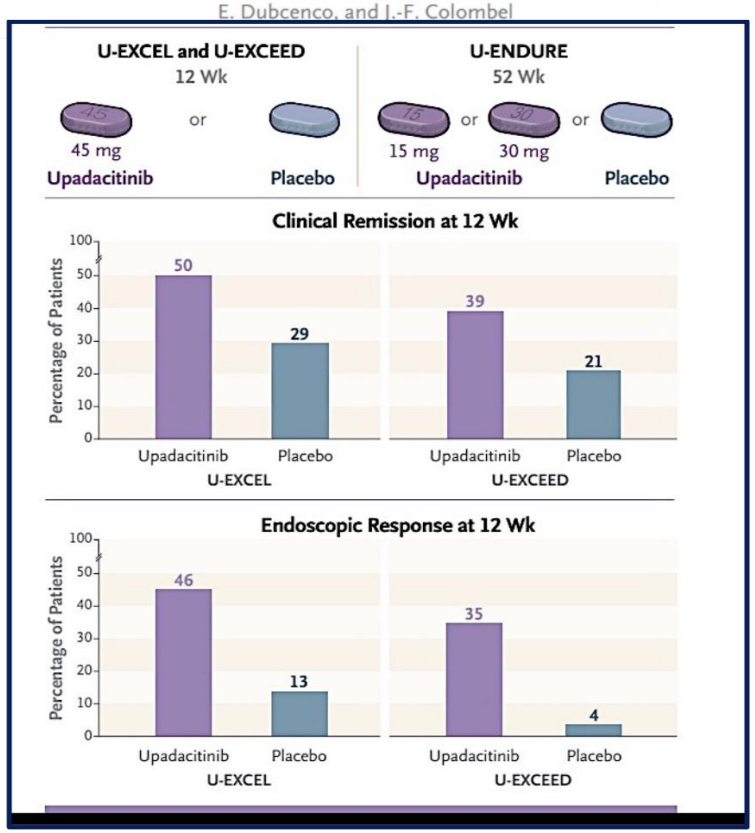


NEJM 2023

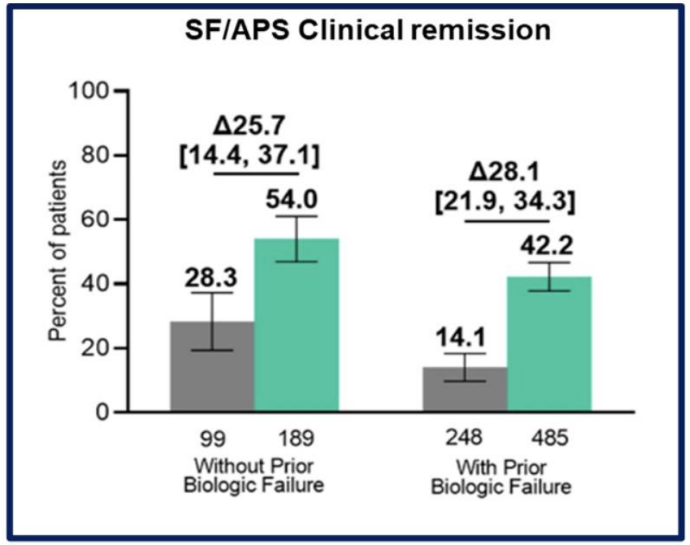
ORIGINAL ARTICLE

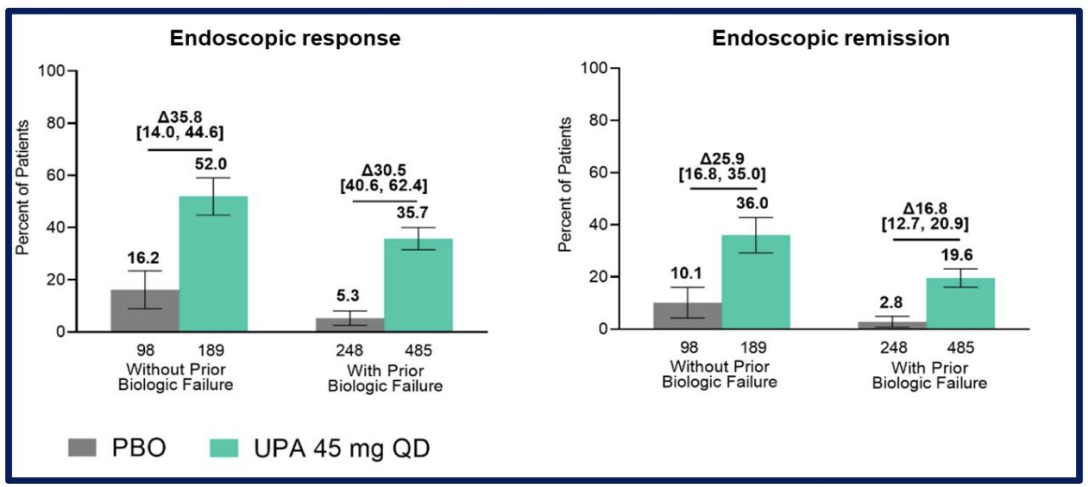
Upadacitinib Induction and Maintenance Therapy for Crohn's Disease

E.V. Loftus, Jr., J. Panés, A.P. Lacerda, L. Peyrin-Biroulet, G. D'Haens, R. Panaccione, W. Reinisch, E. Louis, M. Chen, H. Nakase, J. Begun, B.S. Boland, C. Phillips, M.-E.F. Mohamed, J. Liu, Z. Geng, T. Feng, E. Dubcenco, and J.-F. Colombel



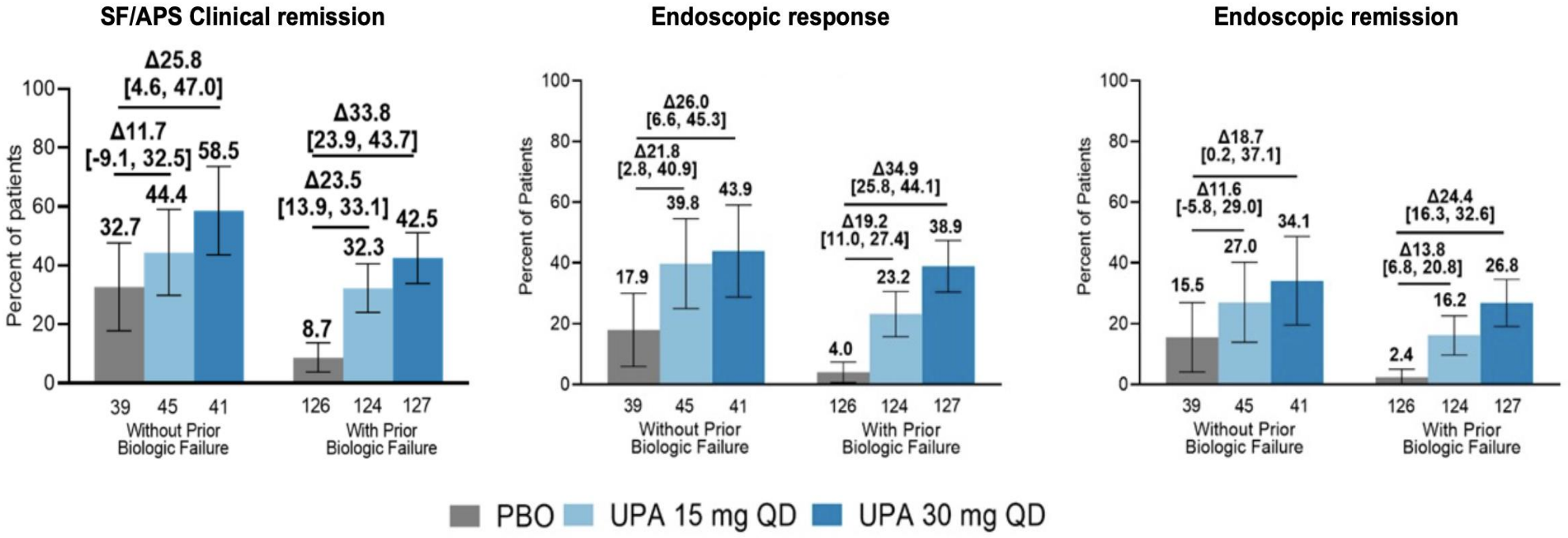
Week 12 - Pooled Induction Data from U-EXCEL and U-EXCEED





ISSUES CLINIQUES ET ENDO SELON L'EXPOSITION ANTÉRIEURE - UPADACITINIB

Week 52 – Maintenance Data from U-ENDURE



FDA requires warnings about increased risk of serious heart-related events, cancer, blood clots, and death for JAK inhibitors that treat certain chronic inflammatory conditions

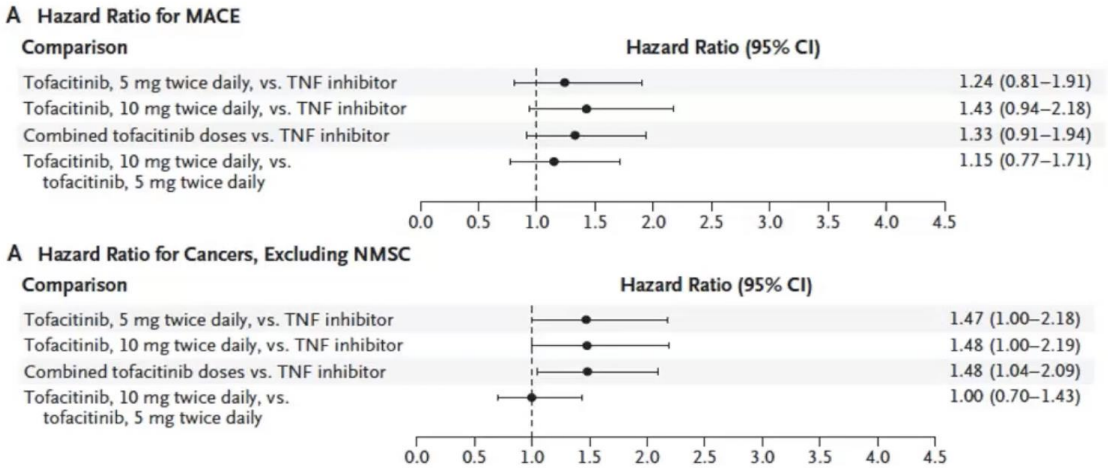
Approved uses also being limited to certain patients

"… we are limiting all approved uses of JAK inhibitors (tofacitinib, upadacitinib, baricitinib) to certain patients **who have not responded or cannot tolerate one or more TNF blockers**"

Cardiovascular and Cancer Risk with Tofacitinib in Rheumatoid Arthritis

ORAL Surveillance Investigators*

The NEW ENGLAND JOURNAL *of* MEDICINE



Event (vs. TNF antagonist)	Tofacitinib 5mg BID	Tofacitinib 10mg BID
Serious infections	1.17 (0.92–1.50)	1.48 (1.17–1.87)
Opportunistic infections	1.82 (1.07–3.09)	2.17 (1.29–3.66)
Hepatic event	1.29 (0.83–2.00)	2.14 (1.43–3.21)
Non-melanoma skin cancer	1.90 (1.04–3.47)	2.16 (1.19–3.92)
Pulmonary embolism	2.93 (0.79–10.83)	8.26 (2.49–27.43)
Venous thromboembolism	1.66 (0.76–3.63)	3.52 (1.74–7.12)
Death	1.49 (0.81–2.74)	2.37 (1.34–4.18)

Ytterberg et al. New Engl J Med 2022

ÉVÉNEMENTS INDÉSIRABLES D'INTÉRÊT – LTE (AD 204 SEMAINES D'EXPOSITION)

Event (E/100 PYs)[a]	PBO n = 89 (PYs = 109.2) (Median exposure = 53.1 weeks)	UPA 15 mg n = 107 (PYs = 173.2) (Median exposure = 79.3 weeks)	UPA 30 mg n = 173 (PYs = 277.8) (Median exposure = 75.0 weeks)
Serious infection	2 (1.8)	3 (1.7)	7 (2.5)
Opportunistic infection, excluding tuberculosis and herpes zoster[b]	0	1 (0.6)	0
Active tuberculosis	0	0	0
Herpes zoster	0	3 (1.7)	12 (4.3)
Adjudicated gastrointestinal perforation	0	3 (1.7)	0
Anaemia	3 (2.7)	3 (1.7)	13 (4.7)
Neutropaenia	1 (0.9)	7 (4.0)	4 (1.4)
Lymphopaenia	0	11 (6.4)	25 (9.0)
Creatine phosphokinase elevation	1 (0.9)	13 (7.5)	13 (4.7)
Hepatic disorder	2 (1.8)	12 (6.9)	27 (9.7)
Renal dysfunction	1 (0.9)	0	2 (0.7)
Malignancies excluding NMSC[c]	1 (0.9)	1 (0.6)	1 (0.4)
Any NMSC	1 (0.9)	0	2 (0.7)
Adjudicated MACE	0	0	0
Adjudicated VTE	0	0	1 (0.4)

AE, adverse event; E, event; LTE, long-term extension; MACE, major adverse cardiovascular event; NMSC, nonmelanoma skin cancer; OL, open-label; PBO, placebo; PY, patient-years; UPA, upadacitinib; VTE, venous thromboembolic event.
Data cut-off date: 01 Aug 2023.

[a]Exposure-adjusted event rates. E/100 PY = number of events per 100 patient-years. Treatment-emergent AEs are those with an onset date on or after the first dose of study drug administration and within 30 days after the last dose of study drug administration per defined cohort/treatment group.

[b]Opportunistic infections (excluding tuberculosis and herpes zoster): esophageal candidiasis (n = 1) in the UPA 15 mg group.

[c]Malignancies excluding NMSC: malignant melanoma (n = 1) in the UPA 15 mg group; malignant fibrous histiocytoma (n = 1) in the UPA 30 mg group. One patient from the UPA 30 mg group had a lymphocyte morphology abnormal coded as lymphoma; lymphoma was ruled out and the patient continues in the study. OP10, 19th Congress of ECCO, February 21-24, 2024, Stockholm, Sweden

COMMENT S'Y RETROUVER?

AGA CLINICAL PRACTICE GUIDELINES

Gastroenterology 2021;160: 2496-2508

A. In adult outpatients with moderate to severe CD, who are *naïve to biologics* the AGA
Recommends the use of infliximab, adalimumab or ustekinumab* over certolizumab pegol (Strong recommendation, moderate certainty of evidence)
Suggests the use of vedolizumab over certolizumab pegol (Conditional recommendation, low certainty of evidence)
B. In adult outpatients with moderate to severe CD, who have never responded to TNFα antagonists (primary non-response), the AGA
Recommends the use of ustekinumab* (Strong recommendation, moderate certainty of evidence)
Suggests the use of vedolizumab (Conditional recommendation, low certainty of evidence)
C. In adult outpatients with moderate to severe CD, who have previously responded to infliximab (secondary non-response), the AGA
Recommends the use of adalimumab or ustekinumab* (Strong recommendation, moderate certainty of evidence)

* Extension pour le risankizumab

Feuerstein et al. Gastroenterology 2021
Singh et al. Gastroenterology 2021

GUIDELINES EN CROHN – COMMENT S'Y RETROUVER?

ECCO

I. Anti-TNF en première ligne

American College of G

I. Anti-TNF ou vedolizumab

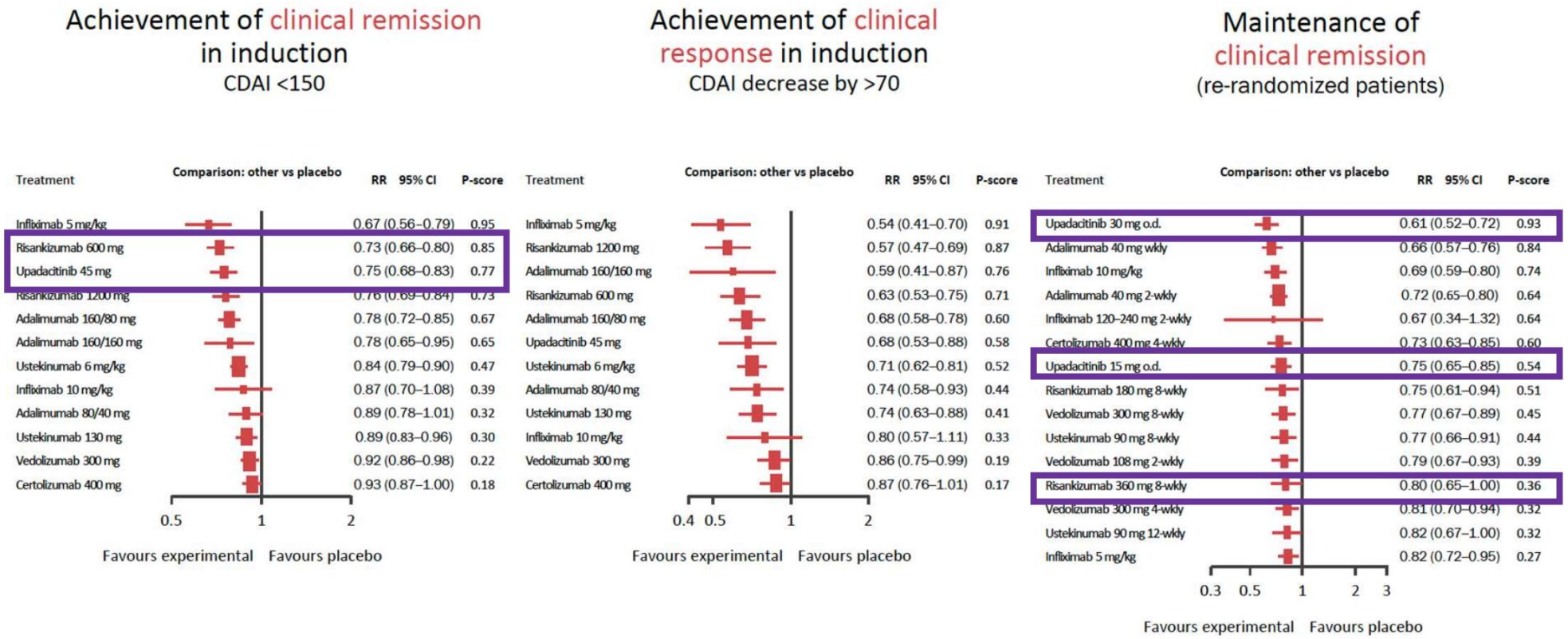
AGA

I. Anti-TNF ou ustekinumab

- Témoigne de la difficulté éprouvée à comparer l'efficacité des tx parmi les études existantes avec design différent
- Méta-analyse en réseau
  - IFX ou ADA en première ligne puis ADA ou risankizumab en 2e ligne (Singh et al Lancet G H 2021)
  - IFX en première ligne mais risankizumab en premier si bionaifs divisé des bioexposés (Barberio et al Gut 2023)

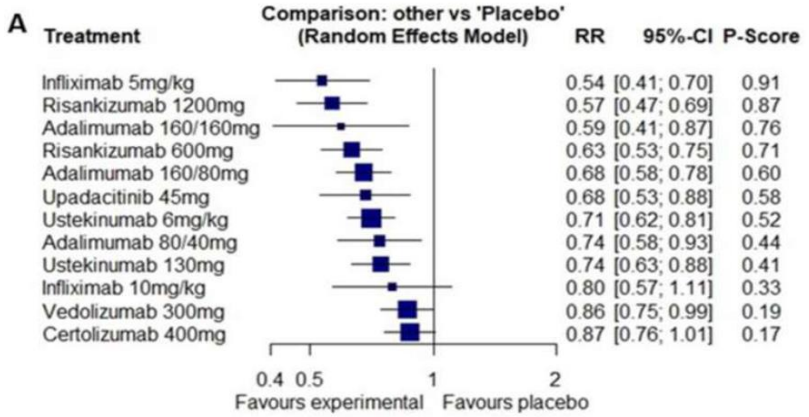
!!! Éval des tx selon leur capacité à induire la rémission clinique mais les données endoscopiques sont prob plus aidantes pour prédire les issues à long terme

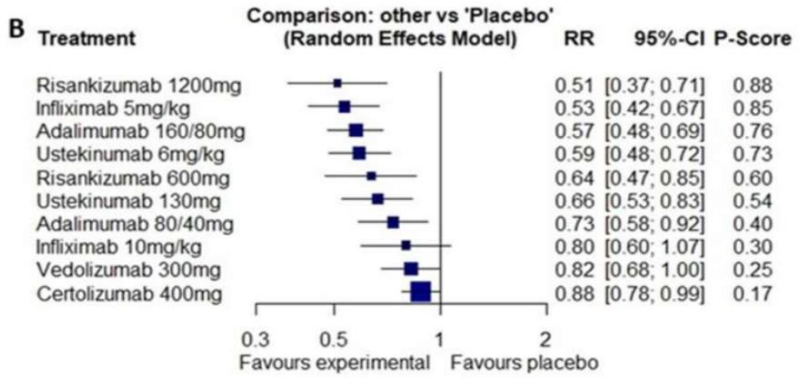
INDUCTION ET MAINTIEN DE LA RÉMISSION EN CROHN LUMINAL : REVUE SYSTÉMATIQUE ET MÉTA-ANALYSE EN RÉSEAU



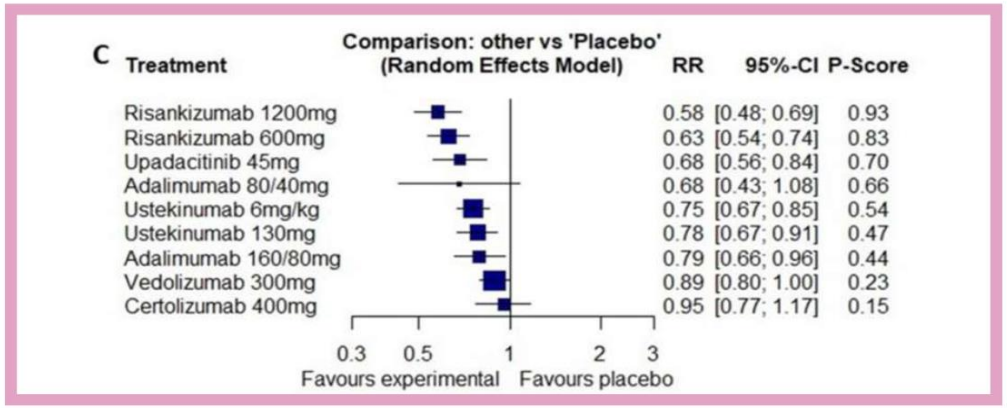
INDUCTION ET MAINTIEN DE LA RÉMISSION EN CROHN LUMINAL : REVUE SYSTÉMATIQUE ET MÉTA-ANALYSE EN RÉSEAU

Patients bio-naïfs





Patients bio-exposés



APPROCHE SUGGÉRÉE

- Considérer comment le bénéfice molécule vs PBO change en présence d'un traitement antérieur avec un anti-TNF
- Exemple en CU :
  - ULTRA2, GEMINI1, VARSITY, True North ont montré que l'induction avec adalimumab, vedolizumab et ozanimod ont eu un plus faible taux de rémission clinique après une thérapie anti-TNF.
  - UNIFI, OCTAVE1et2, U-ACHIEVE/U-ACCOMPLISH ont montré que l'ustékinumab, tofacitinib et upadacitinib n'ont pas eu un plus faible taux de rémission clinique après une thérapie anti-TNF.

APPROCHE SUGGÉRÉE

Mais en Crohn…devrions-nous regarder d'autres issues que la clinique….comme mesures d'issues à long terme?

- Rémission clinique ou guérison muqueuse après l'induction
- Persistance de rémission endoscopique

➢ Donc si on regarde les molécules pour lesquelles nous avons des DONNÉES ENDOSCOPIQUES

- Extend and GEMINI2et3 ont montré que l'adalimumab et le vedolizumab ont des taux de rémission endoscopique plus faibles après une thérapie anti-TNF
- IM-UNITI, SEAVUE et FORTIFY ont montré que l'ustekinumab et le risankizumab n'ont pas des taux de rémission endoscopique plus faibles après une thérapie anti-TNF
- EVOLVE : l'efficacité des anti-TNFs ne semble pas être influencée par l'usage de vedolizumab au préalable

EVOLVE

	UC			CD		
First-line vedolizumab or first-line anti-TNF over 24 months						
	First-line vedolizumab	**First-line anti-TNF**	***p* Value**	**First-line vedolizumab**	**First-line anti-TNF**	***p* Value**
Clinical remission	65.9%	48.6%	0.09	76.6%	68.5%	0.10
Clinical response	88.3%	86.2%	0.64	84.0%	72.1%	0.27
Mucosal healing	86.6%	80.6%	0.66	100%	90.4%	0.12
First-line anti-TNF or second-line anti-TNF at 3 or 6 months						
	First-line anti-TNF	**Second-line anti-TNF**	***p* Value**	**First-line anti-TNF**	**Second-line anti-TNF**	***p* Value**
Clinical remission at 3 months	9.7%	11.0%	0.92	22.9%	49.2%	***0.02***
Clinical response at 3 months	38.4%	44.8%	0.54	30.1%	41.3%	0.52
Clinical remission at 6 months	19.6%	14.7%	0.69	36.2%	74.6%	***<0.01***
Clinical response at 6 months	57.1%	61.1%	0.58	43.5%	74.8%	0.13

p Values in bold italics are statistically significant.
CD, Crohn's disease; TNF, tumor necrosis factor; UC, ulcerative colitis.

- Nombre de pts dans le groupe 2e ligne est petit…
- Effet maximal du vedo lorsqu'utilisé avant un anti-TNF
- L'utilisation du vedo n'impacte pas l'efficacité de l'antiTNF utilisé comme 2e

VEDO VS UST APRÈS UN ANTI-TNF? UST

Observational Study > Aliment Pharmacol Ther. 2020 May;51(10):948-957.
doi: 10.1111/apt.15706. Epub 2020 Apr 6.

The effectiveness of either ustekinumab or vedolizumab in 239 patients with Crohn's disease refractory to anti-tumour necrosis factor

Hadrien Alric [1], Aurélien Amiot [2], Julien Kirchgesner [3], Xavier Tréton [4], Matthieu Allez [5], Yoram Bouhnik [4], Laurent Beaugerie [3], Franck Carbonnel [1], Antoine Meyer [1]

Comparative effectiveness of ustekinumab or vedolizumab after one year in 130 patients with anti-TNF-refractory Crohn's disease.

Townsend T [1], Razanskaite V [2], Dodd S [3], Storey D [1], Michail S [1], Morgan J [1], Davies M [1], Penman D [4], Watters C [4], Swaminathan M [5], Sabine J [4], Chapman A [2], Smith PJ [1], Flanagan PK [4], Reilly I [5], Bodger K [3], Subramanian S [1]

Author information

Alimentary Pharmacology & Therapeutics, 10 Sep 2020, 52(8):1341-1352
https://doi.org/10.1111/apt.16057 PMID: 32955122

VEDO VS UST APRÈS UN ANTI-TNF? SIMILAIRE

› Am J Gastroenterol. 2023 Apr 1;118(4):674-684. doi: 10.14309/ajg.0000000000002068. Epub 2022 Nov 26.

Real-World Evidence Comparing Vedolizumab and Ustekinumab in Antitumor Necrosis Factor-Experienced Patients With Crohn's Disease

Michael D Kappelman [1], Sruthi Adimadhyam [2], Laura Hou [2], Audrey E Wolfe [2], Samantha Smith [2], Andrew L Simon [2], Érick Moyneur [3], Juliane S Reynolds [2], Sengwee Toh [2], Angela Dobes [4], Lauren E Parlett [5], Kevin Haynes [5], Mano Selvan [6], Qianli Ma [6], Vinit Nair [6], Jessica Burris [7], Jennifer E Dorand [4], Ghadeer K Dawwas [8], James D Lewis [9], Millie D Long [1]

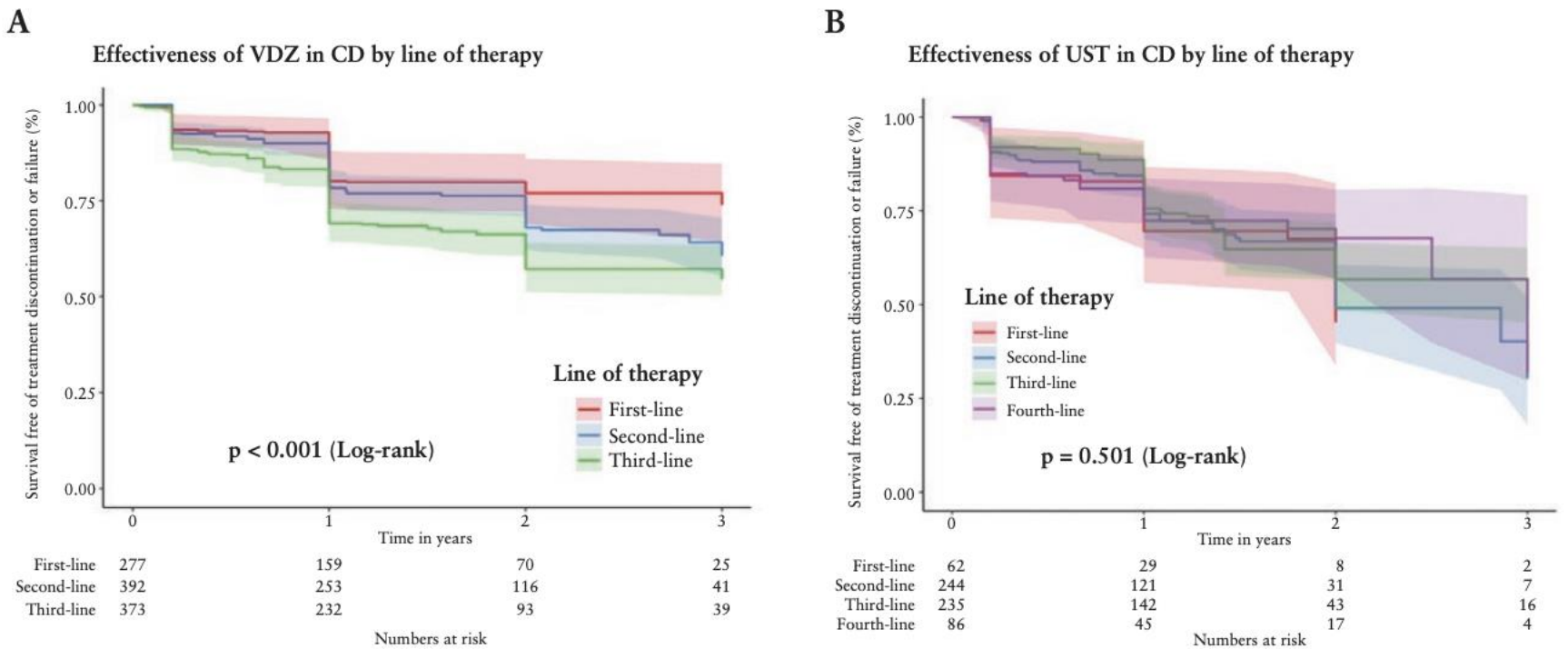
Observational Study › Am J Gastroenterol. 2022 Aug 1;117(8):1279-1287. doi: 10.14309/ajg.0000000000001773. Epub 2022 Apr 13.

An Objective Comparison of Vedolizumab and Ustekinumab Effectiveness in Crohn's Disease Patients' Failure to TNF-Alpha Inhibitors

Sara Onali [1 2], Daniela Pugliese [3], Flavio Andrea Caprioli [4 5], Ambrogio Orlando [6], Livia Biancone [7], Olga Maria Nardone [8], Nicola Imperatore [9], Gionata Fiorino [10], Maria Cappello [11], Anna Viola [12], Maria Beatrice Principi [13], Cristina Bezzio [14], Annalisa Aratari [15], Sonia Carparelli [16], Silvia Mazzuoli [17], Francesco Manguso [9], Laurino Grossi [18], Giorgia Bodini [19], Davide Ribaldone [20], Giammarco Mocci [21], Agnese Miranda [22], Luigi Minerba [1 2], Agnese Favale [1 2], Mauro Grova [6], Ludovica Scucchi [7], Simone Segato [23 24], Walter Fries [12], Fabiana Castiglione [8], Alessandro Armuzzi [25 10], Massimo C Fantini [1 2]; IG-IBD

Biologic Therapy for Inflammatory Bowel Disease: Real-World Comparative Effectiveness and Impact of Drug Sequencing in 13 222 Patients within the UK IBD BioResource

Christina Kapizioni,[a,b,*] Rofaida Desoki,[a,c,*] Danielle Lam,[a,d] Karthiha Balendran,[a,e] Eman Al-Sulais,[a,f] Sreedhar Subramanian,[a] Joanna E. Rimmer,[g] Juan De La Revilla Negro,[a] Holly Pavey,[h,i] Laetitia Pele,[j,k] Johanne Brooks,[l,m] Gordon W. Moran,[n] Peter M. Irving,[o,p] Jimmy K. Limdi,[q,r] Christopher A. Lamb,[s,t] UK IBD BioResource Investigators Miles Parkes,[a] Tim Raine[a]



EFFICACITÉ/INNOCUITÉ COMPARATIVE À LONG TERME UST VS ANTI-TNFS COMME TX DE 2E LIGNE APRÈS ANTI-TNF (COHORTE SUÉDOISE)

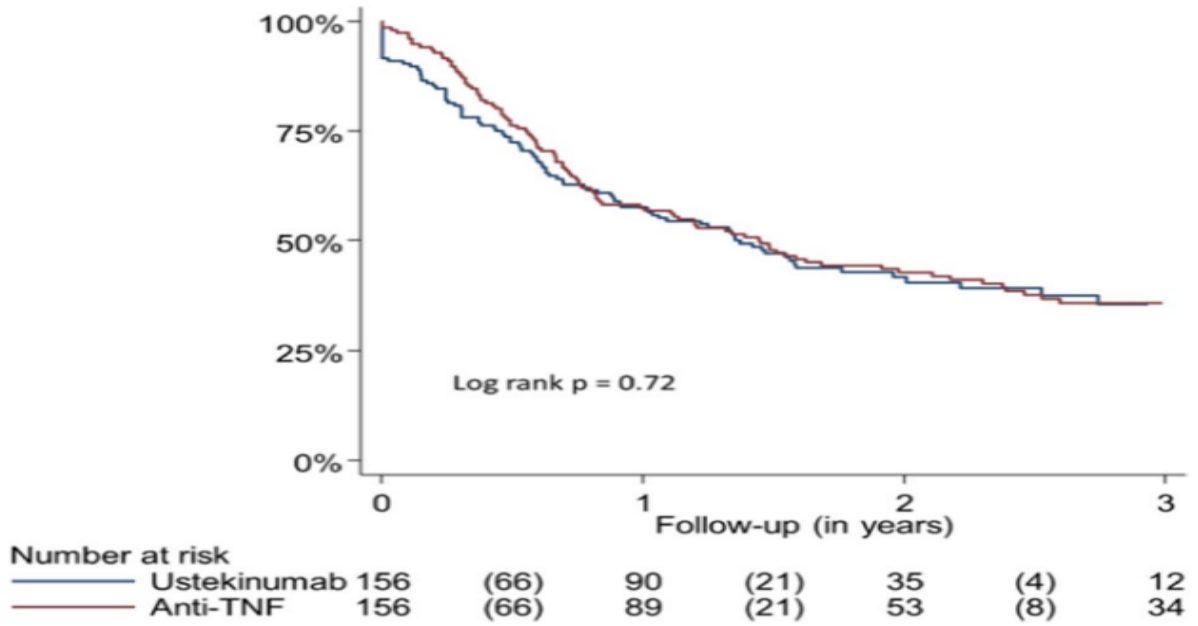


Fig. 1 Kaplan–Meier curves in a propensity score-matched cohort of patients with Crohn's disease illustrating drug survival on second-line biologic treatment

Eriksson et al. Dig Dis and Sciences 2023

- 1ere étude de vraie vie sur la question
- Survie sans HO, chx, nécessité ATB, infections
- Stratification des pts selon la raison d'arrêt du premier anti-TNF (intol ou non réponse)

- CDAI, HBI, endo, biomarqueurs non inclus pour l'analyse

- Survie Rx peut être affectée par l'optimisation….

LIMITATIONS

- Pas de données sur l'utilisation des anti-tnfs en 2e ligne après un tx non anti-TNF…
- Peu de données en première ligne avec anti-IL et inhibiteurs de JAK…
- Chez les bioexposés, données s'appliquent surtout aux pts exposés aux antiTNFs
- Pas d'étude de supériorité IFX vs UST, IFX vs Risankizumab
- Pas d'étude de supériorité Risankizumab vs upadacitinib

ALGORITHME SUGGÉRÉ CROHN MODÉRÉ À SÉVÈRE LUMINAL

En tenant compte des valeurs et préférences du patient (mode d'administration, rapidité, MEI, âge de procréer, etc)

Risque de complications liées à la maladie (sévérité de la maladie)

- Première ligne
  I. Anti-TNF (considérer IMM en combinaison)
  II. Risankizumab ou ustekinumab (si comorbidités ou ci aux anti-TNFs)

- Deuxième ligne (si anti-TNF utilisé en 1er)
  I. Risankizumab » ustekinumab
  II. Upadacitinib
  III. 2e Anti-TNF (si immunogénicité ou intol au premier anti-TNF utilisé)

Risque de complications liées au traitement (comorbidités significatives ex. infections sérieuses antérieures, néoplasie, âge avancé, multiples comorbidités)

- Première ligne
  I. Risankizumab ou ustekinumab
  II. Vedolizumab

- Deuxième ligne
  I. Anti-TNF (en monothérapie)

Singh Nat Rev Gastroenterol Hepatol 2023
Dulai et al Gastroenterology 2024

ALGORITHME SUGGÉRÉ
CROHN MODÉRÉ À SÉVÈRE LUMINAL

En tenant compte des valeurs et préférences du patient (mode d'administration, rapidité, MEI, âge de procréer, etc)

BIONAIFS

- Première ligne
  I. Anti-TNF ou anti-IL
  II. Vedolizumab

- IFX et risankizumab favorisés vs UST, Ada, Vedo
- Recommandations limitées aux pts exposés aux anti-TNFs (design des essais)
- Pas de recommandation quant à la supériorité de l'IFX vs UST
- Pas de supériorité démontrée entre IFX et risankizumab
- Incapacité d'évaluer risankizumab ou upadacitinib

BIOEXPOSÉS

- Non répondeurs primaires
  I. Anti-IL
  II. Vedolizumab

- Non répondeurs secondaires
  I. Anti-IL ou 2e anti-TNF
  II. Vedolizumab

- Recommandations limitées aux pts exposés aux anti-TNFs (design des essais)
- Risankizumab et upadacitinib favorisés vs UST, ada et vedo
- Incapacité à évaluer risankizumab ou upadacitinib
- Pas de supériorité démontrée entre risankizumab et upadacitinib

Singh Nat Rev Gastroenterol Hepatol 2023
Dulai et al Gastroenterology 2024

QUELS SONT LES FACTEURS DÉCISIONNELS À CONSIDÉRER ?

CONSIDÉRATIONS

Choix du patient et mode d'administration souhaité par celui-ci

- Crohn
  - Bionaïf ou bioexposé
  - Présence d'une maladie fistulisante intra-abdominale ou périanale (phénotype)
  - Présence de MEI
  - Désir futur de grossesse
  - Âge du patient, hx d'infections répétées et hx de néoplasie
  - Immunogénicité antérieure
- Perspective du patient (innocuité, efficacité, durabilité, rapidité d'action, cédule et moyen d'administration, accès, coût, etc…)
- Perspective du clinicien (idem + : capacité à induire une rémission sans CS et rémission endoscopique

EN CAS D'ATTEINTE PÉRIANALE

?

MALADIE FISTULISANTE PÉRIANALE

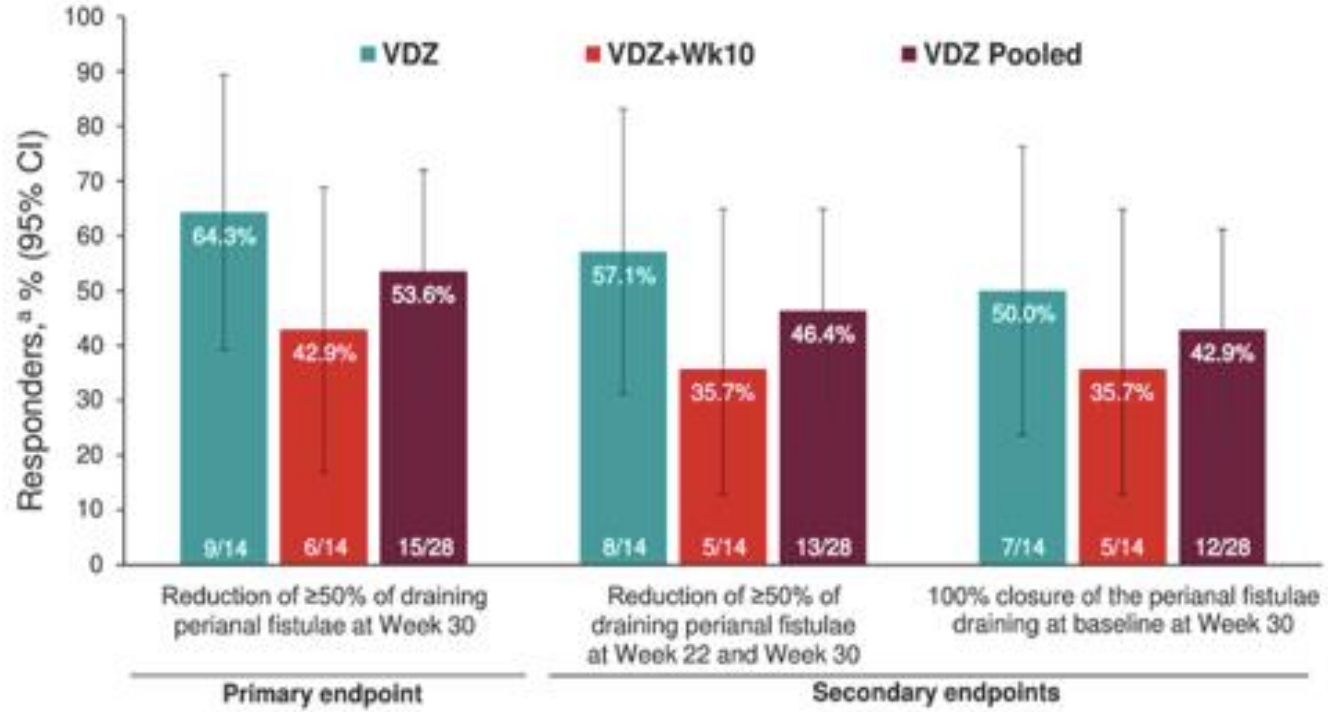
- Combiner un IMM à l'UST ou vedo n'a pas montré d'amélioration significative au niveau de la fermeture des orifices externes et au niveau des niveaux sanguins

Table 3. Univariate and multivariable analyses of factors associated with ustekinumab treatment success

Factors	Univariate analysis, OR (95% CI)	*P* value	Multivariable analysis, OR (95% CI)	*P* value
Sex (female)	1.14 (0.57–2.28)	0.72		
Age (≥35 yr)	1.09 (0.56–2.11)	0.81		
Current smokers	0.79 (0.38–1.63)	0.52		
BMI (kg/m^2)				
<20	1.04 (0.48–2.27)	0.92		
>25	0.92 (0.38–1.63)	0.52		
20–25	Reference			
Immunosuppressive therapy at initiation (no)	1.6 (0.82–3.16)	0.17	1.69 (0.85–3.39)	0.134

Peyrin-Biroulet et al JCC 2022
Chapuis-Biron et al Am J Gastro 2020

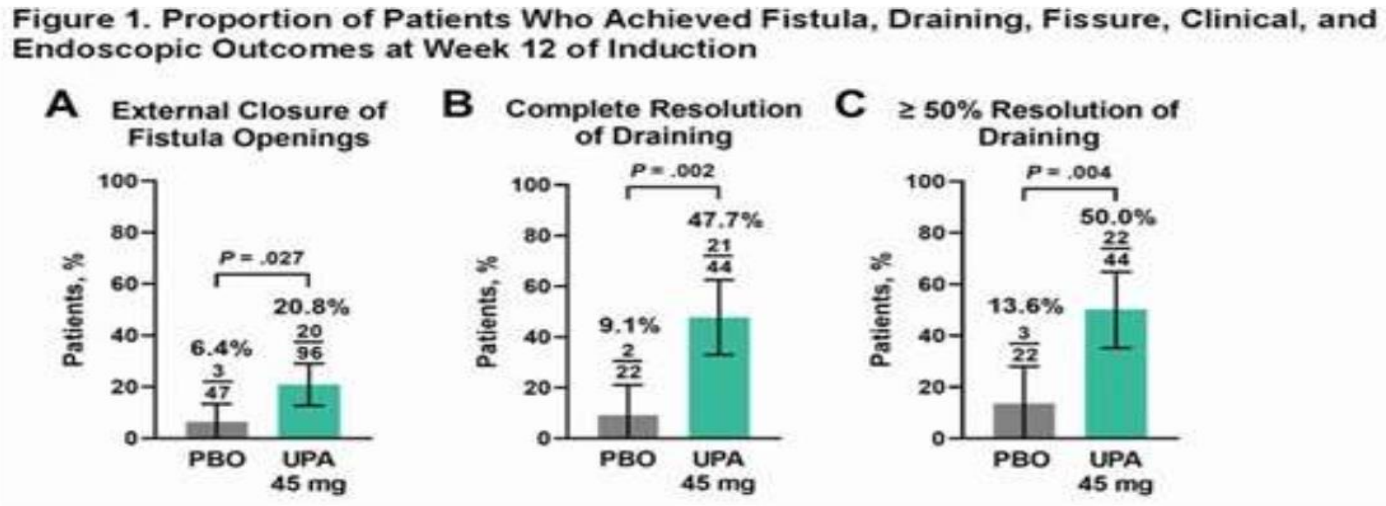
ÉTUDE ENTERPRISE – VDZ EN ATTEINTE PÉRIANALE



The mFAS is defined as all patients from the FAS who had ≥ 1 draining fistula at baseline.
CI, confidence interval; mFAS, modified full analysis set; VDZ, vedolizumab; Wk, week.
[a]Responders are defined as patients with a reduction in the number of draining perianal fistulae (of those draining at baseline) of ≥50% at the visit. Patients with missing data at the visit were counted as nonresponders.

UPADACITINIB EN ATTEINTE PÉRIANALE

Études d'induction U-EXCEL et U-EXCEED (analyse de sous-groupe):
patients randomisés à upadacitinib ou placebo jusqu'à 12 semaines, bénéfices diminués dans l'étude de maintien à 52 semaines



QUELLE EST LA MEILLEURE SÉQUENCE?
OPINIONS

- Garder en tête les facteurs décisionnels : bionaïf ou bioexposé, maladie périanale fistulisante, MEI, âge, hx d'infections répétées ou de néoplasie, désir futur de grossesse, etc
- Pas de différence significative au niveau de la rémission clinique et endoscopique entre UST et ADA chez patients bionaïfs (monothérapie et aucune optimisation) SEAVUE
- Non infériorité du RZB vs UST pour la rem clinique CDAI semaine 24 et supériorité du RZB vs UST pour la remission clinique à la semaine 48 chez les patients avec échec antérieur aux anti-TNFs SEQUENCE
- Non infériorité du mirikizumab vs UST pour la remission Clinique CDAI semaine 52 VIVID-1
- Extend and GEMINI2et3 ont montré que l'adalimumab et le vedolizumab ont des taux de rémission endoscopique plus faibles après une thérapie anti-TNF
- IM-UNITI, SEAVUE et FORTIFY ont montré que l'ustekinumab et le risankizumab n'ont pas des taux de rémission endoscopique plus faibles après une thérapie anti-TNF
- Prochains morceaux du casse-tête : données chez pts exposés à un tx non anti-TNF en première ligne, differences entre les inhibiteurs de l'IL-23 spécifiques, etc…
- Nouvelle frontière : efficacité supérieure avec combinaison de biologiques? Quelle combinaison de classe sera à privilégier?

ALGORITHME SUGGÉRÉ CROHN MODÉRÉ À SÉVÈRE LUMINAL

En tenant compte des valeurs et préférences du patient (mode d'administration, rapidité, MEI, âge de procréer, etc)

Risque de complications liées à la maladie (sévérité de la maladie)

- Première ligne
  I. Anti-TNF (considérer IMM en combinaison)
  II. Risankizumab ou ustekinumab (si comorbidités ou ci aux anti-TNFs)

- Deuxième ligne (si anti-TNF utilisé en 1er)
  I. Risankizumab » ustekinumab
  II. Upadacitinib
  III. 2e Anti-TNF (si immunogénicité ou intol au premier anti-TNF utilisé)

Risque de complications liées au traitement (comorbidités significatives ex. infections sérieuses antérieures, néoplasie, âge avancé, multiples comorbidités)

- Première ligne
  I. Risankizumab ou ustekinumab
  II. Vedolizumab

- Deuxième ligne
  I. Anti-TNF (en monothérapie)

Singh Nat Rev Gastroenterol Hepatol 2023
Dulai et al Gastroenterology 2024

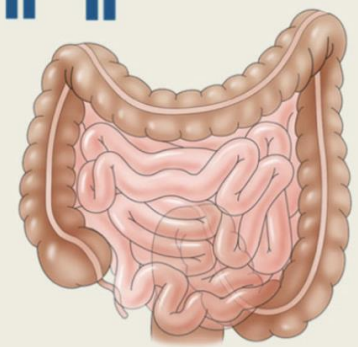
DOIT-ON COMBINER DES THÉRAPIES AVANCÉES?

ÉTUDE EXPLORER

Phase 4, open-label study of vedolizumab, adalimumab, and methotrexate combination therapy in Crohn's disease

Patients

N = 55



Biologic naïve patients with newly diagnosed, moderate to high risk CD

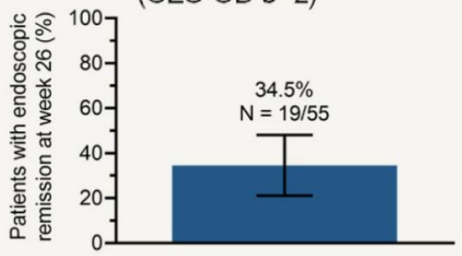
Treatment

Triple combination therapy

- IV vedolizumab 300 mg at weeks 0, 2, and 6 and every 8 weeks until week 102
- SC adalimumab 160 mg at week 0, 80 mg at week 2, and 40 mg every 2 weeks until week 26
- Oral methotrexate 15 mg weekly until week 34

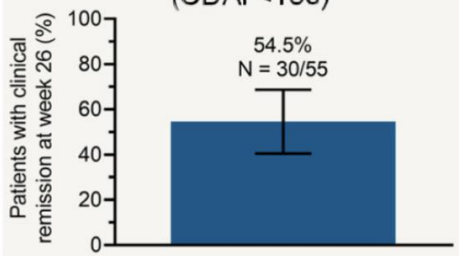
Primary end point

Endoscopic remission at week 26 (SES-CD 0–2)



Secondary end point

Clinical remission at week 26 (CDAI <150)



Post hoc Bayesian analysis[a]

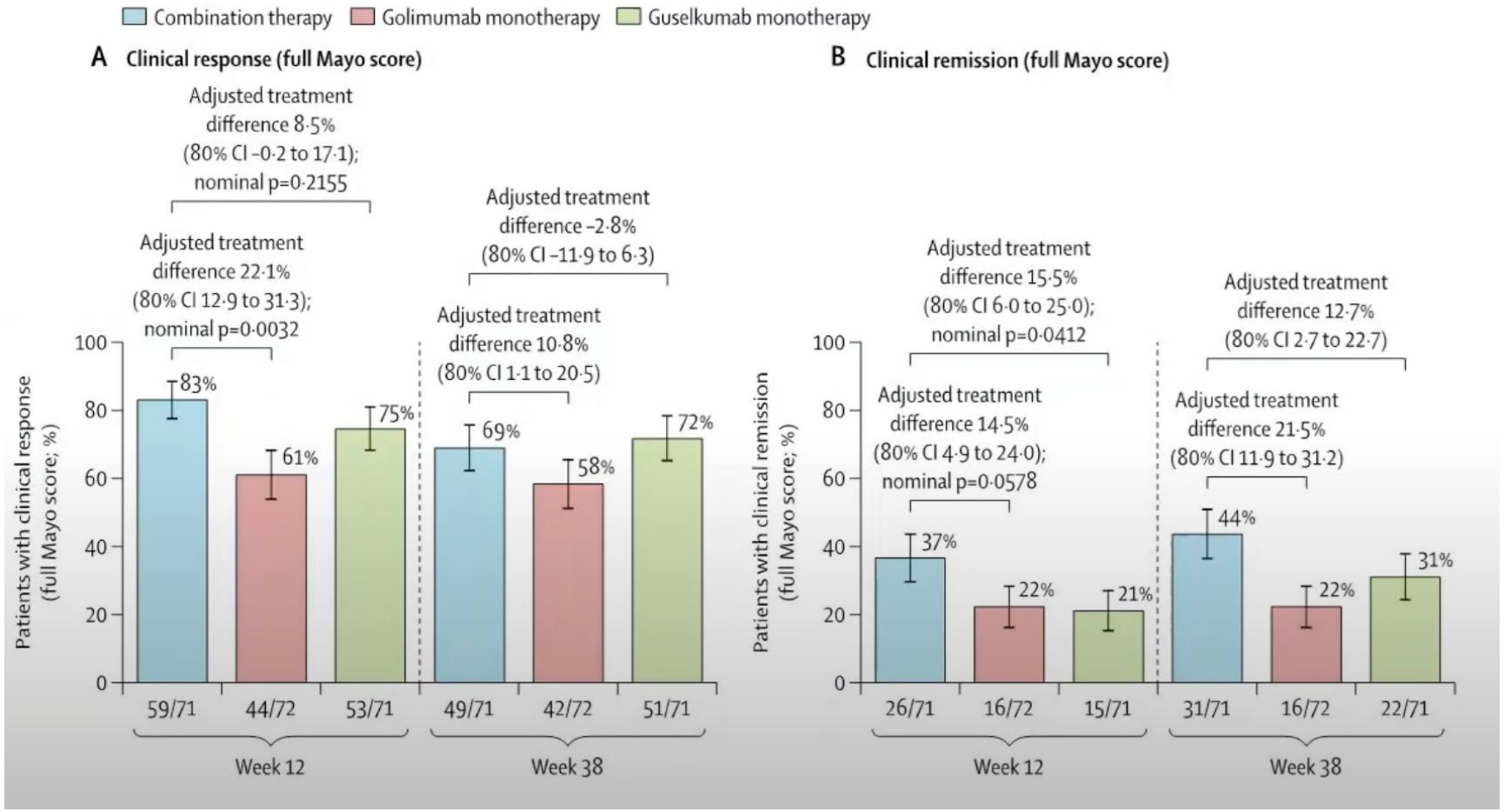
Probability that triple combination therapy produces higher endoscopic remission than benchmark rates for…

- …placebo ≥99.9%
- …vedolizumab monotherapy = 86.3%
- …adalimumab monotherapy = 71.4%

[a]*Beta*(1.667, 5) prior. Posterior mean endoscopic remission rate = 33.5% (95% credible interval: 22.4, 45.7).
CD, Crohn's disease; CDAI, Crohn's Diseas e Activity Index; IV, intravenous; SC, subcutaneous; SES-CD, Simple Endoscopic Score for Crohn's Disease

Clinical Gastroenterology and Hepatology

COMBINAISON DE THÉRAPIES AVANCÉES?



Feagan et al. Lancet Gastroenterol Hepatol 2023

ÉTUDE VICTRIVA

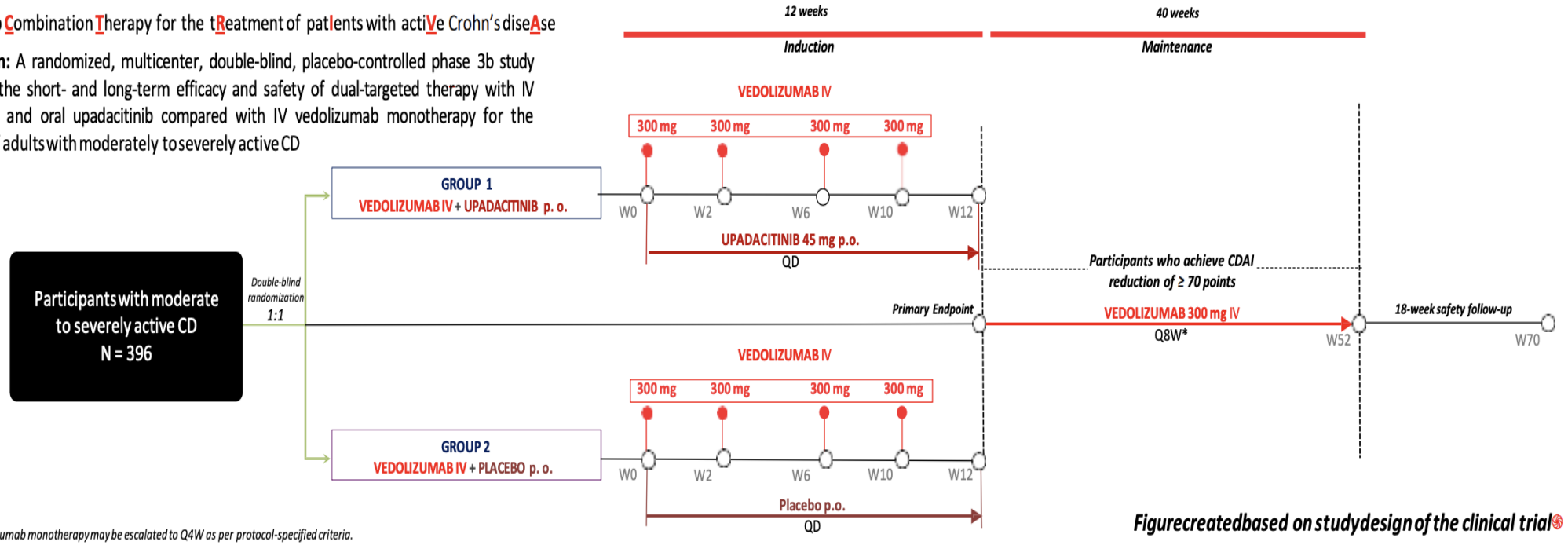
CLINICAL TRIAL FACTSHEET VEDOLIZUMAB-3043: VICTRIVA (NCT06227910)

Takeda

Comparative Study of the Safety and Efficacy of Vedolizumab with and without Upadacitinib in Adults with Moderate to Severe Active Crohn's Disease

Vedolizumab Combination Therapy for the tReatment of patIents with actiVe Crohn's diseAse

Study design: A randomized, multicenter, double-blind, placebo-controlled phase 3b study to evaluate the short- and long-term efficacy and safety of dual-targeted therapy with IV vedolizumab and oral upadacitinib compared with IV vedolizumab monotherapy for the treatment of adults with moderately to severely active CD



*The Q8W vedolizumab monotherapy may be escalated to Q4W as per protocol-specified criteria.

Figure created based on study design of the clinical trial

MOLÉCULES/ÉTUDES D'INTÉRÊT

- Anti-IL23 (anti-p19) : guselkumab et mirikizumab
  - Étude comparative guselkumab vs ustekinumab
- Inhibiteur sélectif de Jak-1 : filgotinib
- Modulateur S1P : ozanimod (stepstone en Crohn), etrasimod
- Anti-beta7 (alpha4beta7 sélectif et alphaEbeta7) : etrolizumab (Bergamot en Crohn)
- JAK/TYK2 (brepocitinib)
- PDE (apremilast)
- Agoniste TLR9 (cobitolimod)

ÉTUDE VOICE

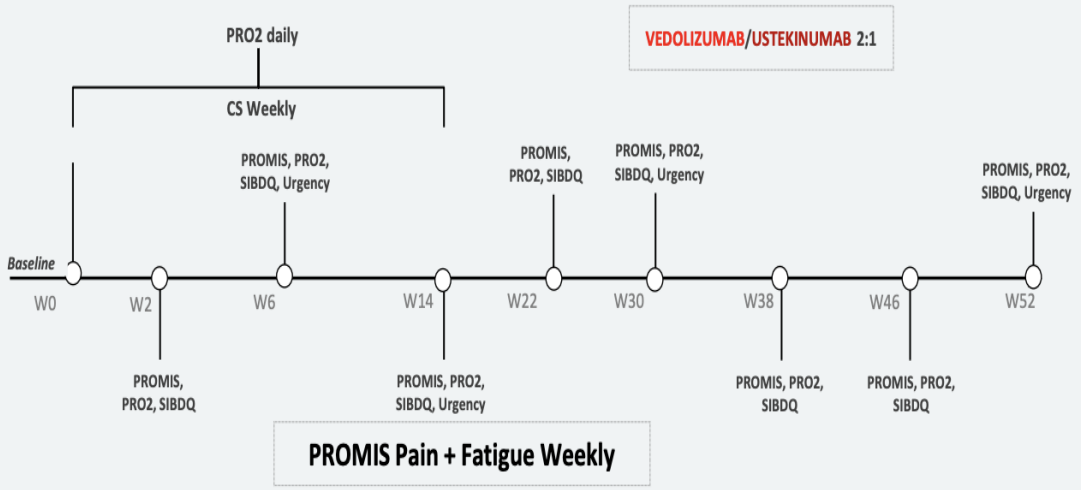
CLINICAL TRIAL FACTSHEET: VOICE (NCT06249555)

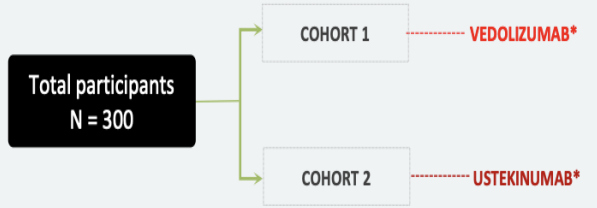
Takeda

Analysis of Response to Vedolizumab and Ustekinumab in Crohn's Disease Using Patient-reported Outcome Measures

VedOlIzumab and Ustekinumab in Participants with Crohn's DisEase

Study design: A prospective, observational, phase 4 study with a reference group in which participants prescribed with vedolizumab or ustekinumab for CD for the first time to explore the time course of response to vedolizumab, as measured by PROMIS Pain interference-SF, other PROMIS domain SFs, and other PRO measures



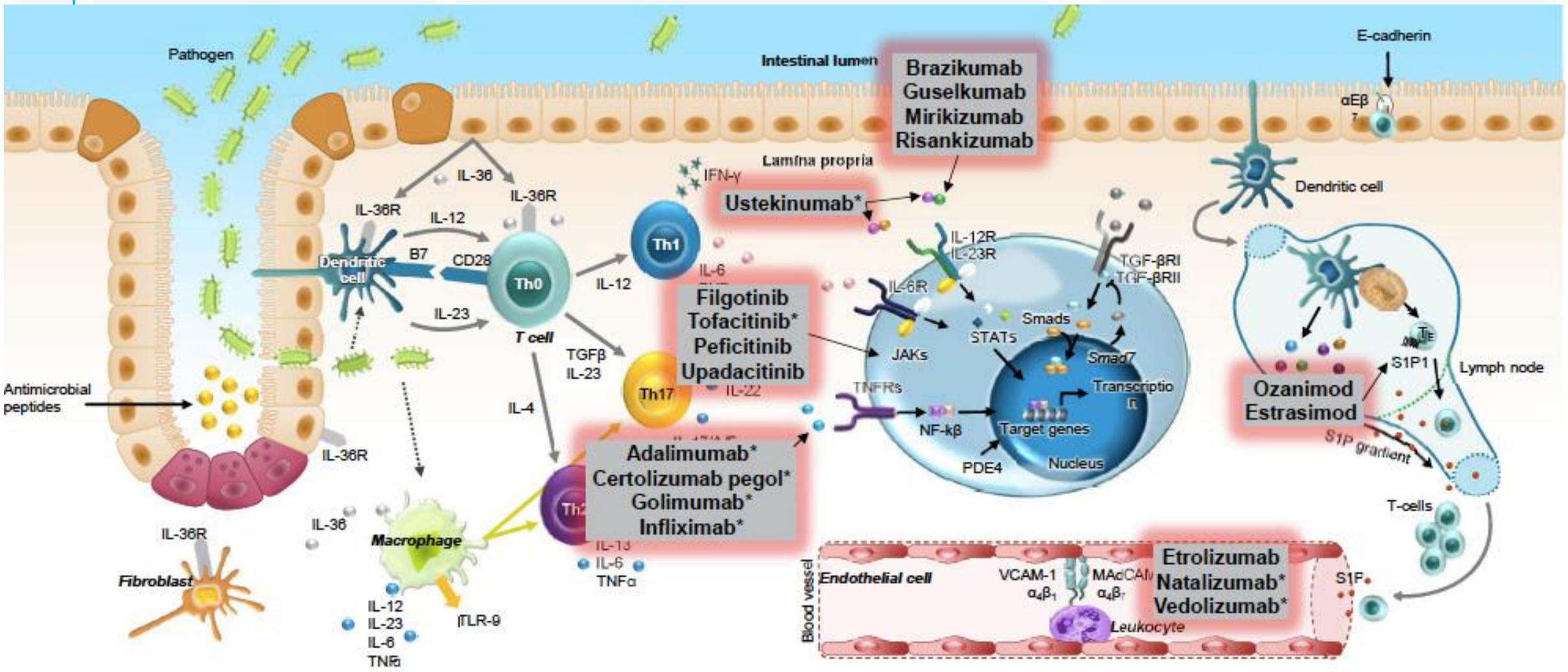


Primary Endpoint: *Time-to-improvement for the primary endpoint will be calculated as the first timepoint at which the pain interference domain T-score shows a 2-point change from the participant's baseline, for both Vedolizumab and Ustekinumab*

Figure created based on the study design of the clinical trial

*Dose, frequency and duration are not mandated as part of the study and are determined by the health care provider.

MOLÉCULES D'INTÉRÊT



Adapted from Coskún M, et al. Tr*ends Pharm Sci* 2017;38:127–42; and Nielsen OH, et al. *Expert Opin Investig Drugs* 2016;25:709–18.

MERCI DE VOTRE ATTENTION!

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