Intérêt des JAKi dans la prise en charge de la PR

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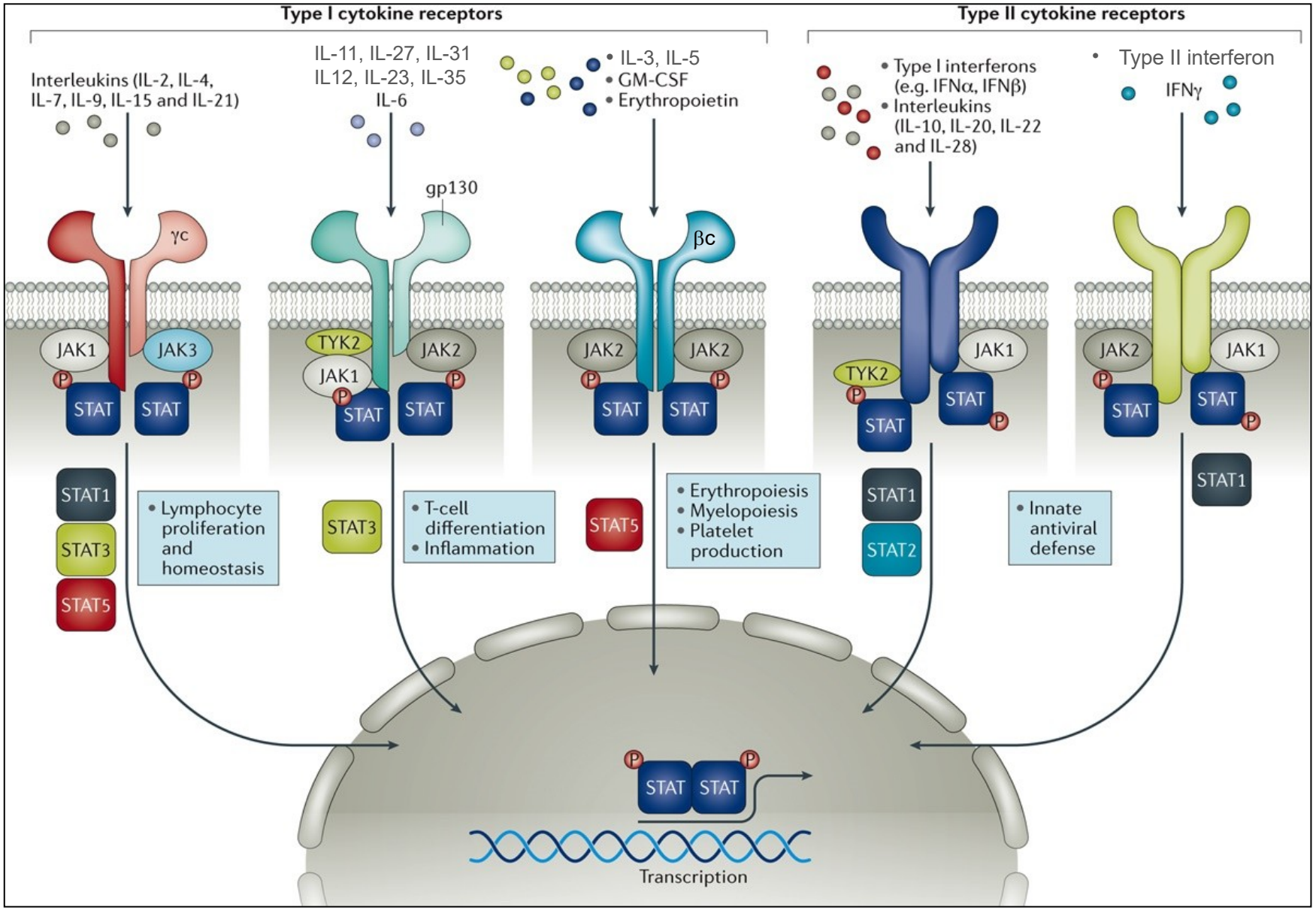
Symposium JAR 2023

Liens d’intérêt

Aucun

Mécanisme d’action

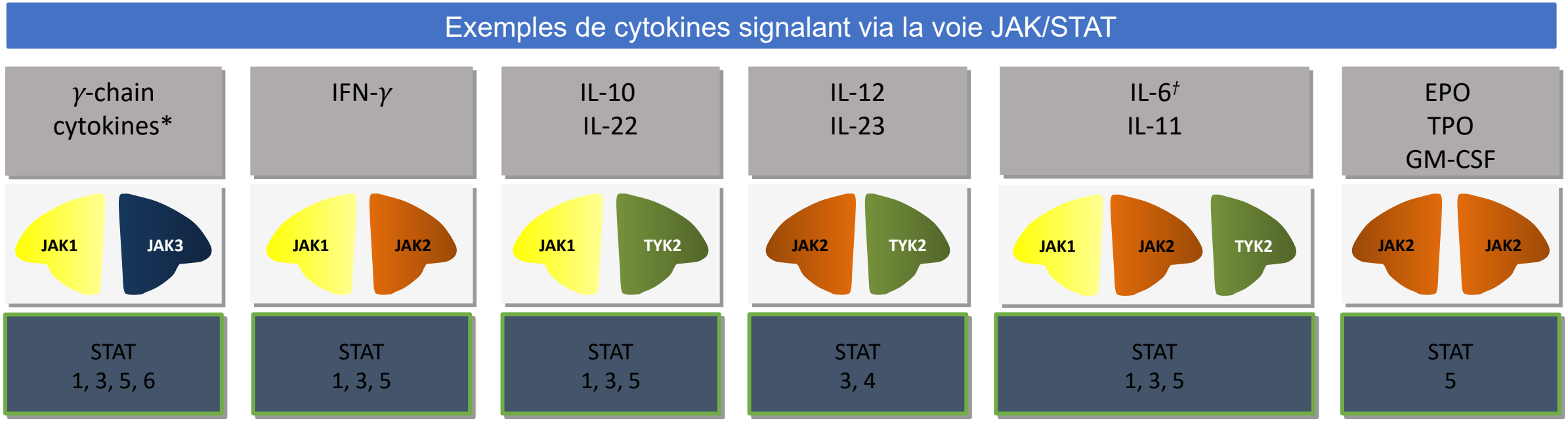
La voie de signalisation JAK/STAT : un système à 4 JAKs et 7 STATs



Winthrop KL. The emerging safety profile of JAK inhibitors in rheumatic disease. Nat Rev Rheumatol. 2017 Apr;13(4):234-243. doi: 10.1038/nrrheum.2017.23. Epub 2017 Mar 2. Erratum in: Nat Rev Rheumatol. 2017 May;13(5):320. PMID: 28250461.

La voie de signalisation JAK/STAT

- **4 membres JAK** :
  JAK1, JAK2, JAK3, et TYK2
- **7 membres STAT** :
  STAT1, STAT2, STAT3, STAT4, STAT5a, STAT5b, STAT6



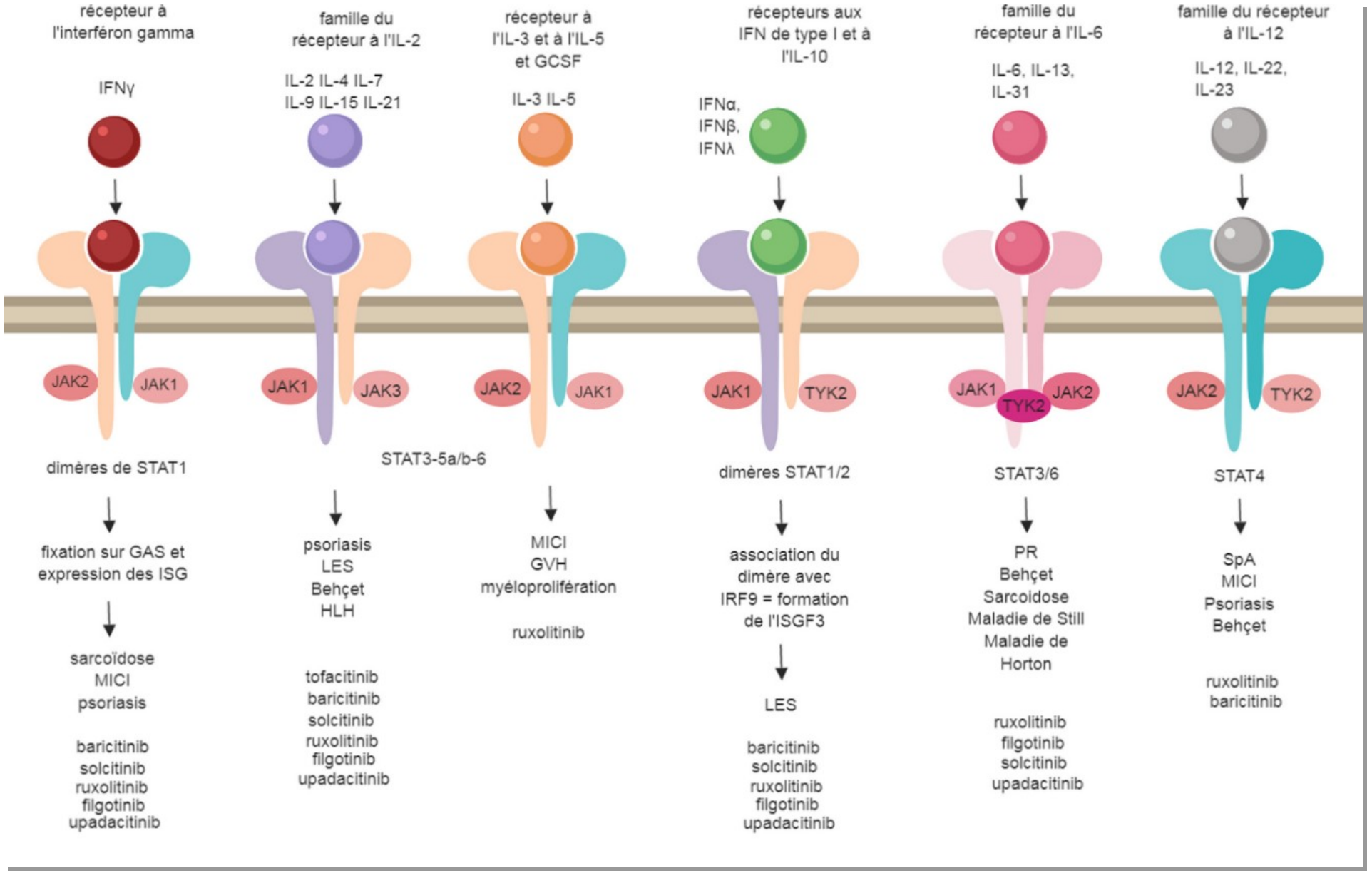
*γ-chain cytokines=IL-2, IL-4, IL-7, IL-9, IL-15, and IL-21.

†Type II cytokine receptors such as those for the gp130 subunit sharing receptors IL-6 and IL-11 as well as IL-10, IL-19, IL-20, and IL-22 mainly signal through JAK1, but also associated with JAK2 and TYK2.

EPO=erythropoietin; GM-CSF=granulocyte-macrophage colony-stimulating factor; IFN=interferon; IL=interleukin; JAK=janus kinase; STAT=signal transducer and activator of transcription; TPO=thrombopoietin; TYK=tyrosine kinase.

O'Sullivan LA, et al. *Mol Immunol*. 2007;44:2497-2506.

Les cytokines impliquées dans la voie JAK-STAT

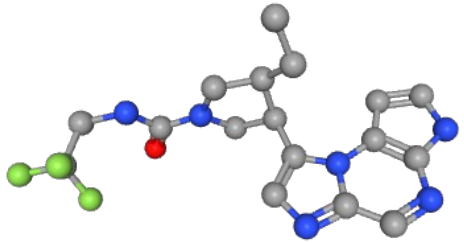


Les inhibiteurs de JAK, Science direct, Tome 40, Numéro 12, Décembre 2019 , Pages 816-825

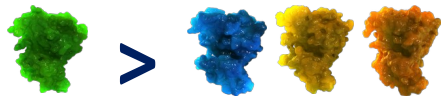
Sélectivité des JAKi

Each JAK inhibitor has different selectivity profiles for JAK1, JAK2, JAK3, or TYK2

Upadacitinib[1]

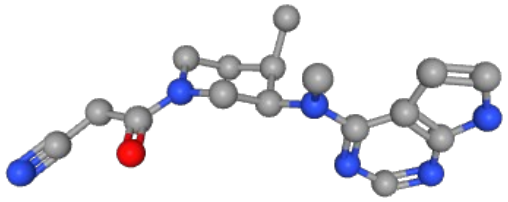


Inhibits activity of JAK1 over JAK2 (~40-fold), JAK3 (> 100-fold) and TYK2 (190-fold)

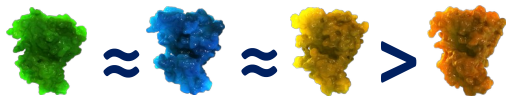


JAK1 JAK2 JAK3 TYK2

Tofacitinib[2]

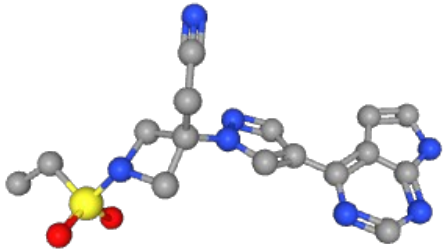


Inhibits JAK1, JAK2, JAK3, and to a lesser extent TYK2

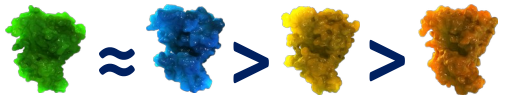


JAK1 JAK2 JAK3 TYK2

Baricitinib[3]

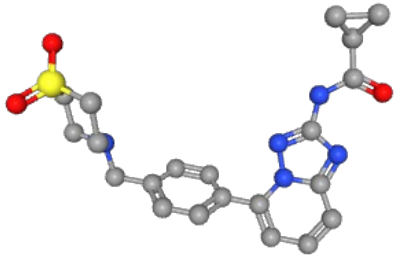


Inhibits activities of JAK1, JAK2, TYK2 and JAK3 with IC_{50} values of 5.9, 5.7, 53 and > 400 nM, respectively

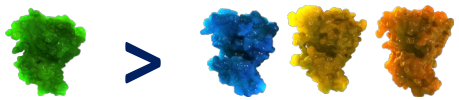


JAK1 JAK2 JAK3 TYK2

Filgotinib[4]



Inhibits activity of JAK1 and showed > 5-fold higher potency of for JAK1 over JAK2, JAK3 and TYK2



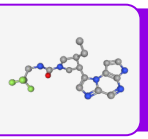
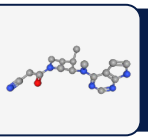
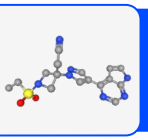
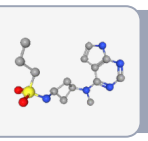
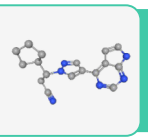
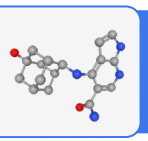
JAK1 JAK2 JAK3 TYK2

JAK, janus kinase; TYK, tyrosine kinase.

1. RINVOQ EU Summary of Product Characteristics 2021;2. Xeljanz EU Summary of Product Characteristics 2021; 3. Olumiant EU Summary of Product Characteristics 2021; 4. Jyseleca EU Summary of Product Characteristics 2021 ; 5. https://pubchem.ncbi.nlm.nih.gov/

½ vie courte Voie orale

Pharmacocinétique des différents JAKi

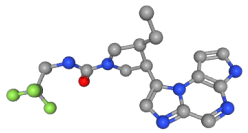
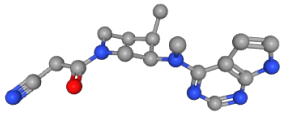
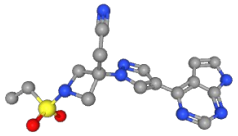
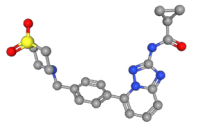
	Biodisponibilité	T_{max}	Demi-vie
 Upadacitinib 15 mg QD[1]	79%	2–4 heures	9–14 heures
 Tofacitinib 5 mg BID[2]	74%	0.5–1 heure	~3 heures
 Baricitinib 4 mg QD[3]	79%	0.5–3 heures	9–13 heures
 Filgotinib 200 mg QD[4]	25-82%	Filgotinib: 2–3 heures Active metabolite: 5 heures	Filgotinib: 7 heures Active metabolite: 19 heures
 Abrocitinib[a] 200 mg QD[5]	~60%	<1 heure	~5 heures
 Ruxolitinib 15 mg BID[6]	95%	1.5 heures	~3 heures
 Peficitinib 150 mg QD[7-10]	~64%	1–2 heures	3.7–7.5 heures

[a]Currently under investigation for treatment of atopic dermatitis
BID, twice daily; QD, once daily

1) RINVOQ EU Summary of Product Characteristics 2021 2) Xeljanz EU Summary of Product Characteristics 2021 3) Olumiant EU Summary of Product Characteristics 2021 4) Jyseleca CHMP Assessment Report 2020 5) MHRA Early Access to Medicines Scheme – Abrocitinib Treatment protocol 2021 6) Jakavi EU Summary of Product Characteristics 2020 7) Tanaka Y, et al. Ann Rheum Dis 2019;78:1320–32 8) Shibata M, et al. Clin Drug Investig 2020;40:469–84 9) Zhu T, et al. Clin Drug Investigation 2020;40:827-38 10) Peficitinib Package Insert 2019

Différentes voies d'élimination des JAKi

All JAK inhibitors, apart from upadacitinib, require some form of dose adjustment for patients with either mild to moderate hepatic and/or renal impairment

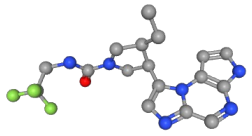
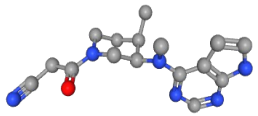
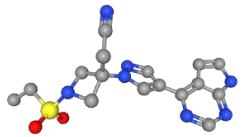
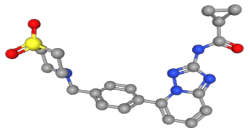
Impairment		Upadacitinib 15 mg QD[1]	Tofacitinib 5 mg BID[2]	Baricitinib 4 mg QD[3]	Filgotinib 200 mg QD[4]
					
Hepatic	Mild				
	Moderate		↓ dose: 5 mg QD		
	Severe				
Renal	Mild				
	Moderate			↓ dose: 2 mg QD • Patients with CrCl 30–60 mL/min	↓ dose: 100 mg QD • Patients with CrCl 15–<60 mL/min
	Severe	Use with caution	↓ dose: 5 mg QD • Patients with CrCl <30 mL/min • Patients under hemodialysis	Patients with CrCl <30 mL/min	Patients with CrCl <15 mL/min

No dose adjustment required | Contraindicated | Dose adjustment recommended

↓, reduce; CrCl, creatine clearance; BID, twice daily; JAK, Janus kinase; mL/min, milliliters per minute; QD, once daily.

1. RINVOQ EU Summary of Product Characteristics 2020; 2. Xeljanz EU Summary of Product Characteristics 2020; 3. Olumiant EU Summary of Product Characteristics 2020; 4. Jyseleca EU Summary of Product Characteristics 2020; 5. https://pubchem.ncbi.nlm.nih.gov/.

Métabolisme et interactions médicamenteuses

	Upadacitinib 15 mg QD[1,2]	Tofacitinib 5 and 10 mg BID[3,4]	Baricitinib 4 and 2 mg QD[5,6]	Filgotinib 200 mg QD[7]
				
CYP3A4 inhibitors (e.g., ketoconazole, clarithromycin, ritonavir)	Use with caution in patients receiving chronic treatment with CYP3A4 inhibitors	↓ Dose by half		
CYP2C19 inhibitors (e.g., fluconazole, fluoxetine, ticlopidine)		↓ Dose by half		
OAT3 inhibitors (e.g., fluconazole, fluoxetine, ticlopidine)			If taking strong OAT3 inhibitors (FDA)	↓ Dose to 2mg QD, if taking strong OAT3 inhibitors (EMA)
CYP1A2 substrate (e.g., alosetron, caffeine, duloxetine)				Caution when co-administered with CYP1A2 substrates with a narrow therapeutic index
CYP3A4 inducers (e.g., rifampin, phenytoin)	Coadministration with strong CYP3A4 inducer (FDA)	Coadministration with strong CYP3A4 inducers(FDA)		
	Patients should be monitored for changes in disease activity (EMA)			
Transporters (e.g., P-gp, BCRP, OATP1B1, OATP1B3, OCT1, OCT2, OAT1, OAT3, MATE1, MATE2K)	Does not inhibit at clinically relevant concentrations	Low potential to inhibit transporters	Caution should be used when leflunomide or teriflunomide are given concomitantly	Caution recommended for coadministration with P-gp or BCRP
				Sensitive OATP1B1 or OATP1B3 substrates: coadministration not recommended

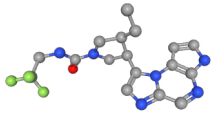
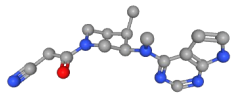
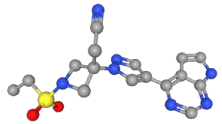
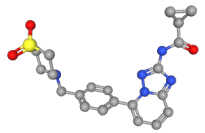
No dose adjustment required Not recommended Dose adjustment recommended

BID, twice a day; CES, carboxylesterase; CYP, cytochrome P450; MATE, multidrug and toxin extrusion; OAT, organic anion transporter; OATP, organic anion transporting polypeptides, OCT, organic cation transporter; QD, once a day

1. RINVOQ EU Summary of Product Characteristics 2021; 2. RINVOQ US Prescribing Information 2021; 3. Xeljanz EU Summary of Product Characteristics 2021; 4. Xeljanz US Prescribing Information 2020; 5. Olumiant EU Summary of Product Characteristics 2020; 6. Olumiant US Prescribing Information 2018; 7. Jyseleca EU Summary of Product Characteristics 2021; 8. https://pubchem.ncbi.nlm.nih.gov/.

Les principaux développements des JAKi (hors abrocitinib)

The number of indications per molecule is not necessarily indicative of lack of benefit in a disease area, but may reflect company CDP strategy.
This development program is not exhaustive.

JAK inhibitor	Chemical Structure	RA	JIA	PsA	AS	nr-axSpA	GCA	SLE	Psoriasis	AD	Alopecia Areata	Ulcerative Colitis	Crohn's Disease
Upadacitinib		✓	■	✓	✓	✓	■	■		✓		✓	Positive CHMP opinion
Tofacitinib		✓	✓	✓	✓				■ ■			✓	■ ■
Baricitinib		✓	■				■	■ ■	■ ■	✓	✓		
Filgotinib		✓		■ ■	■ ■							✓	■ ■

✓ Approved indication[a] ■ Not pursuing marketing approval ■ Primary endpoint met ■ Primary endpoint not met ■ Ongoing trial ■ Trial terminated

AD, atopic dermatitis; AS, ankylosing spondylitis; GCA, Giant cell arteritis; JAK, janus kinase; JIA, Juvenile idiopathic arthritis; nr-axSpA, Non-Radiographic Axial Spondyloarthritis; PsA, psoriatic arthritis; RA, rheumatoid arthritis; SLE, systemic lupus erythematosus.
a. Refers to either EMA, FDA or PMDA regulatory status.
1. Upadacitinib (Adis Insights). Available at: https://adisinsight.springer.com/drugs/800037410 (accessed Feb. 2023); 2. Tofacitinib (Adis Insights). Available at: https://adisinsight.springer.com/drugs/800019029 (accessed Feb. 2023); 3. Baricitinib (Adis Insights). Available at: https://adisinsight.springer.com/drugs/800018131 (accessed Feb. 2023); 4. Filgotinib (Adis Insights). Available at: https://adisinsight.springer.com/drugs/800032685 (accessed Feb. 2023).

Large spectre d'efficacité

Programme de développement dans la PR

UPADACITINIB

	MTX-naïve Signs and symptoms Structure M13-545	MTX-IR Signs and symptoms Structure M14-465	MTX-IR Signs and symptoms M15-555	csDMARD-IR Signs and symptoms M13-549	csDMARD-IR (Japan) Signs and symptoms M14-663[a]	Biologic-IR Signs and symptoms M13-542	Biologic-IR Signs and symptoms M15-925
Type of therapy	Mono	Combo	Mono	Combo	Combo	Combo	Combo
Background	—	MTX	—	csDMARDs	csDMARDs	csDMARDs	csDMARDs
Active comparator	MTX	ADA	MTX	—	—	—	ABA
Arms	• 7.5 mg QD (Japan) • 15 mg QD • 30 mg QD • MTX	• 15 mg QD • PBO • ADA 40 mg EOW	• 15 mg QD • 30 mg QD • MTX	• 15 mg QD • 30 mg QD • PBO	• 7.5 mg QD • 15 mg QD • 30 mg QD • PBO	• 15 mg QD • 30 mg QD • PBO	• 15 mg QD • ABA
Duration of period 1	48 weeks	48 weeks	14 weeks	12 weeks	12 weeks	24 weeks	24 weeks
Sample size	945	1629	648	661	197	499	612

Nombre de patients dans la PR : **N=5191 patients**

[a]Phase 2b/3

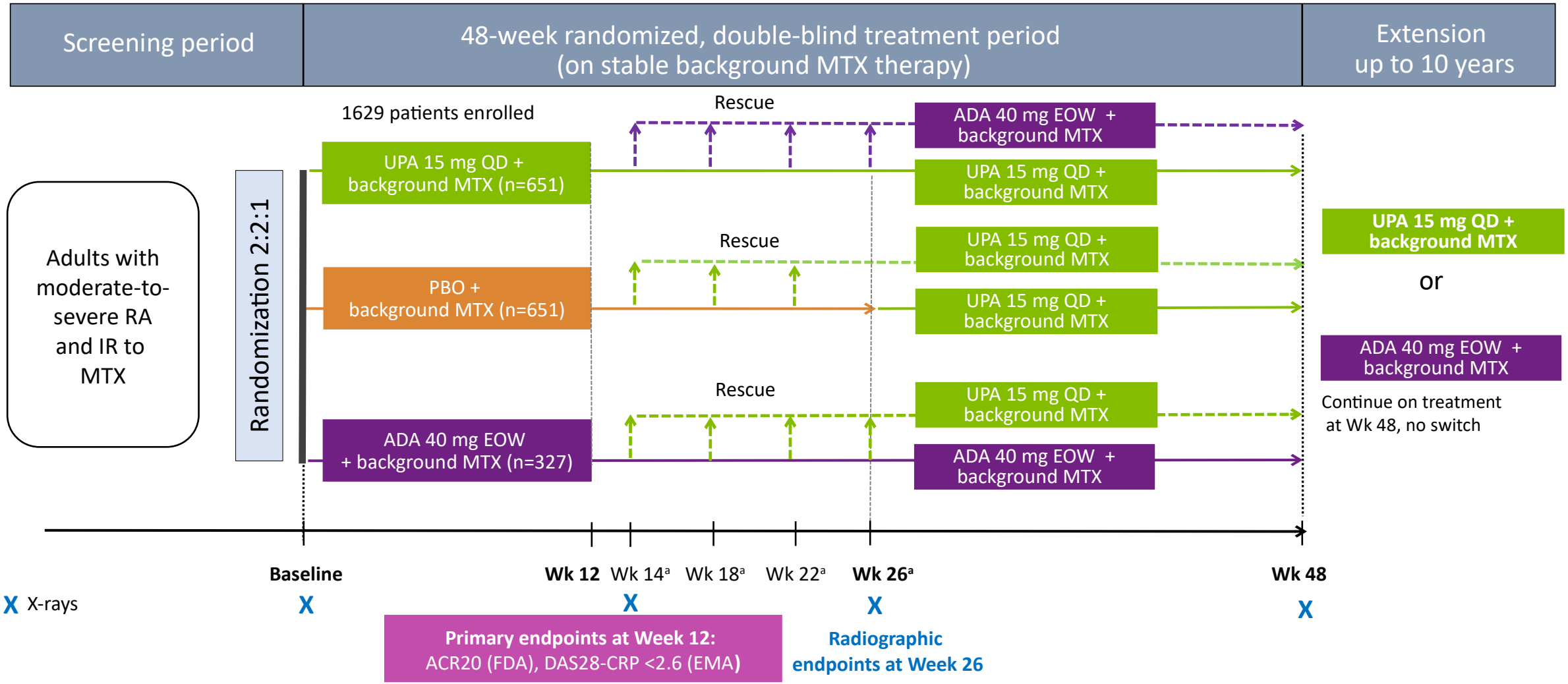
ABA, abatacept; ADA, adalimumab; Combo, combination therapy; csDMARD, conventional synthetic disease-modifying antirheumatic drug; EOW, every other week; IR, inadequate response; Mono, monotherapy; MTX, methotrexate; PBO, placebo; QD, once daily

Efficacité clinique

Étude SELECT-COMPARE

SELECT-COMPARE : Design de l'étude[1,2]

UPADACITINIB



[a]Rescue criteria: At Weeks 14, 18, and 22 if <20% improvement in TJC and SJC; at Week 26 if CDAI >10
ACR20, 20% improvement in ACR criteria; CDAI, Clinical Disease Activity Index; DAS28-CRP, Disease Activity Score of 28 joints with C-reactive protein; EMA, European Medicines Agency; EOW, end of week; FDA, Food and Drug Administration; UPA, upadacitinib; Wk, week

1. Fleischmann, RM et al. Ann Rheum Dis 2019;78:1454–62;
2. Clinicaltrials.gov. NCT02629159

SELECT-COMPARE : Caractéristiques à l'inclusion (1)

UPADACITINIB

Parameter	PBO + MTX (n=651)	UPA 15 mg QD + MTX (n=651)	ADA 40 mg EOW + MTX (n=327)
Demographics			
Female, %	79	80	79
Age (years), mean (SD)	54 (12)	54 (12)	54 (12)
Duration of RA diagnosis (years), mean (SD)	8 (8)	8 (8)	8 (8)
RF-positive and/or anti-CCP-positive, %	88	87	88
Concomitant and prior treatments			
MTX dose (mg), mean (SD)	16.8 (3.8)	17.0 (4.2)	17.1 (3.8)
Prior bDMARD exposure, %[a]	10	8	10
Oral glucocorticoid use, %	60	60	62
Oral glucocorticoid dose (mg), mean (SD)[b]	6.3 (2.4)	6.2 (2.3)	6.5 (2.4)

Full analysis set
[a]Limited exposure (<3 months) or responded to bDMARD but had to discontinue due to toxicity/intolerance (not due to lack of efficacy)
[b]Prednisone equivalent dose in patients receiving oral corticosteroids at baseline
SD, standard deviation

Fleischmann R, et al. Arthritis Rheum 2019;71:1788–800

SELECT-COMPARE : Caractéristiques à l'inclusion (2)

Parameter, mean (SD)	PBO + MTX (n=651)	UPA 15 mg QD + MTX (n=651)	ADA 40 mg EOW + MTX (n=327)
DAS28-CRP	5.8 (0.9)	5.8 (1.0)	5.9 (1.0)
CDAI	40 (13)	40 (13)	40 (13)
TJC68	26 (14)	26 (15)	26 (15)
SJC66	16 (9)	17 (10)	16 (9)
mTSS	36 (52)	34 (50)	35 (47)
Erosion Score	17 (27)	17 (26)	15 (23)
JSN score	19 (26)	18 (25)	19 (26)
hsCRP, mg/L	18 (22)	18 (22)	20 (22)
HAQ-DI	1.6 (0.6)	1.6 (0.6)	1.6 (0.6)
Pain	65 (21)	66 (21)	66 (21)
Morning stiffness duration, min	142 (170)	142 (188)	146 (185)
FACIT-F	27 (11)	27 (11)	26 (11)
SF-36 PCS	33 (7)	33 (7)	32 (7)

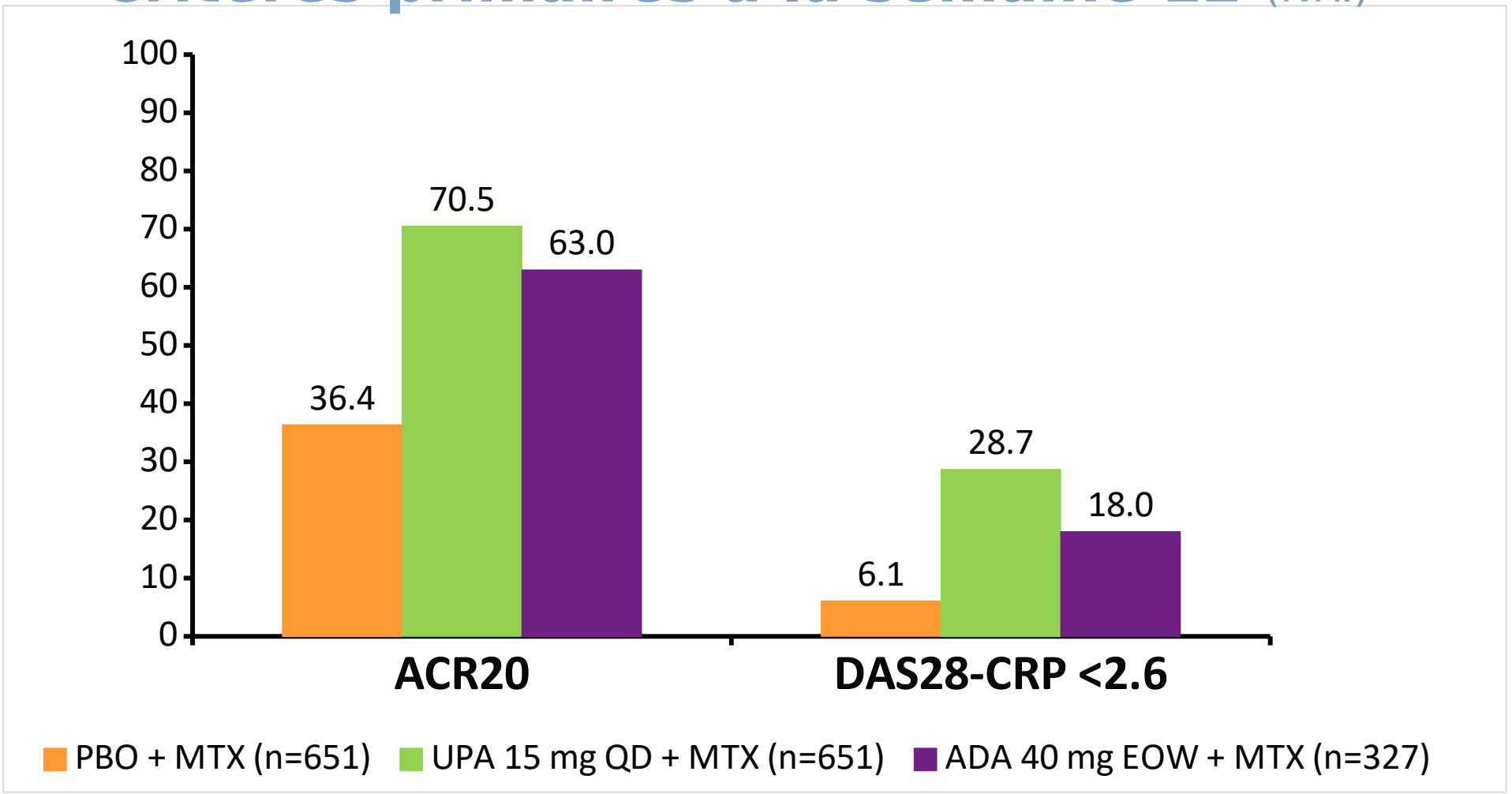
Full analysis set
JSN, joint space narrowing

Fleischmann R, et al. Arthritis Rheum 2019;71:1788–800

SELECT-COMPARE : Résultats d'efficacité

UPADACITINIB

Critères primaires à la semaine 12 (NRI)

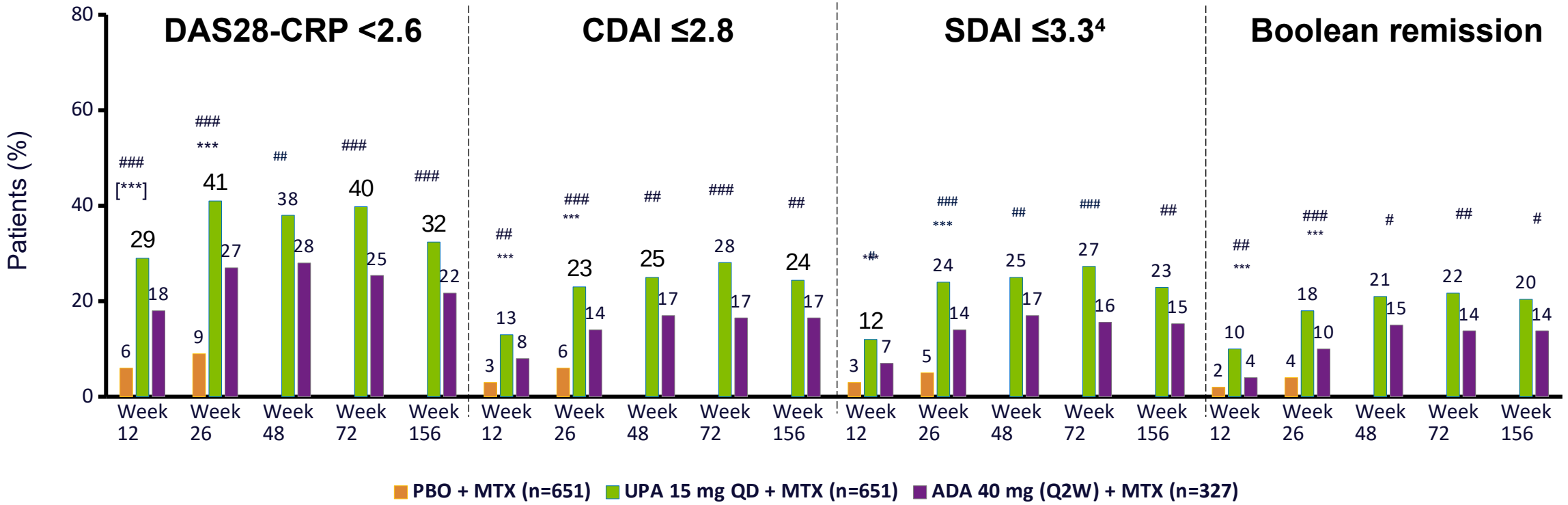


*Population globale d'analyse ***p < 0,001 vs PBO ; Évaluation séparée pour la demande destinée à la FDA et celle destinée à l'EMA ; NRI : Non reponder imputation*

Fleischmann R, et al. Arthritis Rheum 2019;71:1788–800

SELECT-COMPARE : Résultats d'efficacité

Critères de rémission aux semaines 12, 26, 48, 72 et 156 [3]



Significantly higher percentages of patients achieved remission with UPA 15 mg QD + MTX vs ADA 40 mg (Q2W) + MTX, irrespective of remission definition, at 12, 26, 48, 72, and 156 weeks

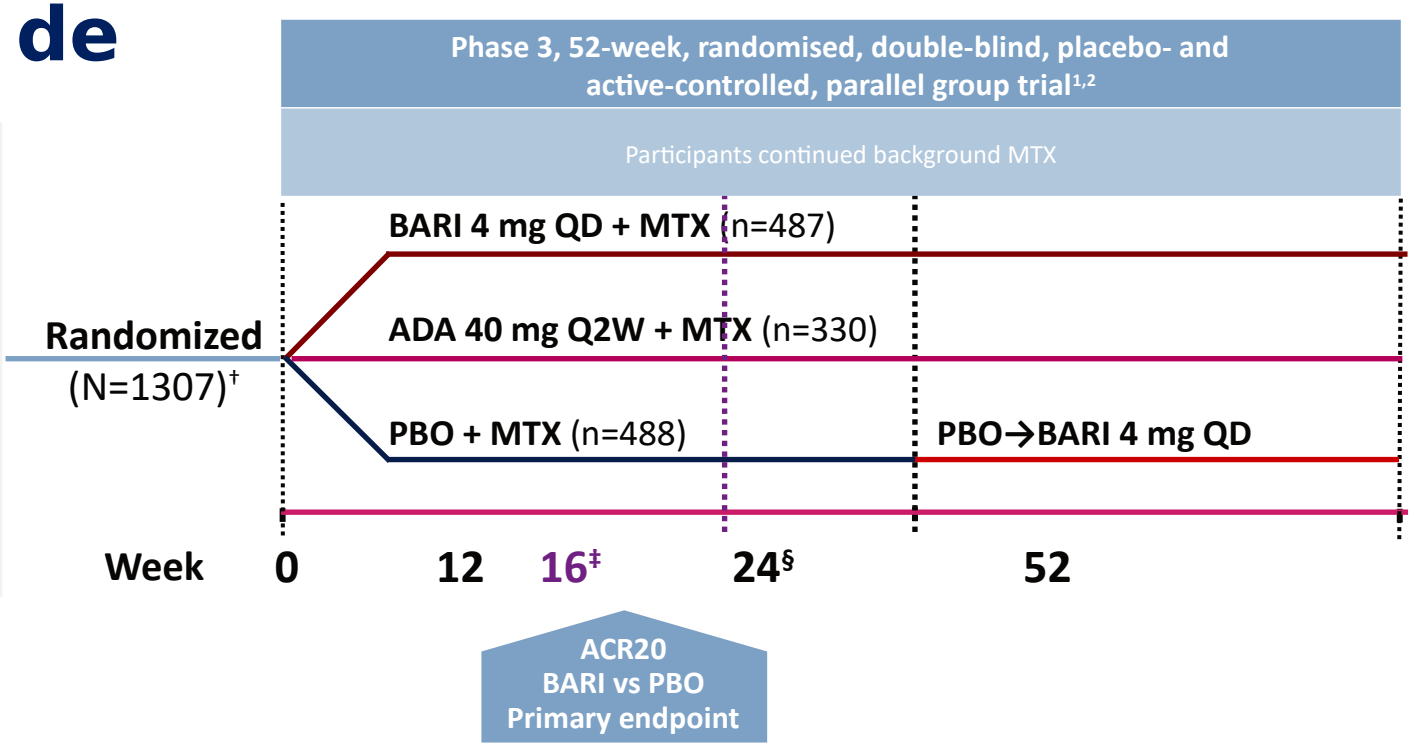
Comparisons adjusted for multiplicity: [***] p<0.001 vs PBO
Comparisons unadjusted for multiplicity: ***p<0.001 vs PBO; #p<0.05; ##p<0.01; ###p<0.001 vs ADA

1. Fleischmann R, et al. Arthritis Rheumatol 2019;71:1788–800;
2. Fleischmann R, et al. EULAR 2020 abstract [THU0201]; 3. Data on file. AbbVie. ABVRRTI72755;
4. Fleischmann R, et al. Arthritis Rheumatol 2019;71:1788–800:Suppl

RA-BEAM : Schéma de l'étude

Patient population (MTX-IR)

- Age ≥18 years
- Active RA: (≥6 of 68 tender joints, ≥6 of 66 swollen joints, and hs-CRP ≥6 mg/L)
- Inadequate response to MTX
  - ≥12 weeks of MTX therapy including ≥8 weeks at stable doses of 15 to 25 mg/week unless lower doses were clinically indicated
  - ≥3 joint erosions or ≥1 joint erosion + seropositive for RF or anti-CCP antibodies



Key endpoints[1,2]

Primary endpoint	Major secondary endpoints (multiplicity-controlled)
ACR20 at Week 12 (BARI vs PBO)	• **ACR20 at Week 12 (BARI vs ADA, superiority)** • ΔHAQ-DI at Week 12 (BARI vs PBO) • SDAI remission (≤3.3) at Week 12 (BARI vs PBO) • **ΔDAS28-CRP at Week 12** (BARI vs PBO and **BARI vs ADA, superiority**) • **ΔmTSS at Week 24 (BARI vs PBO)**

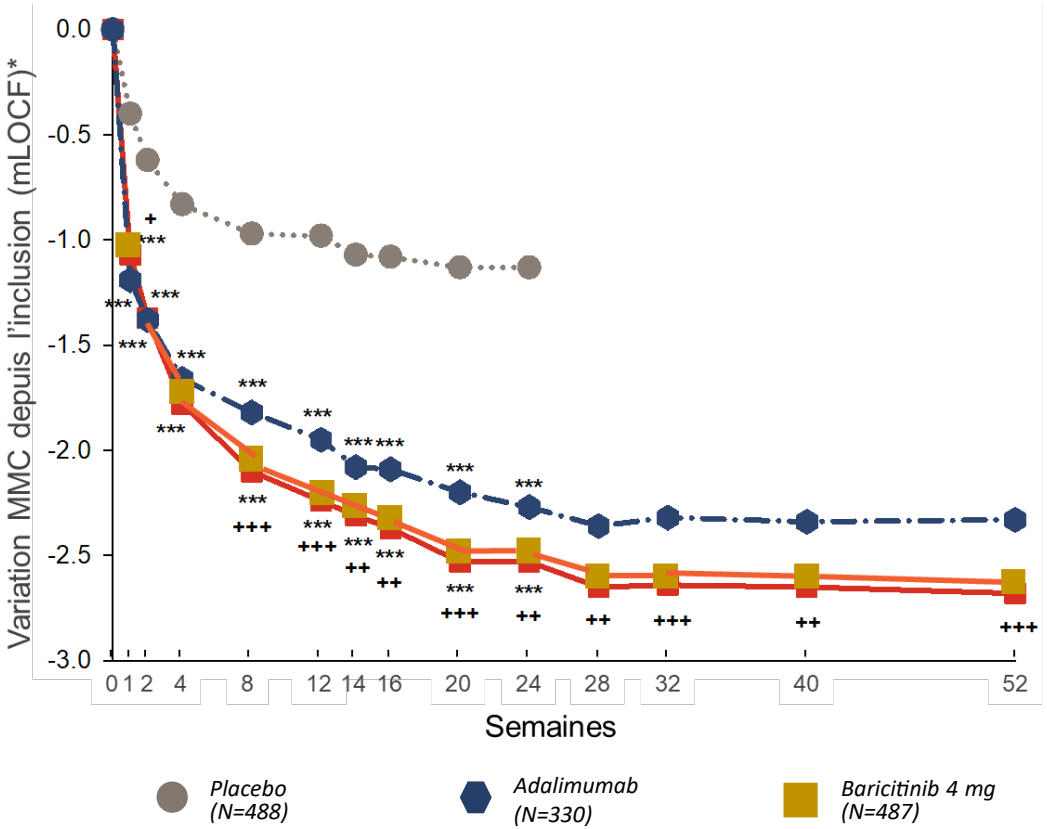
- This is BARI's active comparator study with ADA, with **2 pre-specified superiority comparisons vs ADA**

†Two patients were randomized but not treated, therefore 1305 patients were treated and qualified for analysis; ‡Starting at Week 16, nonresponders (SJC and TJC reduced by <20% from baseline at both Weeks 14 and 16) in the PBO and ADA groups received open-label rescue treatment (BARI 4 mg QD); afterward, rescue treatment was initiated at investigator's discretion on the basis of joint counts; §At Week 24, all participants in PBO group were switched to BARI 4 mg QD and were unaware of the switch.
ACR20, American College of Rheumatology 20% improvement criteria; ADA, adalimumab; BARI, baricitinib; CCP, cyclic citrullinated peptide; DAS28, Disease Activity Score for 28 joint counts; ESR, erythrocyte sedimentation rate; HAQ-DI, Health Assessment Questionnaire-Disability Index; hsCRP, high-sensitivity C-reactive protein; IR, inadequate response; mTSS, modified Total Sharp Score; MTX, methotrexate; PBO, placebo; Q2W; every 2 weeks; QD, once daily; RF, rheumatoid factor; SDAI, Simplified Disease Activity Index; SJC, swollen joint count; TJC, tender joint count.
1. Taylor PC et al. N Engl J Med 2017;376:652–662; 2. NCT01710358. Available at: www.clinicaltrials.gov/ct2/show/NCT01710358 [Last accessed: September 2020].

Baricitinib : étude RA-BEAM

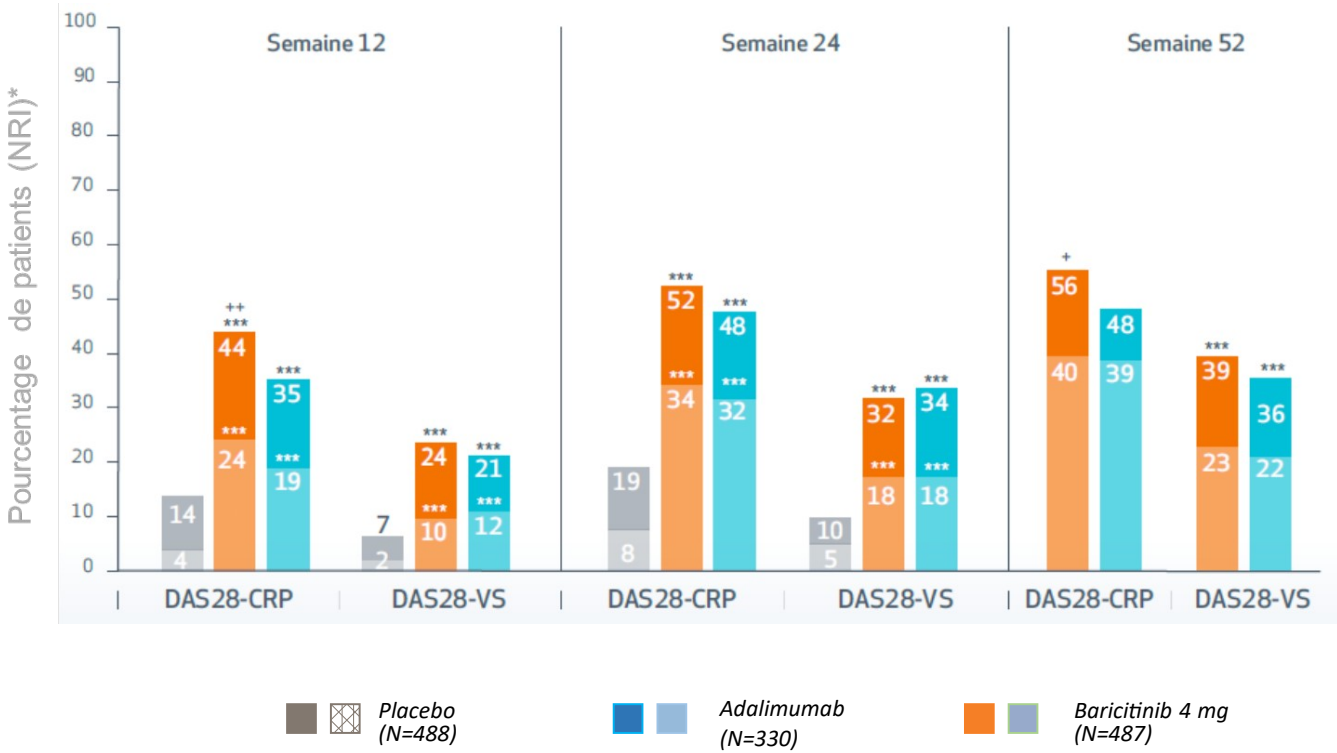
BARICITINIB

Evolution du DAS28-CRP



*vs. adalimumab : ⁺⁺⁺p≤.001, ⁺⁺p≤.01, ⁺p≤.05 ; vs. placebo : ***p≤.001, **p≤.01, *p≤.05 ; *MMC: Moyenne des moindres carrés ; mLOCF: version modifiée du report de la dernière valeur observée*

Faible activité et rémission DAS28



*vs. adalimumab : ⁺⁺⁺p≤.001, ⁺⁺p≤.01, ⁺p≤.05 ; vs. placebo : ***p≤.001, **p≤.01, *p≤.05 ; ; Hauteur totale de chaque barre = DAS28 ≤ 3,2 ; Portion inférieure (ombrée) de chaque barre = DAS28 ≤ 2,6 ; *NRI: imputation en non-réponse*

1. Taylor P. et al. . Baricitinib versus Placebo or Adalimumab in Rheumatoid Arthritis NEJM; 2017;376(7):652-662. 2. Taylor PC et al. Baricitinib versus Placebo or Adalimumab in Rheumatoid Arthritis. New England Journal of Medicine. Supplementary Appendix

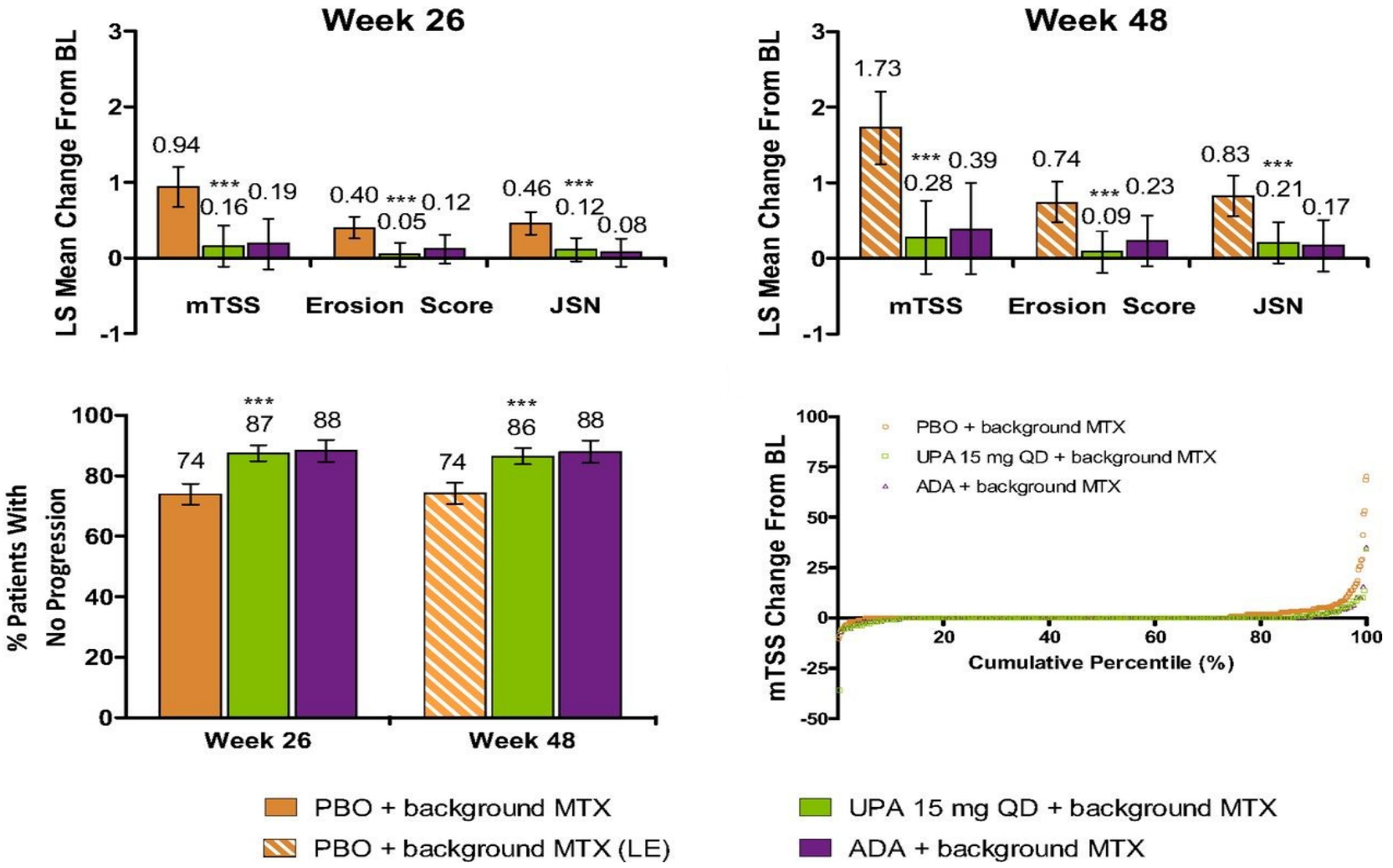
Efficacité structurale

Étude SELECT-COMPARE

SELECT-COMPARE : Efficacité structurale

UPADACITINIB

Inhibition de la progression radiographique



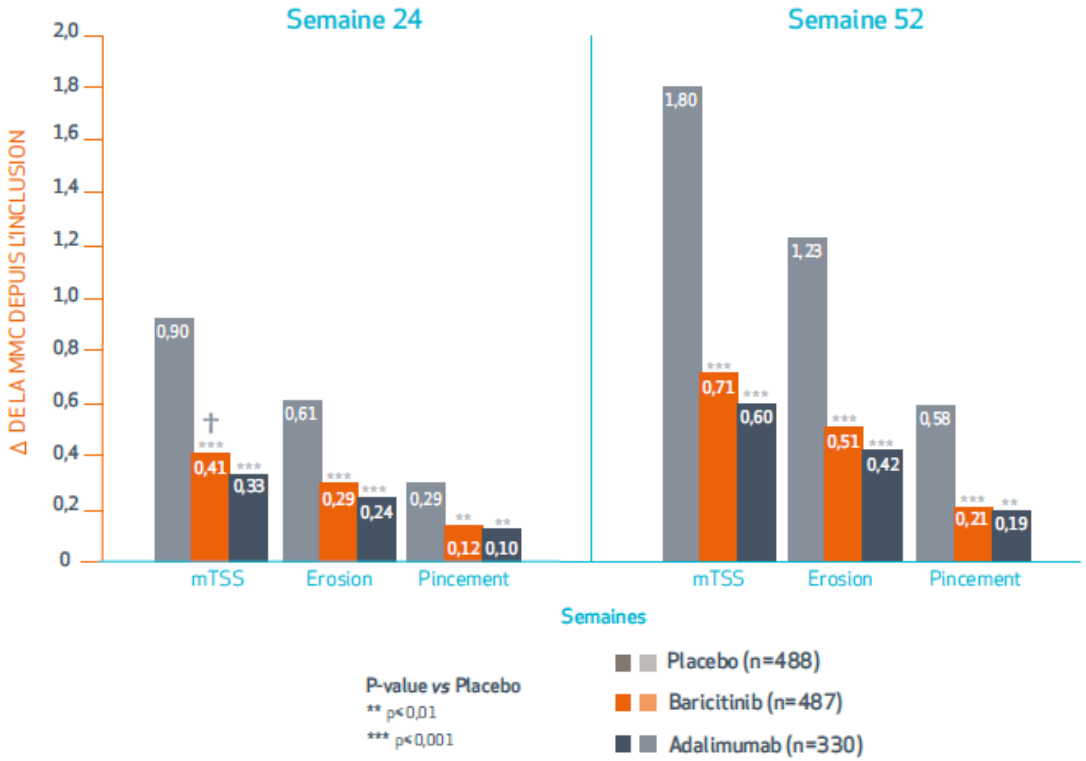
*Treatment groups are by initial randomization. Results based on regarding session 2 *P≤0.05; **P<0.01; ***P<0.001; for UPA vs. PB0 groups, all data at Week 48 were imputed by LE. For patients rescued, data were also imputed by LE.*

1. Fleischmann R et al. Safety and effectiveness of upadacitinib or adalimumab plus methotrexate in patients with rheumatoid arthritis over 48 weeks with switch to alternate therapy in patients with insufficient response. Ann Rheum Dis. 2019 Nov;78(11):1454-1462 and Supplementary data

Baricitinib : étude RA-BEAM

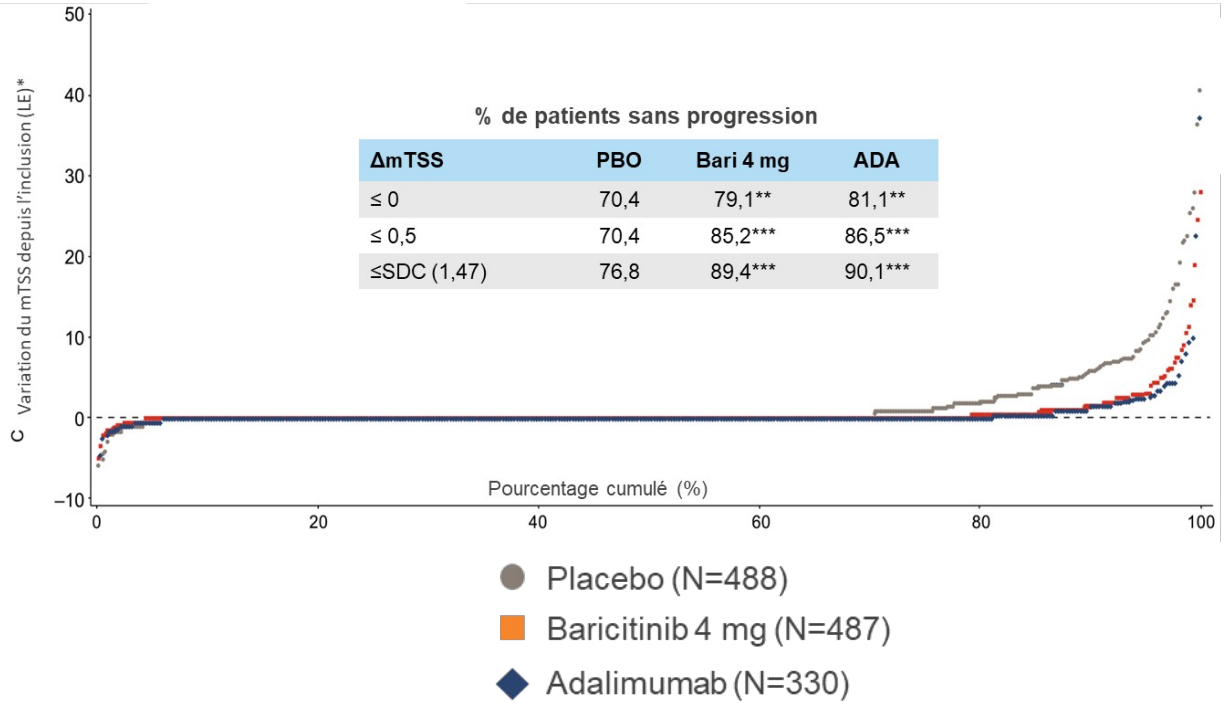
BARICITINIB

Progression radiographique



MMC: Moyenne des Moindres Carrés ; † Résultat statistiquement significatif pour les critères secondaires majeurs, baricitinib vs placebo ou baricitinib vs adalimumab (analyse hiérarchique)

Evolution individuelle du mTSS (vdH) à la semaine 52



% de patients sans progression

ΔmTSS	PBO	Bari 4 mg	ADA
≤ 0	70,4	79,1**	81,1**
≤ 0,5	70,4	85,2***	86,5***
≤SDC (1,47)	76,8	89,4***	90,1***

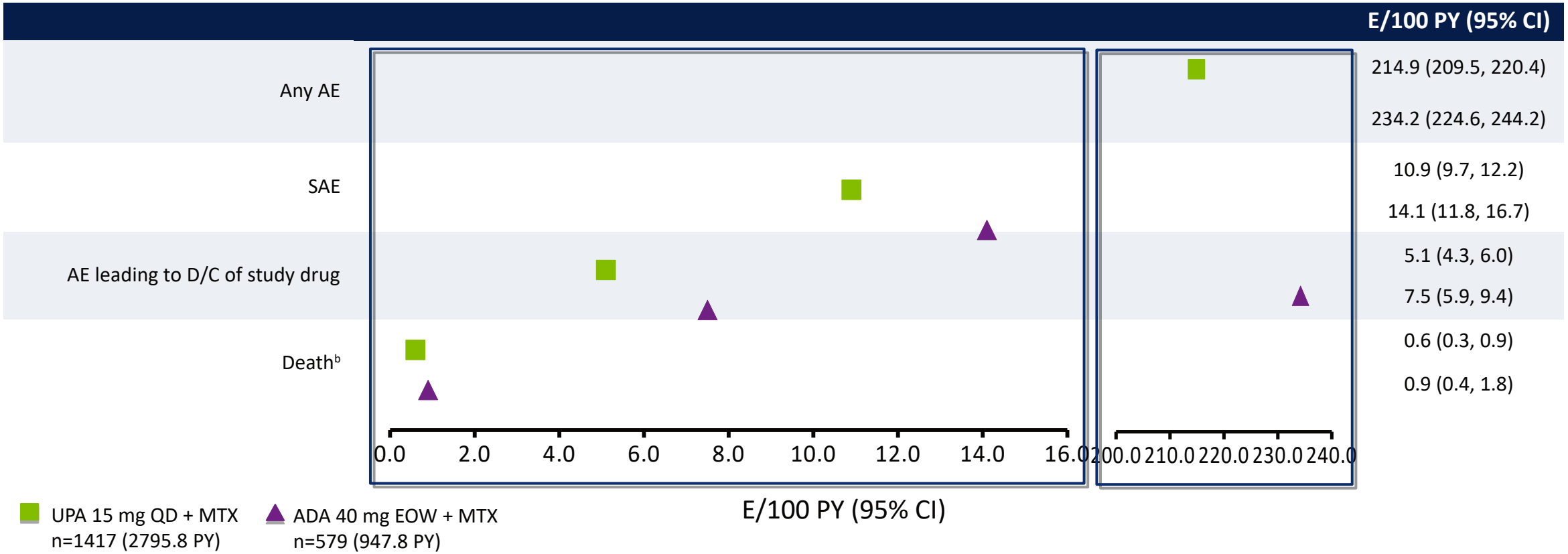
*vs. Adalimumab : ⁺⁺⁺ p≤0,001, ⁺⁺ p≤0,01, ⁺ p≤0,05 ; vs. Placebo : *** p≤0,001 ; ** p≤0,01 ; * p≤0,05 ; * LE: Utilisation de l'interpolation linéaire pour le remplacement des données après traitement de secours ou arrêt ; SDC = plus petite variation détectable (1,98 unités)*

1. Taylor P. et al. . Baricitinib versus Placebo or Adalimumab in Rheumatoid Arthritis NEJM; 2017;376(7):652-662, 2. Taylor PC et al. Baricitinib versus Placebo or Adalimumab in Rheumatoid Arthritis. New England Journal of Medicine. Supplementary Appendix;

Tolérance

Étude SELECT-COMPARE

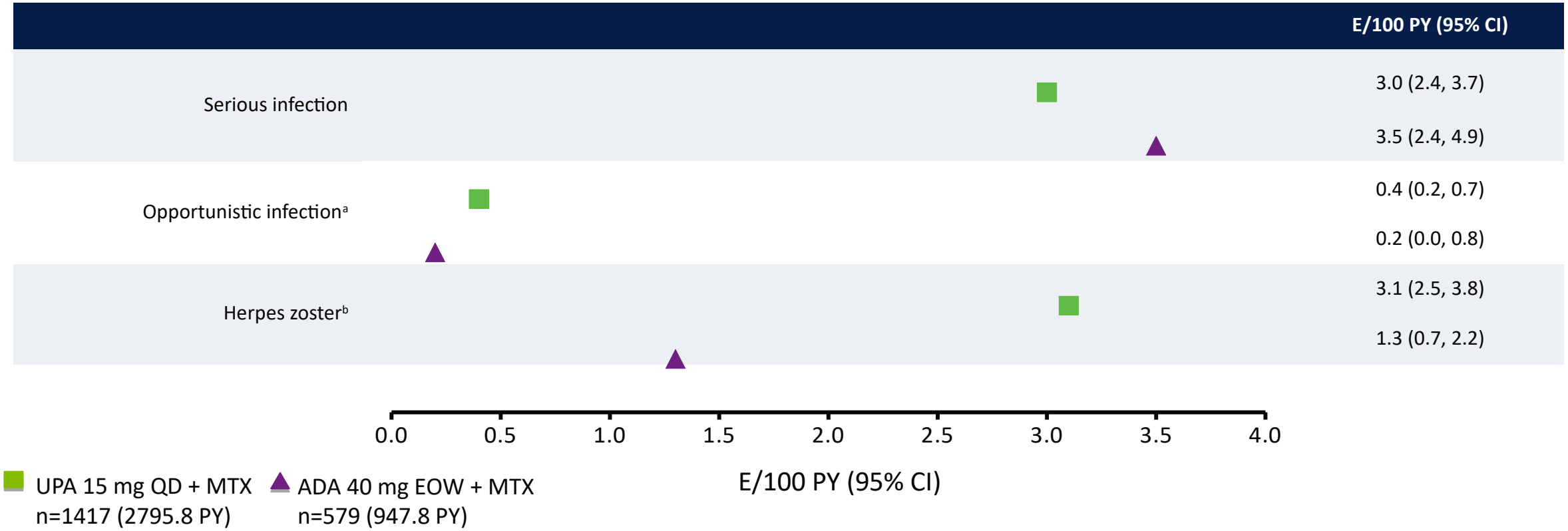
SELECT-COMPARE : Evènements indésirables à S156[a]



TEAE rates were generally similar in the UPA and ADA arms over 156 weeks

Safety analysis set (data cut-off December 26, 2018) [a]Exposure adjusted incidence rates (EAIR) are reported for death; exposure adjusted event rates (EAER) are reported for the remaining events. [b]Deaths (includes non-treatment-emergent deaths) with UPA: 2 deaths (undetermined/unknown), 1 cardiac failure, 1 sudden death, 1 arteriosclerosis coronary artery, 1 meningitis *Listeria*, 1 acute respiratory distress syndrome, and 1 lung carcinoma cell type unspecified Stage IV; ADA: 1 left ventricular failure, 1 craniocerebral injury, 1 colon cancer, 1 mixed connective tissue disease, 1 lung squamous cell carcinoma Stage IV, and 1 undetermined death CI, confidence interval; E/100 PY, events per 100 patient-years

SELECT-COMPARE : Infections à S156



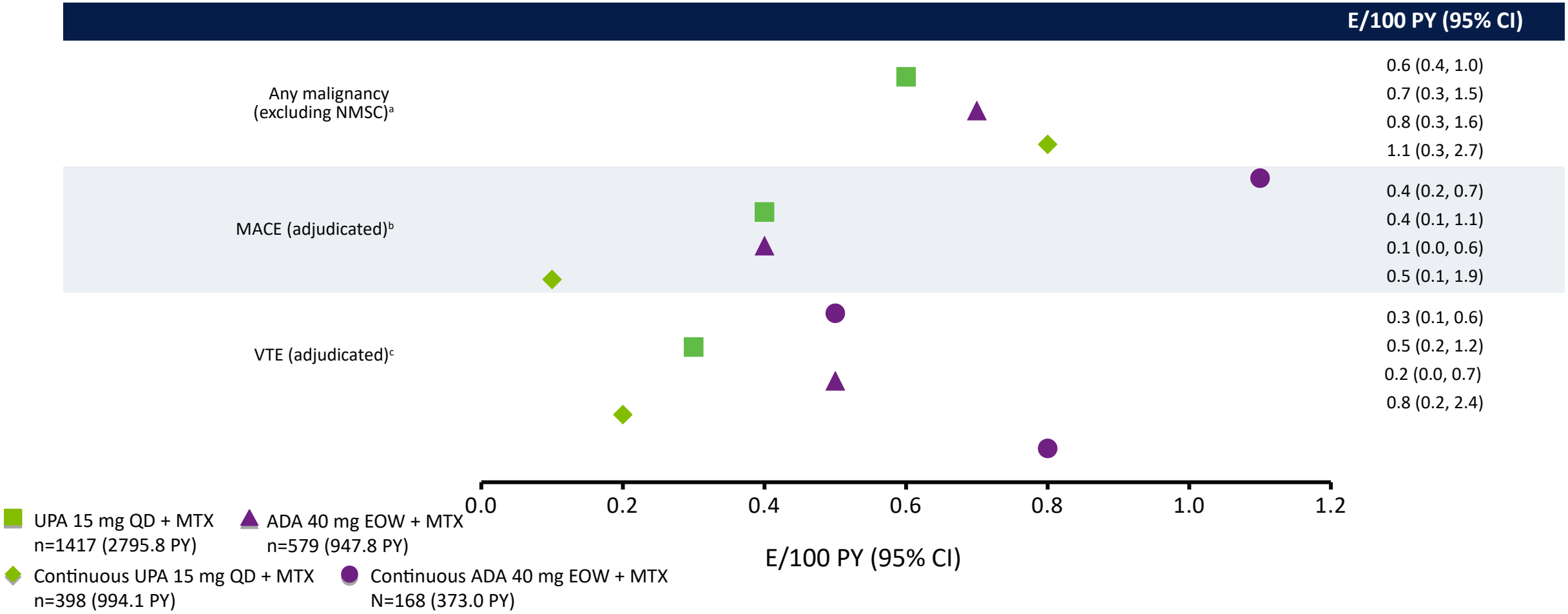
Rates of serious and opportunistic infection were similar in the UPA and ADA arms, although herpes zoster rates were increased with UPA versus ADA

Safety analysis set (data cut-off: December 26, 2018)

[a]UPA: 4 oral candidiasis, 4 esophageal candidiasis, 1 bronchopulmonary aspergillosis, 1 fungal pharyngitis, 1 herpes zoster disseminated, 1 meningitis *Listeria*, and 1 oral fungal infection; ADA: 3 oral candidiasis. [b]Majority of cases on UPA were non-serious and involved 1 or 2 dermatomes

Fleischmann R, et al. EULAR 2021;Poster POS0087

SELECT-COMPARE : Cancer, MACE et VTE à S156



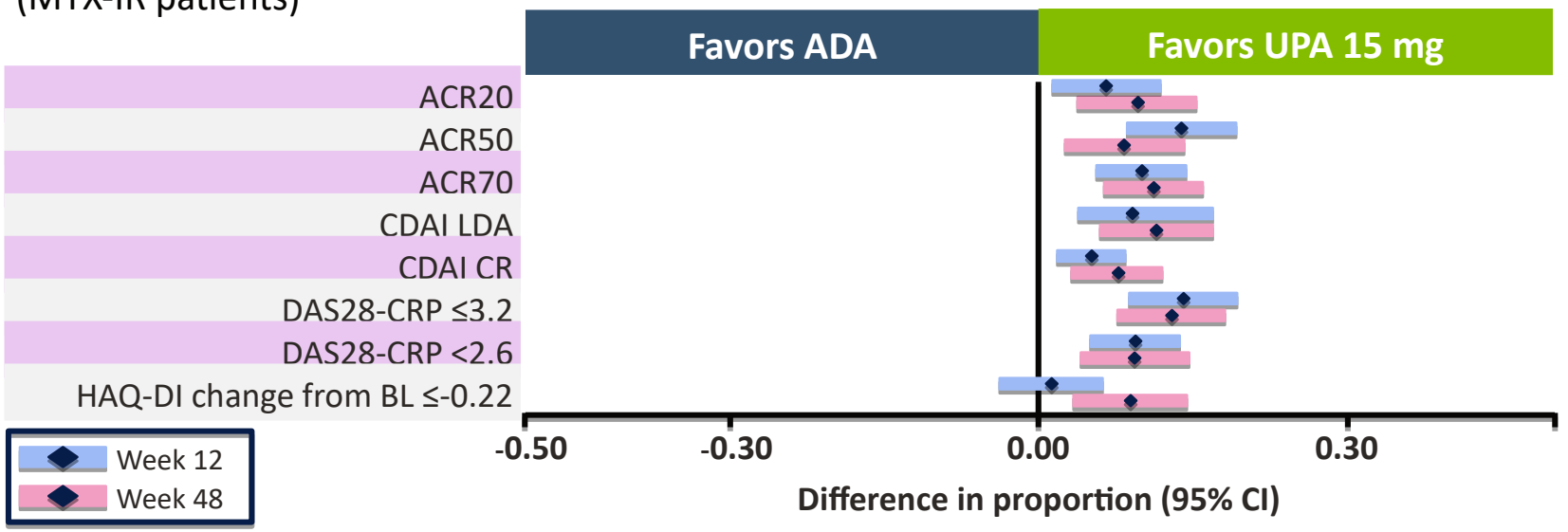
Over 156 weeks, incidence rates of malignancy, MACE, and VTE were comparable for UPA and ADA, including in patients receiving continuous UPA or ADA without rescue or switch

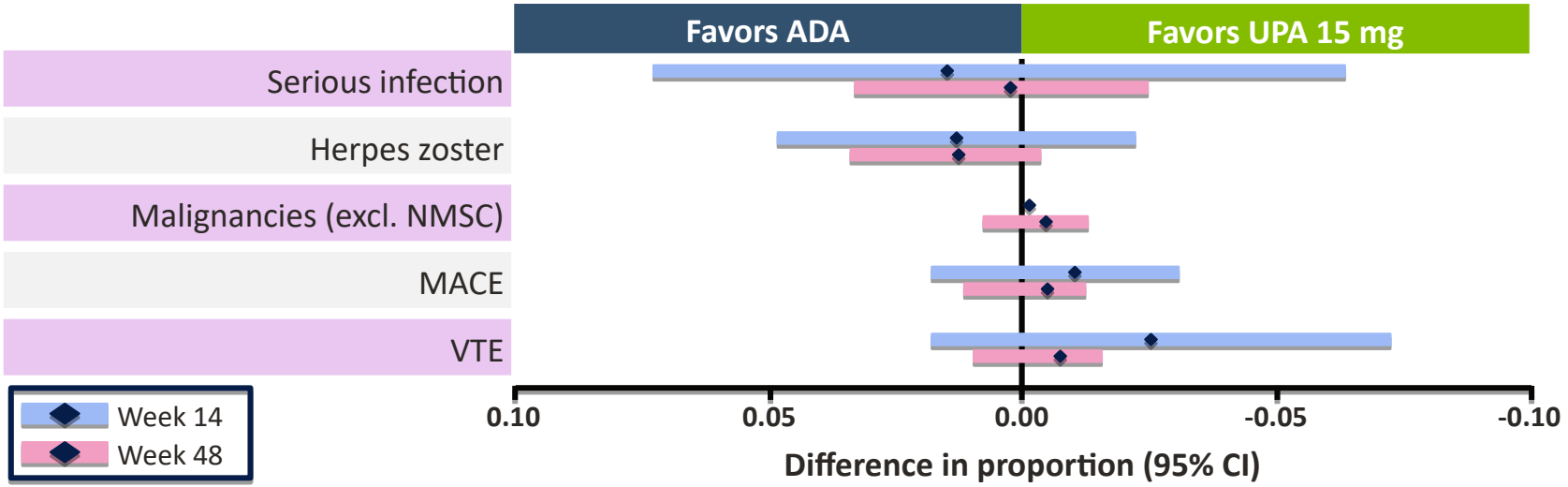
Safety analysis set (data cut-off: December 26, 2018) [a]UPA: 1 laryngeal cancer, 1 endometrial adenocarcinoma, 1 malignant melanoma, 1 gastric adenocarcinoma, and 1 adenocarcinoma of colon; ADA: 1 malignant melanoma, 1 metastatic colon cancer, 1 malignant lung neoplasm, and 1 metastatic colon cancer. [b]Includes CV death, non-fatal MI, and non-fatal stroke; UPA: 1 non-fatal stroke, 3 non-fatal MI, and 1 CV death; ADA: 2 non-fatal strokes and 1 CV death. [c]UPA: 1 DVT, 2 PE, and 1 DVT and PE; ADA: 4 PE and 1 DVT. CV, cardiovascular; MI, myocardial infarction

Fleischmann R, et al. EULAR 2021;Poster POS0087

UPA 15 mg + MTX vs ADA + MTX : Rapport bénéfice/risque

(MTX-IR patients)





Benefit

UPA 15 mg + MTX achieved greater ACR20/50/70 response rates and DAS28-CRP, CDAI remission and CDAI LDA rates compared with those treated with ADA + MTX at Week 12, which were maintained at Week 48[1,2]

Risk

There was an increased rate of HZ with UPA 15 mg + MTX compared with ADA + MTX, but the rate of serious infection, malignancies (excluding NMSC), MACEs, and VTEs were similar between UPA 15 mg and ADA treatment groups[2]

E, event; HZ, herpes zoster; PY, patient-year

1. Fleischmann R, et al. Arthritis Rheumatol 2019;71:1788–800;
2. Conaghan PG, et al. Drug Saf 2021; https://doi.org/10.1007/s40264-020-01036-w

RA-BEAM : Données de tolérance à S24 et S52

BARICITINIB

n (%) patients	Weeks 0–24†			Weeks 0–52†	
	BARI 4 mg QD + MTX **(n=487)**	ADA 40 mg Q2W + MTX **(n=330)**	PBO + MTX **(n=488)**	BARI 4 mg QD + MTX **(n=487)**	ADA 40 mg Q2W + MTX **(n=330)**
Serious AE‡	23 (5)	6 (2)	22 (5)	38 (8)	13 (4)
Any AE	347 (71)	224 (68)	295 (60)	384 (79)	253 (77)
Withdrawal due to AE	24 (5)	7 (2)	17 (3)	36 (7)	13 (4)
Infection	176 (36)	110 (33)	134 (27)	233 (48)	145 (44)
Herpes zoster	7 (1)	4 (1)	2 (<1)	11 (2)	5 (2)
Tuberculosis	0	1 (<1)	0	0	1 (<1)
Serious infection	5 (1)	2 (<1)	7 (1)	10 (2)	5 (2)
Cancer	2 (<1)	0	3 (<1)	3 (<1)	0
Nonmelanoma skin cancer	0	0	1 (<1)	0	0
Breast cancer	1 (<1)	0	1 (<1)	1 (<1)	0
Squamous cell cancer	1 (<1)	0	0	1 (<1)	0
Ovarian cancer	0	0	1 (<1)	0	0
Clear cell renal carcinoma	0	0	0	1 (<1)	0
MACE§	1 (<1)	0	0	2 (<1)	1 (<1)
GI perforation	0	0	0	0	0

- **AEs,** including infection, were more frequent with BARI and ADA groups compared with PBO from Weeks 0–24.
- **Rates of AEs** from Weeks 0–52 were generally similar in BARI and ADA groups.
- **Herpes zoster** was seen in all groups (at a rate of 2% in both the BARI and ADA groups from Week 0–52); most cases occurred in Asia.
- **No events of VTE** were reported

†Starting at Week 16, nonresponders (SJC and TJC reduced by <20% from baseline at both Weeks 14 and 16) in the PBO and ADA groups received rescue therapy (BARI 4 mg QD); afterward, rescue treatment was initiated at investigator's discretion on the basis of joint counts; at Week 24 all participants in PBO group were switched to BARI 4 mg QD; ‡up to time of rescue; §Cardiovascular death, myocardial infarction, or stroke, as adjudicated by an independent cardiovascular committee.

ADA, adalimumab; AE, adverse event; BARI, baricitinib; GI, gastrointestinal; MACE, major adverse cardiovascular event; MTX, methotrexate; PBO, placebo; Q2W, every 2 weeks; QD, once daily; SJC, swollen joint count; TJC, tender joint count; VTE, venous thromboembolism.

Taylor PC, et al. N Engl J Med 2017;376:652–662.

Efficacité en **monothérapie**

Étude
SELECT-MONOTHERAPY

Programme de développement dans la PR

UPADACITINIB

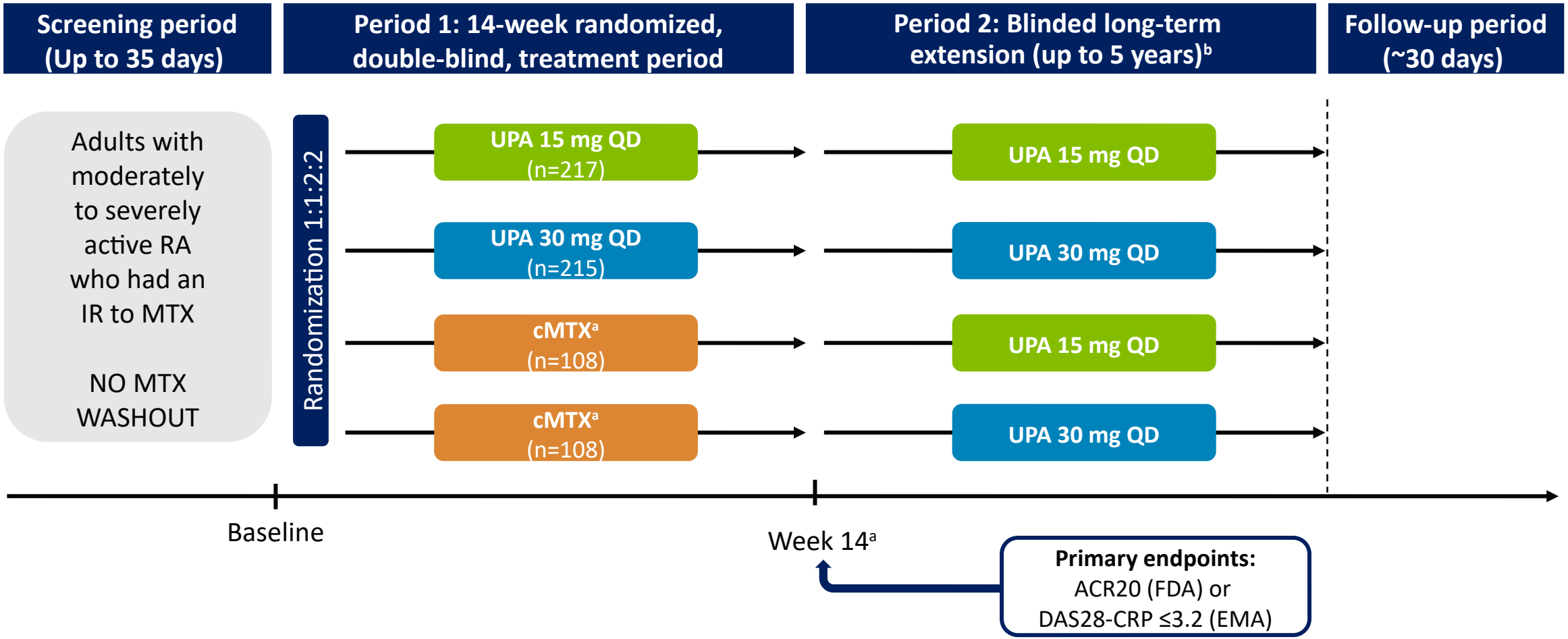
	MTX-naïve Signs and symptoms Structure M13-545	MTX-IR Signs and symptoms Structure M14-465	MTX-IR Signs and symptoms M15-555	csDMARD-IR Signs and symptoms M13-549	csDMARD-IR (Japan) Signs and symptoms M14-663[a]	Biologic-IR Signs and symptoms M13-542	Biologic-IR Signs and symptoms M15-925
Type of therapy	Mono	Combo	Mono	Combo	Combo	Combo	Combo
Background	—	MTX	—	csDMARDs	csDMARDs	csDMARDs	csDMARDs
Active comparator	MTX	ADA	MTX	—	—	—	ABA
Arms	• 7.5 mg QD (Japan) • 15 mg QD • 30 mg QD • MTX	• 15 mg QD • PBO • ADA 40 mg EOW	• 15 mg QD • 30 mg QD • MTX	• 15 mg QD • 30 mg QD • PBO	• 7.5 mg QD • 15 mg QD • 30 mg QD • PBO	• 15 mg QD • 30 mg QD • PBO	• 15 mg QD • ABA
Duration of period 1	48 weeks	48 weeks	14 weeks	12 weeks	12 weeks	24 weeks	24 weeks
Sample size	945	1629	648	661	197	499	612

Nombre de patients dans la PR : **N=5191 patients**

[a]Phase 2b/3
ABA, abatacept; ADA, adalimumab; Combo, combination therapy; csDMARD, conventional synthetic disease-modifying antirheumatic drug; EOW, every other week; IR, inadequate response; Mono, monotherapy; MTX, methotrexate; PBO, placebo; QD, once daily

SELECT-MONOTHERAPY : Design de l'étude

UPADACITINIB



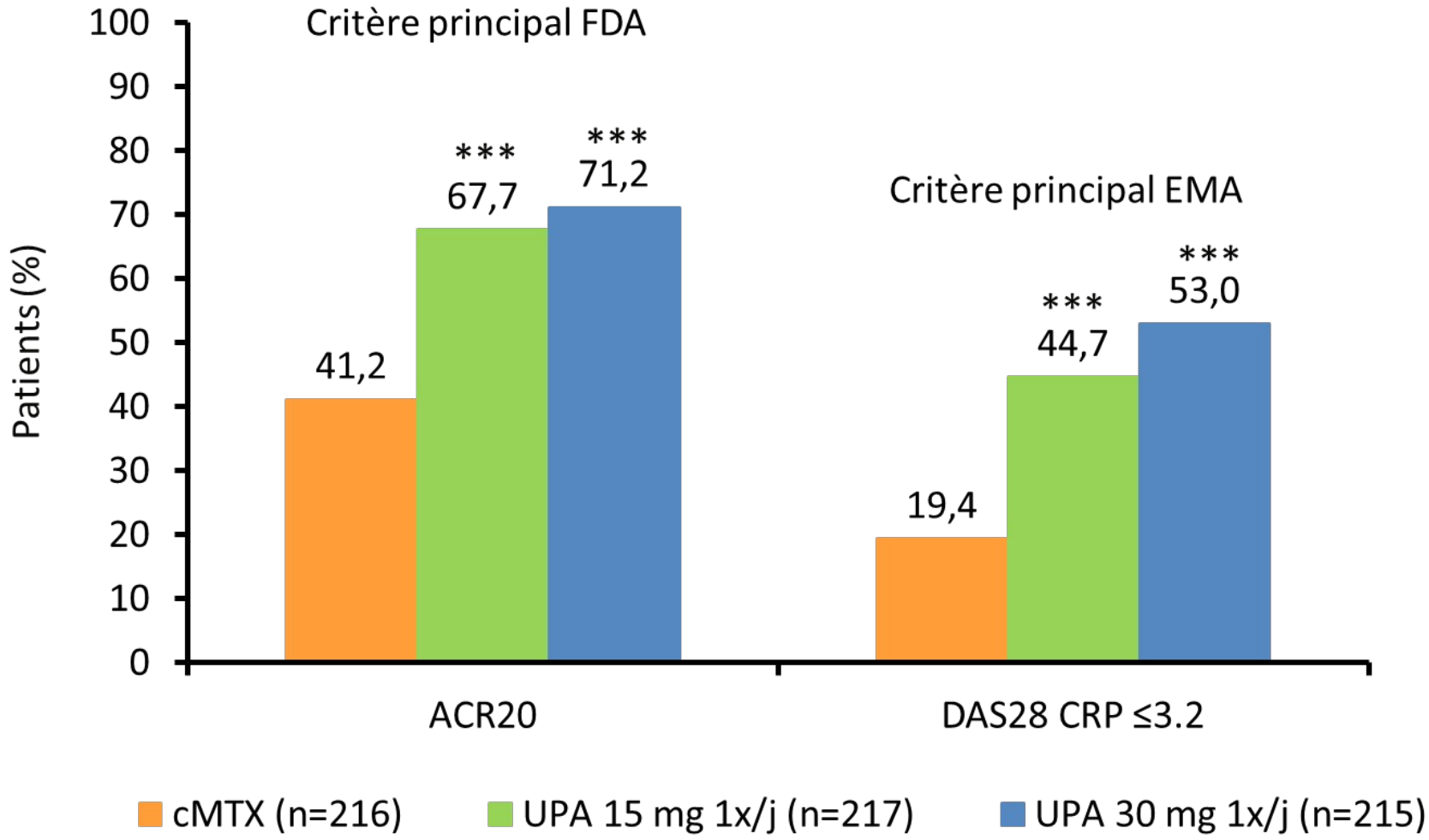
[a]For the primary analysis at Week 14, cMTX data were pooled from both cMTX groups; from Week 14, patients initially randomized to cMTX were switched to UPA 15 mg or 30 mg per prespecified randomization assignment
[b]Visits at Weeks 14, 20, 26, 36, 40, 48, and every 12 weeks thereafter; starting from Week 26, patients with CDAI >10 had background medication(s) adjusted or background csDMARDs could be initiated as rescue
ACR20, 20% improvement in ACR criteria; CDAI, Clinical Disease Activity Index; cMTX, continuing MTX; DAS28-CRP, Disease Activity Score in 28 joints with CRP; EMA, European Medicines Agency; FDA, Food and Drug Administration

Smolen JS, et al. EULAR 2019;Poster THU0191;
Smolen JS, et al. EULAR 2020;Poster THU0213;
Smolen JS, et al. Lancet 2019;393:2303–11

SELECT-MONOTHERAPY : Résultats d'efficacité

UPADACITINIB

Critères primaires à la semaine 14 (NRI)



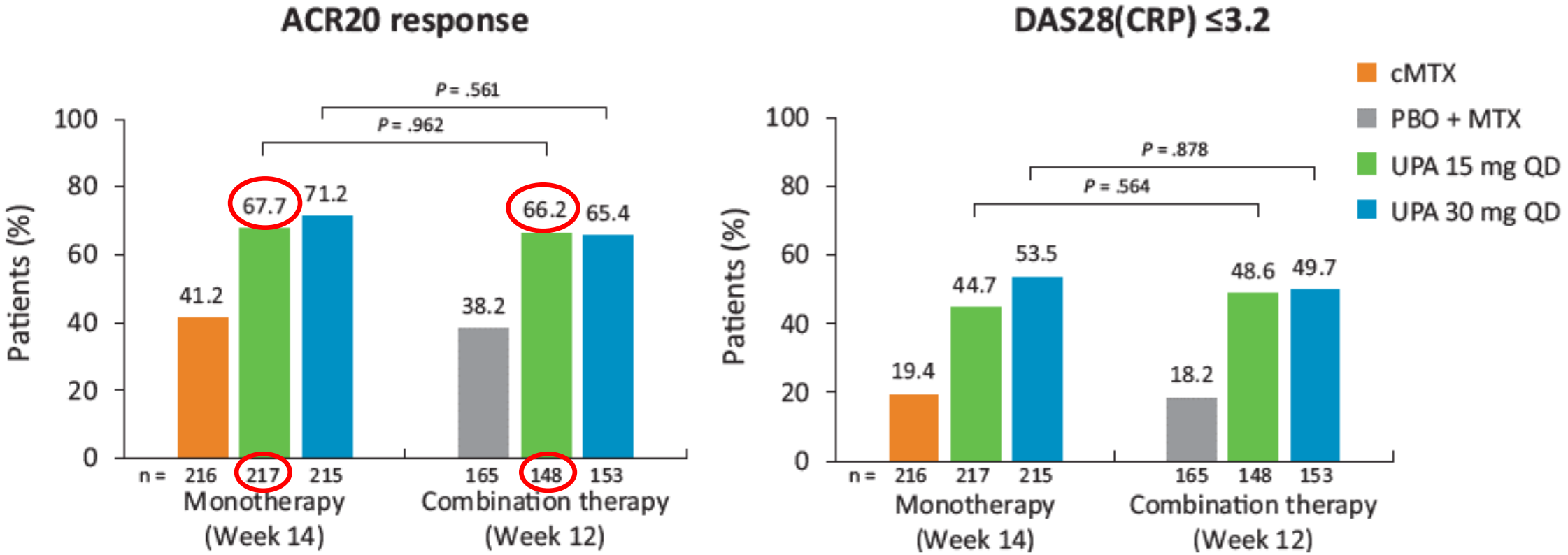
La dose de 30mg n'a pas d'AMM dans la polyarthrite rhumatoïde
*Population globale d'analyse ***p < 0,001 vs cMTX; LDA, Low Disease activity; NRI, non responder imputation ; cMTX : Continuation du MTX*
UPA, Upadacitinib, FDA, U.S. Food and Drug Administration, EMA, european medicines agency

1. Smolen JS, Pangan AL, P Emery et al Lancet 2019; 393: 2303–11

Résultats d'efficacité : monothérapie vs combothérapie

UPADACITINIB

SELECT-MONOTHERAPY et SELECT-NEXT



Des résultats cliniques similaires pour ces deux essais d'upadacitinib en monothérapie et en association au MTX présentant des populations comparables

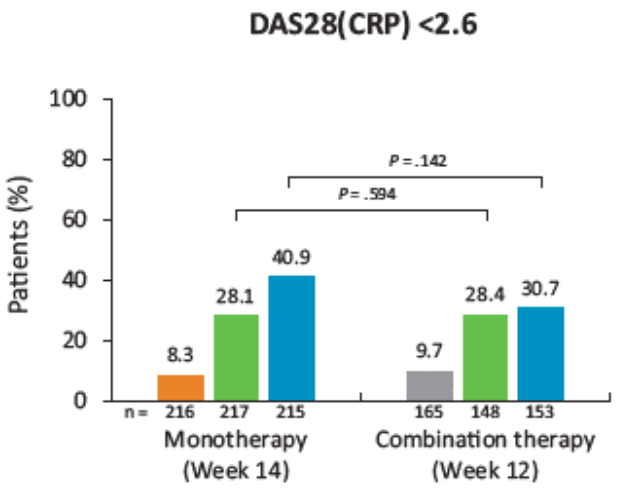
La dose de 30mg n'a pas d'AMM dans la polyarthrite rhumatoïde

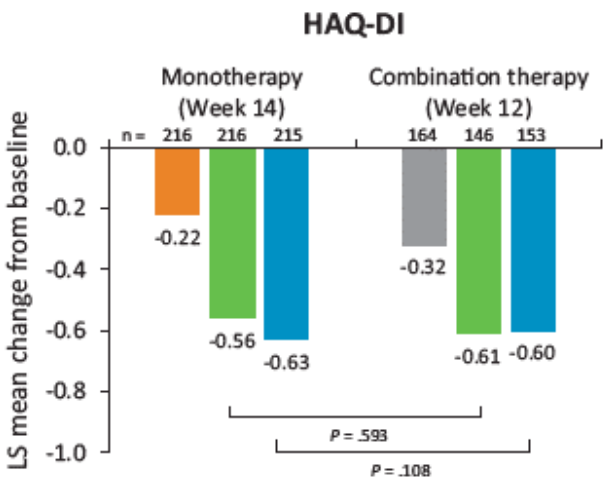
P-values were based on logistic regression (binary outcomes) or ordinary least squares (continuous outcome) analyses for the comparison of the control group-adjusted treatment effects of monotherapy vs combination therapy, adjusting for various demographics (age, sex, race, region, weight, and smoking status) and baseline characteristics (hsCRP, DAS28[CRP], HAQ-DI, RA duration, and RF and anti-CCP positivity). ACR20, 20% improvement in American College of Rheumatology criteria; CCP, cyclic citrullinated peptide; cMTX, continued methotrexate; CRP, C-reactive protein; DAS28, 28-joint Disease Activity Score; HAQ-DI, Health Assessment Questionnaire-Disability Index; hsCRP, high-sensitivity C-reactive protein; MTX, methotrexate; PBO, placebo; QD, once daily; RA, rheumatod arthritis; RF, rheumatoid factor; UPA, upadacitinib.

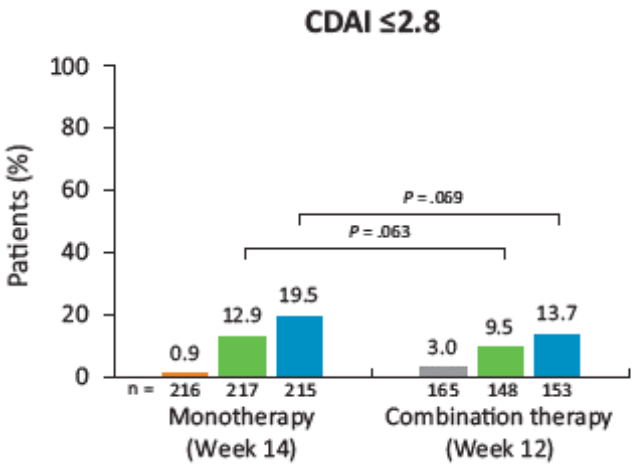
1. Buch M et al., THU0165 A COMPARATIVE ANALYSIS OF UPADACITINIB MONOTHERAPY AND UPADACITINIB COMBINATION THERAPY FOR THE TREATMENT OF RHEUMATOID ARTHRITIS FROM TWO PHASE 3 TRIALS Annals of the Rheumatic Diseases 2019;78:356.

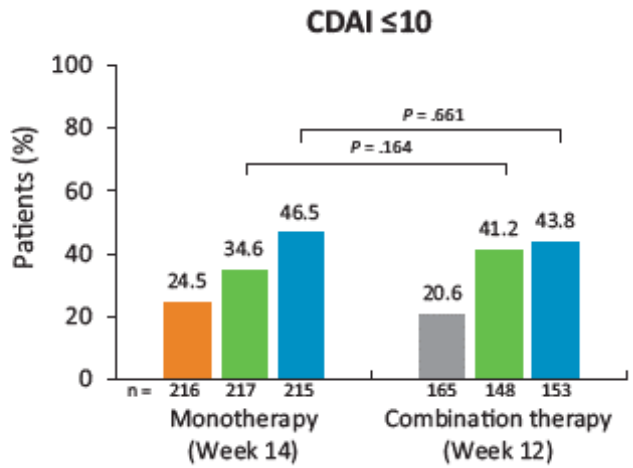
Résultats d'efficacité : monothérapie vs combothérapie

SELECT-MONOTHERAPY et SELECT-NEXT









<u>Des résultats cliniques similaires</u> pour ces deux essais d'upadacitinib en monothérapie et en association au MTX présentant des populations comparables

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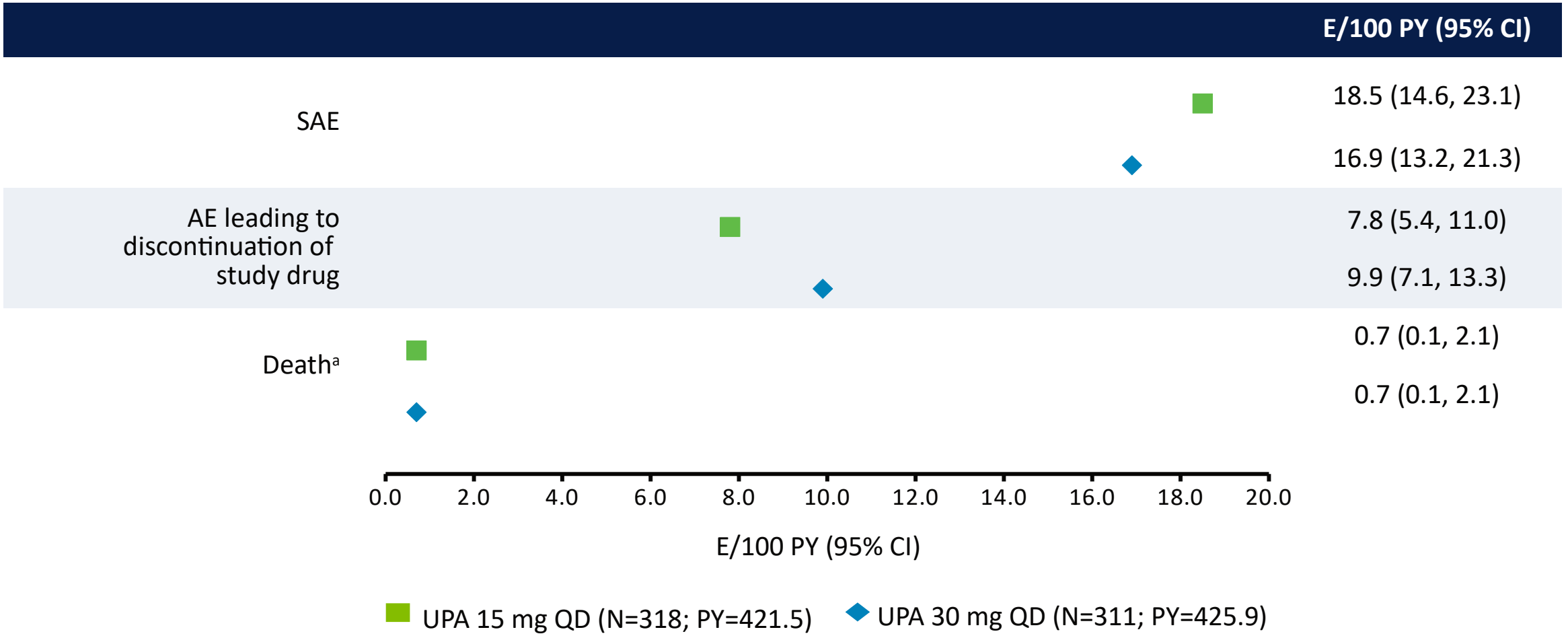
P-values were based on logistic regression (binary outcomes) or ordinary least squares (continuous outcome) analyses for the comparison of the control group-adjusted treatment effects of monotherapy vs combination therapy, adjusting for various demographics (age, sex, race, region, weight, and smoking status) and baseline characteristics (hsCRP, DAS28[CRP], HAQ-DI, RA duration, and RF and anti-CCP positivity). ACR20, 20% improvement in American College of Rheumatology criteria; CCP, cyclic citrullinated peptide; cMTX, continued methotrexate; CRP, C-reactive protein; DAS28, 28-joint Disease Activity Score; HAQ-DI, Health Assessment Questionnaire-Disability Index; hsCRP, high-sensitivity C-reactive protein; MTX, methotrexate; PBO, placebo; QD, once daily; RA, rheumatod arthritis; RF, rheumatoid factor; UPA, upadacitinib.

1. Buch M et al., THU0165 A COMPARATIVE ANALYSIS OF UPADACITINIB MONOTHERAPY AND UPADACITINIB COMBINATION THERAPY FOR THE TREATMENT OF RHEUMATOID ARTHRITIS FROM TWO PHASE 3 TRIALS Annals of the Rheumatic Diseases 2019;78:356.

Tolérance

Étude SELECT-MONOTHERAPY

SELECT-MONOTHERAPY : Evènements indésirables à S84



Data cut-off: February 5, 2019

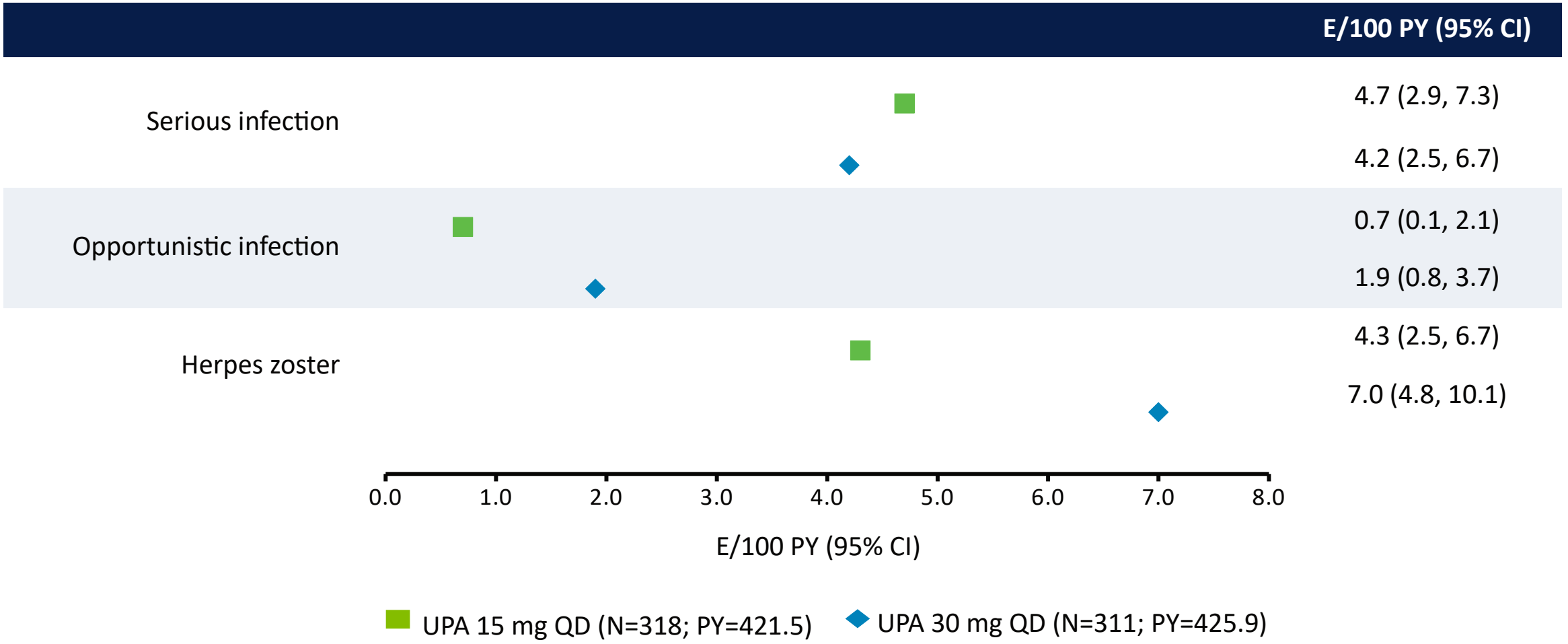
[a]6 deaths occurred, including 1 NTE death; UPA 15 mg, 1 hemorrhagic stroke, 1 sudden cardiac death, 1 congestive cardiomyopathy (NTE); UPA 30 mg, 1 myocardial infarction, 1 cardiorespiratory arrest, and 1 spinal compression fracture

CI, confidence interval; D/C, discontinuation; E/100 PY, events per 100 patient-years; NTE, non-treatment-emergent; SAE, serious AE

Smolen JS, et al. EULAR 2020;Poster THU0213

SELECT-MONOTHERAPY : Infections à S84

UPADACITINIB

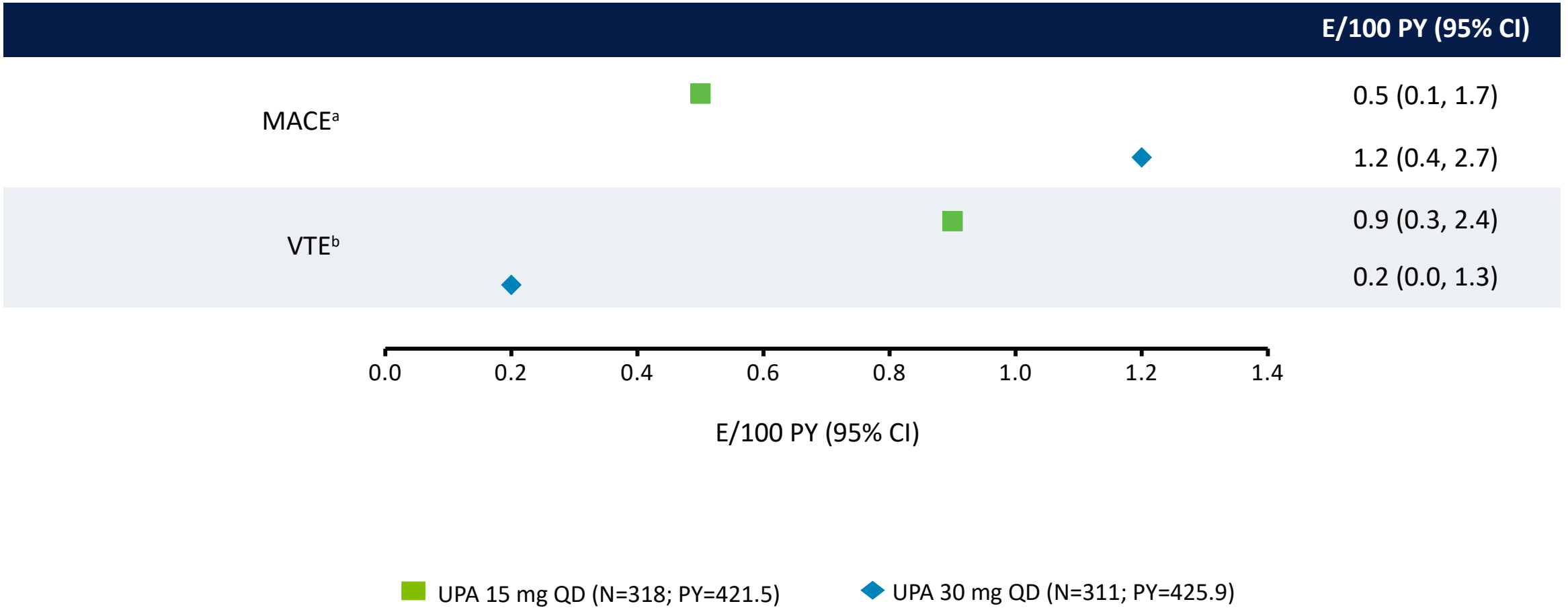


Data cut-off: February 5, 2019

Smolen JS, et al. EULAR 2020;Poster THU0213

SELECT-MONOTHERAPY : MACE et VTE à S84

UPADACITINIB



Data cut-off: February 5, 2019

[a]UPA 15 mg, 2 CV deaths (1 hemorrhagic stroke and 1 sudden cardiac death); UPA 30 mg, 2 non-fatal myocardial infarctions, 2 non-fatal strokes, and 1 CV death (myocardial infarction)

[b]Reported in 5 patients: UPA 15 mg, 2 PE and 2 DVT; UPA 30 mg, 1 DVT

CV, cardiovascular

Smolen JS, et al. EULAR 2020;Poster THU0213

Programme de développement

UPADACITINIB

UPADACITINIB'S SAFETY HAS BEEN ASSESSED:

In **>9,000 subjects** representing **>16,000 PY** of exposure[18-22]

Across RA, PsA, AS, nr-axSpA, UC, and AD[18-22]

UPADACITINIB IS APPROVED:

In 6 indications with 3 different dosing : 15mg, 30mg, and 45mg[18-22]

Approved indication* **Primary endpoint met** **Ongoing trial**

- SELECT-AXIS 1 (Phase II/Phase III)
- SELECT-AXIS 2 Study 1 (Phase III)

- SELECT-PsA 1 (Phase III)
- SELECT-PsA 2 (Phase III)

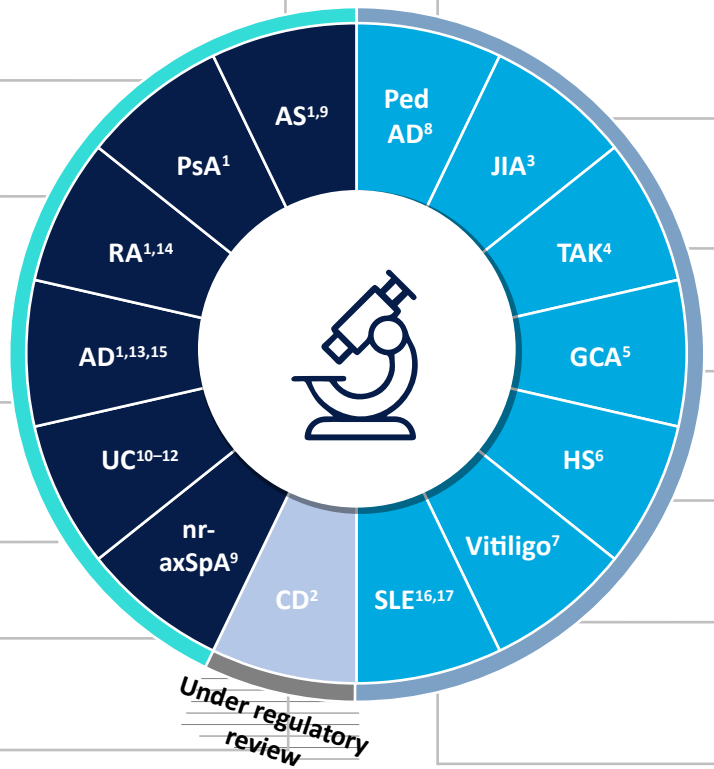
- SELECT-EARLY (Phase III)
- SELECT-NEXT (Phase III)
- SELECT-COMPARE (Phase III)
- SELECT-MONOTHERAPY (Phase III)
- SELECT-BEYOND (Phase III)
- SELECT-CHOICE (Phase III)

- Measure Up 1 (Phase III)
- Measure Up 2 (Phase III)
- AD Up (Phase III)

- U-ACHIEVE (Phase III)
- U-ACCOMPLISH (Phase III)

- SELECT-AXIS 2 Study 2 (Phase III)

- U-EXCEED (Phase III);
- U-EXCEL (Phase III)
- U-ENDURE (Phase III)
- **Note: Under regulatory review**



- NCT03646604 (Phase I)
- NCT03725007 (Phase I)
- NCT04161898 (Phase III)
- SELECT-GCA (Phase III)
- NCT04430855 (Phase II)
- NCT04927975 (Phase II)
- NCT03978520 (Phase II)
- NCT04451772 (Phase II)

References in slide notes: *Refers to either EMA, FDA, or PMDA regulatory status
AD, atopic dermatitis; AS, ankylosing spondylitis; CD, Crohn's disease; EMA, European Medicines Agency; FDA, United States Food and Drug Administration; GCA, giant cell arteritis; HS, hidradenitis suppurativa; JIA, juvenile idiopathic arthritis; NCT, national clinical trial; nr-AxSpA, non-radiographic axial spondyloarthritis; Ped AD, pediatric atopic dermatitis; PMDA, Pharmaceuticals and Medical Devices Agency; PsA, psoriatic arthritis; RA, rheumatoid arthritis; TAK, Takayasu arteritis; UC, ulcerative colitis.

1. Panaccionne et al. UEG Week 2022, October 8–11, Vienna, Austria, P243. 2. Vermeire et al., OP001 presented at UEGW, 8-11 October 2022.

Conclusion : les JAKi

- **Efficaces sur le plan clinique**
- **Efficaces sur le plan structural**
- **Efficaces en monothérapie**
- **Rapidité d'action**
- **Efficacité supérieure au MTX et aux anti-TNF (BARI et UPA)**
- **Rémission fréquente et obtenue rapidement**
- **Pas d'immunogénicité**
- **Facilité d'utilisation avec la voie per os**
- **½ vie courte**
- **Développement clinique qui dépasse la rhumatologie**

A débattre 1/2

- Certains facteurs génétiques influencent la réponse aux biothérapies.
- Ainsi en neurologie certains monoclonaux développés dans la SEP sont efficaces chez les caucasiens sont sans effet chez les afro-caribéens
- Même chose pour certains anti-IL-17.
- A-t-on des données de réponse différente dans des sous-populations afro américaines par exemple ?

A débattre 2/2

- Il y a en Martinique un sur risque cardio vasculaire considérable
- Diabète, HTA, IDM, AVC…sont surreprésentés par rapport à la métropole.
- Comment intégrer ceci dans l'évaluation bénéfice/risque pour une PP ?

Cardiovascular risk factors (%)	
Hypertension	39.6
Diabetes	16.4
Dyslipidemia	15.6
Cardiovascular events	
Familial	24.5
Personal	7.4
Cerebro vascular events	2.8
Myocardial infarction	1.3
Actual smoker	8.7
Body mass index >25	53.3

Cohorte EPPRA
âge moyen 59 ans
99% afro-caribéens