Etude REVERSE

# Avacopan added to standard-of-care therapy in ANCA-associated vasculitis with severe kidney involvement: a randomized, placebo-controlled, double-blinded multicenter superiority study

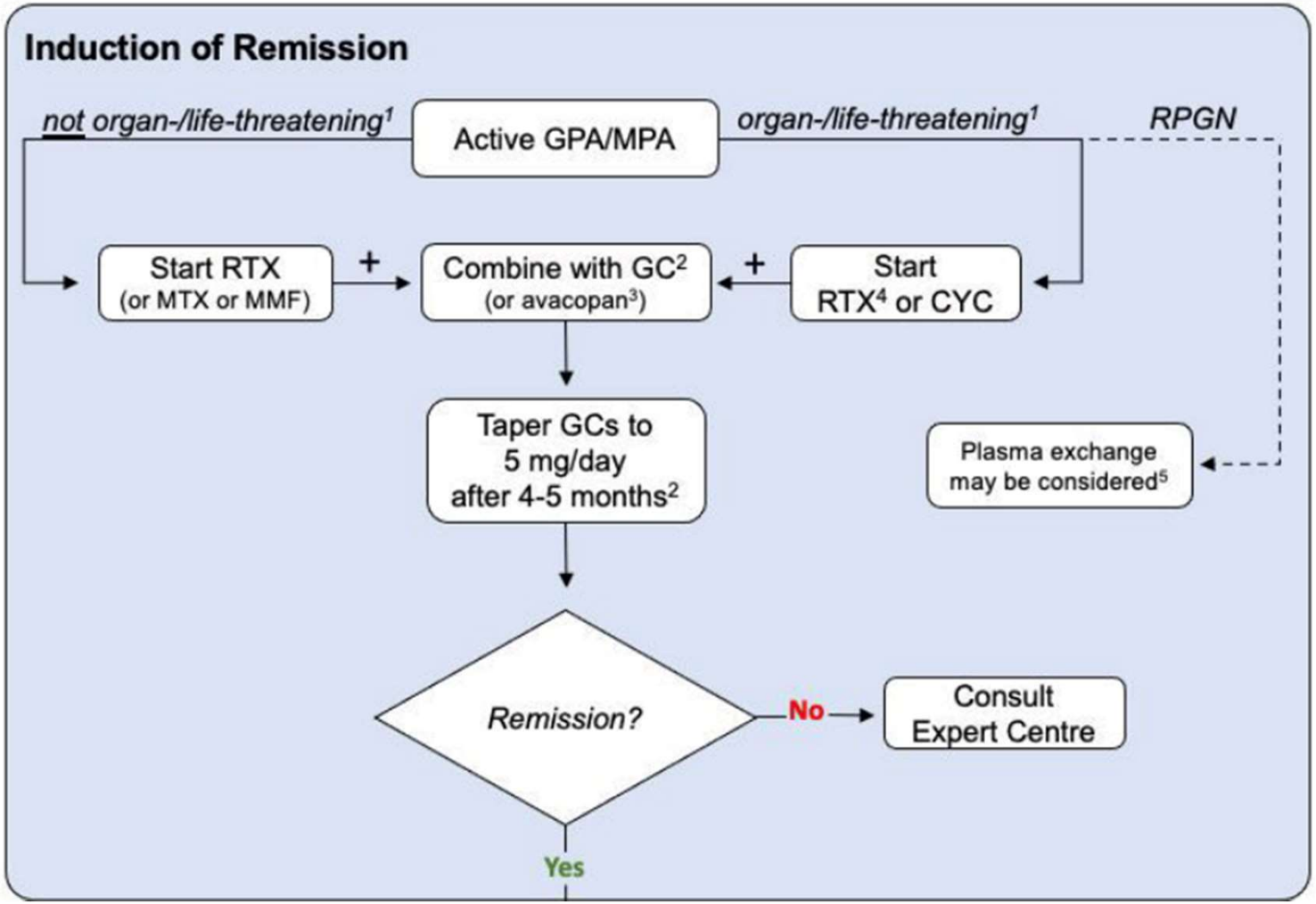
*PHRC-N 2024*

Stanislas FAGUER, Julie BELLIERE

Département de Néphrologie et Transplantation d'Organes

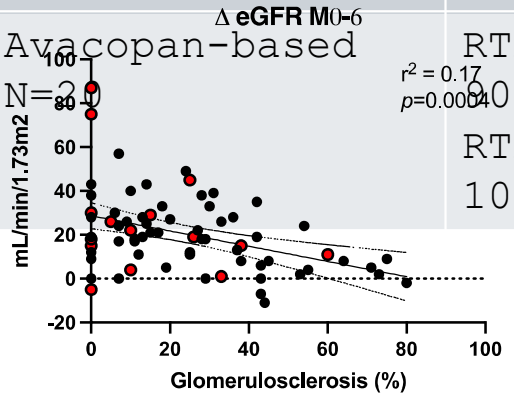
CHU de Toulouse

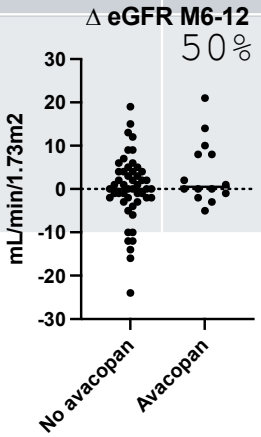
# GNRP – ANCA sévère – recommandations KDIGO 2024

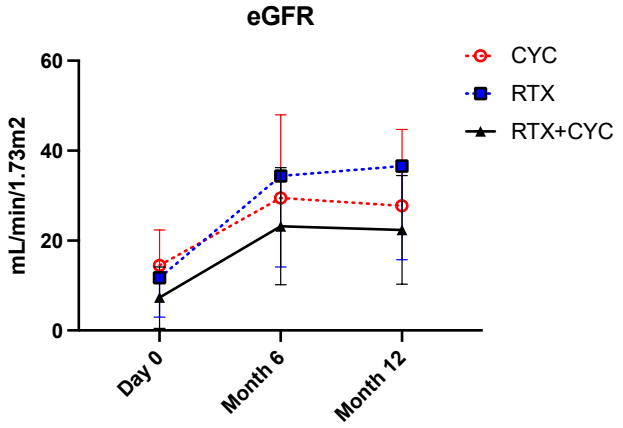


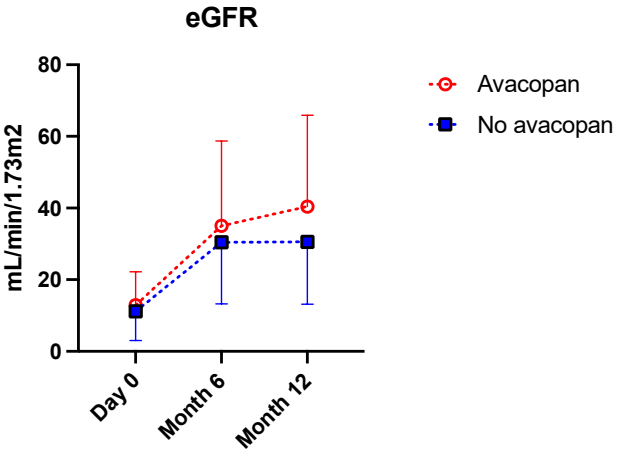
# GNRP – ANCA (DFG < 30 mL/min) et PBR et suivi M6

| | Induction | Aphérèses | Durée cortisone |
|---|---|---|---|
| GCs (haute dose) **N=50** | RTX 56%<br>CYC 30%<br>RTX+CYC 14% | 50% | 15±12 months |
| Avacopan-based N=20 | RTX 90%<br>RTX + CYC 10% | 50% | 1.9±1.8 months |



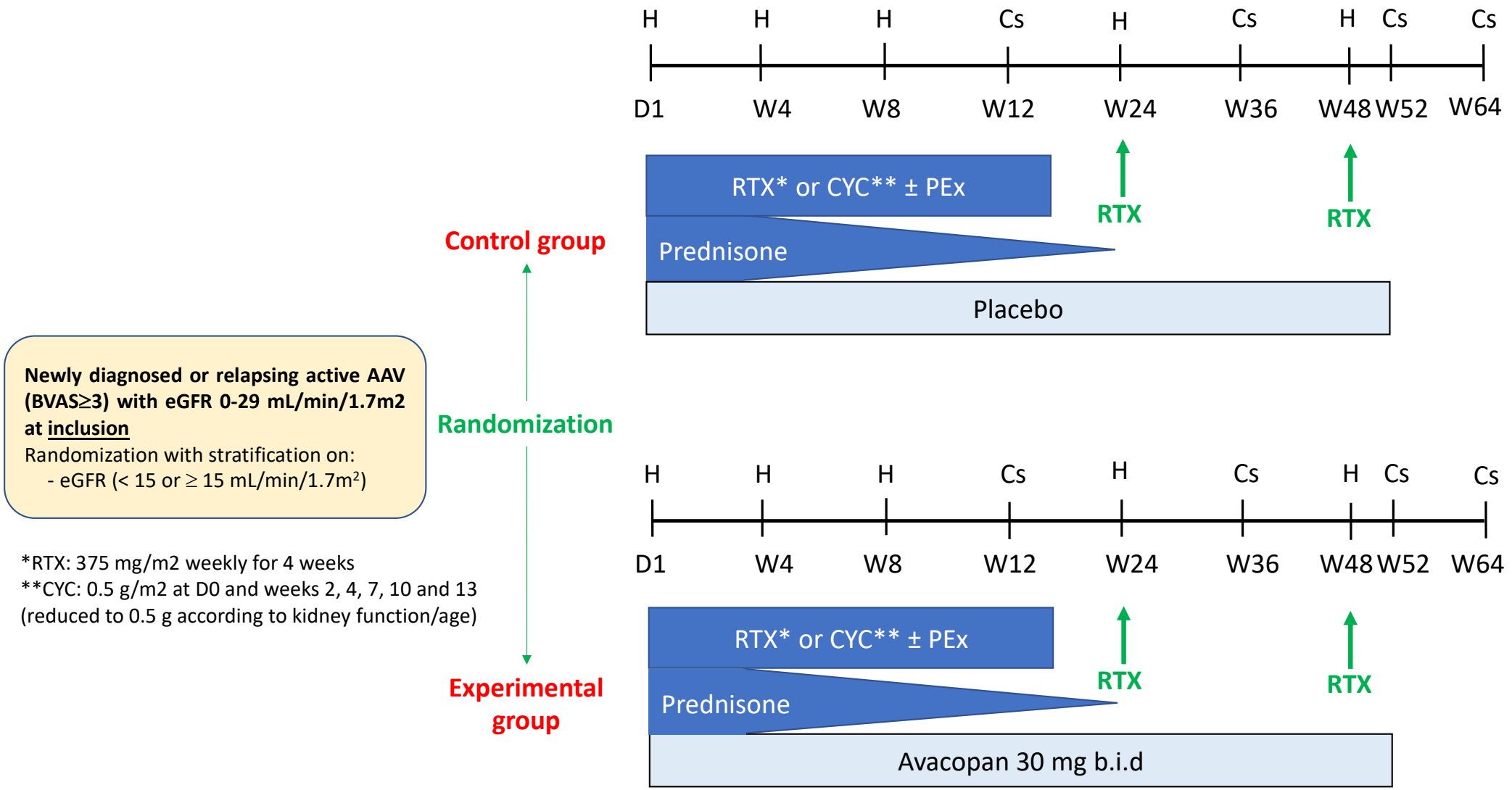




*Faguer et al. So*

# *Hypothèse*

Plutôt qu'opposer GCs et avacopan, la combinaison de GCs (schéma PEXIVAS low-dose) et d'avacopan au cours des atteintes rénales sévères des VAA pourraient être synergique et améliorer le pronostic rénal des patients ainsi qu'optimiser le contrôle de la vascularite systémique.


H H H Cs H Cs H Cs Cs
D1 W4 W8 W12 W24 W36 W48 W52 W64
RTX* or CYC** ± PEx
Prednisone
Placebo
RTX
RTX
Control group
Randomization
Experimental group
Newly diagnosed or relapsing active AAV (BVAS≥3) with eGFR 0-29 mL/min/1.7m2 at inclusion
Randomization with stratification on:
- eGFR (< 15 or ≥ 15 mL/min/1.7m²)
*RTX: 375 mg/m2 weekly for 4 weeks
**CYC: 0.5 g/m2 at D0 and weeks 2, 4, 7, 10 and 13 (reduced to 0.5 g according to kidney function/age)
H H H Cs H Cs H Cs Cs
D1 W4 W8 W12 W24 W36 W48 W52 W64
RTX* or CYC** ± PEx
Prednisone
Avacopan 30 mg b.i.d
RTX
RTX

# *Objectifs*

**Main objective**

To demonstrate an improvement in kidney function at week 52 (eGFR ≥ 30 mL/min/1.7m2; i.e. CKD stage 1-3) in patients with severe forms of AAV-associated RPGN (eGFR 0-29 mL/min/1.7m2 at inclusion) when avacopan is added to GCs-based SOC.

**Main evaluation criterion**

Proportion of patients reaching an estimated glomerular filtration rate ≥30 mL/min/1.7m² (CKD-EPI formula applied to the measure of standardized serum creatinine) at week 52.

# *Objectifs*

**Secondary objectives:**

- To assess **survival** in both groups up to week 64
- To assess in both groups **the vasculitis activity**: Birmingham Vasculitis Activity Score (BVAS) and Vasculitis Damage Index (VDI) at weeks 24, 52 and 64
- To assess in both groups the incidence of **treatment-related adverse events**
- To assess in both groups the **kidney function** (eGFR and proteinuria) at weeks 24, 52 and 64
- To assess in both groups the proportion of **end-stage kidney disease** (chronic dialysis) at weeks 24, 52 and 64
- To assess in both groups the intensity of kidney inflammation (usCD163 and uMCP1; urinary and serum levels of C3a, C5a and factor Bb) at inclusion and at weeks 4, 12, 24 and 52
- Changes in quality of life from baseline to week 64
- To assess the ability of kidney biopsy to predict the renal response to avacopan, in those receiving avacopan (per-protocol analysis)
- **Medico- economic analyses**

# *Inclusion criteria*

- Are male or female, 18 to 85 years of age
- Kidney biopsy before inclusion available (up to 6 weeks before inclusion) or patients agreeing to have a renal biopsy procedure performed no later than prior the visit at week 4
- Have been **newly diagnosed or relapsing active AAV-related RPGN at the time of inclusion** (either granulomatosis with polyangiitis (GPA) or microscopic polyangiitis (MPA), with or without positive ANCA testing)
- Have an active disease (BVAS ≥ 3, with at least one of the 2 renal items of proteinuria (urinary proteinuria/creatininuria > 300 mg/g) and haematuria (>10 RBC/hpf) within the BVAS), and **eGFR 0-29 mL/min/1.7 m2 at inclusion**
- Be planned to receive a SOC induction regimen by rituximab or cyclophosphamide plus glucocorticoids (± plasma exchanges) for the current AAV flare (rituximab or cyclophosphamide may have been started before the inclusion in the study, maximum 2 weeks before the inclusion)

# *Main exclusion criteria*

- Treatment by >3000 mg methylprednisolone or equivalent within the 3 weeks preceding the screening visit
- eGFR before the AAV flare already <35 mL/min/1.7m$^2$
- Glomerulosclerosis >50% or kidney interstitial fibrosis >50%, if results of a kidney biopsy are available. If kidney biopsy is performed after inclusion in the study, the patients will continue the study according to the protocol.
- …

# *Patients*

- **Durée de l'étude / patients:** 15 mois (12 sous avacopan / placebo + 3 mois de suivi/washout)
- **Durée du recrutement:** 36 mois
- Hypothèse principale

*We hypothesized that the incidence of patients reaching an eGFR ≥30mL/min/1.73m2 at week 52 (estimated at 45% in previous multicenter observational cohort) could reach 70% in the experimental group. Thus, a 25% absolute difference between groups in the primary endpoint incidence (45% in the control versus 70% in the experimental group) seems to be a reasonable hypothesis.* ***In addition, given the cost of avacopan (around 71 k€ per 52 weeks of treatment and per patient), a 25% absolute difference between groups was considered as a minimal requirement.***

- **Nombre de sujets nécessaire** (avec 10% de perdus de vue)

➢**130 patients soit 65 par bras**

# *Timeline*

- **Recueil CV – BPC en cours**
- **Dépôt CPP Europe : fin avril (…)**
- **Rédaction** CRF
- Fourniture placebo – avacopan (VIFOR - AMGEN): septembre 2025
- 1ère mise en place: Janvier 2026

**Remerciements**: VIFOR – AMGEN > fourniture gracieuse de l'avacopan et du placebo pour