AVACOPAN
Chronique d'une mort annoncée

Loïc GUILLEVIN

Ancien président de la Commission de la Transparence de la HAS

PARIS, Journée de formation du GFEV

20 novembre 2026

Groupement d'Hôpitaux Paris Centre
COCHIN
BROCA
HÔTEL-DIEU

FVSG

Déclaration d'intérêts

- aucun

EPARGNER LES CORTICOÏDES

Les approaches stratégiques sont toujours d'initiative académique

FVSG

CORTAGE

Traitement des vascularites nécrosantes à partir de 65 ans

Investigateur coordonateur: Pr Loïc Guillevin,
loic.guillevin@cch.aphp.fr

Groupement Hospitalier Paris Centre
COCHIN
BROCA
HÔTEL-DIEU

Groupe Français d'Etude des Vascularites

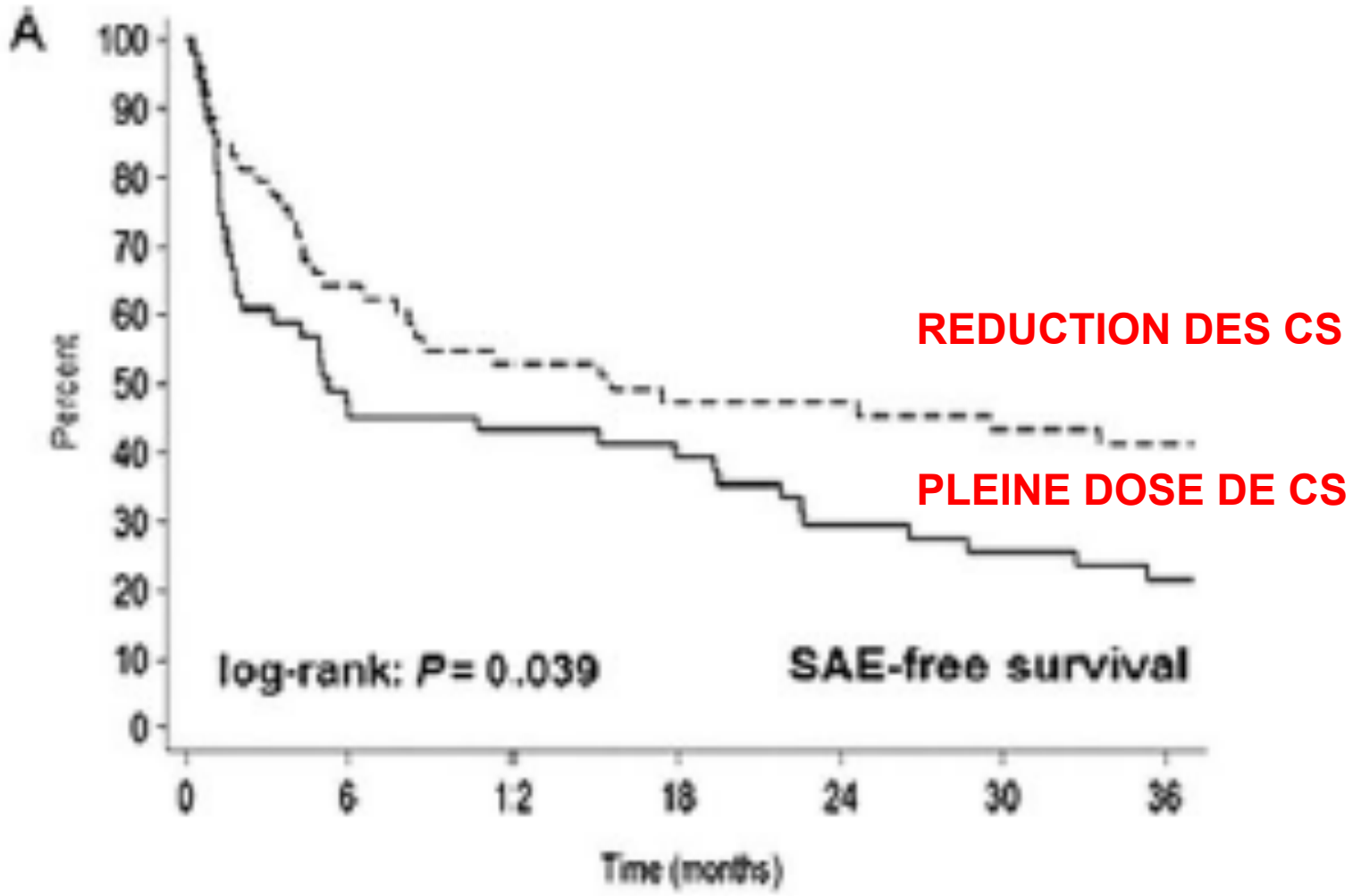
ARTHRITIS & RHEUMATOLOGY
Vol. 67, No. 4, April 2015, pp 1117–1127
DOI 10.1002/art.39011
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2015

Treatment of Systemic Necrotizing Vasculitides in Patients Aged Sixty-Five Years or Older

Results of a Multicenter, Open-Label, Randomized Controlled Trial of Corticosteroid and Cyclophosphamide–Based Induction Therapy

Christian Pagnoux,[1] Thomas Quéméneur,[2] Jacques Ninet,[3] Elisabeth Diot,[4] Xavier Kyndt,[2] Benoît de Wazières,[5] Jean-Luc Reny,[6] Xavier Puéchal,[1] Pierre-Yves le Berruyer,[7] Olivier Lidove,[8] Philippe Vanhille,[2] Pascal Godmer,[9] Olivier Fain,[10] Daniel Blockmans,[11] Boris Bienvenu,[1] Florence Rollot,[1] Séverine Aït el Ghaz-Poignant,[12] Alfred Mahr,[1] Pascal Cohen,[1] Luc Mouthon,[1] Elodie Perrodeau,[13] Philippe Ravaud,[13] and Loïc Guillevin,[1] for the French Vasculitis Study Group


A
100
90
80
70
60
50
40
30
20
10
0
Percent
log-rank: P = 0.039
SAE-free survival
0
6
12
18
24
30
36
Time (months)
REDUCTION DES CS
PLEINE DOSE DE CS

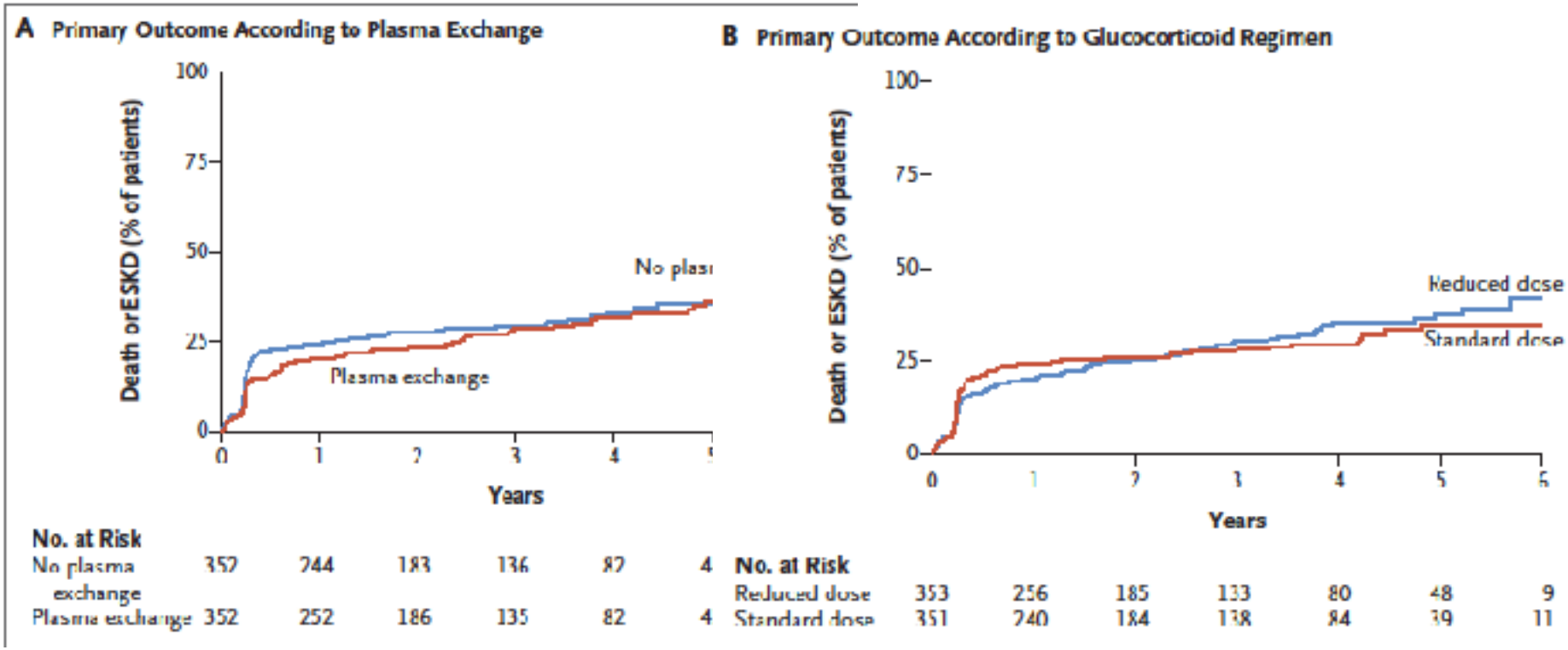
PEXIVAS 2020

- **randomization of PE (+ pulses MPS, CS, CYC or RTX) and randomization of CS dose**



Walsh M NEJM 2020, 382: 622

PEXIVAS



Walsh M NEJM 2020, 382: 622

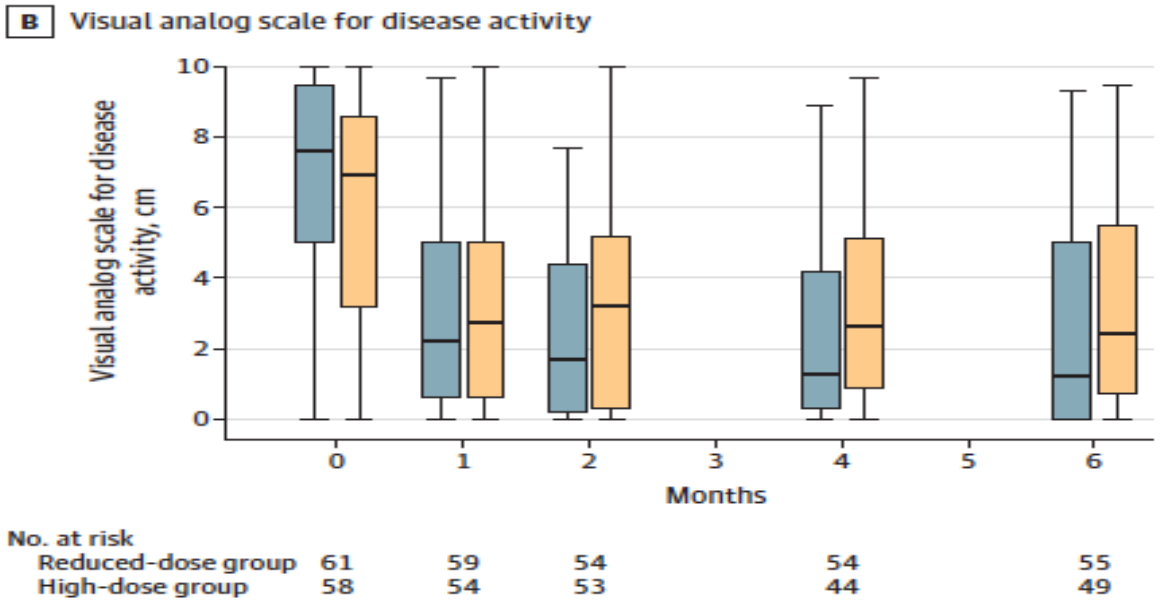
JAMA | Original Investigation

2021

Effect of Reduced-Dose vs High-Dose Glucocorticoids Added to Rituximab on Remission Induction in ANCA-Associated Vasculitis
A Randomized Clinical Trial

Shunsuke Furuta, MD, PhD; Daiki Nakagomi, MD, PhD; Yoshihisa Kobayashi, MD, PhD; Masaki Hiraguri, MD; Takao Sugiyama, MD, PhD; Koichi Amano, MD, PhD; Takeshi Urushibe, MD, PhD; Hajime Kono, MD, PhD; Kazuhiro Kurasawa, MD, PhD; Yasuhiko Kita, MD, PhD; Ryutaro Matsumura, MD, PhD; Yuko Kaneko, MD, PhD; Koji Nimura, MD; Keiju Hiromura, MD, PhD; Shin-ichiro Kayaba, MD, PhD; Yosuke Inoba, PhD; Hideki Hanaoka, MD, PhD; Kei Ikeda, MD, PhD; Hiroshi Nakajima, MD, PhD; for the LoVAS Collaborators

140 malades en deux groupes



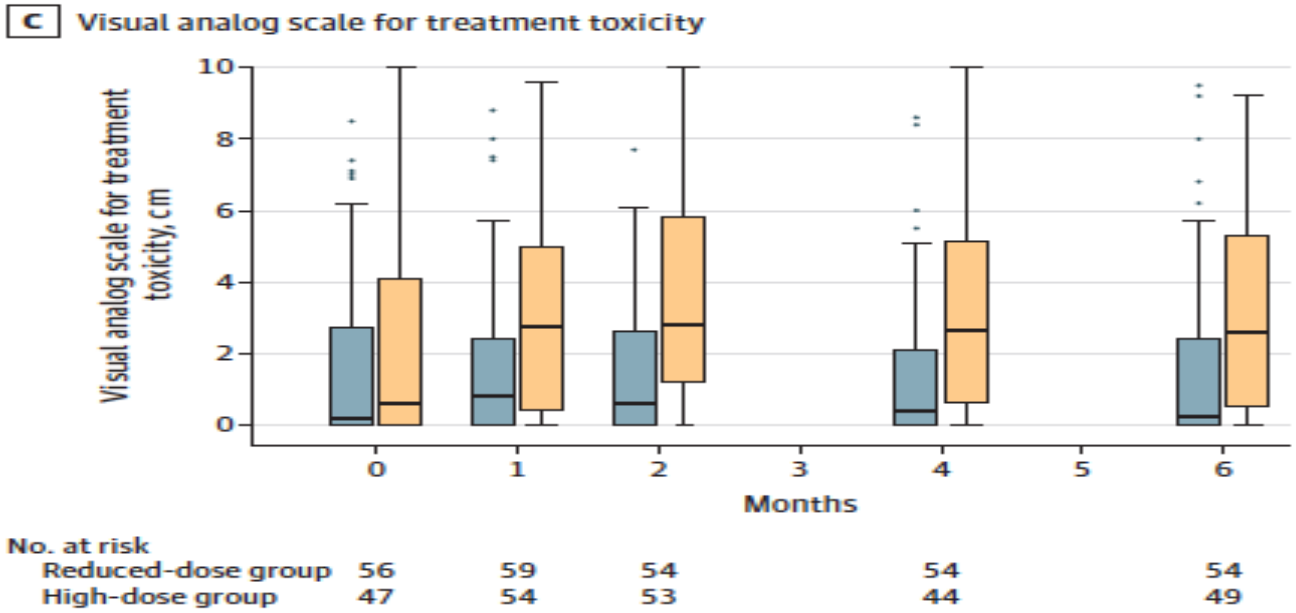
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140 malades en deux groupes

6 MOIS RÉMISSION
dose réduite 71%
Dose pleine 69%



EPARGNER LES CORTICOÏDES

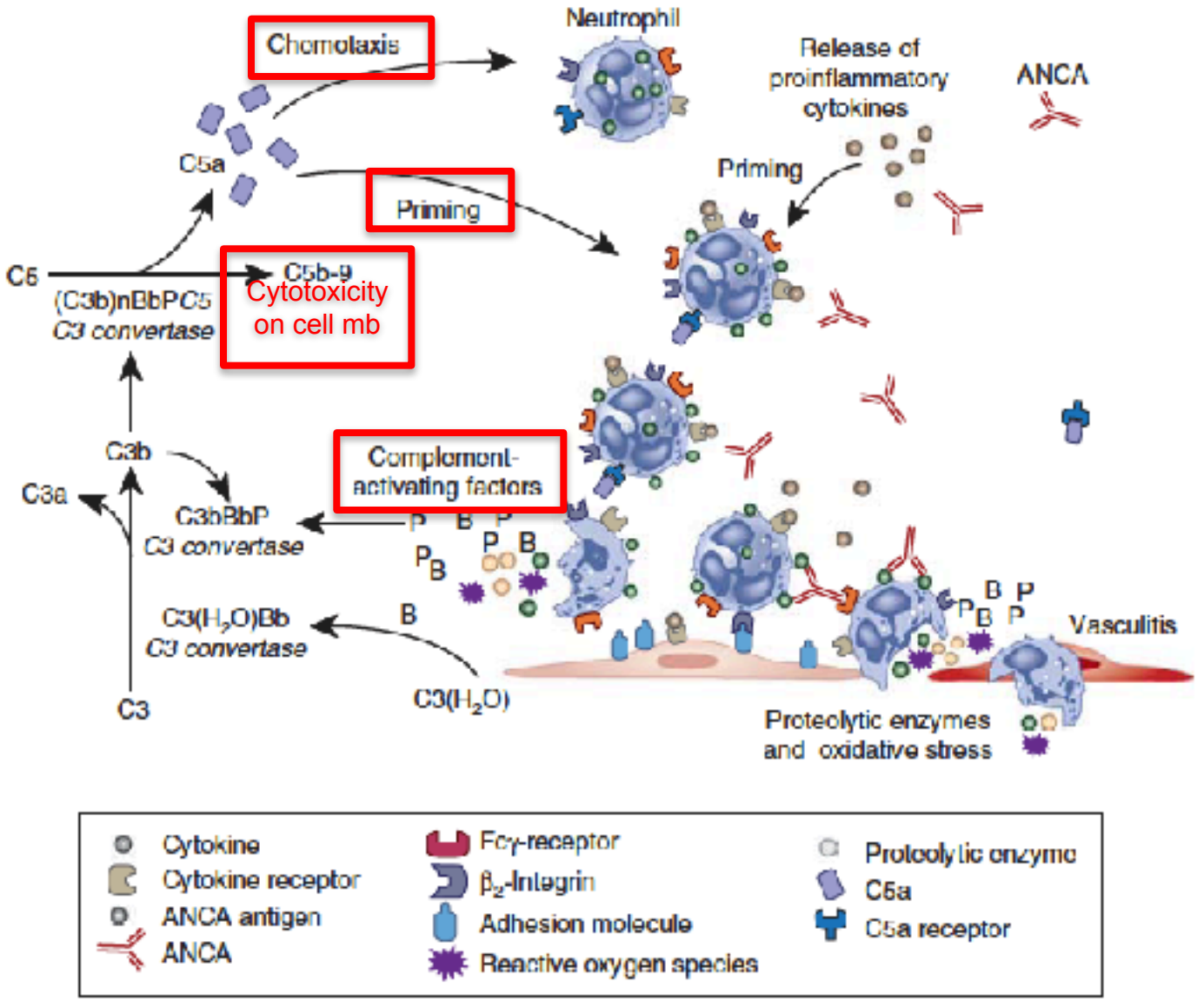
Les approaches médicamenteuses sont généralement d'initiative industrielle

Etude ADVOCATE

Utilisation de l'avacopan (anti-C5aR)
pour l'epargne cortisonique dans la
Vascularite à ANCA

Laboratoires ChemoCentryx

A role for complement in AAV ?

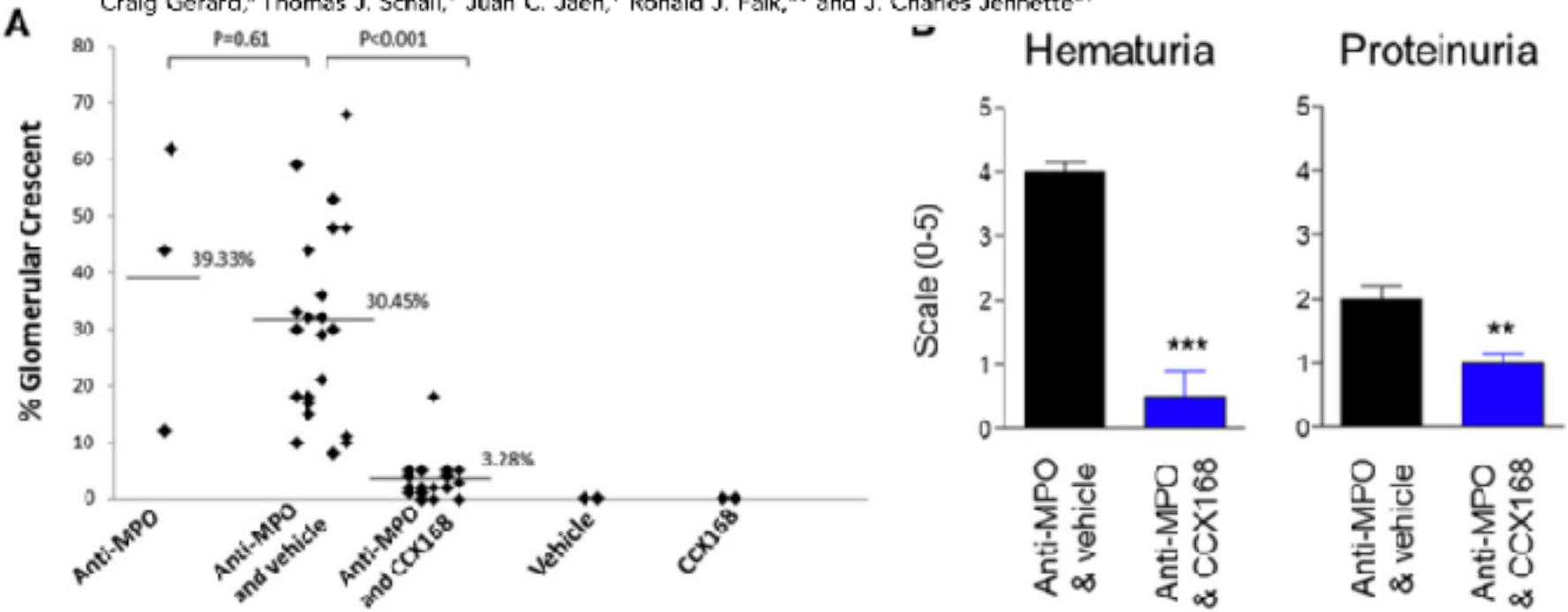


Avacopan (CCX168) : étude pré-clinique

BRIEF COMMUNICATION www.jasn.org

C5a Receptor (CD88) Blockade Protects against MPO-ANCA GN

Hong Xiao,*† Daniel J. Dairaghi,† Jay P. Powers,‡ Linda S. Ertl, † Trageen Baumgart,† Yu Wang,† Lisa C. Seitz,† Mark E.T. Penfold,‡ Lin Gao,§ Peiqi Hu,*† Bao Lu,§ Norma P. Gerard,‖ Craig Gerard,‖ Thomas J. Schall,‡ Juan C. Jaen,‡ Ronald J. Falk,*† and J. Charles Jennette*†



CCX168, an antagonist of human C5aR, reduces the severity of anti-MPO–induced CGN in hC5aR knock-in mice (7 days after anti-MPO injection)

Avacopan (CCX168) : étude clinique de phase 2

CLINICAL RESEARCH | www.jasn.org

Randomized Trial of C5a Receptor Inhibitor Avacopan in ANCA-Associated Vasculitis

David R.W. Jayne,* Annette N. Bruchfeld,† Lorraine Harper,‡ Matthias Schaier,§ Michael C. Venning,‖ Patrick Hamilton,‖ Volker Burst,¶ Franziska Grundmann,¶ Michel Jadoul,** István Szombati,†† Vladimír Tesař,†† Mårten Segelmark,§§ Antonia Potarca,‖‖ Thomas J. Schall,‖‖ and Pirow Bekker,‖‖ for the CLEAR Study Group

Etude CLEAR (Phase 2) : patients VAA avec atteinte rénale

CCX168 (avacopan) : antagoniste oral du C5aR (30 mg x2/j)

N=67 patients en double aveugle

Gp A : placebo+EDX+cort dose standard

Gp B : CCX168+EDX+ cort dose faible

Gp C : CCX168+EDX+placebo (pas de corticoïdes)

Avacopan (CCX168)
étude clinique de phase 2

- Primary endpoint

proportion of patients achieving a >50% reduction in BVAS by week 12 and no worsening in any body system

14 of 20 (70.0%) in the control group,
19 of 22 (86.4%) in the avacopan / reduced prednisone group
17 of 21 (81.0%) in the avacopan without prednisone group

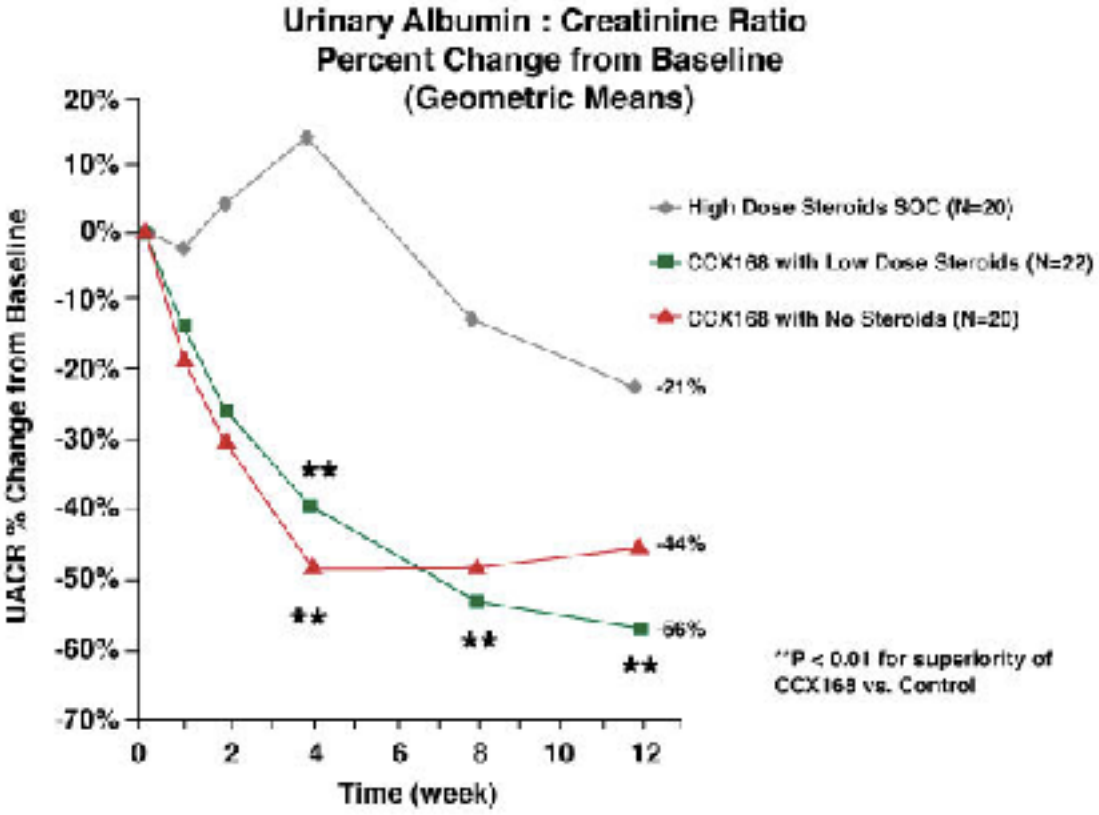
= non inferiority

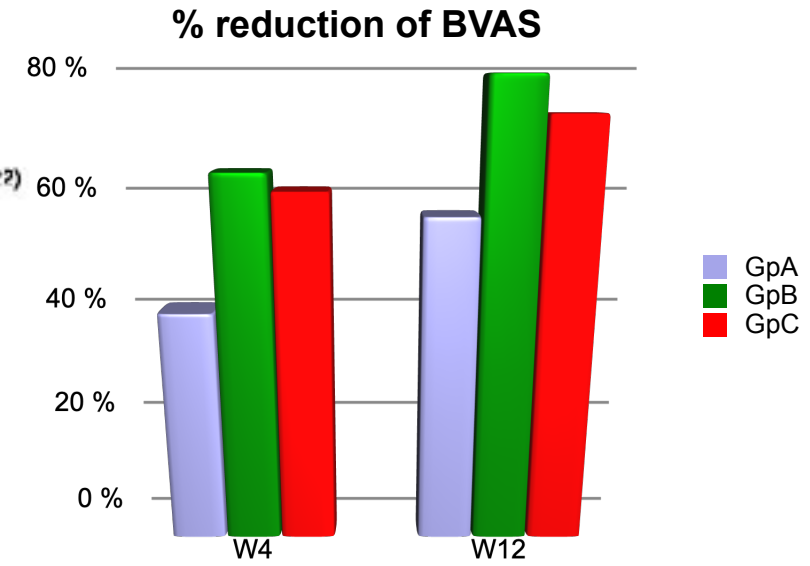
- Safety : no increase in adverse events
  no increase in infectious complications

Jayne, JASN 2017

Avacopan (CCX168)
étude clinique de phase 2

- Secondary endpoints :





Jayne, JASN 2017

Avacopan (CCX168) ADVOCATE
étude clinique de phase 3

Etude randomisée, placebo, contrôlée, internationale
300 inclusions prévues , durée du suivi 12 mois de tt
+ 2 mois suivi

Traitements :
Les deux groupes reçoivent un traitement IS
(CYC/AZA ou RTX) et sont randomisés :

Groupe A : Placebo du CCX168 **+** dose usuelle de prednisone
ou
Groupe B : CCX168 + placebo de la prednisone.

Triple stratification : RTX vs CYC, PR3 vs MPO,
1e poussée ou rechute

C5aR-inhibitor for AAVs (Avacopan)

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ESTABLISHED IN 1812 FEBRUARY 18, 2021 VOL. 384 NO. 7

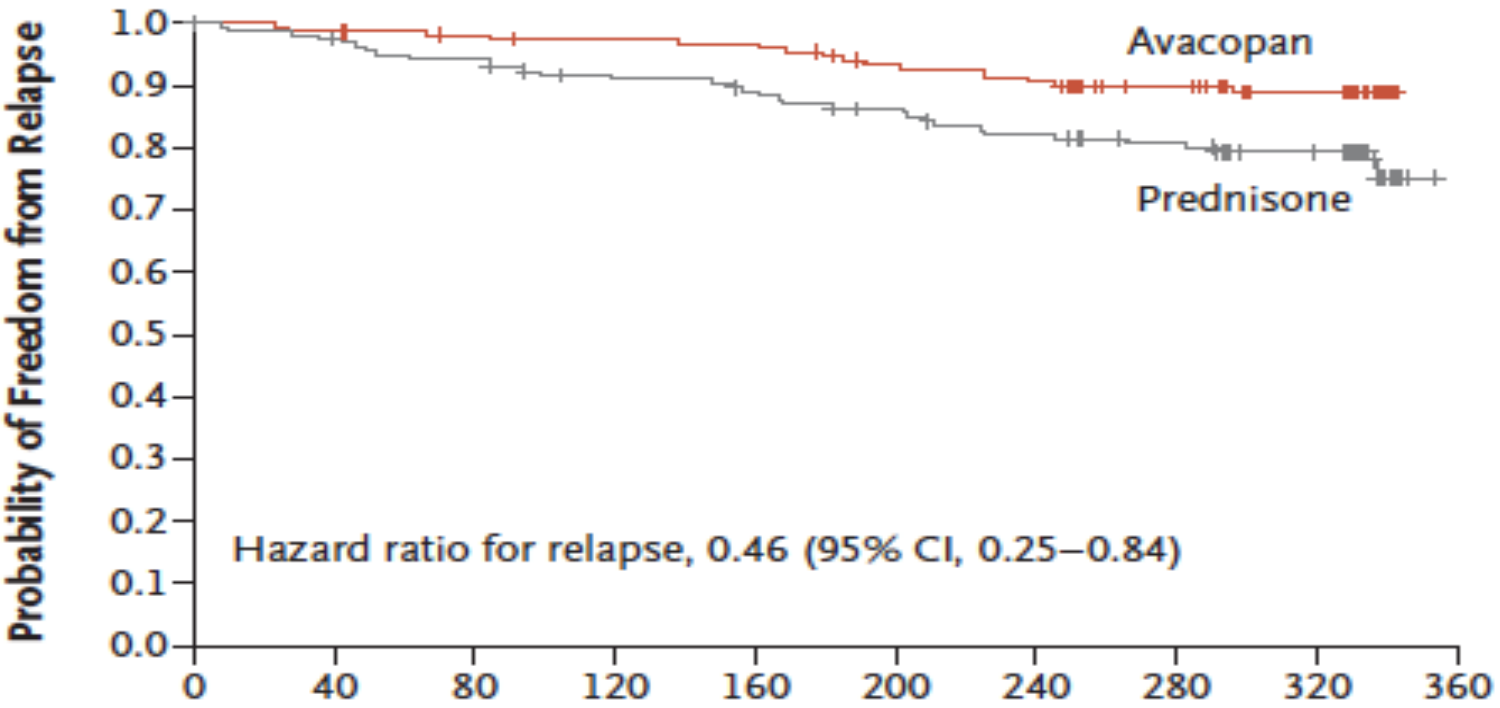
Avacopan for the Treatment of ANCA-Associated Vasculitis

David R.W. Jayne, M.D., Peter A. Merkel, M.D., M.P.H., Thomas J. Schall, Ph.D., and Pirow Bekker, M.D, Ph.D., for the ADVOCATE Study Group*

C5aR-inhibiteur dans les VAA (Avacopan)

- ✓ Avacopan 30 mg x 2 ou placebo
- ✓ Prednisone 60 mg puis diminution au bout de 20 semaines ou placebo
- ✓ Rituximab, 4 semaines
- ✓ OU cyclophosphamide IV puis AZA
- ✓ OU oral cyclophosphamide puis AZA
- ✓ **Pas de traitement d'entretien par le rituximab**

C5aR-inhibitor for AAVs (Avacopan)



No. at Risk										
Avacopan	158	153	149	146	145	133	129	115	92	0
Prednisone	157	151	146	137	133	126	119	111	90	0

C5aR-inhibitor for AAVs (Avacopan)

- ✓ Le bras avacopan n'est pas supérieur au bras prednisone au bout de 26 semaines
- ✓ mais supérieur à 52 semaines
- ✓ Effets secondaires ?

Le parcours du médicament

- ✓ Approbation par la FDA
- ✓ Approbation par l'EMA

- ✓ Approbation par la CT (HAS)
  - ✓ SMR important
  - ✓ ASMR IV
  - ✓ prix 53628 euros/an; remboursé 65% (100% si ALD)

STRATÉGIE INDUSTRIELLE

- Aux USA, le laboratoire Chemocentrix a vendu la molécule à AMGEN (en fait AMGEN a pris le contrôle de Chemocentrix pour 3,7 milliards de dollars).
- En Europe, le médicament est commercialisé par Le laboratoire VIFOR, filiale de CSL, un acteur majeur dans la mise au point de produits dérivés du sang (immunoglobulines)

LES DYSFONCTIONNEMENTS

TROIS DYSFONCTIONNEMENTS

- Une approbation par les autorités de santé contestable pour un médicament non indispensable
- Une toxicité mal évaluée
- Une fraude aux résultats

POURQUOI AVOIR AUTORISÉ CE MÉDICAMENT ?

- Les résultats en termes d'épargne de corticoïdes sont peu convaincants
- La toxicité a été mal évaluée (pas de résultats du plan de gestion de risques (PGR), mis en place le 5 janvier 2024).

LA FRAUDE

C5aR-inhibitor for AAVs (Avacopan)

NDA 214487

CERTIFIED MAIL
RETURN RECEIPT REQUESTED

April 27, 2026

Re: Docket No. FDA-2026-N-1321
PROPOSAL TO WITHDRAW MARKETING APPROVAL; NOTICE OF OPPORTUNITY FOR A HEARING

C5aR-inhibitor for AAVs (Avacopan)

New information shows that the applicant's unblinded study personnel manipulated endpoint results for the phase 3 study, CL010_168, referred to as the ADVOCATE study, which was the sole study used to establish substantial evidence of effectiveness for approval of TAVNEOS.[1] That manipulation was designed to change results that were not statistically significant and make the product look effective when the original analysis did not support that conclusion. If the data as originally analyzed according to the prespecified statistical analysis plan had been submitted to the Agency, the study would not have been viewed as establishing substantial evidence of effectiveness, which is a legal requirement for approval of an NDA. However, in contravention of fundamental principles of good clinical practice regarding the reporting of clinical results as well as FDA's regulations regarding what must be submitted in an NDA, the applicant did not

C5aR-inhibitor for AAVs (Avacopan)

De nouvelles informations montrent que le personnel de l'étude a manipulé les résultats de l'étude de phase 3, référée sous le nom d'ADVOCATE, seule étude ayant permis d'établir une preuve d'efficacité permettant d'approuver la mise à disposition de TAVNEOS.

C5aR-inhibitor for AAVs (Avacopan)

Cette manipulation a été faite pour modifier des résultats qui n'étaient pas statistiquement significatifs et présenter le médicament comme étant efficace alors que l'analyse originale ne permettait pas de conclure ainsi.

C5aR-inhibitor for AAVs (Avacopan)

✓ La FDA a d'abord demandé à AMGEN de retirer le médicament, ce qu'AMGEN a refusé

✓ L'étape suivante a été le retrait de la molécule par décision de la FDA

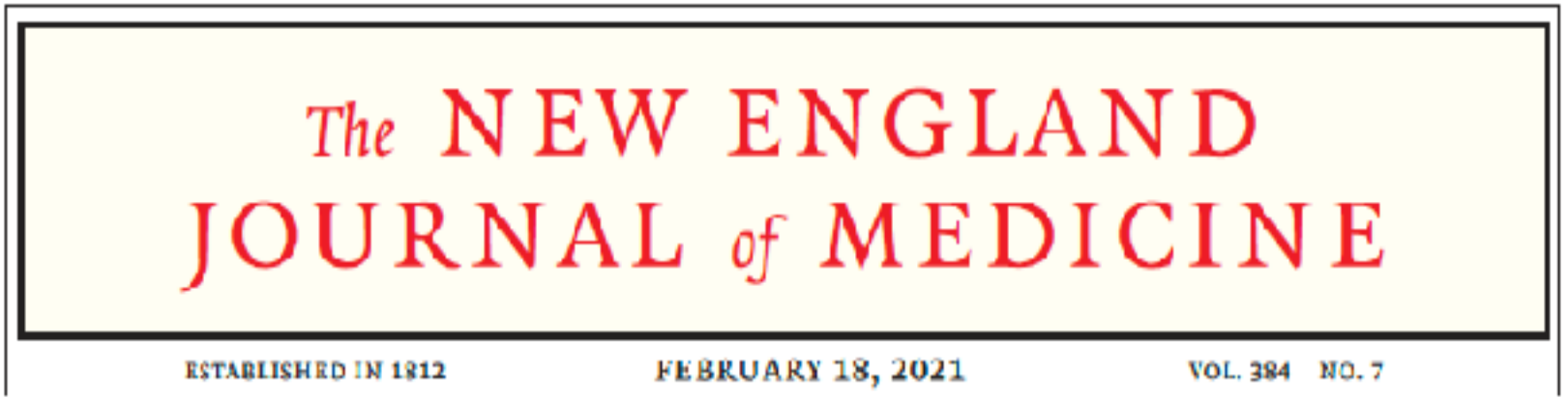
C5aR-inhibitor for AAVs (Avacopan)

- ✓ **En Europe (29 juin 2026)**
- ✓ « EMA recommends revoking marketing authorisation for TAVNEOS ».

- ✓ **En France (16 juillet 2026)**
- ✓ « L'ANSM recommande
  - ✓ Pas de nouveau traitement
  - ✓ Poursuite des traitements en cours
  - ✓ Surveiller la tolérance (foie)».

C5aR-inhibitor for AAVs (Avacopan)

This article has been retracted: N Engl J Med. DOI: 10.1056/NEJMe2608684.



The NEW ENGLAND JOURNAL of MEDICINE

ESTABLISHED IN 1812 FEBRUARY 18, 2021 VOL. 384 NO. 7

RETRACTED: Avacopan for the Treatment of ANCA-Associated Vasculitis

David R.W. Jayne, M.D., Peter A. Merkel, M.D., M.P.H., Thomas J. Schall, Ph.D., and Pirow Bekker, M.D, Ph.D., for the ADVOCATE Study Group[A]

EDITORIAL

Retraction: Jayne DRW et al. Avacopan for the Treatment of ANCA-Associated Vasculitis, N Engl J Med 2021;384:599-609.

Eric J. Rubin, M.D., Ph.D.

The two academic authors of the article by Jayne et al., Avacopan for the Treatment of ANCA-Associated Vasculitis, N Engl J Med 2021;384:599-609,[1] request retraction of the article because, according to an ongoing Food and Drug Administration investigation conducted after publication, and without the knowledge of these two authors, the primary end-point assessments in nine patients were readjudicated after database lock and trial unblinding. This was not disclosed in the article and is inconsistent with proper research conduct. The editors therefore retract the article.

Disclosure forms provided by the author are available with the full text of this editorial at NEJM.org.

This editorial was published on June 29, 2026, at NEJM.org.

1. Jayne DRW, Merkel PA, Schall TJ, Bekker P. Avacopan for the treatment of ANCA-associated vasculitis. N Engl J Med 2021;384:599-609.

DOI: 10.1056/NEJMe2608684

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Le point actuel

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Éditorial

L'avacopan, une question de confiance

Alexandre Terré[a,*], Marie-France Mamzer[b,c], Florian Naudet[d,e]
[a] *Service de médecine interne, centre hospitalo-universitaire Ambroise-Paré, Boulogne-Billancourt, France*

The end for avacopan

On June 29, 2026, *The New England Journal of Medicine* retracted the ADVOCATE trial—the pivotal study of avacopan in ANCA-associated vasculitis, which supported the drug's marketing approval. The retraction—at the request of two academic authors of the study—is the latest instalment in an ongoing controversy surrounding avacopan that could spell the end for the drug.

Avacopan's fate in Europe has been decided. We await the outcome of the FDA hearing. With the retraction of the ADVOCATE trial, the end for avacopan seems inevitable—and patients with ANCA-associated vasculitis seem set to lose access to an effective drug because of the nefarious actions of a few unscrupulous individuals. ■ *The Lancet Rheumatology*

Published Online
July 10, 2026
https://doi.org/10.1016/
S2665-9913(26)00225-0

Kidney Disease: Improving Global Outcomes (KDIGO) responds to the retraction of the ADVOCATE trial of avacopan for the treatment of ANCA-associated vasculitis

Brad H Rovin [1], David R W Jayne [2], Jan-Stephan F Sanders [3], Vladimír Tesar [4], Jürgen Floege [5]

In summary, problems with the conduct and data integrity of the ADVOCATE trial have been identified. The impact of these problems on the trial's efficacy conclusions is still being assessed considering the independant data re-adjudication. Given this situation, KDIGO will reconvene the Evidence Review Team to evaluate the re-adjudicated ADVOCATE data when they become available with real-world data to determine if or how avacopan may be included in the future guideline for the Management of ANCA-associated Vasculitis.

Kidney International
https://doi.org/10.1016/j.kint.2026.08.012

REMARQUES

- ✓ Les traitements sont faits pour aider les malades
- ✓ Le monde académique doit centrer ses activités sur les stratégies visant à améliorer les patients soumis à un traitement.

REMARQUES

- ✓ Les laboratoires pharmaceutiques ont un autre objectif:
  - ✓ trouver de nouveaux médicaments et les commercialiser
  - ✓ modifier les stratégies thérapeutiques grâce à de nouveaux médicaments

REMARQUES

✓ Les médecins expérimentateurs doivent « faire le tri » entre les propositions pharmaceutiques et ne pas faire des choix de peu d'intérêt voire de soutenir des médicaments inutiles et dangereux.

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