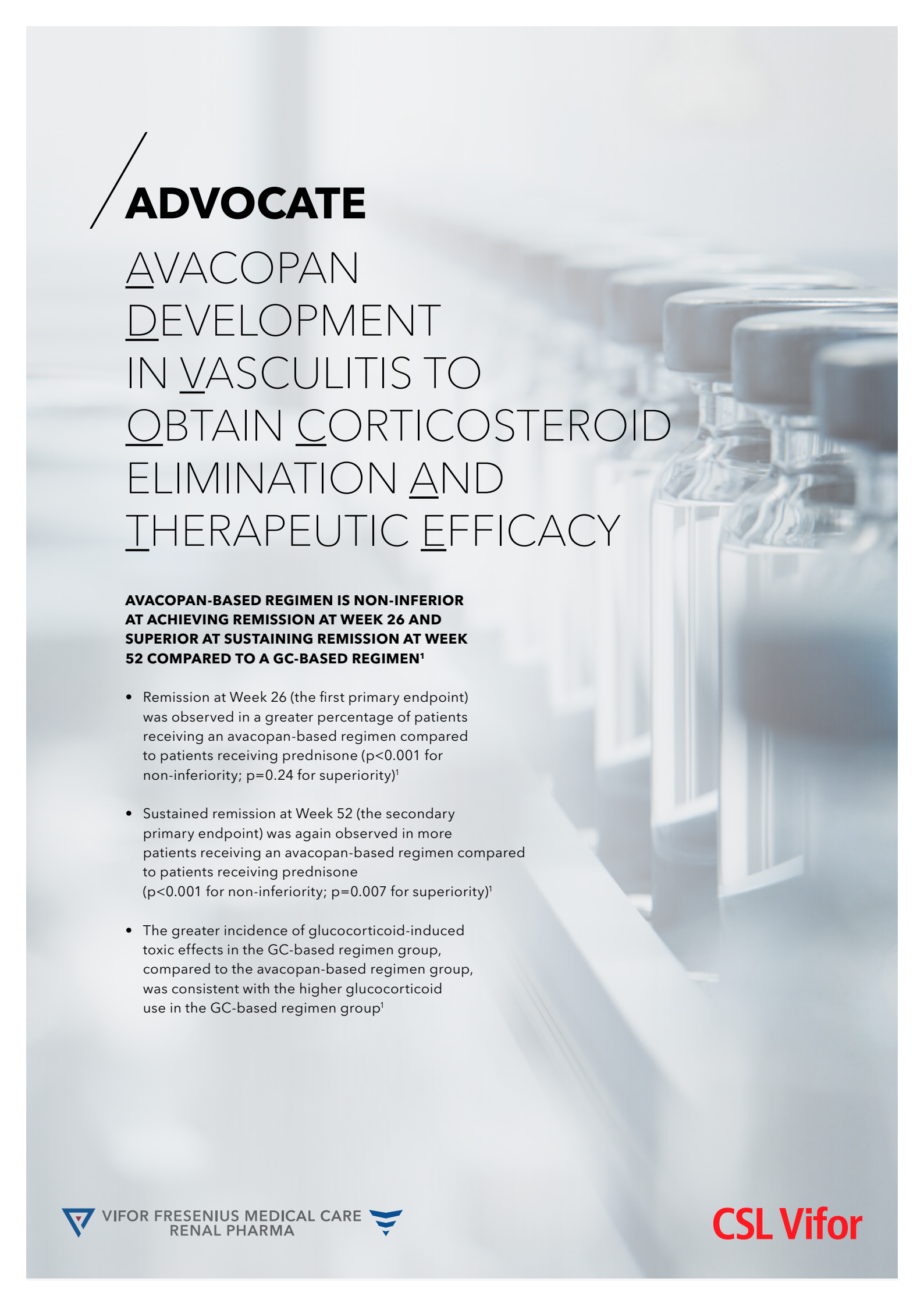
ADVOCATE

AVACOPAN DEVELOPMENT IN VASCULITIS TO OBTAIN CORTICOSTEROID ELIMINATION AND THERAPEUTIC EFFICACY



AVACOPAN-BASED REGIMEN IS NON-INFERIOR AT ACHIEVING REMISSION AT WEEK 26 AND SUPERIOR AT SUSTAINING REMISSION AT WEEK 52 COMPARED TO A GC-BASED REGIMEN[1]

- Remission at Week 26 (the first primary endpoint) was observed in a greater percentage of patients receiving an avacopan-based regimen compared to patients receiving prednisone ($p<0.001$ for non-inferiority; $p=0.24$ for superiority)[1]
- Sustained remission at Week 52 (the secondary primary endpoint) was again observed in more patients receiving an avacopan-based regimen compared to patients receiving prednisone ($p<0.001$ for non-inferiority; $p=0.007$ for superiority)[1]
- The greater incidence of glucocorticoid-induced toxic effects in the GC-based regimen group, compared to the avacopan-based regimen group, was consistent with the higher glucocorticoid use in the GC-based regimen group[1]

VIFOR FRESENIUS MEDICAL CARE RENAL PHARMA

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INTRODUCTION

The activation of the alternative complement pathway and subsequent C5a production is a component of the pathogenesis of ANCA-associated vasculitis. Avacopan is a C5a receptor antagonist that blocks C5a function. The ADVOCATE study evaluated whether an avacopan-based regimen could replace a GC-tapering regimen in the treatment of AAV.[1,2]

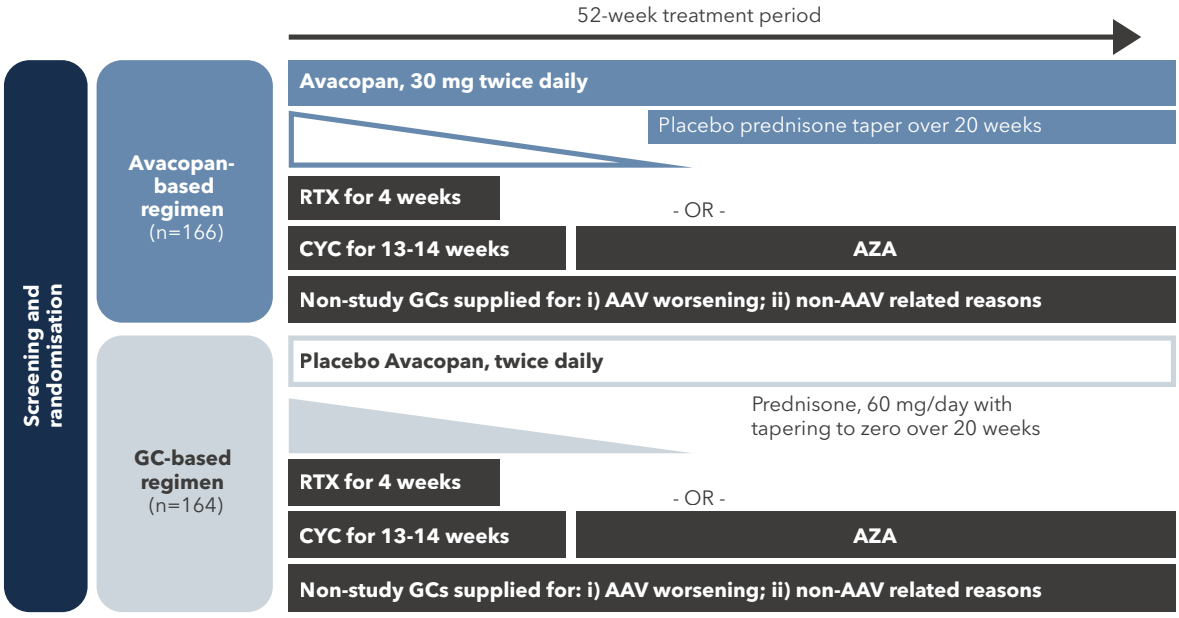
STUDY AIM

Compare the ability of an avacopan-based regimen vs a GC-based regimen to induce and sustain remission in AAV patients[1]

The sponsor of this study was:
ChemoCentryx

STUDY DESIGN

Phase 3, randomised, controlled trial[1-3]



PRIMARY EFFICACY ENDPOINTS[1]

- Clinical remission at Week 26 (defined as BVAS 0 and no receipt of GCs for 4 weeks before Week 26)
- Sustained remission (defined as remission at Week 26 and at Week 52 and no receipt of GCs for 4 weeks before Week 52)

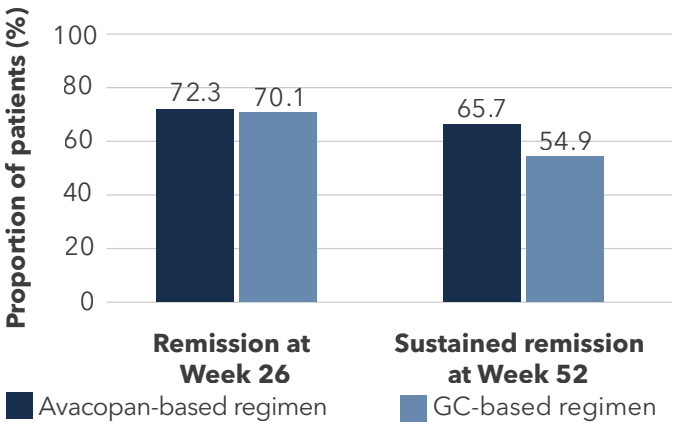
SECONDARY ENDPOINTS[1]*

- GTI scores during the first 26 weeks
- BVAS 0 at Week 4
- Changes from baseline in QoL (SF-36, EQ-5D-5L)
- Relapse
- Change from baseline in eGFR, UACR, urinary MCP-1:creatinine ratio
- VDI

RESULTS

Remission at Week 26 (the first primary endpoint) was observed in a greater percentage of patients receiving an avacopan-based regimen compared to patients receiving prednisone (95% CI, -6.0 to 12.8; p<0.001 for non-inferiority; p=0.24 for superiority).[1]

Sustained remission at Week 52 (the secondary primary endpoint) was again observed in more patients receiving an avacopan-based regimen compared to patients receiving prednisone (95% CI, 2.6 to 22.3; p<0.001 for non-inferiority; p=0.007 for superiority).[1]



Graph adapted from Jayne D, et al. *N Engl J Med* 2021

A 65% reduction in overall GC dose was associated with an avacopan-based regimen. A 16.8 point reduction was seen in GTI-CWS between the avacopan-based regimen and the GC-based regimen (95% CI, -25.6 to -8.0).
A 12.1 point reduction was seen in GTI-AIS between the avacopan-based regimen and the GC- based regimen (95% CI, -21.1 to -3.2).[1]

A total of 16 of 158 patients (10.1%) in the avacopan group and 33 of 157 patients (21.0%) in the prednisone group had relapses. The hazard ratio for relapse after remission (avacopan vs. prednisone) was 0.46 (95% CI, 0.25 to 0.84).[1]

Least-square mean change at Week 52 from baseline in eGFR was 7.3 ml/min/1.73m^2 in the avacopan- based regimen vs 4.1 ml/min/1.73m^2 in the GC-based regimen (difference 3.2 ml/min/1.73m^2; 95% CI, 0.3 to 6.1). Improvement in eGFR was specifically marked in patients with Stage 4 kidney disease.[1]

Improvements in all domains of QoL were noted in the avacopan-based regimen.[1,3]

SAFETY

The number of serious adverse events (excluding events of worsening vasculitis) was 33% higher in the prednisone group than in the avacopan group, a finding consistent with a higher exposure to glucocorticoids in that group, and there were more deaths, life-threatening or serious adverse events, and infections in the prednisone group than in the avacopan group.[1]

CONCLUSION

An avacopan-based regimen is non-inferior at achieving remission at Week 26 and superior at sustaining remission at Week 52 compared to a GC-based regimen.[1]

References & footnotes

AAV, ANCA-associated vasculitis; AIS, Aggregate Improvement Score; ANCA, antineutrophil cytoplasmic antibody; AZA, azathioprine; BID, twice daily; BVAS, Birmingham Vasculitis Activity Score; CI, confidence interval; CWS, Cumulative Worsening Score; CYC, cyclophosphamide; eGFR, estimated glomerular filtration rate; EQ-5D-5L, EuroQol 5-dimension 5-level; GC, glucocorticoid; GTI, Glucocorticoid Toxicity Index; MCP-1, monocyte chemoattractant protein-1; QoL, quality of life; RTX, rituximab; SF-36, Short form 36; UACR, urinary albumin:creatinine ratio; VDI, Vasculitis Damage Index

***Only the key secondary endpoints have been included. For more information, please visit: https://www.clinicaltrials.gov/ct2/home, Identifier NCT02994927**

1. Jayne D, et al. *N Engl J Med* 2021;384(7):599–609.
2. Merkel PA, et al. *JMIR Res Protoc* 2020;9(4):e16664.
3. Jayne D, et al. *N Engl J Med* 2021;384(7):599–609. [Suppl Appendix]