Supplemental Material

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Study Inclusion and Exclusion Criteria

Eligible patients were at least 18 years old and had newly diagnosed or relapsing granulomatosis with polyangiitis (Wegener's) or microscopic polyangiitis according to the Chapel Hill Consensus Conference definitions[1], that required cyclophosphamide treatment (steps 1 and 2), cyclophosphamide or rituximab (step 3), were PR3 or MPO-ANCA positive or ANCA positive by indirect immunofluorescence, had an eGFR of at least 20 mL/min/1.73 m^2, had biopsy-proven renal vasculitis or hematuria (greater than 30 red blood cells per high power field or greater than 2+ by urine dipstick) plus albuminuria (at least 0.5 g/g creatinine) for steps 1 and 2, or had at least one major or three non-major items, or at least two renal items on the BVAS version 3[2] for step 3. Since the BVAS version 3 does not designate "major" items, these were selected to be consistent with the BVAS WG[3].

Patients were excluded if they had severe disease (including rapidly progressive glomerulonephritis, alveolar hemorrhage leading to grade 3 hypoxia, rapid-onset mononeuritis multiplex, or central nervous system involvement), any other autoimmune disease, coagulopathy or bleeding disorder, had received cyclophosphamide within 12 weeks, rituximab within 12 months prior to screening (or 6 months with B-cell reconstitution, CD19 count $>0.01x10^9$/L), cumulative dose of intravenous glucocorticoids greater than 3 g within 12 weeks, or oral glucocorticoids of more than 10 mg per day prednisone equivalent for more than 6 weeks prior to screening.

Study Assessments

The Birmingham Vasculitis Activity Score (BVAS) version 3 was completed during screening, day 1 (baseline), and weeks 4, 12, 16, and 24. The BVAS score was calculated according to the guidelines for the BVAS version 3[2]. First morning urine samples for albumin, monocyte chemoattractant protein-1 (MCP-1), and creatinine were collected at day 1 and weeks 1, 2, 4, 8, 12, 16, and 24. Urine albumin was measured by a nephelometric assay, MCP-1 by ELISA, and creatinine by a kinetic colorimetric assay in a central laboratory (Medpace Reference Laboratory, Belgium). Serum creatinine, for eGFR calculation, and urine red blood cell microscopy were performed regularly over the study course. eGFR (according to the Modified Diet in Renal Disease equation)=$175\times(\text{serum creatinine, mg/dL})^{-1.154}\times(\text{age, years})^{-0.203}\times(0.742 \text{ if female})\times(1.212 \text{ if black})$. The Medical Outcomes Study Short Form-36 version 2 (SF-36) survey and the EuroQOL-5-D-5L (EQ-5D-5L) questionnaire were completed (in step 3 only) at day 1, and weeks 4, 12, and 24. The vasculitis damage index (VDI)[4] was completed on day 1 and weeks 12 and 24.

Safety was monitored at each study visit by assessing adverse events and laboratory data. The incidence of adverse effects commonly associated with glucocorticoid use, including

psychiatric disorders, hypertension, diabetes mellitus/hyperglycemia, weight gain, bone fractures, cataracts, and serious infections was summarized. These effects were selected based on guidance from AAV experts, as well as those reported in patients with AAV[5,6]. For example, infection resulted in 50% of deaths in AAV studies[5], gastrointestinal bleeding in 5%[5]. Also diabetes mellitus (8%[5] and 11%[6]), fractures (3%[5] and 15%[6]), and cataracts (9%[6]) occur frequently. Patient compliance with taking study medication was assessed based on returned capsule counts at each study visit.

Criteria for adjusting the cyclophosphamide dose:

The cyclophosphamide dose was determined by four factors: subject age, estimated glomerular filtration rate, WBC count at the study visit, and WBC count nadir in between dose pulses (where applicable):

Age:

- If <60 years, a full dose was given (unless influenced by the other three factors);
- If 60 to 70 years, the dose was reduced by 2.5 mg/kg;
- If > 70 years, the dose was reduced by 5 mg/kg.

Estimated glomerular filtration rate:

- If ≥30 ml/min, a full dose was given (unless influenced by the other three factors);
- If <30 ml/min, the dose was reduced by 2.5 mg/kg.

WBC count at the time of cyclophosphamide dose (local lab WBC counts):

- If ≥4 x 10^9/L, a full dose was given (unless influenced by the other three factors);
- If 2 to 3.9 x 10^9/L, the dose was reduced by 25%;
- If <2 x 10^9/L, the dose was withheld until the WBC count increased to above 3 x 10^9/L.

WBC count nadir in between cyclophosphamide doses:

- If >3 x 10^9/L, a full dose was given (unless influenced by the other three factors);
- If 2 to 3 x 10^9/L, the dose was reduced by 20%;
- If 1 to 1.9 x 10^9/L, the dose was reduced by 40%;
- If <1 x 10^9/L, the next dose was withheld and further dosing was only given if the WBC was >3 x 10^9/L.

Data Monitoring Committee

An independent external Data Monitoring Committee (DMC) oversaw the study and periodically reviewed safety data. The DMC advised the sponsor regarding transition between steps. At all its visits, the DMC recommended unchanged continuation of the study.

References

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Supplemental Table 1. Treatment Response Based on BVAS for Subgroups*

	Placebo plus 60 mg prednisone control (N=23)	Avacopan plus 20 mg prednisone (N=22)	Avacopan without prednisone (N=22)
All Patients*	14 / 20 (70)	19 / 22 (86)	17 / 21 (81)
Disease Status			
Newly diagnosed patients	11 / 15 (73)	13 / 15 (87)	13 / 15 (87)
Relapsing disease	3 / 5 (60)	6 / 7 (86)	4 / 6 (67)
Type of AAV			
GPA	5 / 10 (50)	11 / 11 (100)	10 / 12 (83)
MPA	7 / 8 (88)	7 / 9 (78)	6 / 8 (75)
ANCA Status			
Anti-PR3 positive	6 / 10 (60)	10 / 10 (100)	6 / 8 (75)
Anti-MPO positive	7 / 10 (70)	9 / 12 (75)	11 / 13 (85)
Disease Location			
Renal ± other disease	13 / 19 (68)	18 / 21 (86)	16 / 20 (80)
Only non-renal disease	1 / 1 (100)	1 / 1 (100)	1 / 1 (100)
Background Treatment			
Cyclophosphamide	11 / 17 (65)	14 / 17 (82)	14 / 16 (88)
Rituximab	3 / 3 (100)	5 / 5 (100)	3 / 5 (60)

*Results are shown for n / N (%), where n = the number of treatment responders and N = the number of patients in the subgroup of patients specified. Treatment response is defined as a decrease from baseline to week 12 in BVAS of at least 50 percent and no worsening in any body system. AAV = ANCA-associated vasculitis; GPA = granulomatosis with polyangiitis; MPA = microscopic polyangiitis; PR3 = proteinase 3; MPO = myeloperoxidase.

Supplemental Table 2. Summary Results of the Short Form-36 version 2 Domains by Study Visit*

Domain	Study Visit	High Dose Steroids SOC Control (N=10)	Avacopan + Low-Dose Steroids (N=14)	Avacopan + No Steroids (N=9)
Role Physical	Baseline	46±10	34±7	60±14
	Week 4	51±7	48±8	76±12
	Week 12	59±5	71±6	84±9
Bodily Pain	Baseline	68±10	61±8	72±12
	Week 4	67±9	75±7	83±9†
	Week 12	81±6	81±6	93±7
General Health	Baseline	45±7	55±4	66±5
	Week 4	48±5	60±5	52±6
	Week 12	51±4	59±5	62±8
Vitality	Baseline	41±6	40±5	55±11
	Week 4	47±5	53±7	60±10
	Week 12	46±4	62±5†	71±8‡
Social Functioning	Baseline	74±6	46±6	82±12
	Week 4	68±10	70±6	84±12
	Week 12	80±7	81±5	96±4
Mental Health	Baseline	66±5	62±5	82±7
	Week 4	68±5	73±6	79±6
	Week 12	65±5	79±6‡	89±4‡
Reported Health Transition (decrease shows improvement)§	Baseline	3.8±0.3	3.9±0.4	3.4±0.3
	Week 4	4.0±0.2	3.2±0.4	3.5±0.4
	Week 12	3.8±0.3	2.9±0.2†	2.9±0.4

*Results are shown for n, the number of patients with a measurement at the time point, and mean±SEM. The physical functioning and role emotional domain results are presented in Table 2.

† $P<0.05$, ‡ $P<0.01$ for change or percent change from baseline differences between avacopan and control groups.

§A decrease in Reported Health Transition corresponds to an improvement in health compared to one year ago.

Supplemental Table 3. Pre-Specified Prednisone Dose Tapering Schedule for the Three Treatment Groups

Study Week	Placebo plus 60 mg prednisone* control	Avacopan plus 20 mg prednisone	Avacopan without prednisone
1	60 mg (or 45 mg for <55 kg subjects)	20 mg (or 15 mg for <55 kg subjects)	0†
2	45 mg	15 mg	0
3	30 mg	10 mg	0
4-6	25 mg	10 mg	0
7-8	20 mg	5 mg	0
9-10	15 mg	5 mg	0
11-14	10 mg	5 mg	0
15-20	5 mg	0	0
≥21	0	0	0

* Prednisone was supplied to study centers as 20 mg and 5 mg tablets, over-encapsulated with hard gelatin capsules.
†Placebo prednisone was given as matching gelatin capsules.