

# RAVE

## RITUXIMAB FOR ANCA-ASSOCIATED VASCULITIS

A Phase II/III, double-blinded, placebo-controlled study of rituximab in Wegener's Granulomatosis and Microscopic Polyangiitis

### STUDY INFORMATION SHEET

Clinical Phase	II/III
Protocol Chairs	John Stone, MD, MPH (The Johns Hopkins University) Ulrich Specks, MD (The Mayo Clinic)
Accrual Objective & Period	200 participants over 30 months
Study Duration	The common closing date will be 18 months after the last participant is enrolled in the trial.
Study Design	This is a randomized, multicenter, double-blinded, placebo-controlled trial in patients with severe AAV. Two hundred participants will be randomized 1:1 to either the control or the experimental group.
Primary Study Objective	To determine the efficacy of rituximab (375 mg/m <sup>2</sup> ) and glucocorticoids in the induction of remission.
Secondary Objective	To compare the safety profile of rituximab (375 mg/m <sup>2</sup> ) with that of conventional therapy.
Inclusion Criteria	<ol style="list-style-type: none"><li>1. <b>Age:</b> They must be over 15 years of age.</li><li>2. <b>Diagnosis Type:</b> They must be diagnosed with WG or MPA according to the definitions of the Chapel Hill Consensus Conference.</li><li>3. <b>Screening Diagnosis:</b> They must be newly diagnosed patients, or they must have a disease flare that fulfills inclusion criteria 4, 5.</li><li>4. <b>Disease Activity / Severity:</b> disease that would normally require treatment with CYC.</li><li>5. <b>ANCA Status:</b> They must be positive for either PR3-ANCA or MPO-ANCA at the screening.</li></ol>
Exclusion Criteria	<ol style="list-style-type: none"><li>1. <b>Diagnosis:</b> They are diagnosed with Churg Strauss syndrome as defined by the Chapel Hill Consensus Conference.</li><li>2. <b>Disease Severity:</b><ol style="list-style-type: none"><li>a. <b>Limited Disease:</b> They have limited disease that would not normally be treated with CYC.</li><li>b. <b>Severe Disease:</b> They require mechanical ventilation because of alveolar hemorrhage.</li></ol></li><li>3. <b>Co-Morbidities:</b><ol style="list-style-type: none"><li>a. <b>Allergies:</b> They have a history of severe allergic reactions to human or chimeric monoclonal antibodies.</li><li>b. <b>Infection (Systemic):</b> They have an active systemic infection.</li><li>c. <b>Infection (Deep Space):</b> They have, or have been diagnosed as having, a deep-space infection, such as osteomyelitis, septic arthritis, or pneumonia complicated by emphysema or lung abscesses, within 6 months of randomization.</li><li>d. <b>Infection (Blood-Borne):</b> They have active hepatitis B or active hepatitis C or a documented history of HIV, hepatitis B, or hepatitis C.</li><li>e. <b>Liver Disease:</b> They have acute or chronic liver disease that is deemed sufficiently severe to impair their ability to participate in the trial.</li></ol></li></ol>

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Exclusion Criteria  
(continued)

- f. **Renal Disease:** They have a history of documented anti-GBM disease.
- g. **Malignancy:** They show current evidence of malignancy or have a history of a malignancy that Active or history of malignancy in last 5 years. Individuals with squamous cell or basal cell skin carcinomas and individuals with cervical carcinoma in situ may be enrolled if they have received curative surgical treatment.
- h. **Uncontrolled disease:** They show evidence of other uncontrolled disease, including drug and alcohol abuse, which could interfere with participation in the trial according to the protocol.

4. **Diagnostics:**

- a. **WBCs:** They have a white blood cell count that is less than 4,000/mm<sup>3</sup>.
- b. **Platelets:** They have a platelet count that is less than 120,000/mm<sup>3</sup>.
- c. **Liver Function Tests:** They have an ALT or AST level greater than 2.5 times the upper limit of normal that cannot be attributed to underlying AAV disease.
- d. **Creatinine:** They have a serum creatinine level greater than 4.0 mg/dL that is attributed to renal failure from a current flare. Individuals with stable renal failure from the previous episode of active disease may be included in the study if the flare involves other organ systems.
- e. **Thiopurine Methyltransferase:** They are deficient in one or both of the alleles for TPMT.
- f. **Human Antichimeric Antibodies:** They have had any history of HACA formation.
- g. **Pregnancy test:** positive

5. **Treatments**

- a. **CYC (adverse effects):** They are intolerant to CYC—i.e., they have previously suffered the adverse effects of conventional therapy that preclude CYC use. These effects may include CYC-induced hemorrhagic cystitis, bone marrow hypoplasia, or malignancy.
- b. **CYC (Recent Use):** They have used CYC, oral or IV, within the past 4 months unless they started oral CYC 1 week prior to enrollment. They cannot have received IV CYC within the past 4 months of enrollment.
- c. **Monoclonal Antibodies:** They have had any previous treatment with rituximab or Campath-1H.
- d. **Plasma-exchange:** They who have been treated with plasma-exchange within the 3 months preceding the screening visit
- e. **Vaccines:** They have had a live vaccination fewer than 4 weeks before randomization.

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Summary of Study  
Procedures

**Screening:** procedures to establish inclusion/exclusion criteria.

**Baseline:** procedures to establish baseline values for efficacy outcome (BVAS/WG) and other outcomes of interest: immediately after randomization but before receiving any treatment.

**Remission induction phase:** from the first administration of study treatment through month 6. BVAS/WG scores and the rate of selected adverse events obtained during this period will be analyzed toward the primary analysis. Participants may be crossed over to the other treatment arm should they be considered treatment failures.

**Remission maintenance phase:** beginning after month 6 through the common closing date (18 months after enrollment of the last participant). Efficacy and safety outcomes obtained during this period will be analyzed toward secondary endpoints. Participants who experience severe flares during this period will be treated with open label rituximab. After month 18, the investigator may treat participants based on best medical judgment.

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Treatment Description	<p><b>Glucocorticoids:</b> Glucocorticoids will be given to both treatment arms. Participants will receive a 1-day course of intravenous glucocorticoids, followed by oral prednisone; the IV glucocorticoids may be repeated up to a maximum of 3 days at the discretion of the investigator. The prednisone will be tapered so that by month 6 all participants in clinical remission will be off glucocorticoids.</p> <p><b>Remission induction phase (month 1 through months 3 to 6):</b> The experimental arm will receive intravenous infusions of rituximab (375 mg/m<sup>2</sup>/week times 4) and daily CYC placebo plus oral prednisone. The control arm will receive CYC (2 mg/kg, with doses modified for renal dysfunction) and four weekly infusions of rituximab placebo plus oral prednisone.</p> <p><b>Remission maintenance phase (months 3 to 6 through month 18):</b></p> <ul style="list-style-type: none"><li>- The experimental arm will switch from daily CYC placebo to AZA placebo.</li><li>- The control arm will switch from daily CYC to AZA (2 mg/kg/day).</li><li>- After completion of the month 18 visit, treatment will be according to best medical judgment.</li></ul>
For Additional Information or Enrollment Inquiries	<p>Please see <a href="http://www.immunetolerance.org/RAVE">www.immunetolerance.org/RAVE</a> for list of clinical sites and contacts.</p>
Sponsors	<p><b>RAVE is an Immune Tolerance Network study.</b> Supported by the NIH, FDA and Genetech, Inc.</p>

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