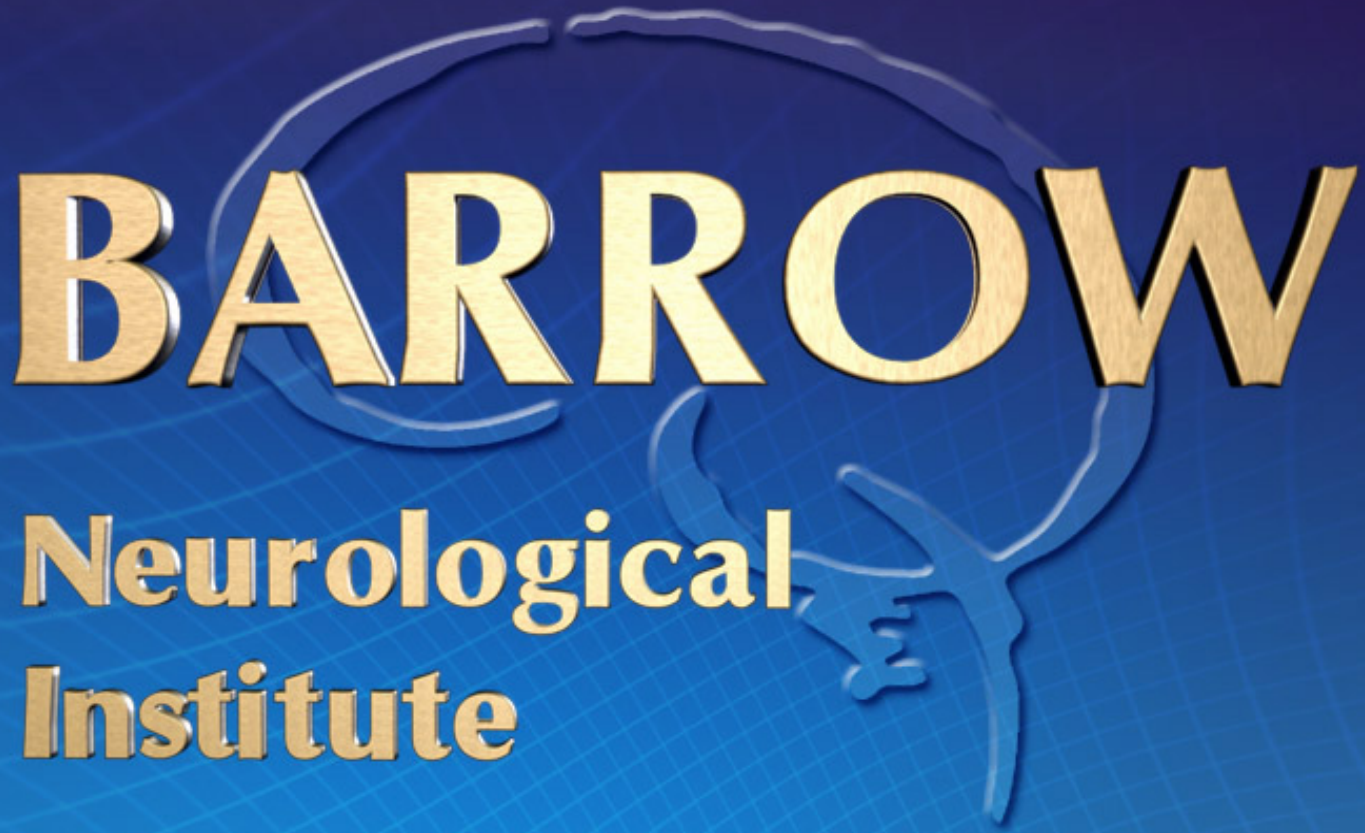


"unlocking the mysteries…"

Timothy Vollmer, MD
Van den Burgh Chair
Division of Neurology

Protocol BHT-3009-01

- **Placebo-controlled trial of BHT-3009 alone or combined with Atorvastatin in patients with multiple sclerosis**

- **Centers:**
  - **Barrow Neurological Institute – Tim Vollmer, M.D.**
  - **Montreal Neurologic Institute – Jack Antel, M.D.**
  - **University of Southern California – Les Weiner, M.D.**
  - **University of British Columbia – Joel Oger, M.D.**

Objectives & Endpoints

- Safety
- Determine Phase 2 dose
- Immune response
- Disease activity markers

- Clinical & lab evaluation
- MRI
- Safety
- Optimal biological dose
- Antibodies
- T cell proliferation, cytokines, subsets
- qPCR of PBMC RNA

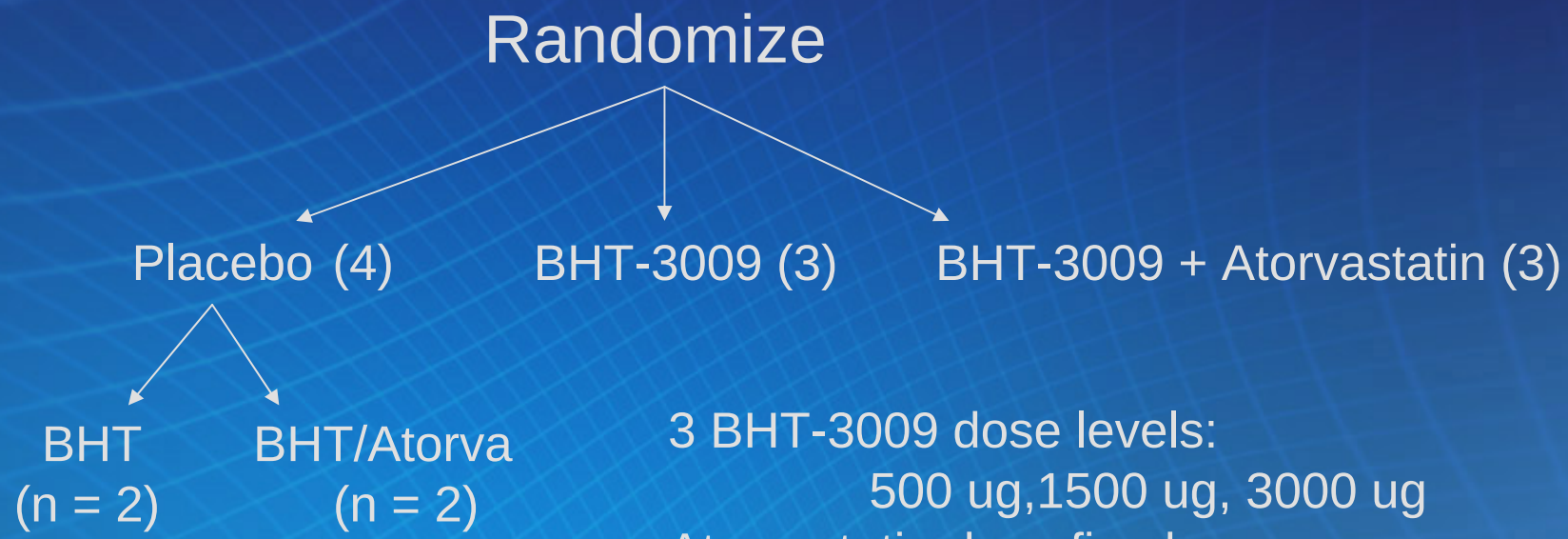
Patients

- Definite diagnosis of multiple sclerosis by the McDonald criteria.
- Patients with relapsing remitting MS or secondary progressive MS are eligible.
- 1-5 Gd+ lesions on MRI or relapse in last 2 years or disease worsening in last 2 years
- Clinically stable for $\geq$ 1 month before screening evaluation and during screening.
- EDSS $\geq$ 2.5 and 7.0
- Adequate hematopoietic, renal and hepatic function

Study Design

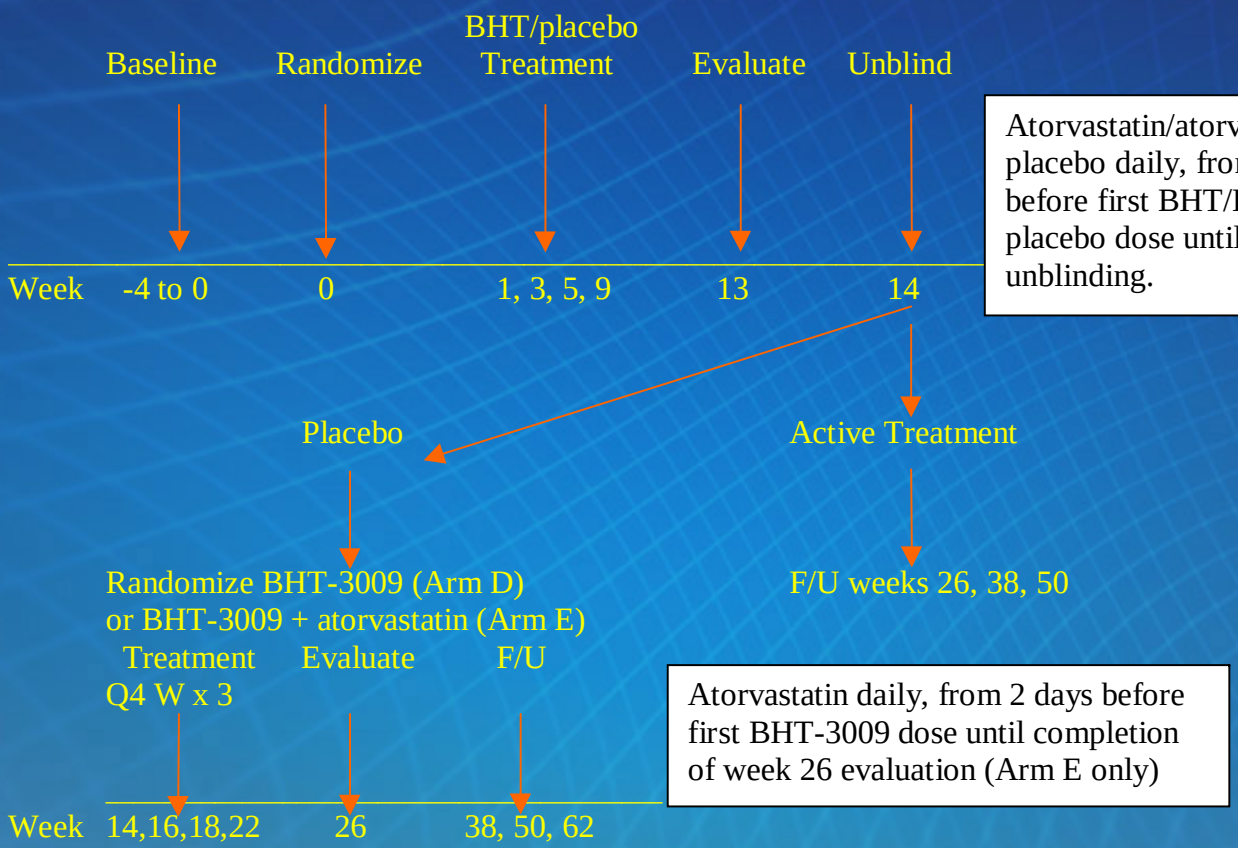
- Three arms
  - Placebo-4 Patients
  - BHT-3009-3 Patients
  - BHT-3009+Atorvastatin-3 Patients
- Randomized
- Double-blind
- Placebo-controlled
- Cross-over from placebo to active
- Repeated for three doses of BHT-3009

BHT-3009-01 SCHEMA



3 BHT-3009 dose levels:
500 ug,1500 ug, 3000 ug
Atorvastatin dose fixed:
80 mg/day
10 patients per BHT-3009 dose level
30 patients

Treatment Schedule



Safety Monitoring

- **Physical exam & AE evaluation**
  - Baseline, before each treatment, every 12 weeks follow-up
  - EDSS at baseline (2), end of treatment, relapse/progression
  - Monitor for 2 hours after each injection
  - Phone contact 3 days after each injection
- **MRIs**
  - Baseline (2), every 4 weeks on treatment, every 12 weeks follow-up
- **Routine labs**
  - CBC, chemistries, LDL cholesterol, CK

Data Safety Monitoring Board

- Review safety data after each dose cohort
  - Approve initiating next higher dose group
- Review Serious Adverse Events as they occur
- Review patients who exceed action limits
  - MRI: Any patient with $\geq$5 Gd+ lesions above baseline values on two sequential regularly scheduled scans
  - Relapses: Two patients with relapses during treatment time
  - Progression: Two patients with progression during treatment time

DSMB Members

- Gary Cutter, Statistician, Birmingham, AL
- Hillel Panitch, Neurologist, University of Vermont
- Mark Freedman, Neurologist, University of Ottawa
- Tony Traboulsee, MRI, U British Columbia

Separate 15 Year Follow-Up Study

BARROW Neurological Institute

- Begin in year 1
  - Familiarize patients with process and encourage participation
- Questionnaire completed at home
  - Paper or on line
  - New conditions (cancer, hematologic, autoimmune)
  - Status of MS
- Administered by NARCOMS
- Database
  - All BHT-3009 protocols
  - Protocols using same vector backbone

NARCOMS Overview:

- **Project of the CMSC Initiated 1996**
- **Paper-based (40%) and Internet Cohorts (60%)**
- **Participants complete comprehensive questionaire every 6 months.**
- **24,755 - Total active participants as of May 2004**
- **3,320 – Total 2003 new enrollments**
- **22,798* – Total update questionnaires sent out in Spring 2004**
- **Is the largest database of MS patients in the world**

*Enrollments received within 6 months of update cycle are not yet eligible to be sent an update questionnaire.

Staff of NARCOMS

- Timothy Vollmer, MD – Director
- Tuula Tyry, PhD, MAED – Program Manager
- Olympia Hadjimichael, MPH – Program Coordinator
- Stacy Oswald, BS – Technical Writer
  - MSQR Coordinator
- Donnie Dante, MS – Research Assistant
- Carlene Wesley – Research Assistant
- Alicia Minard – Research Assista
- Gary Cutter, PhD
  - Statistical support
- Ruth-Ann Marrie, MD
  - Fellow - 1 year appointment (starting July 1, 2004)

Immune Monitoring

- Antibodies
  - ELISA (MBP, PLP, MOG)(Immunosciencelab)
  - Microarrays (Bayhill/Stanford)

T Cell Function

- Central facility
  - Montreal Neurological Institute
  - Cells frozen at each site and shipped to Montreal
- Antigen-specific responses
  - MBP, PLP, MOG – protein & peptides
- T cell proliferation by CFSE dye dilution assessed by flow cytometry
  - CD4+ cells
- Intracellular cytokines
  - IL-4, IL-5, TNFα and IFNγ
- Primary IL7 T cell proliferation assay

Cell Phenotype

- **Central facility**
  - **USC core facility**
  - **Centers ship fresh blood to USC**
- **4 color flow cytometry**
  - **T cell, B cell & DC phenotype and activation state**
  - **CD3, CD4, CD4/CD3, CD8, CD8/CD3, CD4/CD8 ratio, CD19/CD3-, CD19, CD4/25, CD3/25, CD4/154, CD3/154, CD4/80/3, CD4/86/3, CD4/62L/45RA, CD8/62L/45RA, CD4/62L/45RO, CD8/62L/45RO CD40, CD28, CCR5, CXCR3, CTLA4 (CD152), HLA-DR.**

Inflammation Markers

- Peripheral blood gene expression
  - Source Precision (Boulder, CO)
  - RT/PCR
- Pilot study at Barrow
  - Examine 70 markers
  - Cytokines (e.g IL-1, 4, 6, 10, 13)
  - Chemokine markers (e.g CCL-1, CXCR3, CCR5)
  - CD markers (e.g CD86)
  - Osteopontin

BHT-3009 and MBP Expression

- Althea Technologies, San Diego
  - Performed pre-clinical GLP tests
- BHT-3009
  - PCR of peripheral blood
  - 1, 3, 14, 28 and 119 days after injection
- MBP
  - RT/PCR
  - 1 and 14 days after injection

BARROW Neurological Institute

Questions?

St. Joseph's Hospital and Medical Center
CHW