

OBA Protocol #1007-1053
Phase 1 /2 Randomized,
Blinded, Placebo-Controlled,
Sequential Dose Escalation Study of the
Safety and Pharmacodynamics of
BHT-3034, an Acetylcholine Receptor
Tolerizing Plasmid

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Outline

- Background
 - BHT-DNA plasmids
- Proposed mechanism of action of BHT-3034
- Review of animal studies
 - Expression of transgene
 - Early vs late disease
 - Lack of evidence for exacerbation
 - Selection of dose range
 - Interim toxicology study results
- MG and unmet medical need
 - Alternative therapies
- Proposed patient population
 - Ocular and mild generalized MG
 - Corticosteroid use during study

Rationale

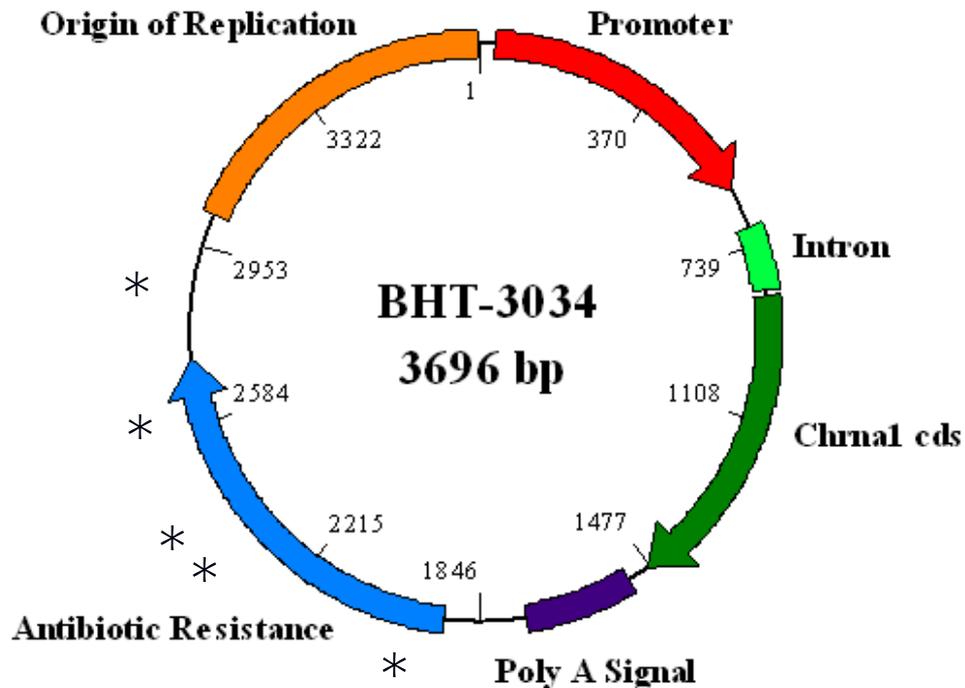
- Pathogenesis of MG
 - Autoimmune process directed against extracellular domain of α chain of human nicotinic acetylcholine receptor (AChR), leading to muscular weakness
- BHT-3034 is a DNA plasmid expression vector encoding the extracellular domain of the α chain of AChR
- Goal: Antigen-specific tolerance to AChR
- Potential advantage: leave intact other immune responses and immune surveillance

Other BHT-DNA Plasmids

- BHT-3009 for multiple sclerosis
 - OBA Protocol #0403-633: RAC Meeting June 8, 2004
 - Completed Phase 1 and Phase 2 studies
 - No safety signals seen in >200 MS patients dosed for up to one year
- BHT-3021 for type 1 diabetes
 - OBA Protocol #0604-769: RAC Meeting June 21, 2006
 - Ongoing Phase 1 study (T1D)
 - No safety signals seen in >50 T1D patients dosed weekly for 12 weeks

BHT-3034 Plasmid

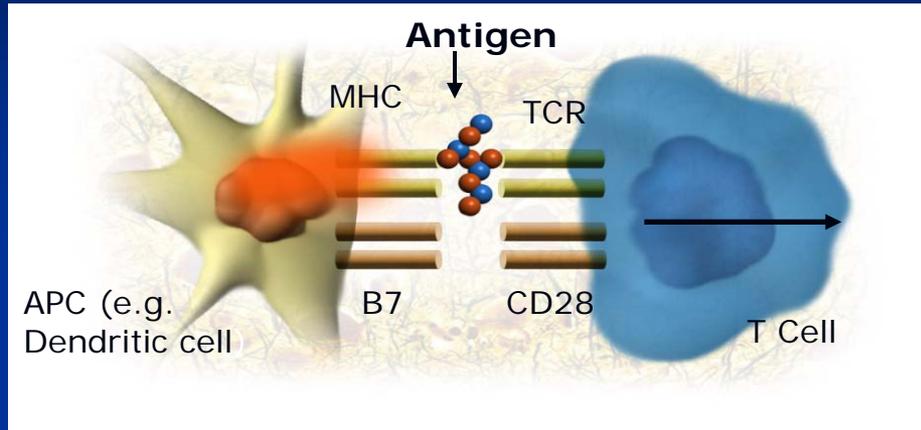
Figure 1 – Structural Diagram of BHT-3034



Features	Position (bp)
Promoter	32-621
Intron	702-834
Chn1a1	845-1483
Poly A signal	1527-1751
Antibiotic Res	1924-2718
Origin	3018-3691

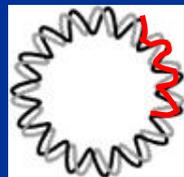
Proposed mechanism of BHT-DNA Induced Tolerance

Immunizing vaccine (adjuvant) →

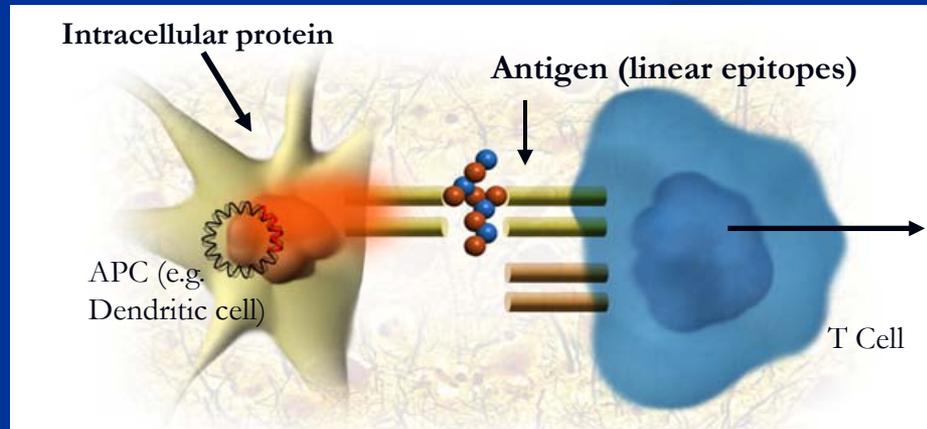


Activation:

- ↑ proliferation
- ↑ IFN- γ
- ↑ autoantibodies



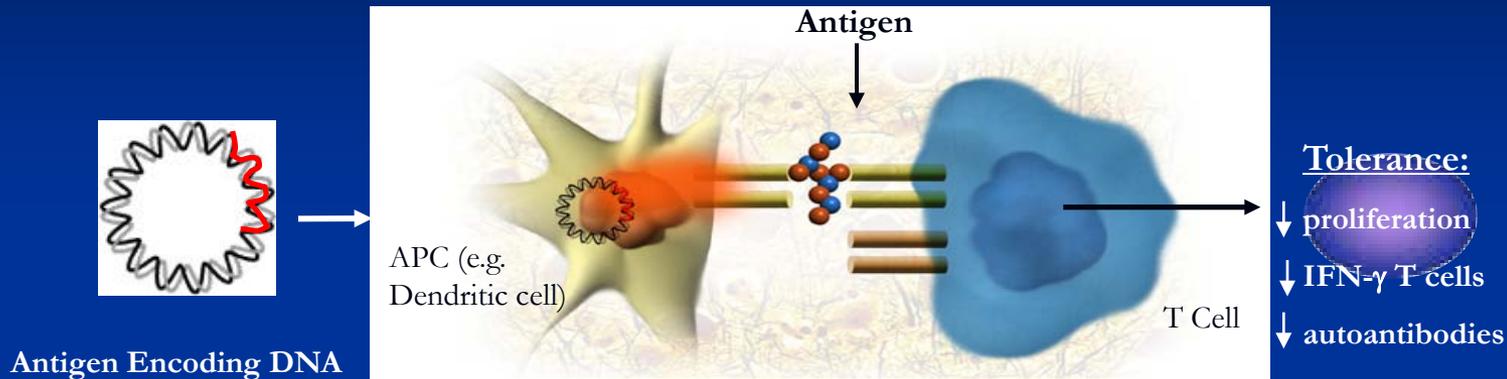
Tolerizing DNA Vaccine →



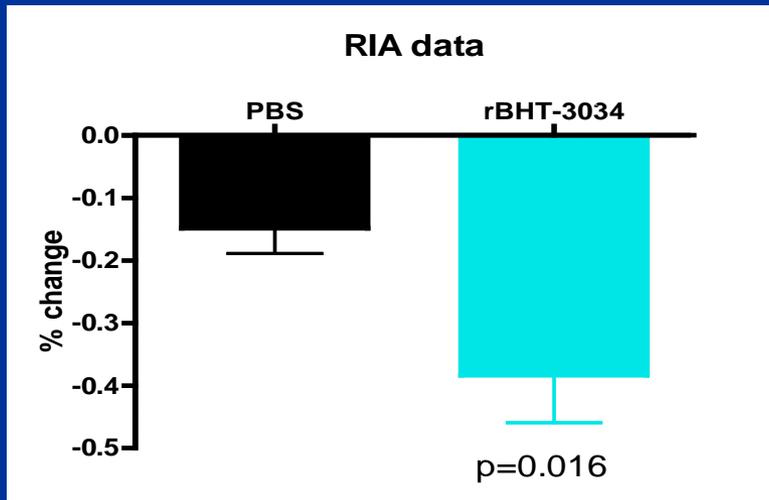
Tolerance:

- ↓ proliferation
- ↓ IFN- γ T cells
- ↓ autoantibodies

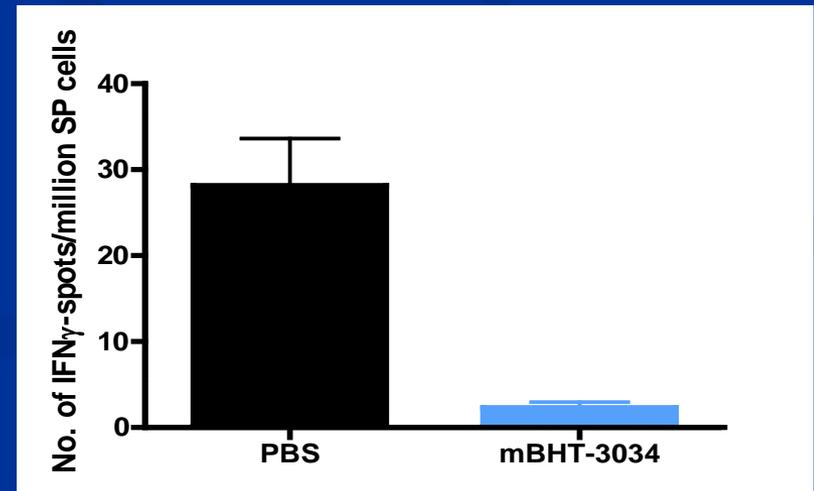
BHT-3034 Therapy Reduces B cell and T cell Responses



Antibody Reduction



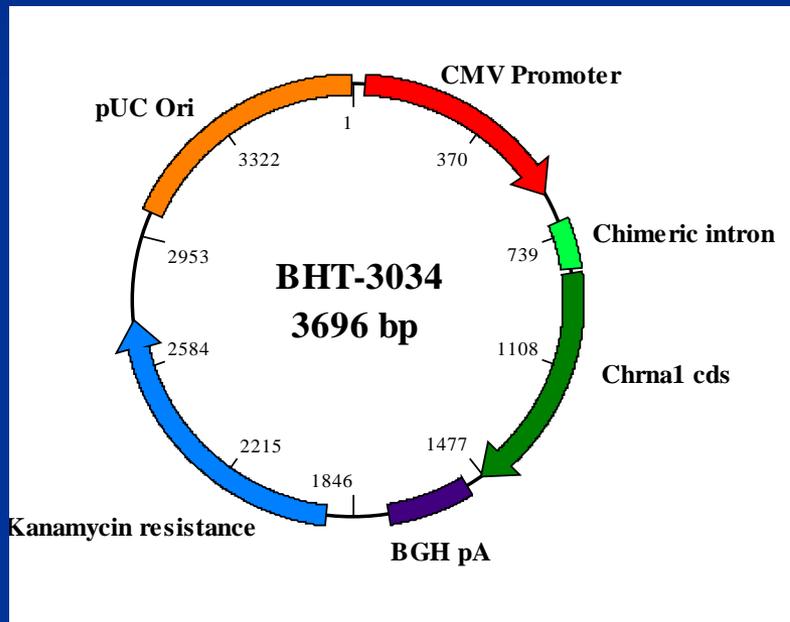
Decreased T cell Number



Animal Models and Species

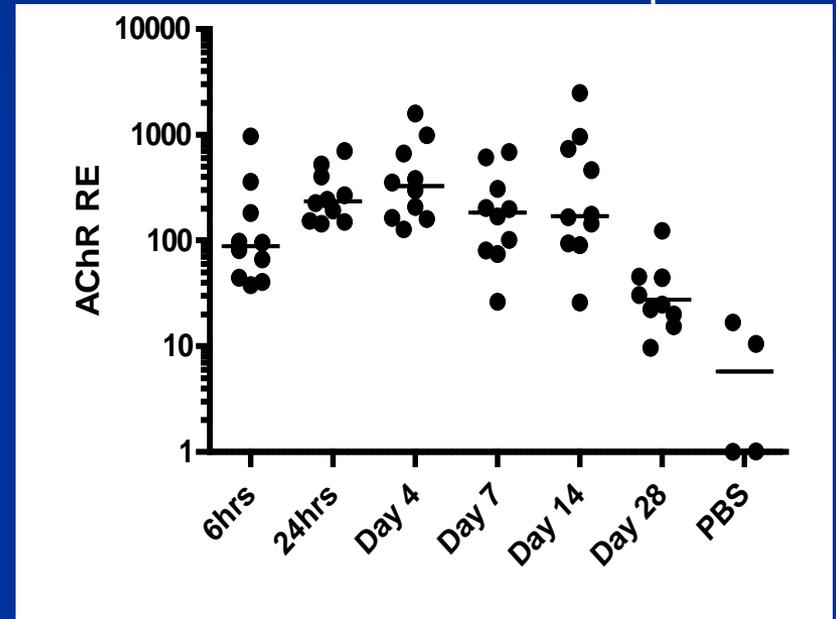
- Pharmacology studies performed in mice (C57Bl/6) and rats (Lewis)
 - Gold standard for studies of MG
 - Genetically susceptible animals
 - Antigen specific induced disease model
 - Similar to human disease
 - Animals develop anti-AChR antibodies, complement deposition at NMJ, T cell involvement, progressive muscle weakness
 - Two species differ in dominant epitopes
- Toxicology study performed in Lewis rats used in efficacy EAMG studies.

BHT-3034 Expression Peaks Within One Week



IM Injection

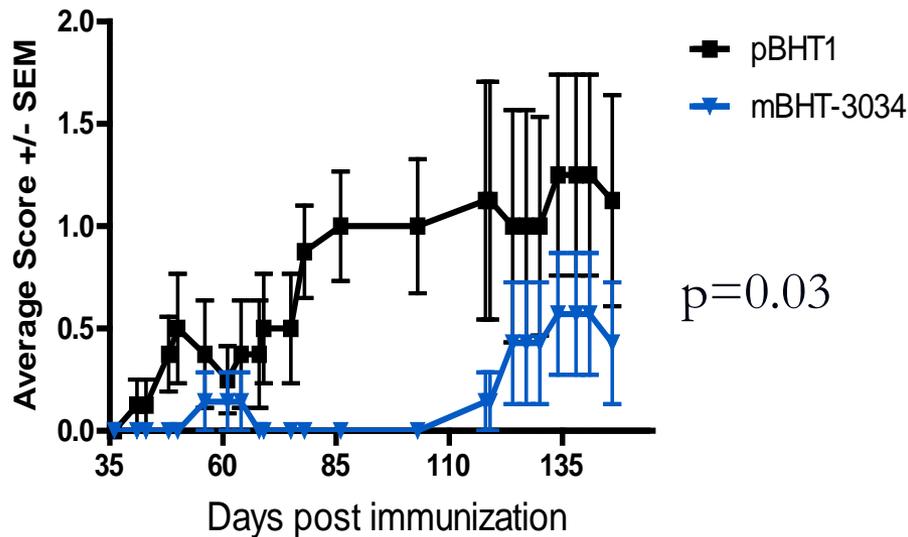
BHT-3034 Muscle Expression



Weekly Injections intended to maintain constant levels of peak expression

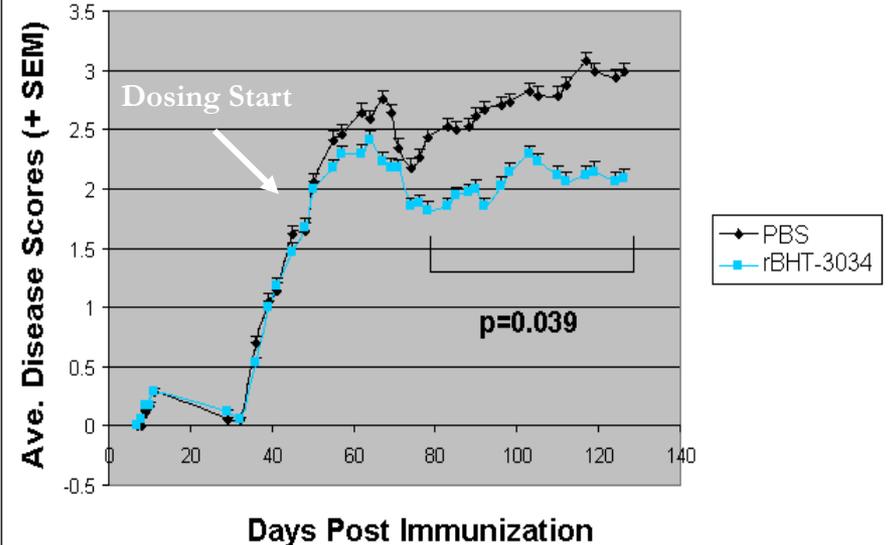
BHT-3034 Suppresses Disease in EAMG Studies

Mouse “Prevention” Study



Weekly IM injections
50 μ g Dose
n=7-8

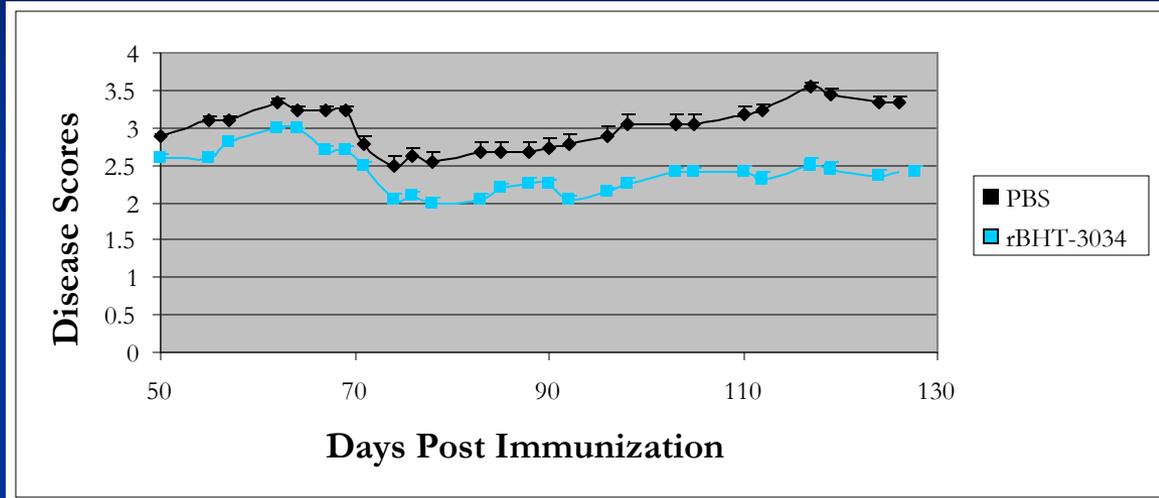
Rat “Treatment” Study



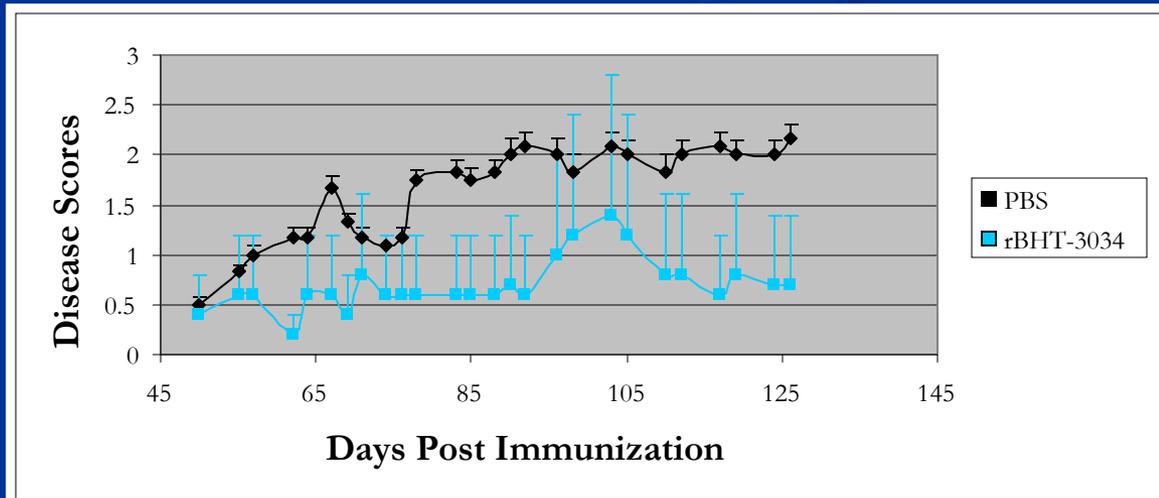
Weekly IM injections
250 μ g Dose
n=17

BHT-3034 is More Effective Treating Early/Mild Disease in Rat EAMG Study M20

Rats ≥ 2 at Start of Therapy (n=12)

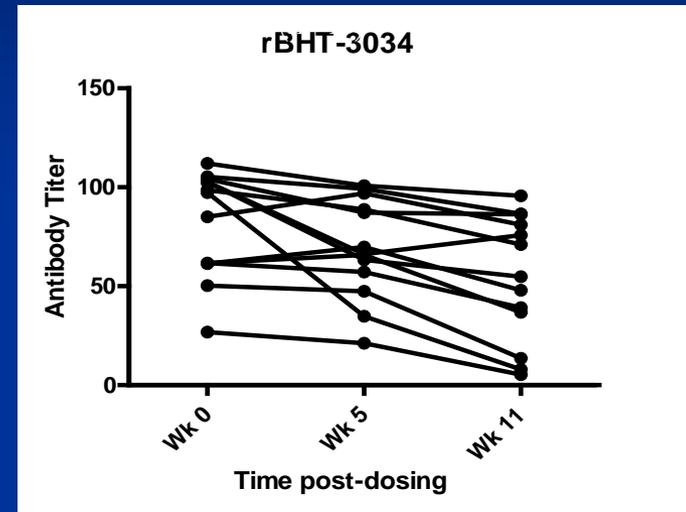
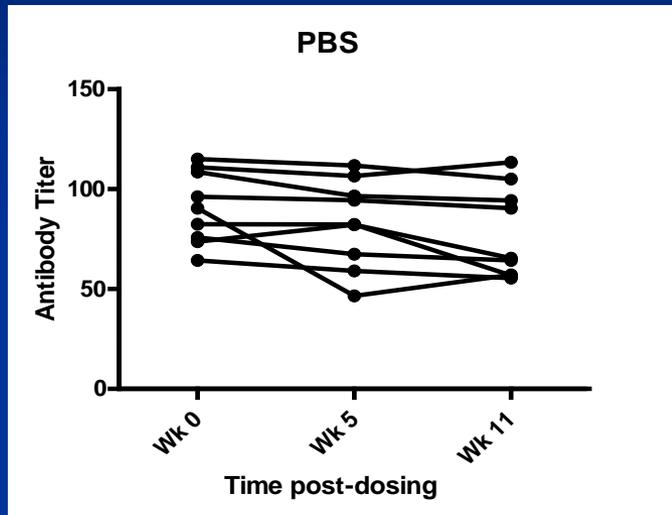


Rats ≤ 1 at Start of Therapy (n=5)

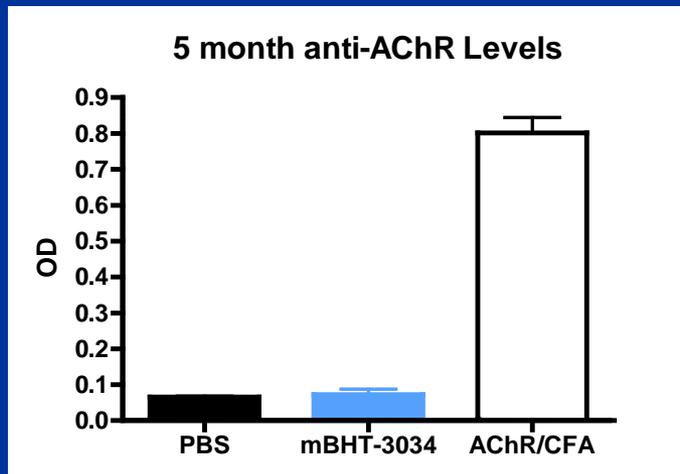


BHT-3034 Does not Induce anti-AChR Antibodies

EAMG Study M20 (Rat)



Mouse Immunogenicity Study (healthy C57Bl/6 mice)



Weekly dosing for 5 months in C57Bl/6 mice (n=5). No anti-AChR Antibodies induced

Toxicology Study Design

13 week GLP repeat dose (QW) toxicology study in Lewis Rat

Dose levels: 0.25mg, 1.0mg

Dose regimen: Weekly IM dosing

Endpoints: Clinical observations; body weights; food consumption; full necropsy with organ weights; complete tissue panel histopathology; clinical chemistry; immune cell phenotyping; hematology and clotting analysis.

10 Week Interim data:

- No deaths on study
- No adverse clinical symptoms associated with drug
- No differences in average body weight or food consumption
- Necropsy performed Sept 1

Phase 1/2 Dosing is Supported by Efficacy and Safety Study Dose Regimens

Rationale for Weekly Dosing:

- Effective in rat and mouse EAMG studies
- Effective in pre-clinical studies for other autoimmune diseases
- Effective in BHT-3021 Trial in T1D
- Consistent with expression profile

Rationale for Clinical Dose Range:

- MRSD is 1.0-4.0 mgs (based on tox NOAEL with 10X safety margin)
- Anticipated starting dose of 0.2 mgs (50-200X safety margin)
- Active doses in BHT-3009 and BHT-3021 Trials are in 1.0mg range
- Highest clinical dose proposed (10 mg) approaches practical limit based on concentration limits of DNA and the maximum IM dose volume.
- No safety signals in 3-6mg doses (12x weekly) in T1D Trial

Myasthenia Gravis Summary

- Most common NMJ disorder
 - Prevalence 1/10-20K
 - AChR-Ab discovered in 1973
 - Clinical features
 - Ptosis, diplopia in 90%
 - Only 15% remain purely ocular; most generalize in 2-3 yrs
 - Bulbar, truncal, proximal > distal limb involvement
 - Respiratory weakness in 30%, crisis in 20%
 - Diagnosis
 - Edrophonium test, Rep stim/SFEMG, AChR-Ab, MuSK-Ab
 - Chest CT/MRI for thymoma
 - Treatment
 - Pyridostigmine, corticosteroids, azathioprine, cyclosporine, mycophenolate, tacrolimus
 - Crisis: Plasma exchange, IVIG

Corticosteroids

- Marked improvement in >80% of patients
 - 28% remission
 - 53% normal ADLs, minor symptoms

Favorable response in approximately 80%

- 15% improved with functional limitations
- Remainder refractory
 - Pascuzzi et al. *Ann Neurol* 1984;15:291
- Maximal benefit in 5-6 mo

Immunosuppressive agents

Medication	Controlled studies
Azathioprine	+
Cyclosporin	+
Mycophenolate	+
Cyclophosphamide	+
Tacrolimus	+
IVIg	+

Mycophenolate mofetil

Randomized, double-blinded, controlled studies in generalized AChRAb+ MG

	MSG-Roche	Aspreva
Patients (n)	80	136
Duration	3 mo/6 mo open label	9 mo
MM dose	1250 mg bid vs. placebo	1000 mg bid vs. placebo
Prednisone at entry	None	≥ 20 mg qd or qod equivalent
Prednisone during study	20 mg qd	Tapered to 7.5 mg qd or 15 mg qod
Primary outcome	Δ QMG score	Reaching MMS or PR from wks 32-36

Mycophenolate mofetil

- MSG-Roche study
 - n=39 on pred/placebo; 41 on pred/MM
 - No significant difference in Δ QMG at 3 mo
 - -4.4 on MM vs. -3.6 on placebo (p=0.71)
 - No significant difference in 2° outcomes
 - MG-ADL, MMT, SF-36, AChRAb levels
 - MM was well tolerated
 - Diarrhea in 16%, infection in 13% in blinded phase on MM
- Muscle Study Group. *Neurology* 2008;71:394

Mycophenolate mofetil

- Aspreva study
 - n=88 on pred/placebo; 88 on pred/MM
 - n=144 completed study
 - No significant difference in reaching treatment response of MMS/PR
 - 44.3% on MM vs. 38.6% on placebo (p=0.541)
 - No significant difference in 2° outcomes
 - QMG, MG-ADL, SF-36, global assessments
 - Trend for greater prednisone dose reduction, decline in AChRAb, hospitalizations if on MM, but not significant
 - MM overall well tolerated
 - Headache (12%), nausea (9%) most common side effects
 - One death related to study drug (pneumonia in MM group)
- Sanders et al. *Neurology* 2008;71:400

The “muddle” of the MM trials

- Greater than expected response to prednisone alone
 - MSG study did not select prednisone-resistant patients
- Potential confounding factors
 - Rigorous definition of response in Aspreva study for which there was no preliminary data
 - Short duration of studies: 12, 36 weeks
 - Older patients, more men
 - Duration of disease (up to 3 years)
 - Benatar & Rowland. *Neurology* 2008;71:390

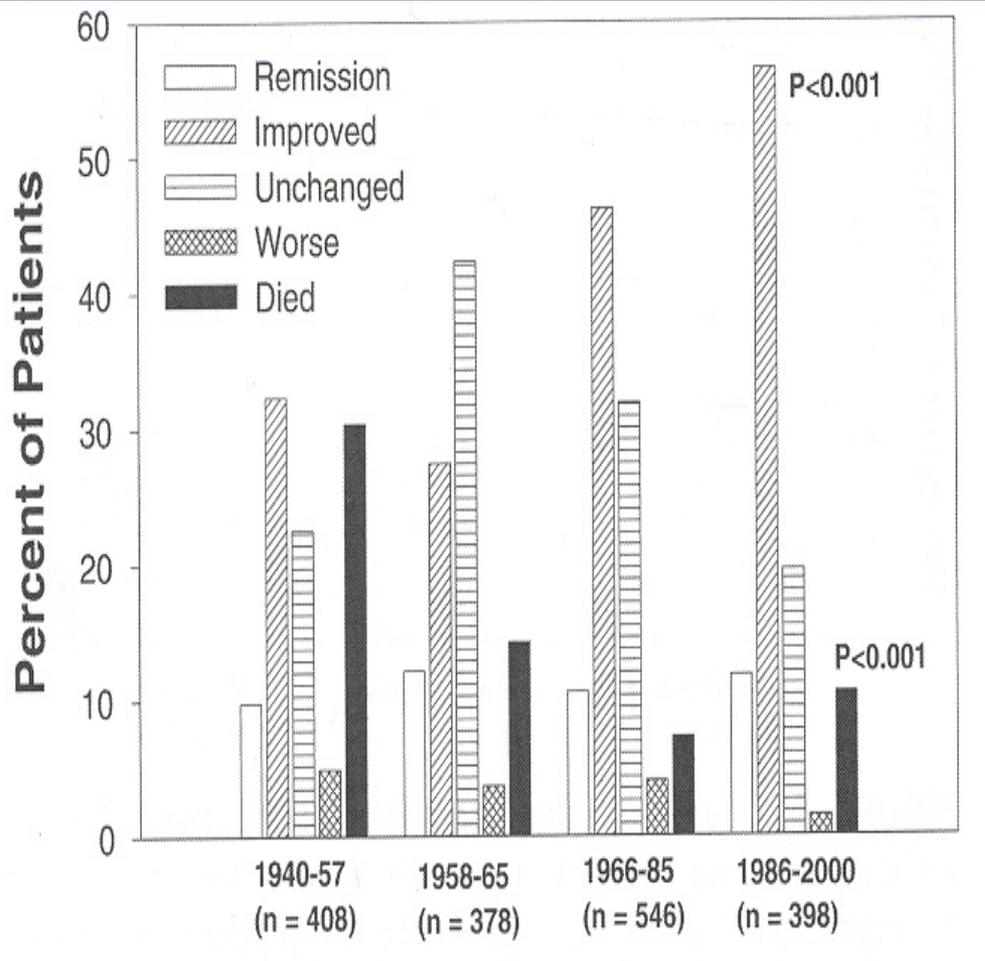
Immunosuppressive agents

Medication	Major adverse events
Prednisone	HTN, DM, weight gain, bone loss, cataracts, ulcers, psychologic disorders
Azathioprine	Fever, abdominal pain, hepatotoxicity, n/v, anorexia, leukopenia, skin rash
Cyclosporin	Hirsutism, tremor, gum hyperplasia, HTN, hepatotoxicity, nephrotoxicity
Cyclophosphamide	Alopecia, leukopenia, n/v, skin discoloration, anorexia, hemmorrhagic cystitis, malignancy
Tacrolimus	Hyperglycemia, HTN, headache, hyperkalemia, nephrotoxicity, diarrhea, n/v

Lifetime Course of MG

Grob et al. *Muscle Nerve* 2008;37:141

David Grob, MD, 1919-2008



Transternal thymectomy effect on remission

■ 1940-57

- Significant effect (20% vs. 10%)

■ 1958-1965

- Similar remission and improvement rates

■ 1966-2000

- Slightly higher mortality and lower remission rates in thymectomy group

P values
vs. 1940-57

Unmet Need: Ocular and Mild Generalized MG

- Ocular MG
 - ~60% of patients symptomatic on pyridostigmine alone
 - Many patients unwilling to initiate treatment with corticosteroids or other immunosuppressives
 - 50-60% of patients → generalized disease within 1-2 years
- Mild Generalized MG
 - Chronic disease → chronic therapy
 - Spontaneous remission rare; remission with aggressive Rx ~20%
 - Adverse effects of chronic therapy with corticosteroids or other immunosuppressives
- BHT-3034 has the potential to
 - ↓ symptoms of MG
 - ↓ need for corticosteroids or other immunosuppressives
 - ↓ progression of ocular to generalized disease

Proposed Study Population

- Adults, ages 18-75, inclusive
- MG by standard diagnostic criteria
- Ocular or mild generalized disease
- Within 18 months of symptom onset
- AChR antibody +
- Symptomatic (not well controlled on current Rx)
- Stable acetylcholinesterase inhibitor and corticosteroid use (if applicable)
- No other immunosuppressives, cell-depleting Rx

Corticosteroid Use During Study

- Inclusion
 - Corticosteroid use up to 20 mg/day prednisone (or equiv.) allowed
- Concomitant medication
 - For those on steroids, “effort should be made to keep the dose of corticosteroid constant throughout the study, and in particular throughout the Evaluation Period.”
 - For those not on steroids, effort should be made to optimize symptom control without use of corticosteroids, in particular throughout the Evaluation Period.”
 - If steroid dose \geq 60mg/day prednisone for \geq 7 consecutive days, then study drug should be discontinued
- Reflects variation in clinical practice with respect to steroid use (dose, adjustment, schedule)
 - Strict algorithm considered impractical for Phase 1 /2 study designed for safety and pharmacodynamic endpoints
- Provides strict boundary to ensure subject safety
 - Safety of low-moderate dose steroids supported by animal study
- Acknowledge standardizing steroid use will be important in later studies