

# EPITOME

## Efficacy of Prednisone In the Treatment of Ocular Myasthenia

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Muscle Study Group

# Study Sites

- Emory University - Michael Benatar
- Duke University - Don Sanders
- UT Southwestern - Gil Wolfe
- University of Kansas - Rick Barohn
- University of Virginia - Ted Burns

# Background

- Definition of ocular myasthenia
- Impact on quality of life
- Goals of therapy
  - Restore state of clear vision
  - Reduce the risk of progression to GMG
- Options for therapy
  - Symptomatic (cholinesterase inhibitors)
  - Immune suppressive (prednisone)
- Clinical equipoise

# Clinical Questions

- Is Prednisone effective in alleviating the symptoms of ocular myasthenia in patients who have failed to respond to pyridostigmine?
- Is low to moderate dose Prednisone tolerable and safe in patients with ocular myasthenia?
- Does prednisone reduce the risk of progression to generalized MG in patients with ocular myasthenia?
- What are the relative merits of low/moderate and high dose prednisone?

# Specific Aims

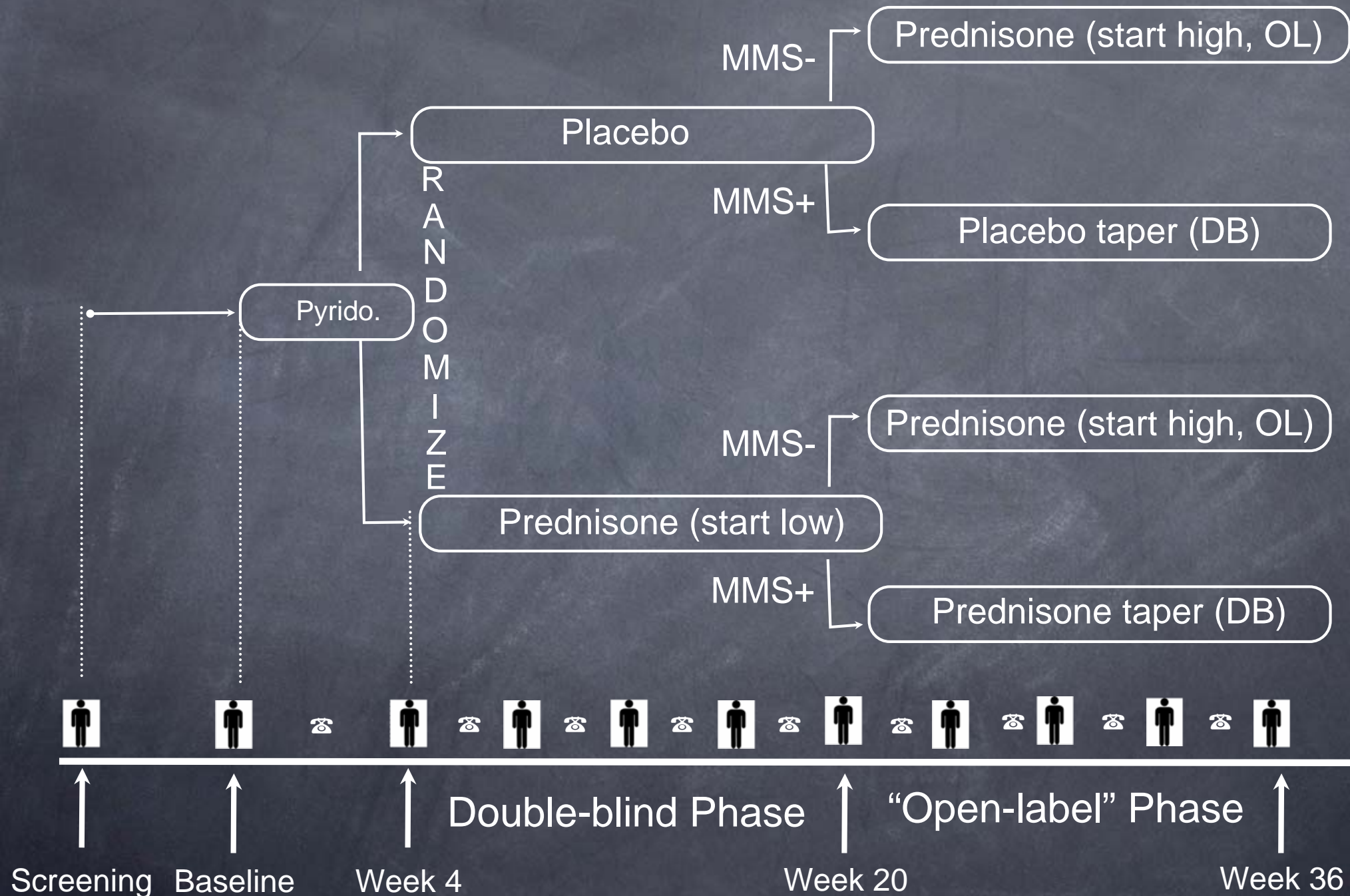
- Primary Aim
  - Compare adjustable-dose prednisone v. placebo with respect to frequency of treatment failures
  - Treatment failure
    - Failure to achieve sustained MMS within 4 months of double-blind treatment period, or
    - Toxicity leading to drug discontinuation
  - Outcome combines measures of efficacy and tolerability

# Specific Aims

- Secondary Aims
  - Safety/tolerability of adjustable-dose prednisone
    - Frequencies of drug discontinuation, participant withdrawal and individual adverse events
  - Efficacy of adjustable-dose prednisone
    - Time to sustained MMS, time to ocular-QMG=0
  - Impact of treatment on health-related QoL
- Exploratory Aims
  - Time to progression to GMG
  - Descriptive examination of efficacy and safety of high-dose prednisone strategy

# Study Overview

- Randomized, double-blind, placebo-controlled trial
- Patients with newly diagnosed OM
- Initial trial of pyridostigmine, titrated to maximum efficacy/tolerability
- Randomization (1:1) to the addition of prednisone (start low) or placebo
- Study drug titration over a period of 4 weeks
- Open label rescue with high dose prednisone for those who fail to remit and do not develop AEs
- Sustained MMS is the primary efficacy outcome measure



# Power

- Sample size: N=88 (includes 10% loss to follow-up)
- Preliminary data
  - Treatment failure in prednisone group  $\geq 35\%$
  - Treatment failure in placebo group  $\geq 69\%$
- Power
  - At least 80% (often 90%) to detect group difference in failure rates of 30-35%

# Inclusion Criteria

- Weakness confined to EOM, eyelid levator or orbicularis oculi
- At least one abnormal diagnostic test (AChR antibody, RNS, SFEMG, Tensilon or ice test)
- Normal brain MRI (if supportive diagnostic test is the tensilon or ice test)
- Inadequate prior trial of pyridostigmine
- Age  $\geq 18$
- Capable of providing informed consent
- Identifiable PCP to assist with management of medical complications

# Exclusion Criteria

- Disease duration > 2 years
- Steroids within 90 days of randomization
- Prior treatment with immune suppressive therapy
- IVIg or PLEX within 90 days of randomization
- Prior thymectomy or thymoma
- Contra-indications to steroids
- Unwillingness to be randomized to prednisone if symptoms respond inadequately to pyridostigmine
- Pregnant or lactating
- Untreated medical / psychiatric disorder
- Receipt of investigational drug within 30 days

# Pyridostigmine Treatment

- Initiated at 30mg t.i.d.
- Dose increments every 3 days if troublesome or functionally limiting symptoms persist
- Addition of anti-muscarinic agent permitted
- Goal is to optimize symptomatic response within 4 weeks of treatment
- Weekly telephone calls to assist participants with dose titration
- Randomization of those who fail to achieve “MMS”
- Dose to remain constant once enter double-blind phase of trial

# Prednisone (double blind)

- Start 10mg QoD
- Increase to 10mg QD after 2 weeks
- Upward titration by 10mg every 2 weeks, for maximum of 40mg/day
- Dosage adjustments determined by efficacy and tolerability
- Goal of therapy is sustained MMS without unmanageable adverse events

# Outcome Measures

- Primary
  - Proportion of treatment failures within 4 months of double-blind treatment
  - Treatment failure = failure to attain sustained MMS OR the occurrence of AE that require prednisone discontinuation
- Secondary
  - Time to sustained MMS
  - Time to ocular-QMG score of zero
  - Change in QoL (NEI-VFQ, 10-item supplement, INQoL)
  - Occurrence of adverse events

# Adverse Events

- Prophylaxis against steroid-related AEs
  - Vitamin D, calcium and bisphosphonate
  - Diet, exercise, use of PPI
- Aggressive monitoring for steroid-related adverse events
  - Monitoring of weight and blood pressure
  - Glucose tolerance tests
  - T-spine x-rays and DEXA scans
  - Ophthalmological evaluations for glaucoma and cataracts

# “Open-label” Phase

- Sustained MMS at end of double-blind phase
  - Yes --> double-blind taper of study drug
  - No --> rescue therapy with high dose prednisone (60mg/day)
- 4 week duration of open-label phase (to mirror duration of double-blind phase of low dose prednisone)
- Prednisone dose tapered according to tolerability and efficacy
- Aggressive monitoring for steroid-related AEs

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