HT-100: Delayed-Release Halofuginone Hydrobromide for Duchenne Muscular Dystrophy

PPMD Connect
Baltimore, MD
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Acknowledgements and Funding

Thank you DMD community!

- Action Duchenne
- Charley’s Fund
- Coalition Duchenne
- Cure Duchenne
- Duchenne Now
- The Duchenne Research Fund
- Harrison’s Fund
- Hope for Gus
- Hope for Javier
- The Jain Foundation
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- Nash Avery Foundation
- Parent Project Muscular Dystrophy
- Pietro’s Fight
- Ryan’s Quest
- Suneel’s Light
- Two Smiles One Hope
- Zubin’s Wish

DART therapeutics
Absent dystrophin does not directly cause motor dysfunction.

**ABSENT DYSTROPHIN**

- Branched fibers
- Muscle degeneration
- Abnormal muscle architecture
- Decreased force production
- Decreased muscle strength and motor function

**Normal to DMD**

- Absent dystrophin
- Does not directly cause motor dysfunction

**Biophys J. 2010 February 17; 98(4): 606–616.**
The goal of chronic therapy in DMD…tipping the balance

DMD muscle

Normalization
Degeneration

Inflammation
Necrosis
Fibrosis

Drug + DMD muscle

Normalization
Degeneration

Regeneration

Inflammation
Necrosis
Fibrosis
DMD cocktail should include drugs in at least 3 “therapy buckets”

Membrane and DGC stabilization
- Dystrophin gene or mRNA repair/replacement
- Utrophin upregulation
- α-dystrobrevin, α7 integrin upregulation
- Other membrane-stabilizing drugs

Normalizing muscle microarchitecture and function
- Abnormal Calcium homeostasis: Stretch activated Ca^{++} channels; Ryanodine Rc
- Inflammation
- Exercise-triggered muscle ischemia
- Abnormal fibrosis
- Oxidative damage to myofibers
- Failure of muscle regeneration

Improving remaining muscle
- Myostatin inhibitors
- SARM
- IGF-1 modulators
HT-100 is derived from an ancient compound

4730 B.C
- Chang Sang (Dichroa Febrifuga): Earliest records of clinical use

1940-1950
- ~600 plants tested for antimalaria activity. High activity in D. febrifuga

1960
- Febrifugine the active compound
- >130 derivatives synthesized

1980s-present
- Halofuginone a veterinary drug

1993-2006
- Clinical relevance discovered
- First clinical trials

2012
- Halo develops HT-100 by manufacturing enteric coated HF to enhance GI tolerability
How does HT-100 work?

- **HT-100 has anti-fibrotic effects**
  - Reduces fibrosis in MD independent of the mutation or muscle type including cardiac muscle
  - Inhibits Smad3 phosphorylation downstream in the TGF-β signaling pathway
  - Inhibits secretion of pro-fibrotic cytokines by T-cells and macrophages
  - HT-100 has antifibrotic effect only in abnormal fibrotic tissue

- **HT-100 has anti-inflammatory effects**
  - Inhibits T-cell secretion of cytokines, indirectly decreasing abnormal TGF-β pathway signaling
  - Decreases muscle necrosis and degeneration

- **HT-100 improves muscle regeneration**
  - HT-100 enhances myotube fusion via the PI3K/Akt and MAPK/ERK pathways
HT-100 tips the balance

DMD muscle

Normalization
Degeneration

HT-100+DMD muscle

Normalization
Degeneration

Regeneration
Inflammation
Necrosis
Fibrosis

Regeneration
Inflammation
Necrosis
Fibrosis
Evidence of efficacy in DMD and other animal models

- Young *mdx* mice
  - Decreases collagen type I deposition in diaphragm and heart
  - Decreases muscle degeneration and increases muscle regeneration in diaphragm
  - Prevents posterior cardiac wall thickness and wall motion abnormalities
  - Prophylactic effect: treated mice performed as well in RotaRod measure of coordination and balance as wild type mice, and significantly better than untreated mice

- Old *mdx* mice
  - Reduced collagen content in skeletal, diaphragm and heart
  - Improved voluntary running capacity and decreased exercise-induced muscle fiber damage
  - Improved respiratory function

- Positive results in models of other muscular dystrophies, as well as other fibrotic diseases
Comprehensive pre-clinical safety package

- Genetic Toxicology Studies:
  - Several \textit{in vitro} studies, all negative

- Safety Pharmacology Studies:
  - CNS (SD rats) & Cardiovascular (beagle dogs), all negative

- GLP Toxicology Studies:
  - 2 x pilot dose range finding in SD rats and beagle dogs
  - 2 x four week studies in SD rats and beagle dogs
  - 3 and 6 months studies in rats and beagle dogs (pre-GLP)
  - 1 year in SD rats (pre-GLP)
  - 2 year carcinogenicity studies in mice and SD rats (pre-GLP)

- Development and reproductive toxicity (all negative except for effects on maternal health):
  - Repro organ testing in SD rats, rabbits and beagle dogs

- ADME/PK studies
  - Good bioavailability, moderate to long $\frac{1}{2}$ life
  - The combination of very low dose given, almost no significant metabolism, and no CYP450 inhibition indicates very low drug interaction potential
Extensive clinical history

- Multiple studies with topical administration, providing evidence of anti-fibrotic effects in humans (scleroderma, GvsHD)

- Four studies of oral administration in humans, including two studies with long-term dosing
  - Ascending dose, healthy volunteers (n=26)
  - Split dose, healthy volunteers (n=8)
  - Solid tumors (n=24)
  - Bladder cancer (n=24)
HT-100: Enhanced tolerability

- Consistent finding from preclinical and clinical studies: dose limitation is GI tolerability (nausea and vomiting)
- HT-100 developed to address this issue: enteric coated tablet bypasses the stomach where tolerability response occurs
  - Successful studies in most sensitive animal model reduced N/V events 3-4 fold
Clinical program for DMD

1. Phase Ib: Single- and multiple-dose pharmacokinetic and safety/tolerability study in broad population of DMD boys
   - Clinical Trial started in June 2013

2. Phase Ila: Open-label extension study
   - Already developed and being submitted by the sites to their IRBs for seamless continuation of therapy after Ib completion

3. Phase I Ib/III pivotal study: Randomized, controlled study in well-defined patient population
An Open-label, Single And Multiple Ascending Dose Study To Evaluate The Safety, Tolerability And Pharmacokinetics Of HT-100 In Patients With DMD, followed by a Phase IIa Open label Extension Study
Study Design: Key Elements

- Phase Ib: Open-label, non-randomized, single and multiple ascending dose study
- Multicenter (5 sites)
- N = 30 (max)
- Multiple dose cohorts (up to 5)
  - Minimum of 3 subjects/cohort age 7-10, ambulatory, and on stable dose of corticosteroids
- Pharmacovigilance Team for inter-cohort safety reviews and dose escalation decisions
- Phase IIa: 6-month extension trial – separate but immediate
Study Flow:
Staggered Dose Escalation from SAD to MAD

Single Ascending Dose (SAD) Phase

- 5 µg/kg BID → 1 wk washout
- 20 µg/kg → 1 wk washout
- 10 µg/kg BID → 1 wk → 1 wk washout
- 5 µg/kg BID → 1 wk → 1 wk washout

Multiple Ascending Dose (MAD) Phase

- Dose TBD → 1 wk washout
- ≤80 µg/kg/day → 1 wk → 1 wk washout → 30 days dosing
- Dose TBD → 1 wk washout → 30 days dosing

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Main Inclusion and Exclusion Criteria

INCLUSION
- 6-20 years of age
- Ambulatory or non-ambulatory.
- Diagnosis of DMD confirmed by biopsy, genetic testing or family history
- On stable corticosteroid therapy or corticosteroid naïve

EXCLUSION
- Any substantial change in
  - prophylaxis/treatment with angiotensin converting enzyme inhibitors within 3 months
  - or any medication that may affect muscle function within 1 month
  - or prophylaxis/treatment with human growth hormone within 18 months of dosing
- Cerebral arterial or venous malformation
- FVC <55% of predicted
- Symptomatic cardiomyopathy, asymptomatic evolving cardiomyopathy, or a QTc ≥450 msec or >480 msec if bundle branch block is present.
- History of severe allergic or anaphylactic reactions
OBJECTIVES

- Primary
  - To assess the safety and tolerability of single and multiple escalating doses of HT-100 administered by mouth to boys with DMD.

- Secondary
  - To assess the PK profile of HT-100 following oral administration of single and multiple escalating doses to boys with DMD.
  - To assess the safety, tolerability, and early effects of HT-100 administered continuously for 4 weeks in a broad DMD population.
HT-100 Tablets & Dosage Strengths

**Tablet Size**
- Small, round tablets; ~3/16” diameter
- Comparable size to NECCO® candy dots
- Administer with fluids

**Dosage Strengths**
- 75 µg (white tablet)
- 225 µg (yellow tablet)
- 300 µg (red tablet)
# Clinical Study Visit Schedule

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**Dr Visit:** If not joining Extension Study

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Participating Clinical Sites
HT-100 will be a pivotal trial candidate in 2014.
Acknowledgements

Halo Team

Marc Blaustein, CEO
Diana Escolar, CMO
Ernie Bush, Safety and Toxicology
Mark Pines, CSO
Jane Davis Golden, Project Manager
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