The BRAVE Study: A Phase 2 Trial to Assess the Efficacy and Safety of MNK-1411 in Duchenne Muscular Dystrophy

Parent Project Muscular Dystrophy
JOIN THE FIGHT. END DUCHENNE.

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Mallinckrodt Pharmaceuticals

Disclaimer

This presentation is for the investigational drug MNK-1411.

This presentation is for educational purposes only and not for promotional purposes.

This presentation may be discussed with patients, parents and caregivers only.

MNK-1411 A Melanocortin Receptor Agonist

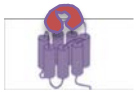
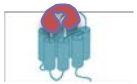
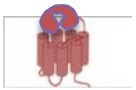
What are Melanocortin Receptors (MCRs)?

They are a family of G-protein-coupled receptors that bind Melanocyte-stimulating hormones and Adrenocorticotropic hormone.

There are 5 known MCR subtypes, each with a distinct distribution throughout the body.

And what is an Agonist?

A Receptor Agonist is a substance which binds to receptors and causes receptor activation.

		Cellular Expression
MC1R		**Leukocytes, Central Nervous System (CNS) cells, kidney cells, muscle cells, many other cells**
MC2R		**Adrenal cortical cells**
MC3R		**Leukocytes, CNS cells, kidney cells, muscle cells, many other cells**
MC4R		**CNS cells**
MC5R		**Leukocytes**

References available upon request.

MNK-1411 A Melanocortin Receptor Agonist

MNK-1411 has been reported to activate all 5 known melanocortin receptors (MCRs) to generate certain biological responses.

		Cellular Expression	Believed Functions
MC1R		Leukocytes, CNS cells, kidney cells, muscle cells, many other cells	Reduce inflammation/ Effecting how the immune system responds
MC2R		Adrenal cortical cells	Formation of steroids
MC3R		Leukocytes, CNS cells, kidney cells, muscle cells, many other cells	Reduce inflammation, modulate kidney function
MC4R		CNS cells	Reduce inflammation, preservation of neuronal structure and/or function
MC5R		Leukocytes	Immunoregulatory effects

While the exact mechanism of action of MNK-1411 is not fully understood, further investigation is being conducted. This information is based on nonclinical data and the relationship to clinical benefit is unknown.

References available upon request.

MNK-1411 A Melanocortin Receptor Agonist

What is MNK-1411?

- The active ingredient in MNK-1411 is a man-made shortened form of the natural hormone corticotropin (also called ACTH).
- Products in this class were initially developed because ACTH was known to stimulate production of cortisol, and cortisol was thought to have anti-inflammatory effects.
- When the receptor mediating the effects of ACTH in the adrenal gland was identified,

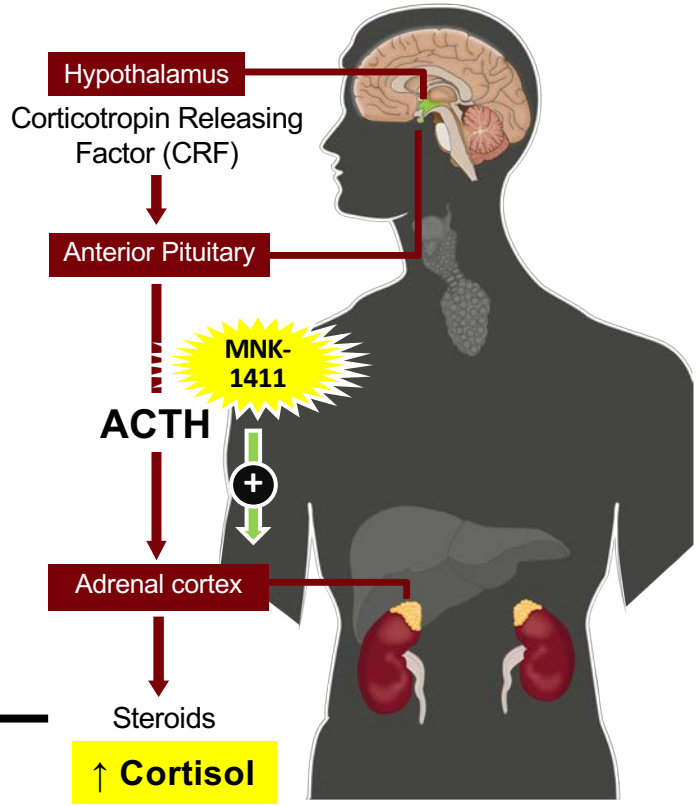
  4 related receptors were discovered that also can respond to ACTH; the family of melanocortin receptors (MCRs).
- MCRs thought to play an important role in regulating inflammation and modulating immune response.

References available upon request.

MNK-1411 A Melanocortin Receptor Agonist

How is this activation believed to work?

MNK-1411 activates in such manner that the body produces its own natural steroid (cortisol).



- **Potential suppression of inflammation**
- **Potential immune modulation**

References available upon request.

Hypothesis for how MNK-1411 may work in Duchenne

- Muscles from patients with Duchenne show inflammation around injured muscle, and reduction of inflammation is a treatment approach being studied.

- Treatment with oral corticosteroids has been shown to slow Duchenne disease progression.

References available upon request.

Hypothesis for how MNK-1411 may work in Duchenne

- MNK-1411 has the potential to reduce muscle damage and/or promote muscle regeneration via:
  - Direct effects on cells of the immune system to reduce muscle inflammation
  - Indirect effects to reduce muscle inflammation via stimulation of endogenous cortisol (a naturally produced corticosteroid)
  - Possible direct effects on certain types of muscle cells seen in damaged muscle

- Preliminary experiments in Mdx mice suggest MNK-1411 reduces inflammation (measured by Magnetic Resonance Imaging (MRI) and muscle histology) and may reduce abnormal gait.

This information is based on preclinical data and its clinical relevance is unknown.

References available upon request.

The Brave Study

The BRAVE Study: Objectives

BRAVE is a Phase 2 study in boys with Duchenne who are 4-8 years old:

- The primary objective of this study is to determine the effect of MNK1411 on motor function, measured by the 10 m walk/run
- The secondary objectives of the study include assessing the effect of MNK1411 on additional measures of motor function (NorthStar Ambulatory Assessment, other timed function tests, muscle strength), and safety and tolerability
- To explore potential effects of MNK-1411 on
  - Pulmonary function
  - Surrogate markers associated with DMD

Because there is likely overlap in the mechanism of action of exogenous glucocorticoids and the hypothesized mechanism of action of MNK-1411 in DMD, it is not feasible to study MNK-1411 as an adjunctive therapy to the standard of care (pharmacologically administered corticosteroids).

The BRAVE Study: Summary

- Multi-Center, Randomized, Parallel Group, Placebo-Controlled, Double-Blind Study in ~132 Patients with Duchenne Ages 4-8

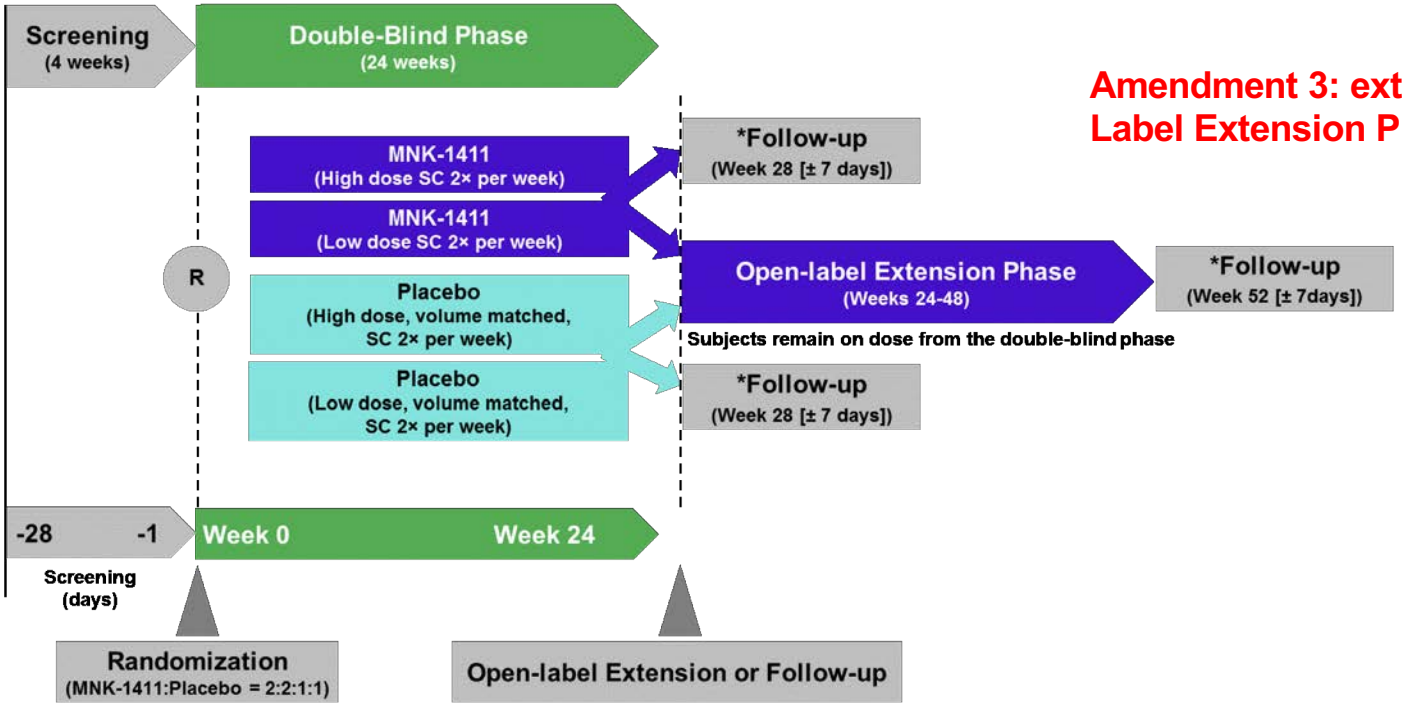
- 4 dose arms:
  - 2 active doses (“low” and “high”) and 2 volume matched placebo groups
  - Dosing is flat but weight based (< 20 kg or ≥ 20 kg)
  - “High” dose was modeled to result in cortisol exposure roughly equivalent to usual dose of pharmacologically administered steroid (~ 0.75 mg/kg/day prednisone equivalent); “Low” dose is 50% lower
  - Patients to be randomized 2:1 (MNK-1411:placebo)

The BRAVE Study: Summary

- Visits at: Screening (Day-28 to Day -1), Baseline (Day 0), Week 4, Week 8, Week 12, Week 16, Week 24, Week 28 (follow up for boys who do not enter the optional open-label extension (OLE))

- 24-week open-label extension offered to patients who complete 24-week double blind treatment
  - All patients on active treatment, they retain dose assignments from the double-blind phase
  - Visits for OLE: Baseline at Week 24 (Drug dispensed for OLE), Week 28, Week 36, Week 48 (end of open-label treatment), Week 52 (follow-up visit)

The BRAVE Study: Design



Amendment 3: extension of Open Label Extension Phase

*All subjects will have a follow-up visit at 28 (±7) days after their last dose of study drug. Subjects who complete the study and do not enter the open-label extension will have their follow-up visit at approximately Week 28. Subjects who complete the open-label extension will have their follow-up visit at approximately Week 52.

The BRAVE Study: Key Inclusion Criteria

- Patients ≥4 and ≤8 years of age
- Diagnosis of Duchenne muscular dystrophy confirmed by complete dystrophin deficiency (by immunofluorescence and/or immunoblot), or identifiable mutation in the DMD gene where reading frame can be predicted as "out of frame", or complete dystrophin gene sequencing consistent with DMD AND a typical clinical profile consistent with DMD
- Patients taking approved treatments for DMD (by a Health Authority) that target dystrophin gene mutations (e.g., eteplirsen or ataluren) may be enrolled in the study if they have been on a stable dose for 30 days prior to the first dose of study drug, and plan to remain on that dose throughout the study

The BRAVE Study: Key Exclusion Criteria

- Patients with symptomatic cardiomyopathy or who are unable to complete the 10m walk/run test at baseline

- Patients who have had previous systemic treatment with corticosteroids within 2 months prior to the screening visit. Exception: In subjects who were down-titrated to a physiological dose of corticosteroids (ie, 3 mg/m2 of prednisone or deflazacort) a maximum of 1 month of no greater than a physiological dose followed by 1 month completely off corticosteroids prior to the screening visit will be acceptable for study entry. Transient previous use of corticosteroids will be evaluated on a case-by-case basis by the sponsor or designee. The use of topical or intra-articular corticosteroids is permitted during the study.

- Patients with Type 1 or Type 2 diabetes mellitus.

The BRAVE Study: Key Exclusion Criteria

- Patients with a history of chronic active hepatitis including acute or chronic hepatitis B, or acute or chronic hepatitis C.
- Patients with a history of tuberculosis (TB) infection, any signs/symptoms of TB, or any close contact with an individual with an active TB infection.
- Patients with known immune compromised status (not related to disease/condition under study), including but not limited to, individuals who have undergone organ transplantation or who are known to be positive for the human immunodeficiency virus.

The BRAVE Study: Endpoints

- **Primary:** Δ from baseline for 10m walk/run at week 24

- **Secondary:**
  - Δ from baseline for NorthStar Ambulatory Assessment at weeks 4, 8, 12, 16 & 24
  - Δ from baseline for Time to climb 4 stairs at weeks 4, 8, 12, 16 & 24
  - Δ from baseline for Time to stand from supine at weeks 4, 8, 12, 16 & 24
  - Δ from baseline for 10m walk/run timed at weeks 4, 8, 12, 16
  - Δ from baseline for Quantitative Muscle testing at weeks 4, 8, 12, 16 & 24
  - Safety and tolerability

- **Exploratory:**
  - Δ from baseline for Pulmonary function at weeks 4,12 & 24

The BRAVE Study: Current status

- Participating sites in US, Mexico, Spain, Italy, Serbia, Bulgaria and Israel initiated so far

- 25 patients randomized, 4 patients in screening phase and 1 patient finished treatment phase and entered the Open Label Phase

- Amendment 3 to include an extension of the Open Label Extension period to allow for patients to continue receiving IMP if wished for after the double-blind treatment period ended, until either the product is approved and marketed or MNK would cease development of MNK-1411

- Regulatory and EC approvals for additional countries expected between now and fall of 2019

Thank you!

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