



# The Brave Study

Presentation Date: 29 June 2018

# Agenda

- **About Mallinckrodt ARD Inc.**
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# Mallinckrodt at Our Core



**OUR MISSION**  
MANAGING COMPLEXITY.  
IMPROVING LIVES.

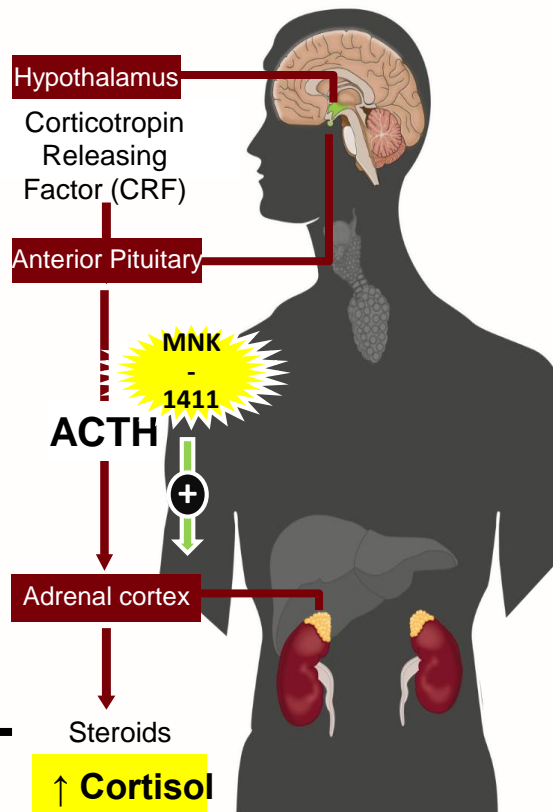
**OUR VALUES**  
QUALITY. INTEGRITY. SERVICE.

**OUR HALLMARKS**  
ACCOUNTABLE. COMPETITIVE.  
COLLABORATIVE.  
HIGH PERFORMING.  
TRUSTWORTHY.

# 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 known 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; this family of receptors are called melanocortin receptors (MCRs)
- ▶ Laboratory studies suggest that MCRs are expressed on certain cells of the immune system, muscle cells, nerve cells, and other cell types



- **Suppression of inflammation**
- **Immune modulation**

References available upon request

# Hypothesis for how MNK1411 may work in Duchenne



- ▶ MNK-1411 has not yet been studied in Duchenne Muscular Dystrophy
- ▶ Muscles from patients with Duchenne show foci of inflammation around injured muscle, and reduction of inflammation is a treatment approach being studied
- ▶ Treatment with exogenous corticosteroids has been shown to slow Duchenne disease progression
- ▶ MNK-1411 has the potential to attenuate 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 MNK1411 reduces inflammation (by MRI and muscle histology) and may reduce abnormal gait

# Scope of the study

## ▶ **Protocol Title:**

- A Multicenter, Randomized, Parallel Group, Double Blind, Multiple Dose, Placebo Controlled Study to Assess the Efficacy and Safety of MNK-1411 in Male Subjects 4 to 8 Years of Age With Duchenne Muscular Dystrophy

## ▶ **Countries:** ~15 across Europe, North America, Latin America and the Middle East

## ▶ **Sites:** ~50

# 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

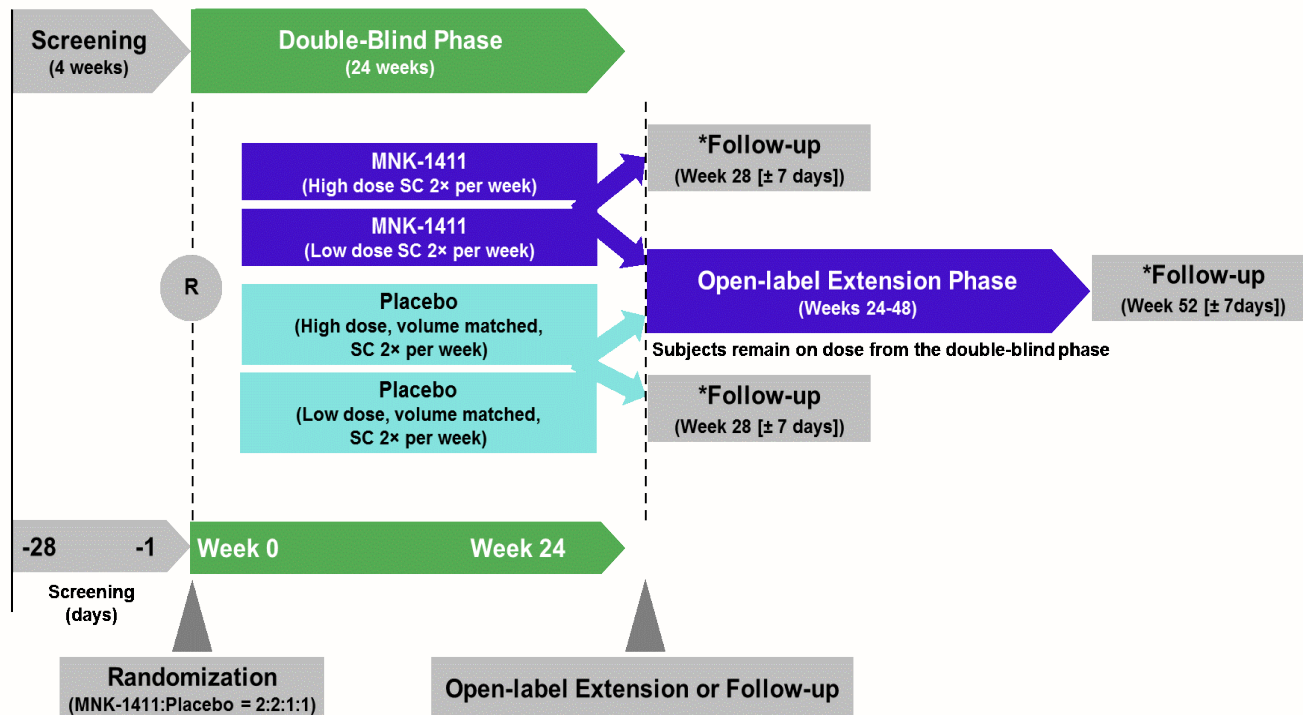


- ▶ Multi-Center, Randomized, Parallel Group, Placebo-Controlled, Double-Blind Study in ~132 Patients with Duchenne Ages 4-8
  
- ▶ 4 dose arms:
  - 2 active doses (“low” and “high”) and 2 volume matched placebo groups
  - Dosing is flat but weight based ( $< 20$  kg or  $\geq 20$  kg)
  - “High” dose was modeled to result in cortisol exposure roughly equivalent to usual dose of pharmacologically administered steroid ( $\sim 0.75$  mg/kg/day prednisone equivalent); “Low” dose is 50% lower
  - Patients to be randomized 2:1 (MNK1411:placebo)
  
- ▶ 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)
  
- ▶ 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



\*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  $\geq 4$  and  $\leq 8$  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 treatment with corticosteroids (if the steroid therapy was taken transiently, the investigator may consult with the sponsor regarding potential eligibility). Inhaled corticosteroids will be permitted if given at a stable dose for the 3 months prior to the first dose of study drug and the subject will remain on that dose throughout the study. The use of topical or intra-articular corticosteroids is permitted during the study.
- ▶ Patients with Type 1 or Type 2 diabetes mellitus.
- ▶ 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:**  $\Delta$  from baseline for 10m walk/run at week 24
  
- ▶ **Secondary:**
  - $\Delta$  from baseline for NorthStar Ambulatory Assessment at weeks 4, 8, 12, 16 & 24
  - $\Delta$  from baseline for Time to climb 4 stairs at weeks 4, 8, 12, 16 & 24
  - $\Delta$  from baseline for Time to stand from supine at weeks 4, 8, 12, 16 & 24
  - $\Delta$  from baseline for 10m walk/run timed at weeks 4, 8, 12, 16
  - $\Delta$  from baseline for Quantitative Muscle testing at weeks 4, 8, 12, 16 & 24
  - Safety and tolerability
  
- ▶ **Exploratory:**
  - $\Delta$  from baseline for Pulmonary function at weeks 4, 12 & 24

## The BRAVE Study: Current status



- ▶ Four sites out of approximately 15 now initiated in US.
- ▶ Ex-US Regulatory and EC approvals expected between June and early 2019.
- ▶ Currently recruiting sites in: US, Canada, Mexico, UK, Spain, Belgium, Italy, Portugal, Rumania, Bulgaria, Serbia, Croatia, Poland, Israel and Turkey.



thank you!