MoveDMD[SM]: A Phase 1/2 Clinical Trial with CAT-1004 in Boys with Duchenne Muscular Dystrophy

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Catabasis Pharmaceuticals

March 23, 2016

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A return to health

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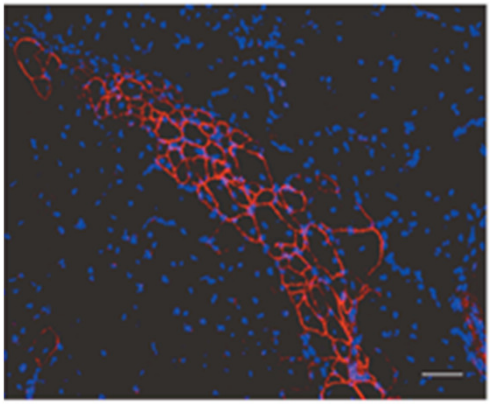
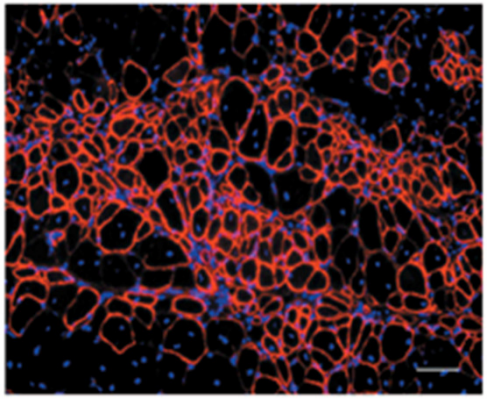
Inhibition of NF-κB Produces Disease-Modifying Effects in Duchenne Muscular Dystrophy

Intact NF-κB levels



with wild type MDSC implanted

Reduced NF-κB levels



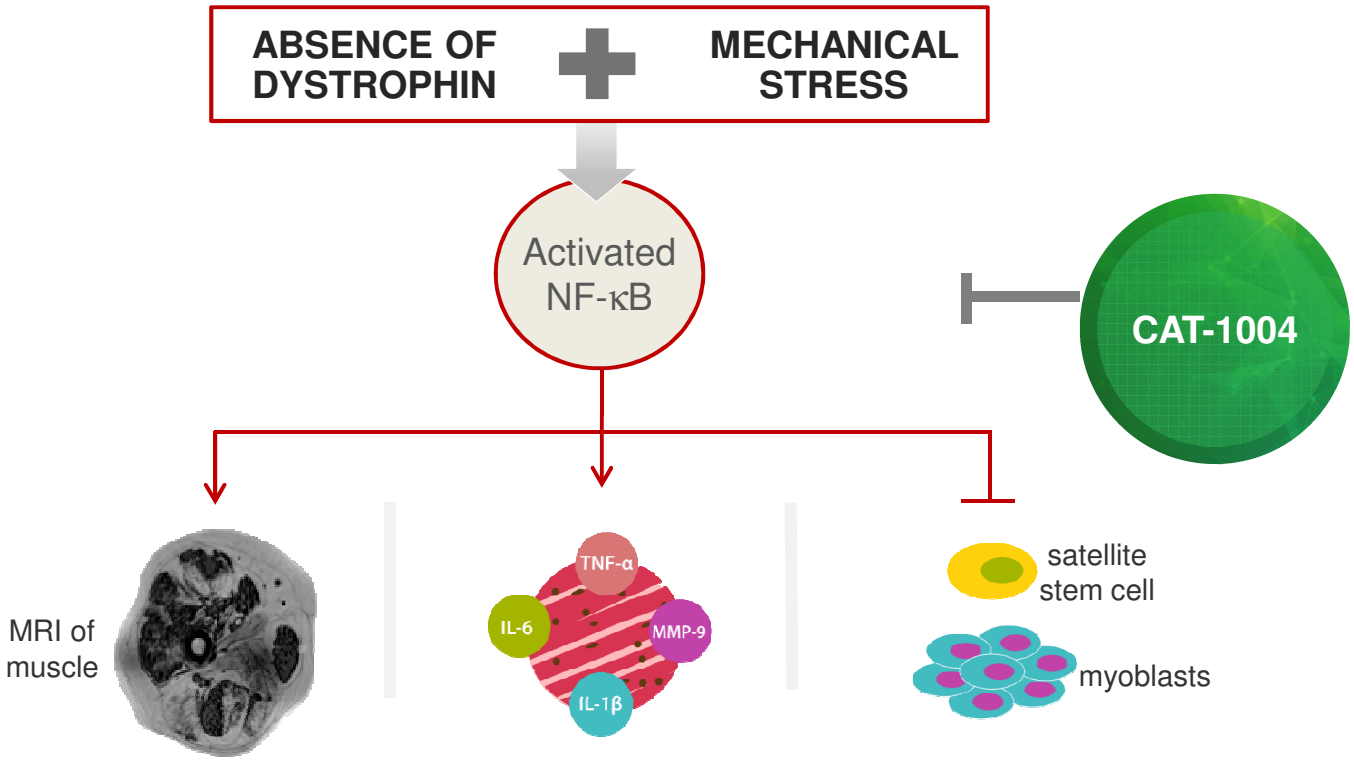
with *p65*$^{+/-}$ MDSC implanted

8-week-old *mdx*/SCID mice
Engraftment was determined by immunostaining for dystrophin (red)

Lu et al., 2012, Mol. Therapy

- NF-κB is chronically activated in Duchenne due to lack of dystrophin and elevated NF-κB is seen before the onset of fibrosis
- ~50% reduction in NF-κB observed to have disease-modifying effects
  - Reduced muscle degeneration
  - Enhanced muscle regeneration
  - Improvement in muscle mass and function
- Inhibition of NF-κB seen to have a positive effect on dystrophin-production in models with baseline dystrophin production
- CAT-1004 is being developed to target NF-κB in Duchenne muscular dystrophy

CAT-1004 Inhibits NF-κB and Shows Disease-Modifying Effects in DMD Models



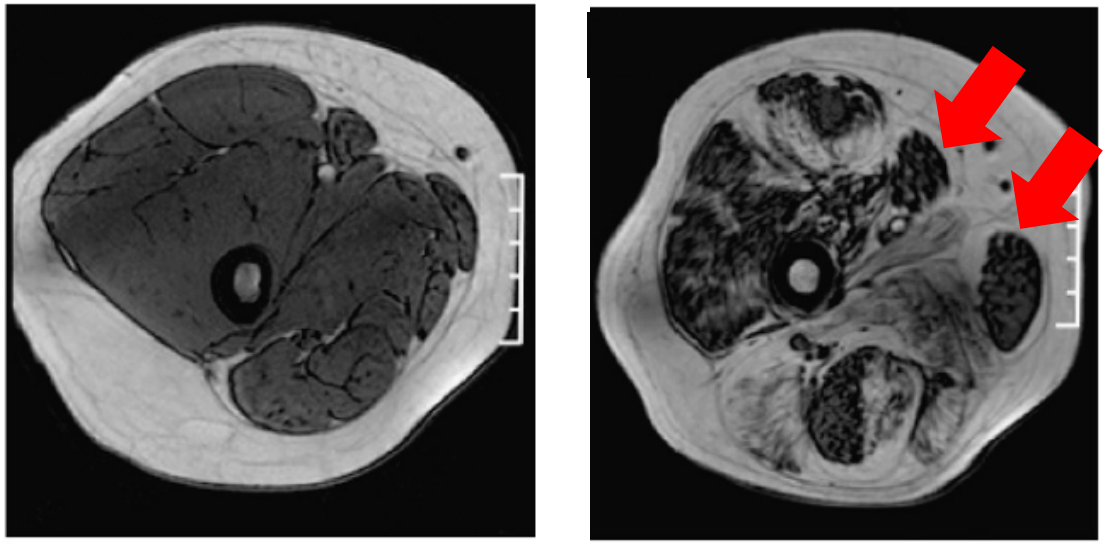
CAT-1004 pre-clinical studies *(Sweeney et al.)*	Reduced muscle degeneration	Reduced inflammation and fibrosis	Enhanced muscle regeneration
	✓	✓	✓

Activated NF-κB – Not Just Absence of Dystrophin – Plays a Central Role in DMD Pathophysiology

Cross section of thigh

Unaffected

DMD



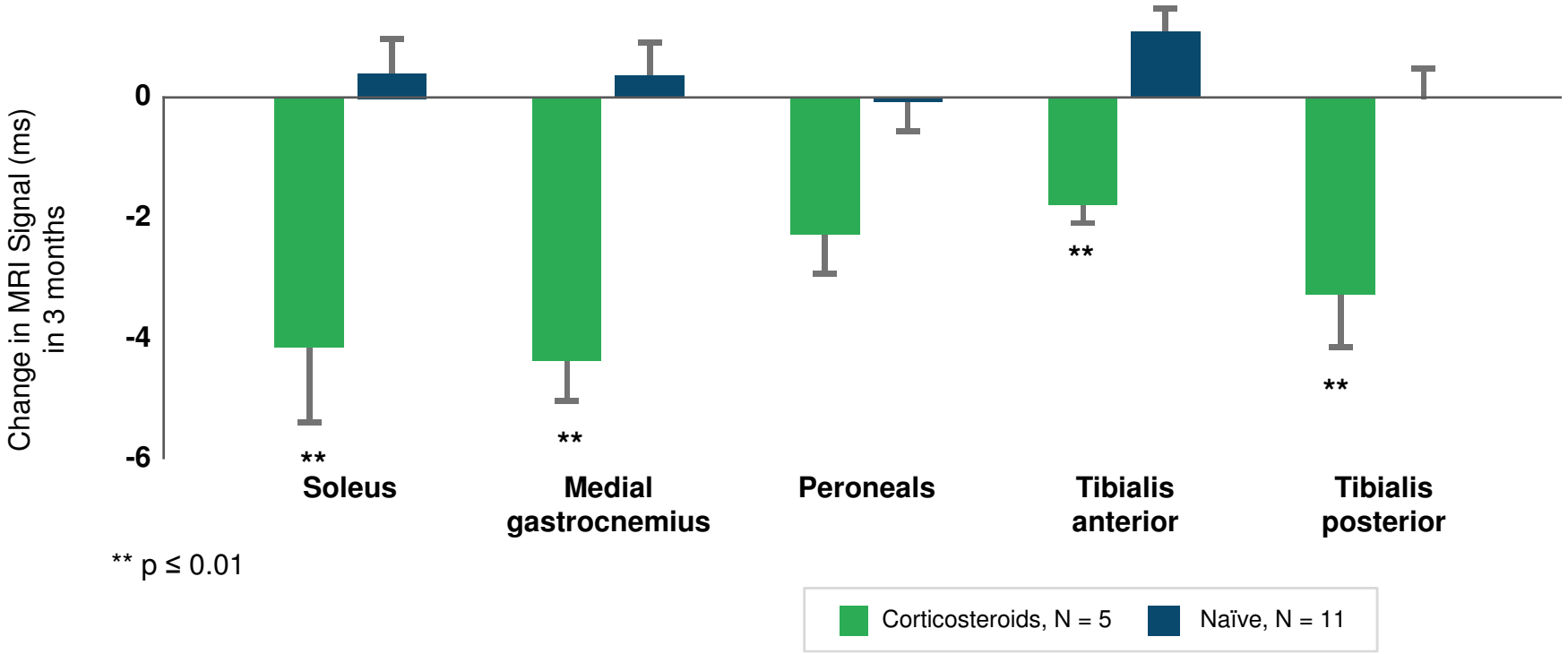
Ages 12 - 14

- Mechanical stress activates NF-κB in muscles
- Muscles with less mechanical stress (red arrow) are relatively protected – even in the absence of dystrophin

Akima et al. 2012, Neuromuscul Disord

MRI Able to Identify Early Changes in Muscle Pathology in Small Patient Numbers in an Objective and Quantitative Manner

Comparison of MRI in Lower Leg Muscles in Corticosteroid-Naïve vs. Corticosteroid-Treated Boys with DMD Ages 5 – 7 Years Old



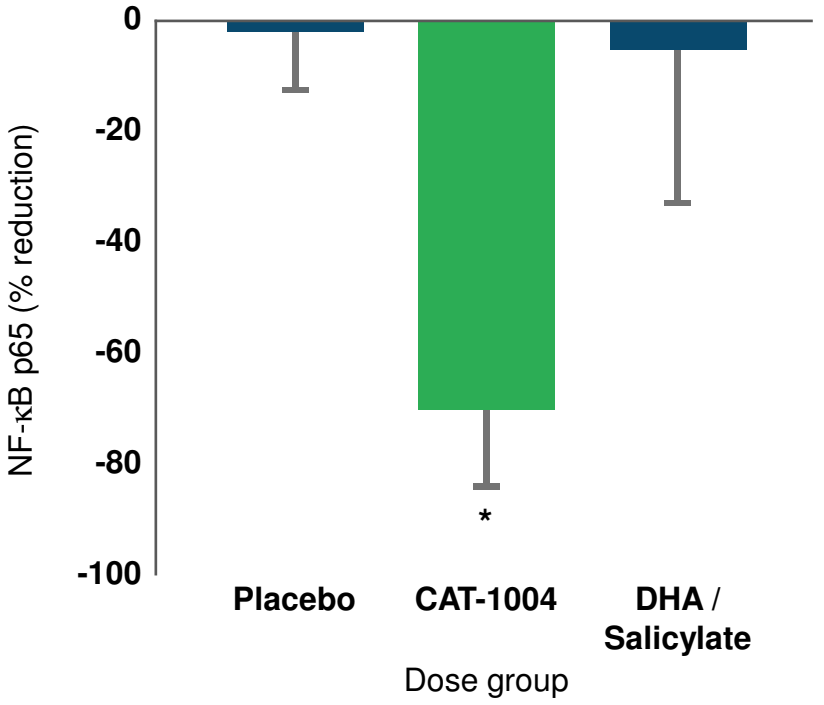
- Data from ImagingDMD
  - MRI signal correlates with functional measures
  - MRI signal increases continuously with age

Arpan et al Neurology 2014 83:1-7

Phase 1 Trials in Adults: Safety, Tolerability and Significant Inhibition of Activated NF-κB

- **Design:**
  - Three completed Phase 1 trials
    - Single and multiple ascending dose trials
    - Biomarker trial
  - 79 adult subjects treated with CAT-1004
- **Results:**
  - No safety signals and good tolerability
  - Significantly reduced expression of NF-κB-target gene set after 14 days of dosing
  - Significant reductions in NF-κB biomarker activity compared to placebo or the co-administration of the bioactives, salicylate and the omega-3 fatty acid, DHA
  - The effect seen with CAT-1004 is not seen when salicylate and the omega-3 DHA are taken at the same time

Phase 1 Clinical Data
Inhibition of Activated NF-κB



3-way crossover design, 9 subjects
* p<0.005

MoveDMD[SM] Trial: Initial Assessment of Safety and Pharmacokinetics in DMD

- Key objectives:
  - Assess safety in 3 cohorts of boys age 4 -7 with Duchenne
    - Cohort 1 – 17 mg/kg per day
    - Cohort 2 – 33 mg/kg per day
    - Cohort 3 – 67 mg/kg per day
  - Assess pharmacokinetics in pediatric patients under various dietary conditions
    - On Day 1 and Day 7 single doses administered with high or low-fat diet in random sequence
  - Compare pharmacokinetics in pediatric and adult population
  - Assess whether pediatric exposures are similar to those at which NF-κB inhibition was observed in adults

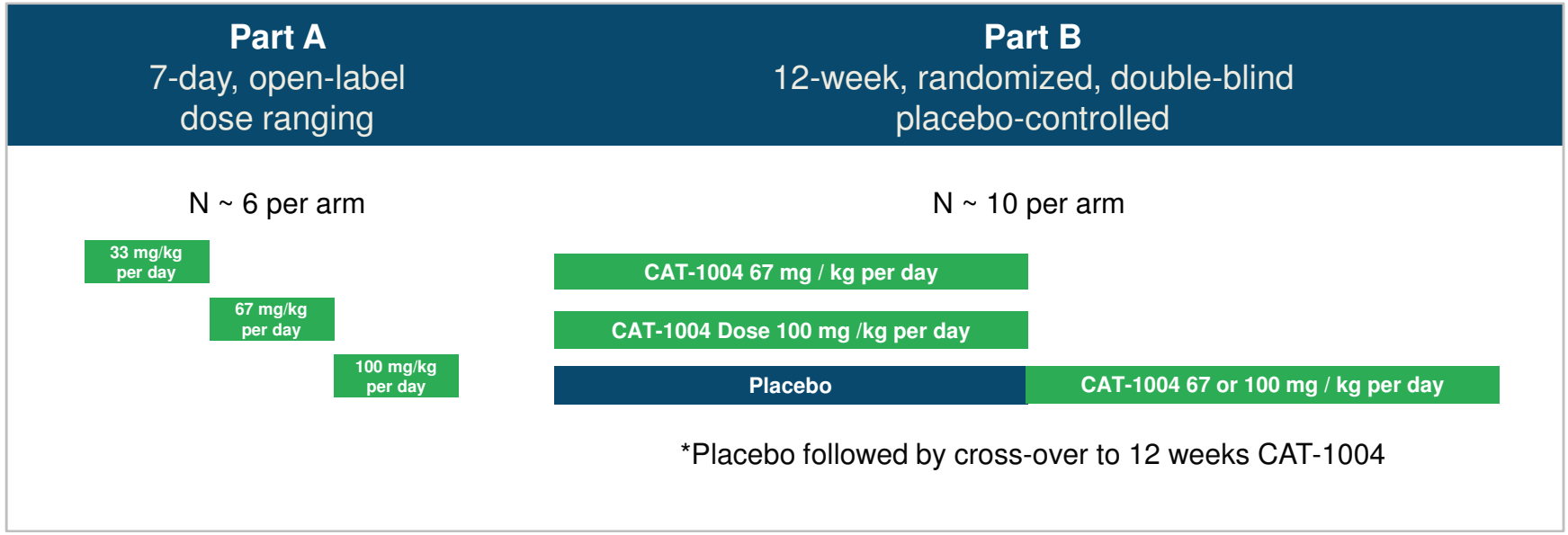
MoveDMD Trial Objectives and Design

Part A (1 week of treatment):

- Assess the safety and PK of CAT-1004 in ~18 boys with Duchenne aged 4-7
- Identify doses of CAT-1004 that have plasma exposures known to have effects on NF-κB

Part B (12 weeks of treatment):

- Assess the safety of CAT-1004 in ~30 boys with Duchenne over 12 weeks
- Measure the efficacy of CAT-1004 versus placebo on MRI, timed functional tests (10 meter walk/run, 4 step climb, time to stand), North Star, PODCI, muscle strength



MoveDMD Study Population

Initial approach is to assess safety, pharmacokinetics and MRI as a biomarker of inflammation in young boys not on steroids

Inclusion Criteria

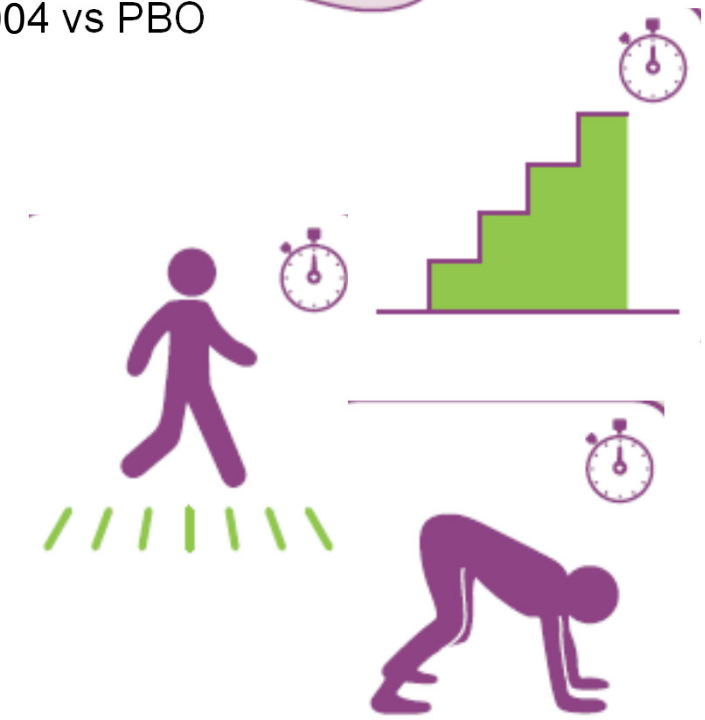
- Diagnosis of DMD based on a clinical phenotype with increased serum CK and the presence of a mutation in the dystrophin gene known to be associated with a DMD phenotype
- Ambulatory
- Age ≥4 years and <8 years
- Adequate immunization for varicella and influenza

Exclusion Criteria

- Use of corticosteroids within prior 6 months to treatment initiation or planning to initiate steroid therapy within the next 6 months
- Abnormal GGT, creatinine, hemoglobin <10.5 g/dL
- Ongoing immunosuppressive therapy

Move DMD Endpoints: Assessments of Disease

- MRI assessments (primary endpoint):
  - T2 as measure of muscle damage
    - Prior to initiation of Part A
    - Baseline and endpoint of Part B: 12-week CAT-1004 vs PBO
- Functional assessments
  - Timed functional tests:
    - 10 meter walk / run, 4-step climb, time to stand
  - North Star Ambulatory Assessment
  - PODCI
  - Limited muscle strength testing



  - Timing
    - Prior to initiation of Part A / Part B dosing
    - At baseline, monthly and endpoint of 12-week CAT-1004 vs PBO

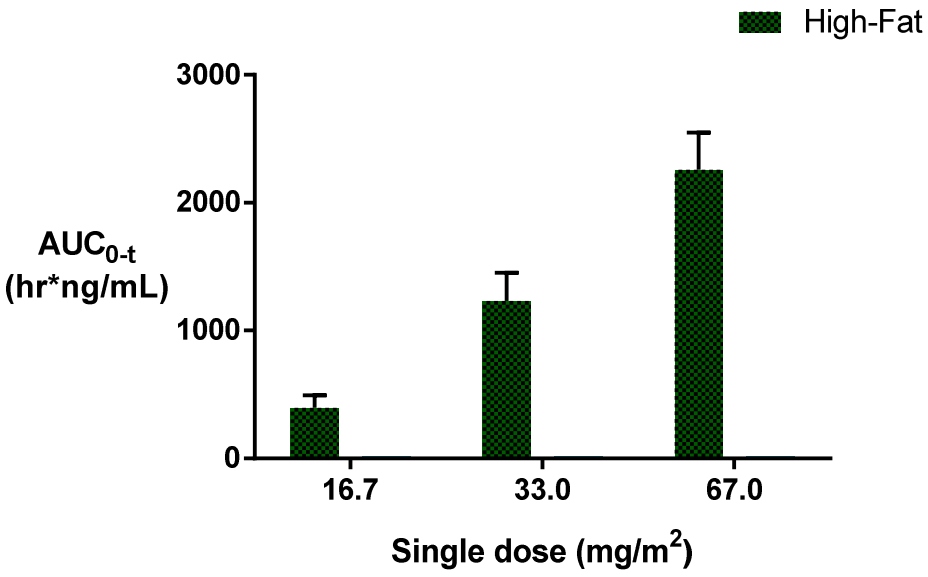
MoveDMD:
Safety and Tolerability

- Generally well tolerated
  - No serious adverse events, no discontinuations
  - All patients able to take CAT-1004 capsules
  - Adverse events (AE) predominantly mild, most common AE was diarrhea
- Assessments:
  - Laboratory: no trends or safety issues in liver, renal, hematology
  - Physical exam, EKG, vitals: no safety issues
- Adverse events (7 days):

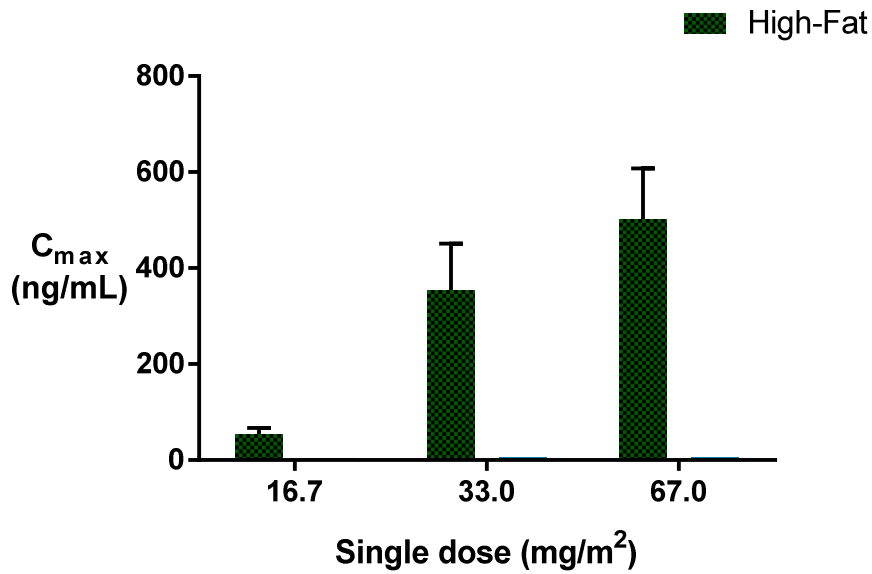
	33 mg/kg n=5	67 mg/kg n=6	100 mg/kg n=6	Total n=17
Diarrhea	0	0	4	4
Feces soft	1	1	1	3
Abdominal pain upper	1	0	1	2

Pharmacokinetics: Dose-Dependent Increases in Exposure, with Modest Effect of Meal Composition

Dose dependent AUC



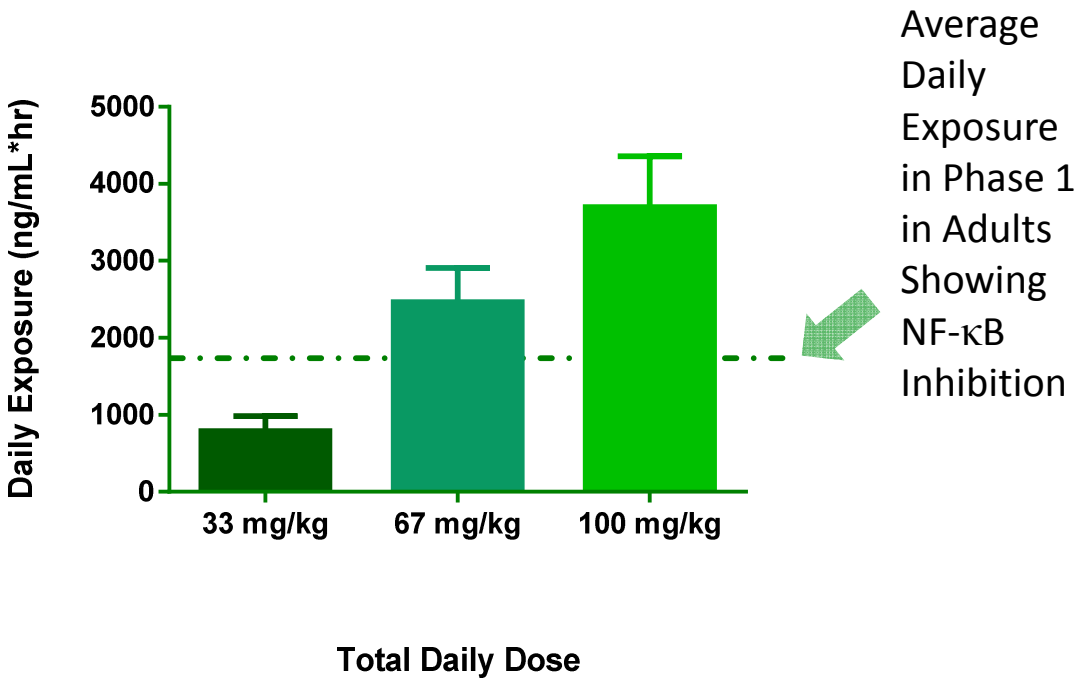
Dose dependent C_{max}



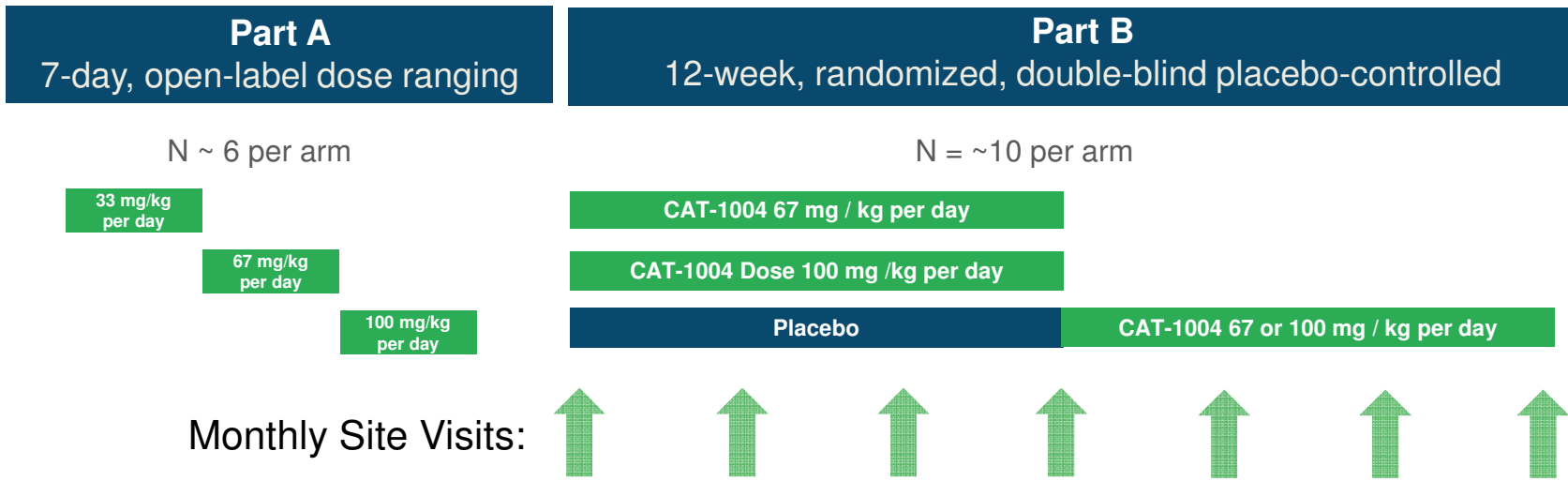
- With single doses of 33 mg/kg there were minimal differences in AUC or C_{max} when CAT-1004 was administered either with a high-fat or a low-fat meal
- A total daily dose of 67 or 100 mg/kg can be administered with food as 33 mg/kg either 2 or 3 times daily

Comparison of Exposures in Pediatrics and Adults

- In Phase 1 in adults, changes in expression of NF-κB driven genes were observed at a dose of approximately 33 mg/kg BID
- In the MoveDMD study, when doses of 33 mg/kg were given BID or TID (total daily doses of 67 or 100 mg/kg), systemic exposures were reached at which NF-κB inhibition were observed in adults



Design of MoveDMD Part B



Inclusion/Exclusion: Similar to Part A

Safety: Monitored by investigators, Sponsor and Data Safety and Monitoring Committee

Sites: University of Florida; Shriners, Portland OR; CHOP, Philadelphia PA; Nemours Children's Hospital, Orlando FL; UCLA, CA

Key Endpoints: Changes in Magnetic Resonance Imaging (MRI) of muscles at 12 weeks

- Changes in appropriate Timed Function Tests (10 meter walk/run, 4 step climb, time to stand), North Star, PODCI, muscle strength at 12 weeks
- Assess safety, tolerability and pharmacokinetics

Move DMD

CAT-1004: Potential Disease-Modifying Oral Therapy for Duchenne Muscular Dystrophy

CAT-1004

- No safety signals and generally well tolerated at all 3 doses tested
- Plasma exposure levels consistent with those previously observed in adults at which inhibition of NF-κB was observed, and which are higher than exposure levels in animal models at which disease modifying effects were seen.
- These results support initiation of Part B of the trial, which is planned to be a 12-week, double-blind, placebo-controlled efficacy of 67 mg / kg and 100 mg / kg CAT-1004 trial in approximately 30 boys aged 4 – 7 with confirmed DMD (those who participated in Part A plus additional patients).
- Based on inhibition of activated NF-κB, CAT-1004 may reduce inflammation and muscle degeneration with potentially positive longer-term effects on muscle regeneration and function in DMD patients regardless of mutation type.

Thank You!

- Patients and families
- Patient groups
- ImagingDMD Investigators and Staff
- For questions: joanne.donovan@catabasis.com
- Thanks to our partners for grant support for patient travel:

Part A

Parent Project Muscular Dystrophy

LEADING THE FIGHT TO END DUCHENNE

Part B

MDA®

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