ASPIRO Study
Interim data as of December 21, 2017

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AT132 OVERVIEW

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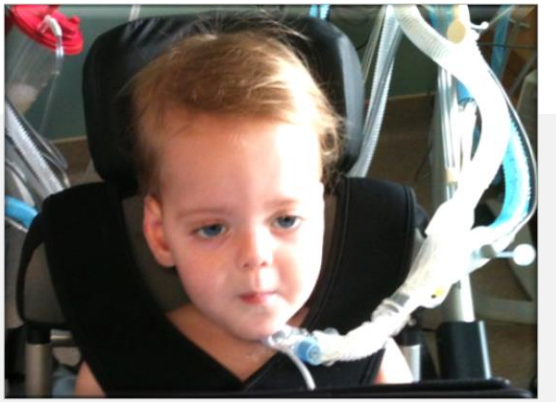
XLMTM Overview

A fatal disease with no treatment options



Serious, life-threatening rare disease	➤ Significant impairment of respiratory and neuromuscular function ➤ Estimated 50% mortality by 18 months ➤ Incidence: 1 in 50K newborn males
Monogenic, well-understood biology	➤ MTM1 gene encodes myotubularin, an enzyme required for normal development and function of skeletal muscle
Target for AAV gene therapy	➤ AAV8 effectively penetrates skeletal muscle ➤ Muscle tissue is otherwise reasonably healthy and exhibits no dystrophic or inflammatory change
Clear clinical measures	➤ Multiple endpoints to evaluate neuromuscular and respiratory function ➤ Developmental milestones ➤ Muscle biopsy

Source: *Hnia, Beggs, et al. J Clin Invest. 2011, Joshua Frase Foundation. McEntagart, 2002*

AT132 Clinical Development Program

RECENSUS

Retrospective Medical Chart Review of Patients with XLMTM
N=140

- Characterize aspects of the disease and medical management of XLMTM
- Identify potential outcome measures for ASPIRO
- Initial presentation Q1:17; First publication Q4:17

INCEPTUS

Prospective Natural History Run-in Study in XLMTM Patients
N≈16

- Longitudinal baseline and within-patient control for ASPIRO
- Facilitates enrollment in and operational aspects of ASPIRO
- Prelim. data shared Q4:17

ASPIRO

A Phase 1/2 Clinical Study in XLMTM Patients
N=12

- Assessment of safety and tolerability and preliminary efficacy
- Focus on neuromuscular & respiratory measurements
- First patient dosed Q3:17; Positive interim data reported for Cohort 1 in Q1:18

- Orphan Drug Designation received from FDA and EMA
- Rare Pediatric Disease and Fast Track designations granted by FDA

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ASPIRO: TO ASPIRE…

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ASPIRO Phase 1/2 Clinical Study

Open-label, ascending-dose, safety and preliminary efficacy study

Inclusion Criteria

- Subject is male
- <5 yrs old, or enrolled in INCEPTUS
- Genetically confirmed XLMTM
- Requires ventilator support

Key Efficacy Assessments

Neuromuscular

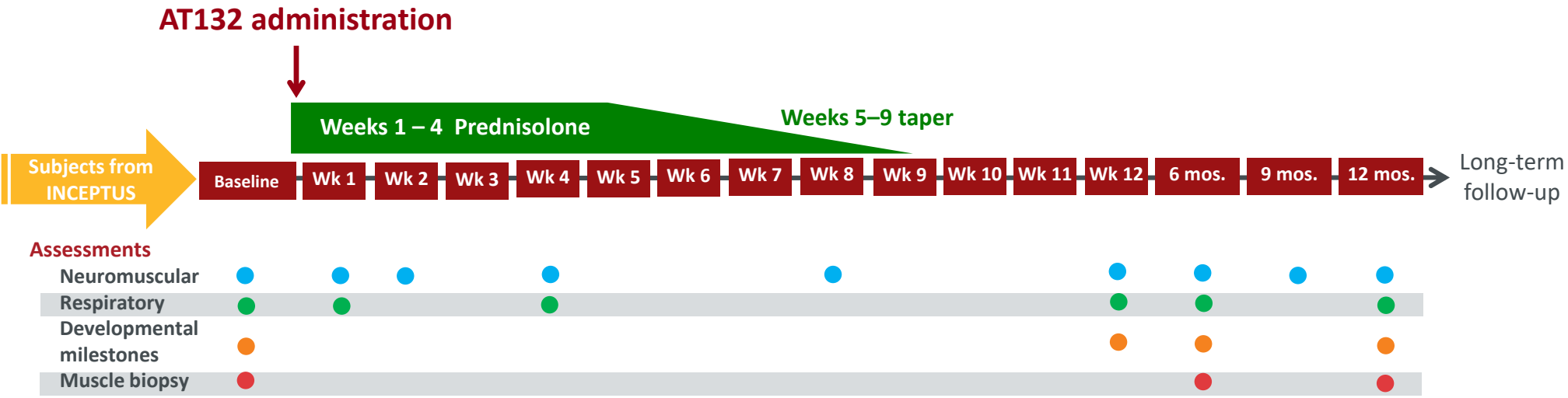
- CHOP INTEND
- MFM-20
- Bayley III
- Muscle biopsy
- Developmental milestones

Respiratory

- Max Inspiratory Pressure (MIP)
- Ventilator use
- Respiratory sprinting

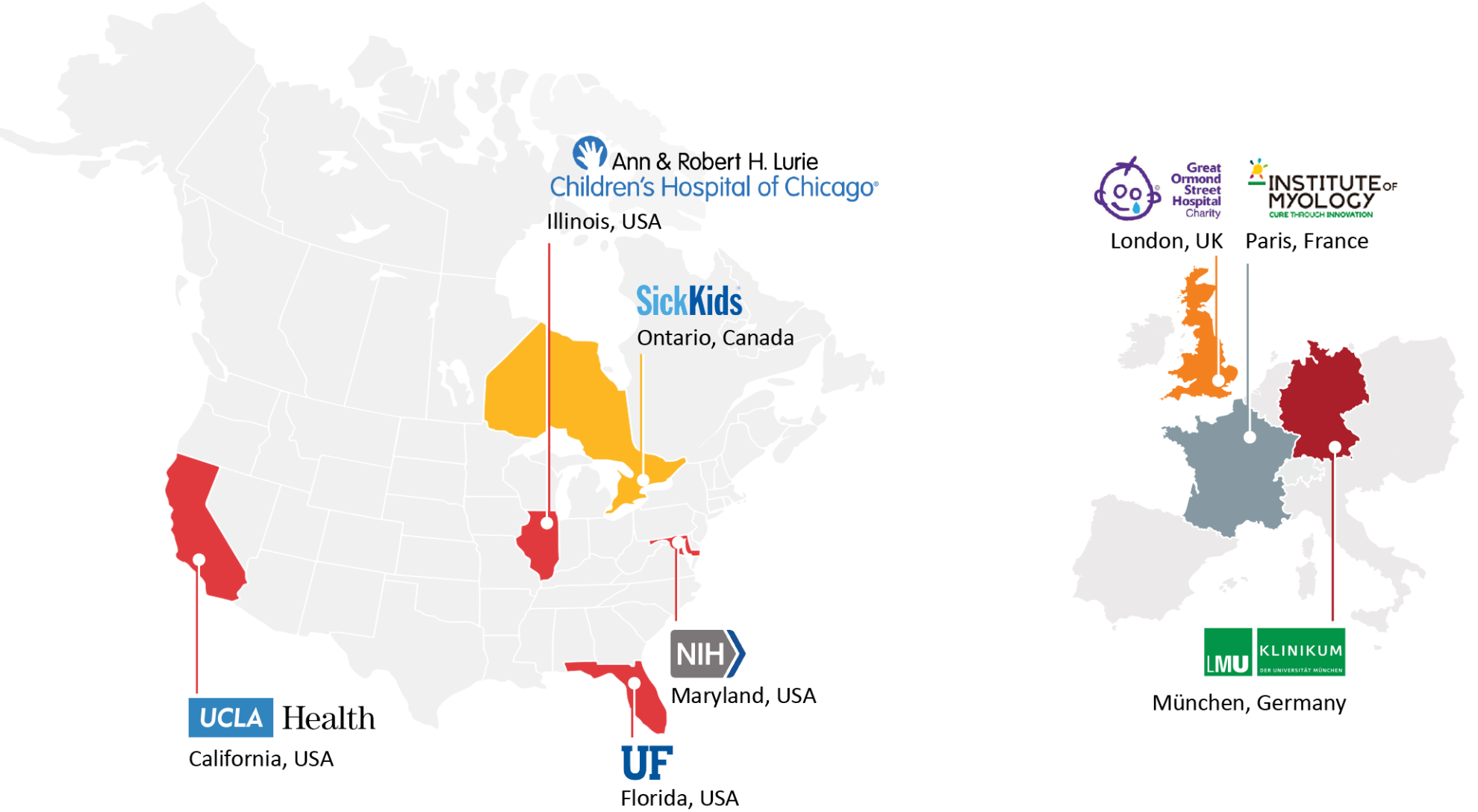
Design

- N=12, roll-over from INCEPTUS
- 3 ascending-dose cohorts (3 active plus a delayed-treatment concurrent control)
- Doses: $1x10^{14}$, $3x10^{14}$, $5x10^{14}$ vg/kg



ASPIRO Clinical Study Sites

Same study sites as INCEPTUS natural history run-in study



ASPIRO Cohort 1

All four Cohort 1 patients rolled over from INCEPTUS to ASPIRO

	Subject Number	Age at ASPIRO Baseline (yrs)	Age at baseline and follow up duration				
			0 -12 months	1 year	2 years	3 years	4 years
Cohort 1 1×10^{14} vg/kg	Pt 1	0.8					
	Pt 2	4.1					
	Pt 3	2.6					
	Pt 4 (Ctl)	4.0					

INCEPTUS Natural History Run-in Study
ASPIRO Follow-up

- Ventilator status at baseline:
  - Patient 1: 12 hours of BiPAP per day
  - Patient 2: 17 hours of invasive ventilation per day
  - Patient 3: 24 hours of invasive ventilation per day
  - Patient 4: 12 hours of BiPAP per day

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SAFETY AND TOLERABILITY

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AT132 Safety and Tolerability Profile at 1 x 10^{14} vg/kg

- No tolerability issues during study drug administration
- Two serious adverse events (SAEs), both in Patient 3
  - Hospitalization for pneumonia (week 2), not treatment-related
  - Hospitalization for GI infection and elevated troponin levels (week 7), is responding to IV steroids and supportive care; probably treatment-related
- Two possibly/probably treatment-related adverse events (AEs)
  - Patient 1
    - Mild, clinically asymptomatic exacerbation of preexisting hyperbilirubinemia, resolved; possibly treatment-related
  - Patient 2
    - Clinically asymptomatic liver enzyme elevation, controlled by extended steroid coverage; probably treatment-related
- Two additional non-treatment related AEs

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NEUROMUSCULAR FUNCTION

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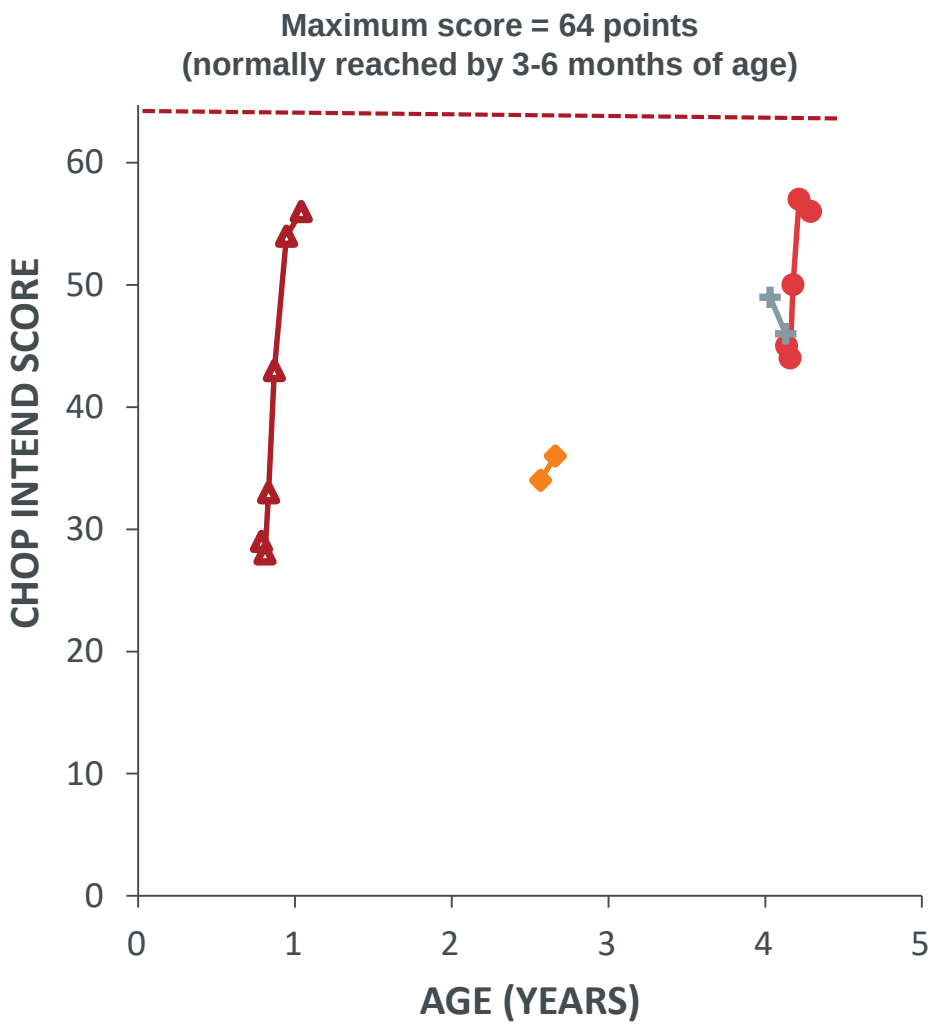
Significant Improvements in Neuromuscular Function as Assessed by the CHOP-INTEND Scale



CHOP-INTEND score				
Pt #	Median score in INCEPTUS	Baseline Score in ASPIRO	Most recent score (Wk)	Change from baseline (%)
1	29	29	56 (Wk 12)	27 (93%)
2	45	45	56 (Wk 8)	11 (24%)
3	28	34	36 (Wk 4)	2 (6%)
4 (Control)	49	49	46 (Wk 4)	-3 (-6%)

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Multiple Motor Milestones Achieved at 12 Weeks in First Treated Patient

First-year developmental milestones in healthy children	Patient 1	
	Baseline	Week 12
Rolling over	–	+
Head Control	–	+
Sitting unassisted >5 sec	–	+

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RESPIRATORY FUNCTION

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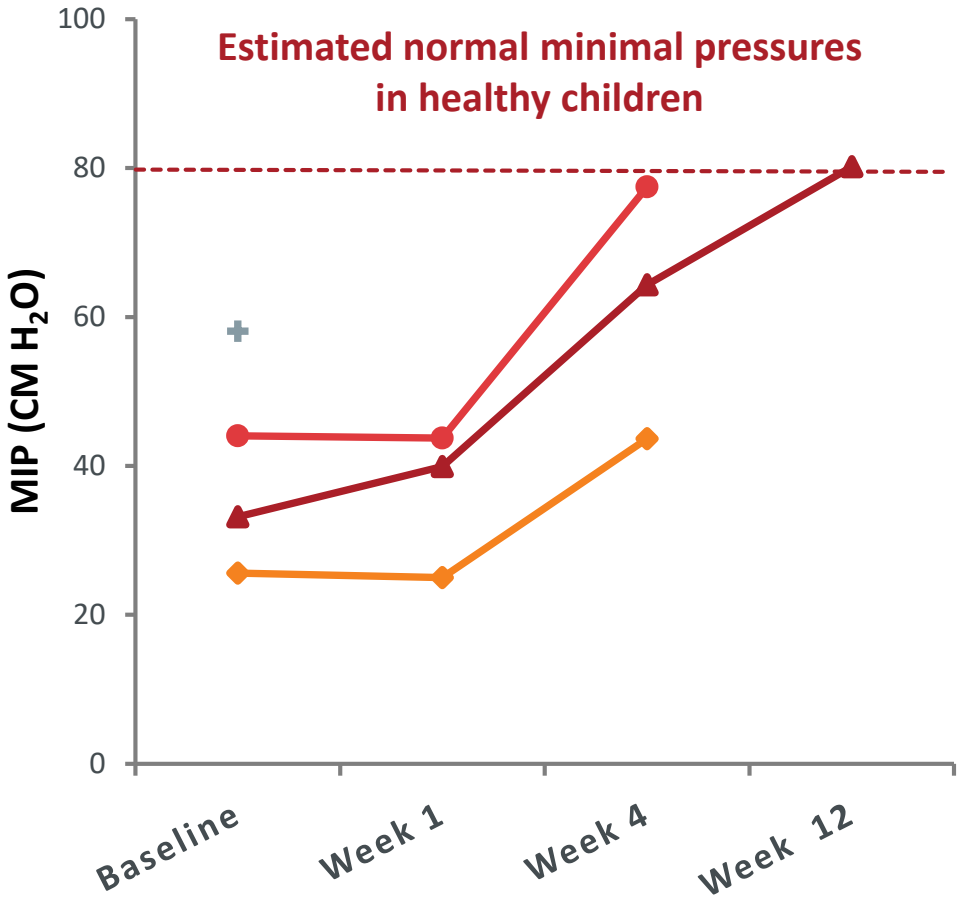
Significant Improvements in Respiratory Function as Assessed by Maximal Inspiratory Pressure (MIP)



Maximum Inspiratory Pressure (cmH_2O)				
Pt #	Median Pressure in INCEPTUS	Baseline Pressure in ASPIRO	Most recent Pressure (Wk)	Change from baseline (%)
1	29	33	80 (Wk 12)	47 (142%)
2	34	44	77 (Wk 4)	33 (76%)
3	24	26	44 (Wk 4)	18 (70%)
4 (Control)	65	58	--	--

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QUALITATIVE ASSESSMENTS

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Progressive Qualitative Improvements Observed in Disease Severity in All Treated Patients

- Increased trunk and limb strength and activity
  - Early indicator of gross muscle function improvement
  - Velocity and accuracy of movement has also improved
- Reductions in ventilator settings (pressure, rate and volume of mechanical ventilation) Patients 1 and 2
  - First step toward weaning off mechanical ventilation
- Improvements in airway clearance control (swallowing, coughing)
  - Critical for reducing aspiration risk
- Increased vocalization – improved ability to communicate with caregivers
- Initial exposure to oral feeding (Patient 1)

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PATIENT 1
CHOP INTEND VIDEO ASSESSMENTS
BASELINE VS WEEK 12

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ASPIRO Key Findings and Program Next Steps

- Six adverse events to date (3 treatment-related); all resolved or responding to treatment
- Significant improvements in neuromuscular function as assessed by the CHOP-INTEND scale
- Multiple developmental milestones achieved at 12 weeks in Patient 1
- Significant improvements in respiratory function as assessed by Maximal Inspiratory Pressure (MIP)
- Progressive qualitative improvements observed in disease severity in all treated patients
- Interim efficacy and safety data review underway with independent Data Monitoring Committee prior to initiating enrollment of next cohort
- Next study update is scheduled for Q2:18

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