

A close-up photograph of a young child with dark hair and a tracheostomy tube, looking towards a woman whose face is partially visible in profile on the right. The child is wearing a blue garment. The woman has dark hair and is looking at the child. The background is blurred.

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ASPIRO Update

August 2018

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THERAPEUTICS

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Safe Harbor

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A close-up photograph of a young child with dark hair and a tracheostomy tube in their neck. The child is looking towards the right. In the background, a woman's face is partially visible, looking towards the child. The image has a soft, warm tone. In the bottom left corner, there are overlapping geometric shapes in shades of blue, purple, and red.

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Robust Internal Large-scale cGMP Manufacturing

High quality clinical material produced in-house since inception of clinical programs

Large-scale cGMP capacity

- 2x500L bioreactor scale
- Internal process & analytical development, fill/finish, and QC testing
- Additional capacity (~5,000L) possible in existing lease footprint

Robust process

- Mammalian serum-free suspension culture process
- Demonstrated scalability, reproducibility, applicability across constructs/products
- Excellent yields and impurity profiles

Commercial readiness

- Facility designed and commissioned to support global licensure
- Same process, facility, and scale utilized from inception of clinical studies
- BLA readiness and validation efforts underway, consistent with recent FDA gene therapy guidance



Today's Discussion

Continued progress in ASPIRO

- Clinical data update
- Muscle biopsy results
- Program next steps



Clinical Data Update

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ASPIRO Phase 1/2 Clinical Study

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

Key Efficacy Assessments		
Neuromuscular	Respiratory	Muscle Biopsy
➤ CHOP INTEND	➤ MIP	➤ Vector copy number
➤ MFM-20	➤ Ventilator use	➤ Protein expression
➤ Developmental milestones		➤ Histology

Enrollment Status		
Pt #	Baseline Age (yrs)	Data (wks)
1	0.8	24
2	4.1	24
3	2.6	24
4*	4.0	24
5	1.0	4
6	0.8	4
7	0.8	-

* Untreated control

AT132 Administration



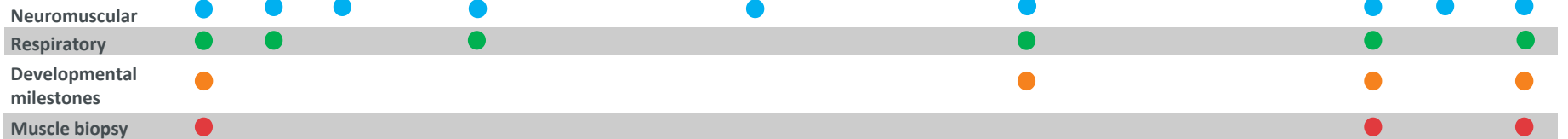
Weeks 1 – 8 Prednisolone 1mg/kg/day

Weeks 9–16 taper

INCEPTUS
Subjects



Assessments



CHOP-INTEND = Children's Hospital of Philadelphia Infant Test of Neuromuscular Disorders;
MFM-20 = Motor Function Measure 20; MIP = Maximum Inspiratory Pressure

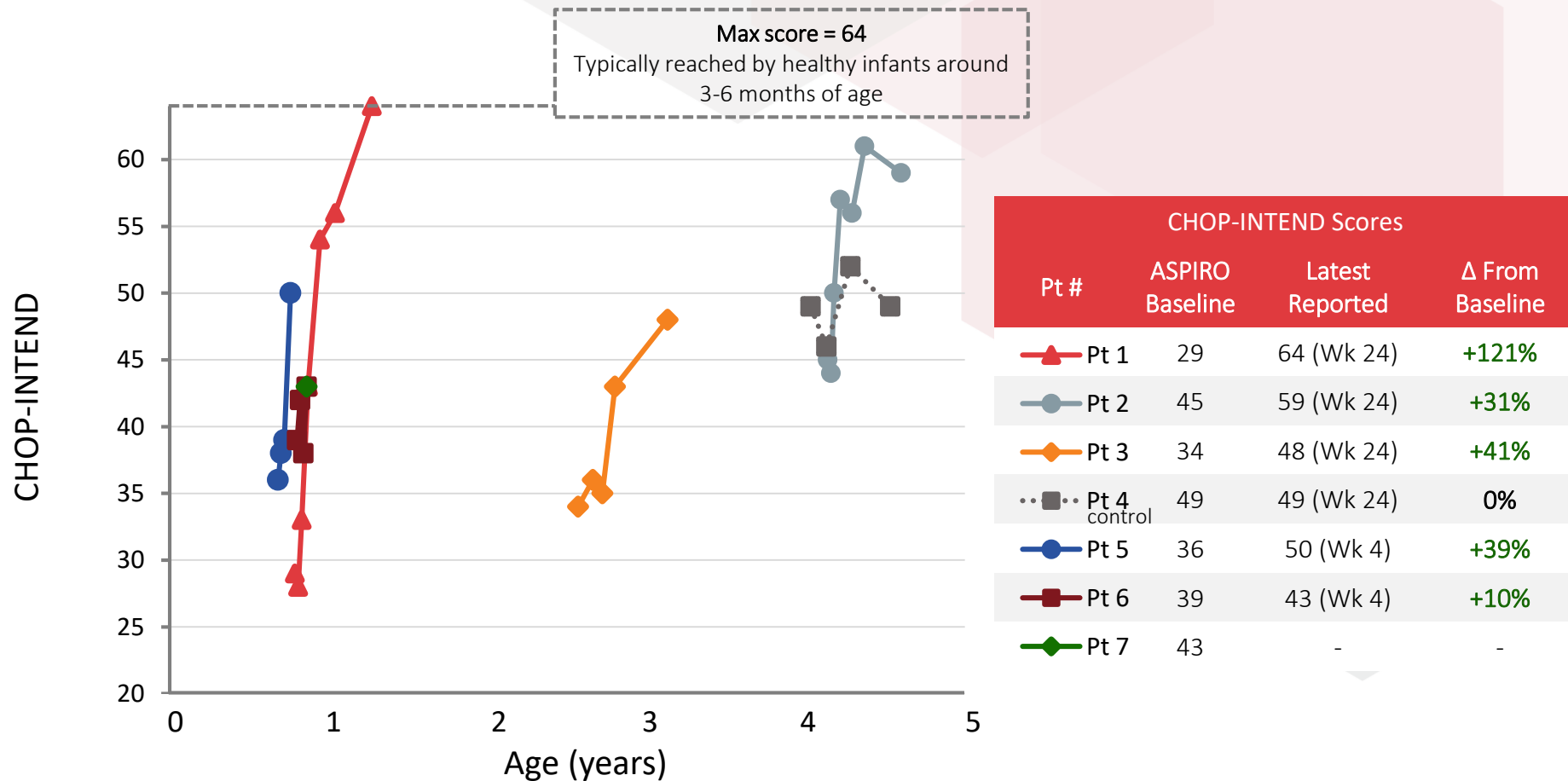
Updated ASPIRO Data Set

New information since ASGCT presentation (May 16, 2018)

- Efficacy out to week 24 in Patient 3
- Muscle biopsy:
 - Baseline and Week 24 biopsies for Patients 1, 2, and 3
- Safety findings:
 - No new treatment-related serious adverse events

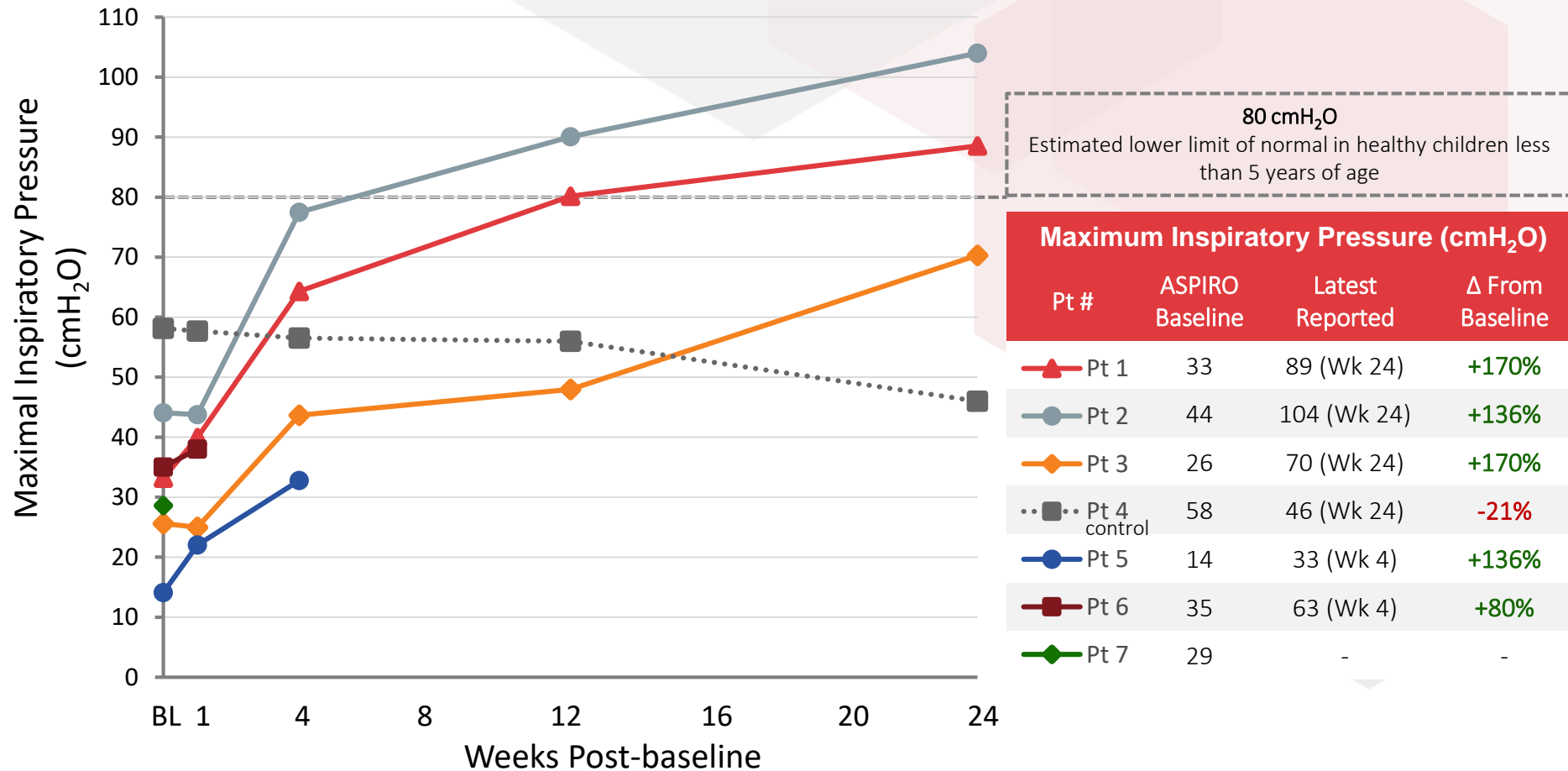
Significant Improvements in Neuromuscular Function

All treated patients show clinically meaningful increases in CHOP-INTEND scores



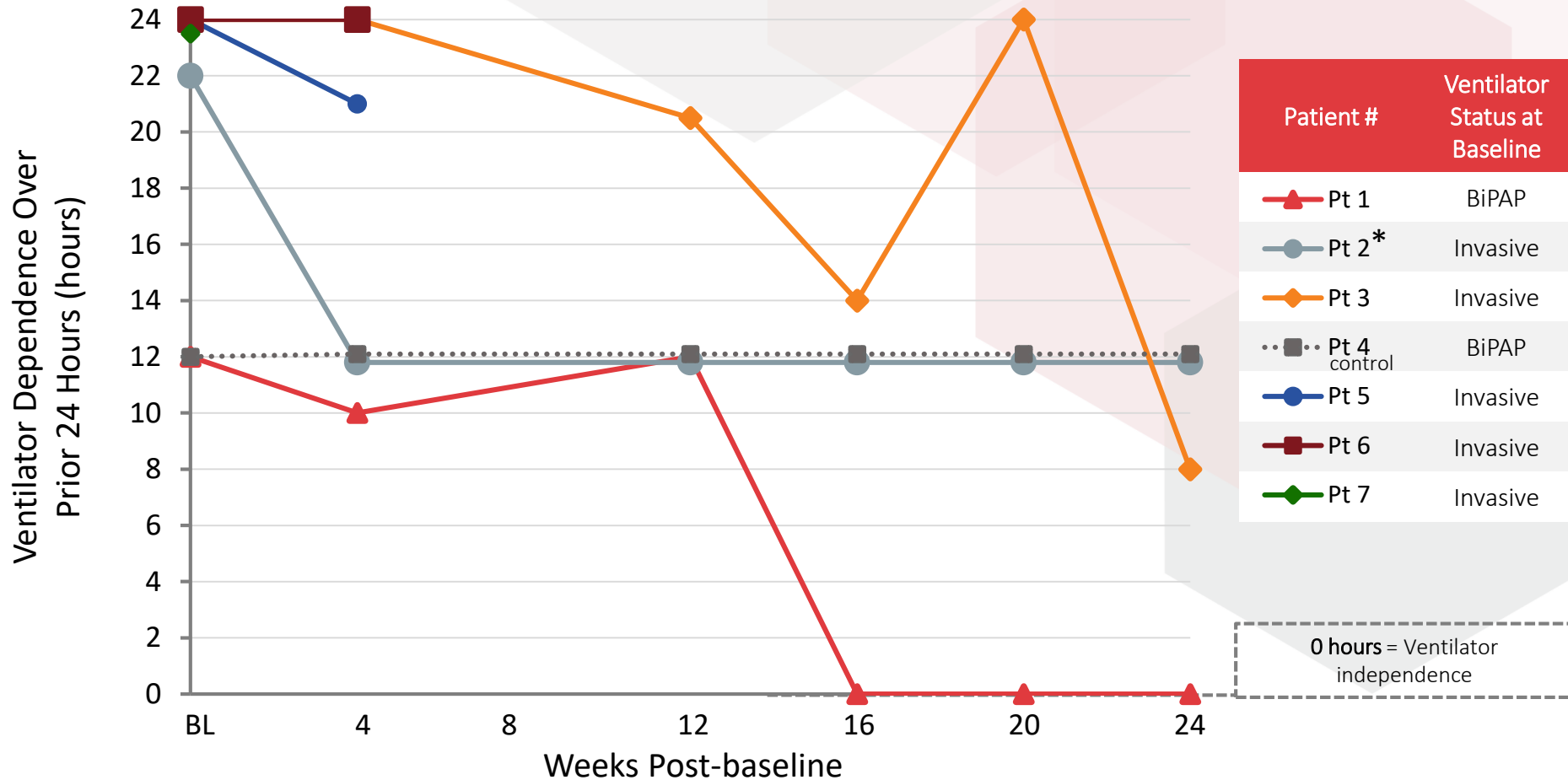
Significant Improvements in Respiratory Function

All treated patients show clinically meaningful increases in MIP



By Week 24, Significant Reductions in Ventilator Use in 3/3 Patients

Ventilator independence achieved by Patient 1 at Week 16



* Subsequent to the Week 24 assessment, Patient 2 successfully achieved ventilator independence.



Muscle Biopsy Results

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AT132 Preclinical Data Summary

Completed Studies

Murine model

- Dose ranging and biodistribution
- Doses: 2.5×10^{13} to 2.0×10^{14} vg/kg

Canine model

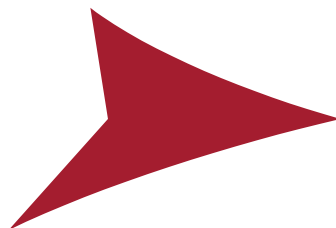
- Dose ranging and biodistribution
- Doses: 3×10^{13} to 5×10^{14} vg/kg

Non-human primates

- Toxicology and biodistribution
- Dose: 8×10^{14} vg/kg

Key Conclusions

- Dose dependent improvements in protein expression, function, and survival
- Full histopathological correction at high doses
- Durable efficacy >5 years in canine model
- No safety findings up to 8×10^{14} vg/kg in NHP tox



ASPIRO Muscle Biopsy – Vector Copy Number

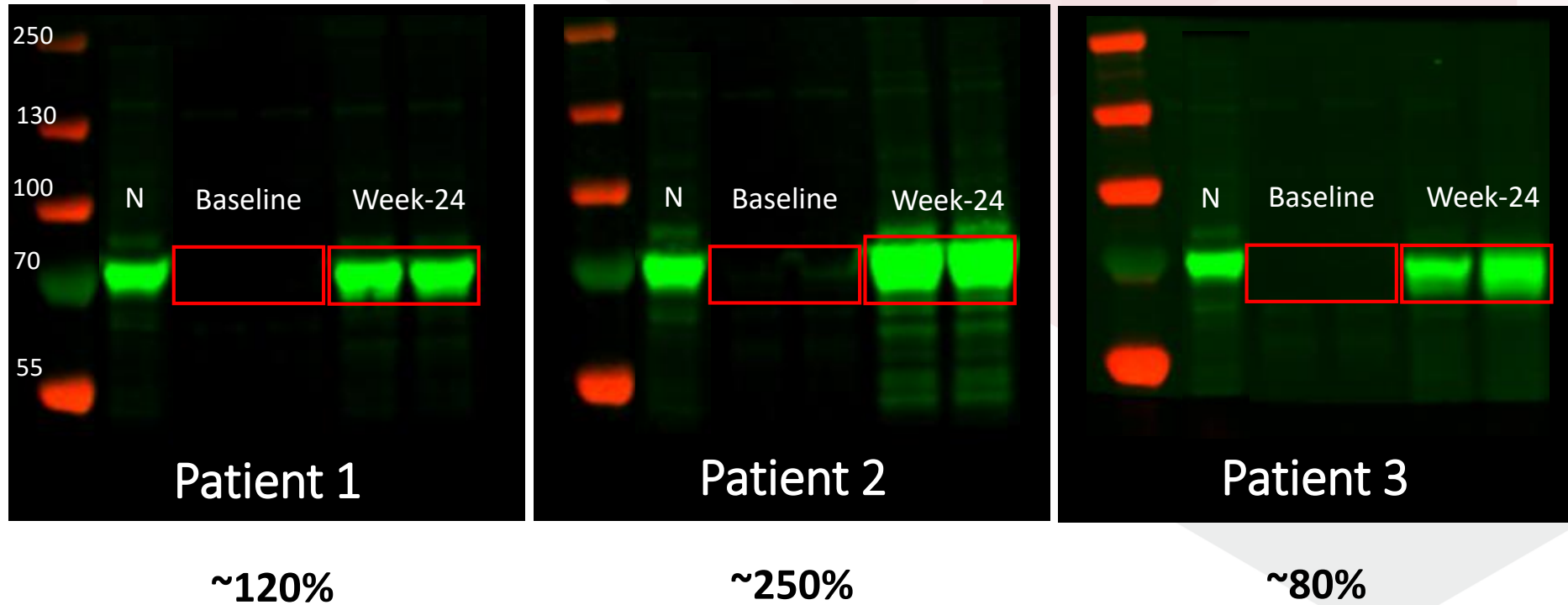
Unprecedented Tissue Transduction at 1×10^{14} vg/kg

	Patient	Baseline	Week 24
Vector Copy Number (per diploid genome)	1	BLOD	6.2
	2	BLOD	7.1
	3	BLOD	2.7

BLOD = Below limit of detection

ASPIRO Muscle Biopsy – Protein Expression

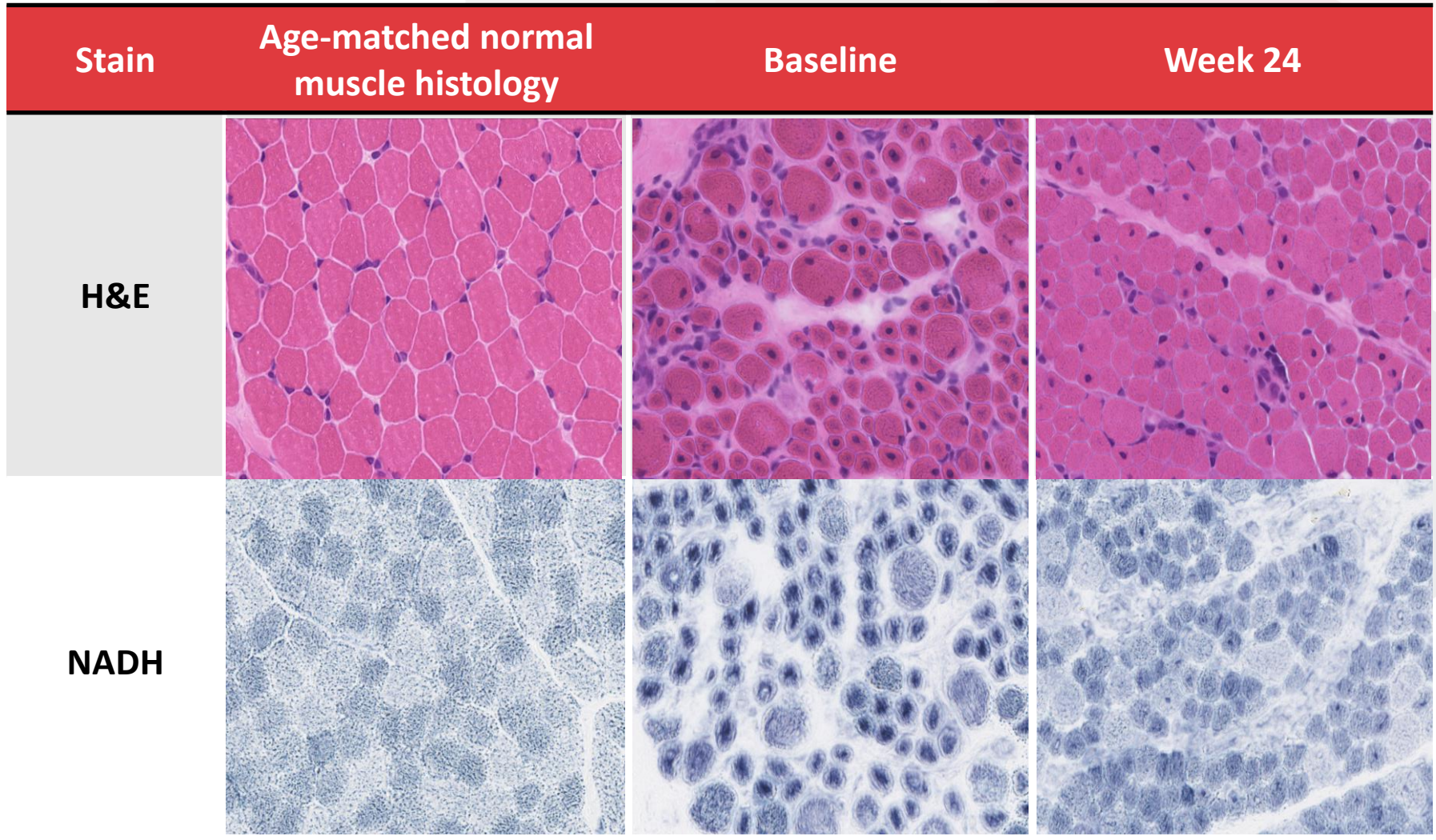
Robust Myotubularin Levels at Week 24



Expression levels calculated as a percentage of Normal (N)

Patient 1: Histological Improvements

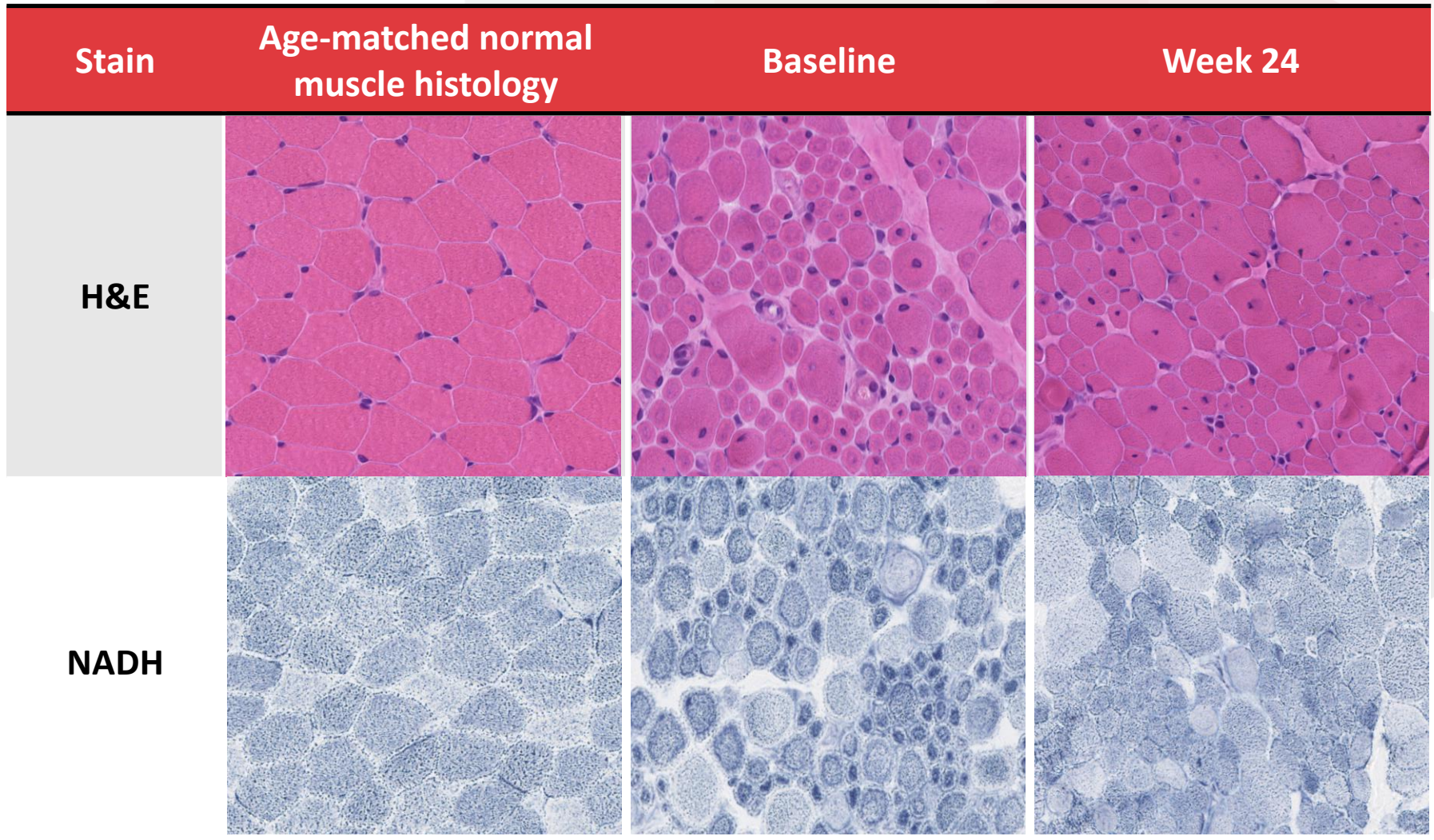
Significantly improved organelle localization and myofiber size



H&E = Hematoxylin and eosin; NADH = Nicotinamide adenine dinucleotide

Patient 2: Histological Improvements

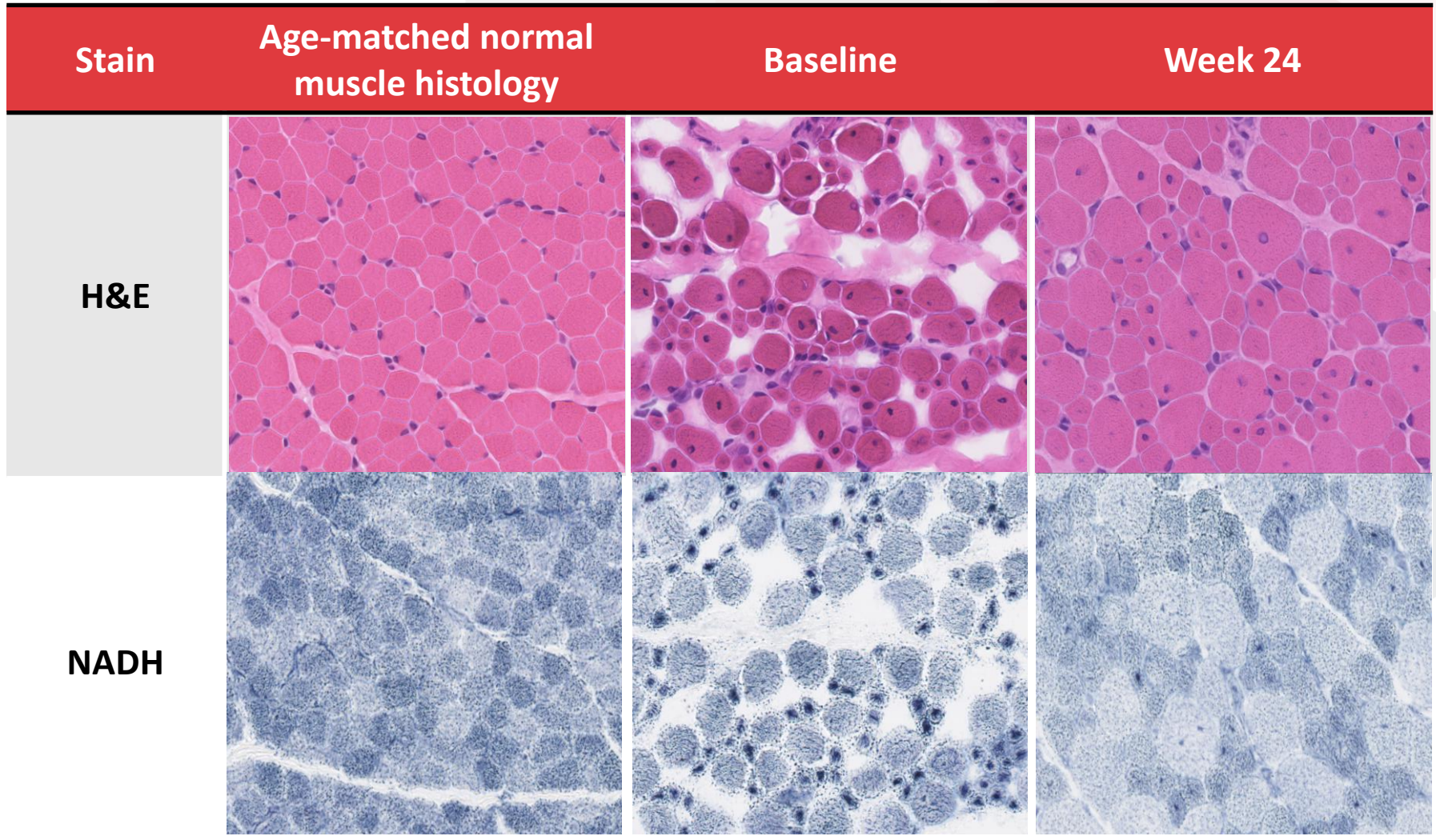
No apparent organelle mislocalization and improved myofiber size



H&E = Hematoxylin and eosin; NADH = Nicotinamide adenine dinucleotide

Patient 3: Histological Improvements

Significantly improved organelle localization and myofiber size



H&E = Hematoxylin and eosin; NADH = Nicotinamide adenine dinucleotide

ASPIRO Summary

- Efficacy gains continue in all treated patients
 - Clinically meaningful improvements in CHOP-INTEND scores and MIP in all treated patients
 - Significant reductions in ventilator use in 3/3 patients by Week 24
- No new treatment-related serious adverse events
- Muscle biopsy results consistent with marked functional improvements
 - Transduction: unprecedented vector copy number in target tissue
 - Expression: robust protein expression as evidenced by Western blots
 - Histopathology: significant improvements in myofiber size, nuclear peripheralization, and organelle localization

ASPIRO Next Steps

- Continue with planned dose-escalation to 3×10^{14} vg/kg
- Cohort 2 sentinel patient expected to be dosed in coming weeks
- Next update planned at World Muscle Society, Oct 2-6, 2018

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