Endocrinologic and Metabolic Drugs Advisory Committee (EMDAC) Meeting

Biologics License Application (BLA) 125460 for VIMIZIM (elosulfase alfa)

November 19, 2013

Introduction

Henry Fuchs, MD

Chief Medical Officer
BioMarin Pharmaceutical Inc.

Agenda

Introduction	**Henry Fuchs, MD** Chief Medical Officer BioMarin Pharmaceutical Inc.
Description of MPS IVA	**Christian Hendriksz, MB ChB, MSc, MRCP, FRCPCH** Birmingham Children's Hospital NHS Foundation Trust, United Kingdom Principal investigator, Phase 1/2, Phase 3 Trials
Clinical Trial Results	**Christine Haller, MD** Senior Group Medical Director BioMarin Pharmaceutical Inc.
Risk Benefit Assessment	**Christian Hendriksz, MB ChB, MSc, MRCP, FRCPCH**
Conclusion	**Henry Fuchs, MD**

External Experts

Ken Berger, MD	New York University School of Medicine, André Cournand Pulmonary Physiology Laboratory, Bellevue Hospital New York, NY
Paul Harmatz, MD	Children's Hospital and Research Center Oakland, CA
William G. Mackenzie, MD	A.I. DuPont Hospital for Children Wilmington, DE
Gillian Shepherd, MD	New York Presbyterian Hospital New York, NY
Janet Wittes, PhD	Statistics Collaborative, Inc. Washington, DC

Disclosures

Dr. Kenneth Berger

Dr. Paul Harmatz

Dr. Christian Hendriksz

Dr. William G. Mackenzie

Dr. Gillian Shepherd

Dr. Janet Wittes

- Are compensated consultants
- Have no financial interest in BioMarin or the outcome of this meeting.

Overview

- Morquio A Syndrome is a rare inherited disorder
- Prevalence in the US is approximately 800 patients
- Elosulfase alfa is a novel enzyme replacement therapy

Mucopolysaccharidoses (MPS) Disorders

- Caused by inability to produce specific enzymes
- Results in progressive damage throughout body
- Includes several identified syndromes, which differ in the deficient enzyme, accumulated intracellular products, and clinical manifestations
- Common features include skeletal dysplasia, impaired stature, and motor dysfunction
- Only three syndromes with approved treatment
- Two of these therapies developed by BioMarin; Aldurazyme for MPS I and Naglazyme for MPS VI

MPS IVA (Morquio A Syndrome)

- Caused by mutations in gene for GALNS
- Progressive accumulation of glycosaminoglycans (GAGs) leads to multisystemic impairment
- Differs from other MPS diseases
  - Greater bone and joint deformities
  - Less pronounced visceral organomegaly
  - No cognitive impairment
- No approved treatment other than supportive care

Elosulfase Alfa (BMN 110)

- Recombinant form of human GALNS
- Identical to naturally occurring enzyme in amino acid sequence and N-linked glycosylation
- Taken up into lysosomes and increases catabolism of the GAGs
- Reduces progressive accumulation of GAGs and improves signs and symptoms
- Proposed Indication: Treatment of MPS IVA
- Recommended Dose: 2.0 mg/kg; weekly IV infusion

Summary

- Enormously challenging disease to study
  - Extremely rare, debilitating, complicated
  - Limited to no outcome data at start of program
  - Widely variable disease in phenotype, state of progression
- Overcame obstacles to demonstrate favorable risk:benefit
  - Well-conducted Phase 3 trial, clinical endpoint widely used
  - Significant effect on challenging primary endpoint
  - Data in most other domains, but not all, supportive
  - Main important side effect infrequent and manageable
- Sponsor commitment to Morquio A continues as with MPS I, MPS VI
  - Post-approval registry
  - Post-approval risk management plan
  - Document long-term outcomes

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Description of MPS IVA

Christian Hendriksz, MB ChB, MSc, MRCP, FRCPCH

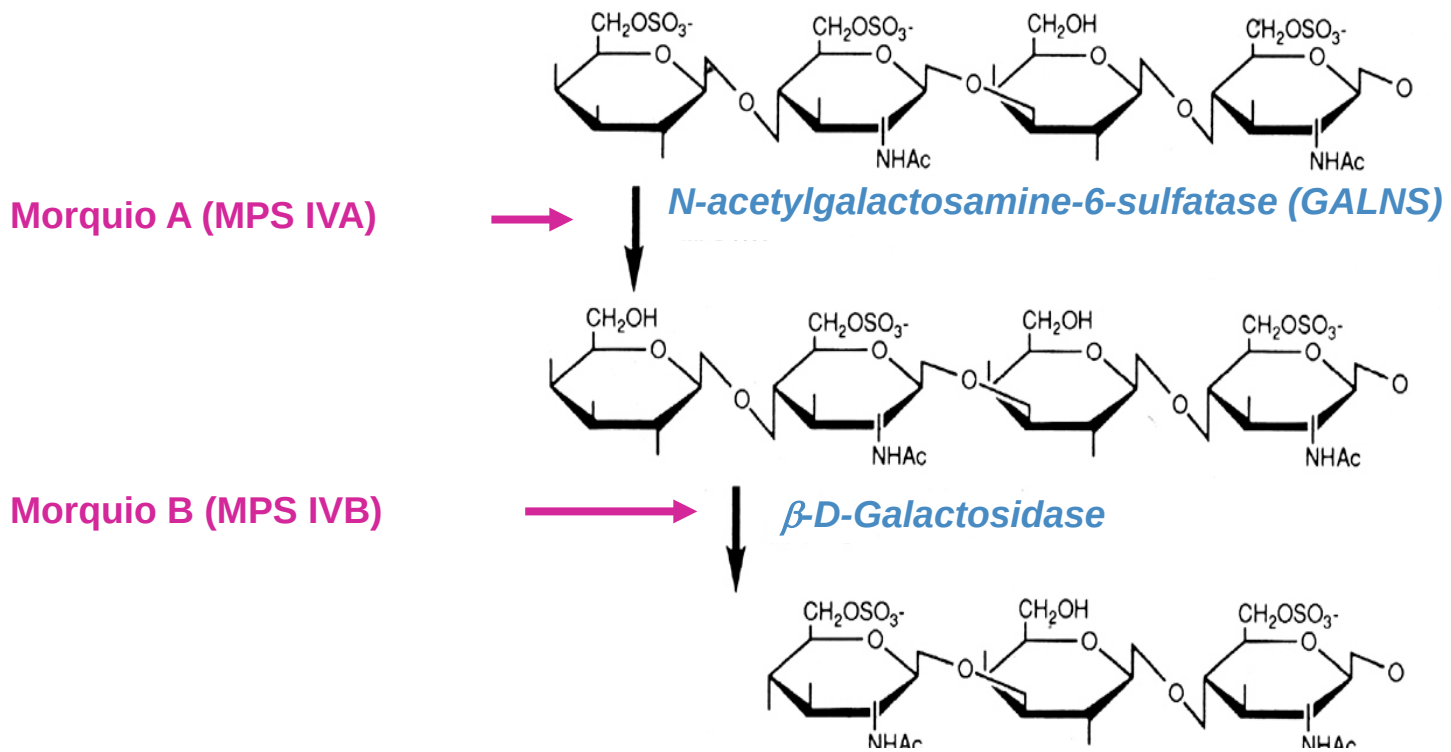
Birmingham Children's Hospital
NHS Foundation Trust, United Kingdom
Principal Investigator, Phase 1/2, Phase 3 Trials
Clinical Director – Acute Medicine, Salford Royal NHS Foundation Trust

MPS IVA – Disease Overview

- Rare autosomal recessive lysosomal storage disorder
- Caused by deficient activity of *N*-acetyl-galactosamine-6-sulfatase (GALNS)
- Progressive disease that leads to devastating multisystemic clinical impairments and early death
- Only supportive treatments exist:
  - Surgery
  - Symptom control
  - Minimizing secondary complications
  - Physical therapy

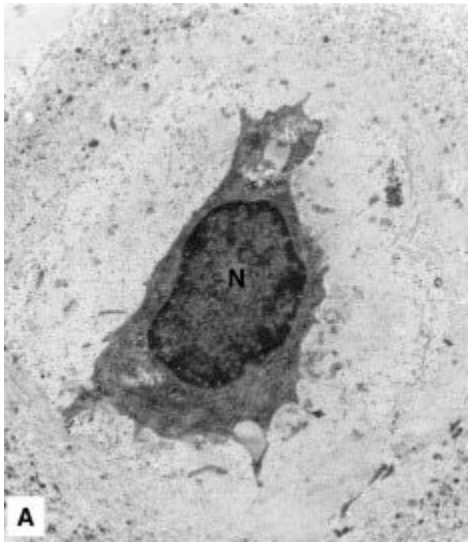
Specific Biochemical Deficiency in MPS IVA is Well-Characterized

- **GALNS deficiency causes a block in the sequential breakdown steps of glycosaminoglycans**



Neufeld, EF and Muenzer, J. *The Mucopolysaccharidoses*. Part 16: Chapter 136. In Valle, D, et al. (Eds.), The Online Metabolic & Molecular Bases of Inherited Disease. Germany: The McGraw-Hill Companies; 2001-2006.

MPS IVA Disorder – GAG Accumulates in Lysosomes



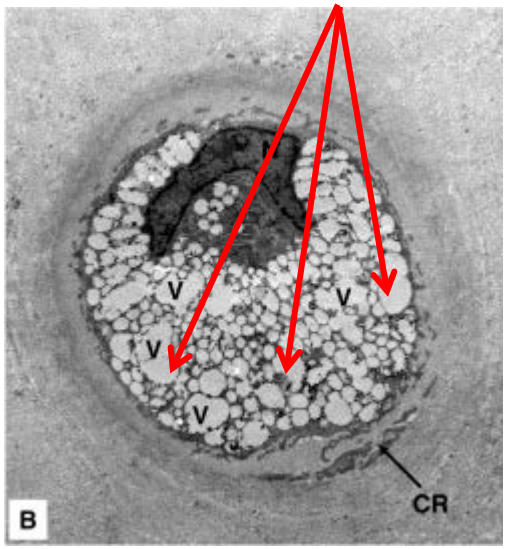
Unaffected cell

Insufficient lysosomal enzyme activity impairs lysosomal degradation of the GAGs keratan sulfate and chondroitin-6-sulfate

Accumulation of GAGs leads to lysosomal engorgement and disruption of normal cell function

Cellular dysfunction results in the progressive multisystemic morbidities that are the hallmark of this disorder

Lysosomes engorged with undegraded KS



Cell with GAG accumulation in lysosomes

Banks et al. *Molecular Genetics and Metabolism* 97 (2009) 196–201.

MPS IVA is Clinically Heterogeneous

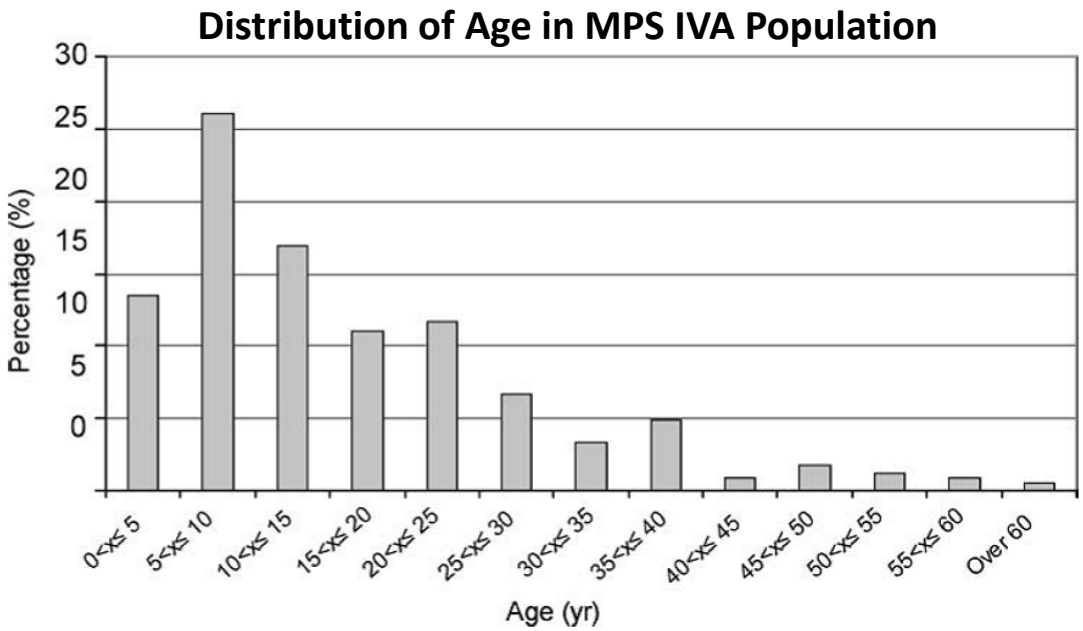
Ages 18, 34, 54, 33, 7

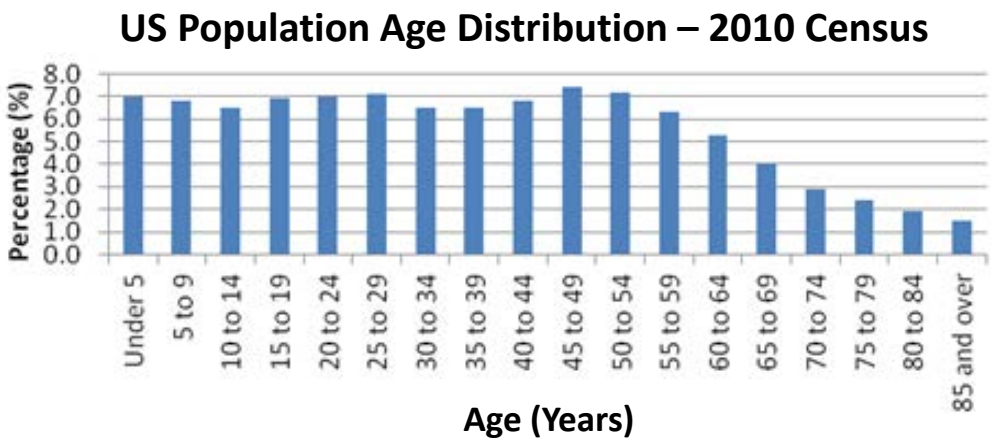
- Broad spectrum of clinical manifestations
- Median age of diagnosis is 3-5 years
- Over 185 mutations in the GALNS gene identified to date
- No pre-dominant mutation
  - Most common allele <9%
- Molecular heterogeneity leads to phenotypic diversity

The Human Gene Mutation Database, http://www.hgmd.org; Tomatsu et al, *Hum Mutat*, 2005.

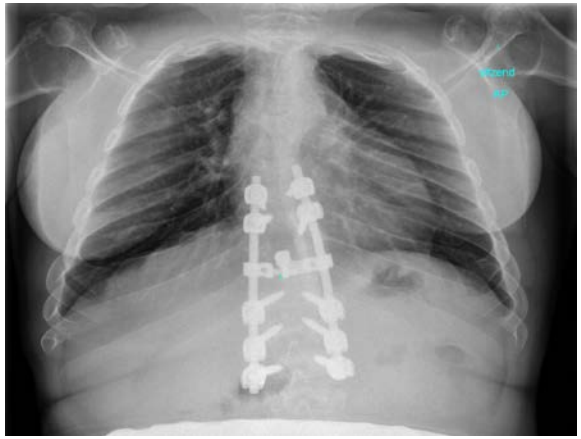
Life Expectancy is Reduced

- Most patients usually do not survive beyond 30s
- Major causes of mortality:
  - Pulmonary complications
  - Cervical instability and myelopathy
  - Cardiac complications
  - Complications associated with surgery and general anesthesia





Musculoskeletal Manifestations

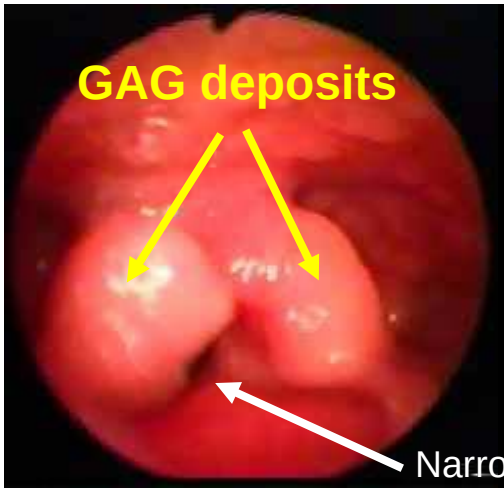


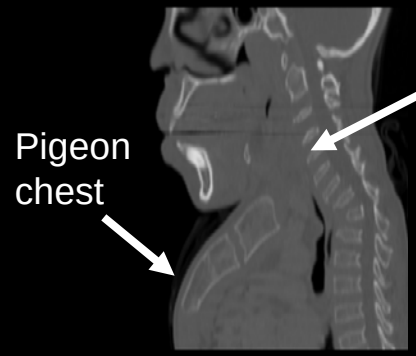
Images courtesy of Christina Lampe, MD, and Ralph Lachman, MD

- **Skeletal dysplasia**
  - **Spinal abnormalities**
  - **Pectus carinatum (pigeon chest)**
  - **Hip dysplasia**
  - **Genu valgum (knock knees)**
  - **Joint laxity and degeneration**
- **Frequent surgeries**
  - **Complicated**
  - **Long recovery**
  - **Increase caregiver burden**
- **Unlikely to change in short term**

Dhawale et al, *J Pediatr Orthop*, 2012; White, *Curr Orthop Prac*, 2012 ; Dhawale et al, *J Pediatr Orthop B*, 2012; Tomatsu et al, *Curr Pharm Biotechnol*, 2011.

Respiratory System Manifestations

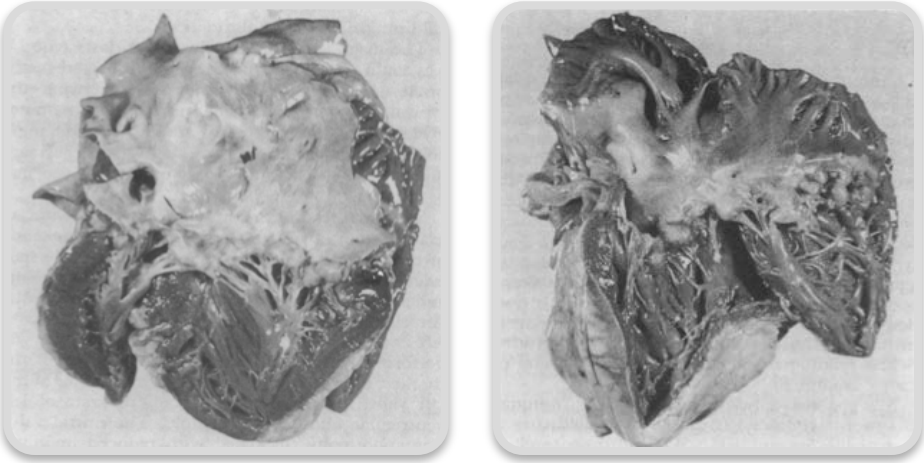




- **Upper airway obstruction**
- **Narrow/torturous trachea and bronchi**
- **Excessive and thickened secretions**
- **Restricted thoracic space due to skeletal deformities and muscular weakness**
- **Recurrent pulmonary infections**
- **Respiratory failure and early death**

Hendriksz et al, *J Inherit Metab Dis*, 2012; Tomatsu et al, *Curr Pharm Biotechnol*, 2011; Walker et al, *Thorax*, 2003; Pelley et al, *Respir Care*, 2007 ; Semenza and Pyeritz, Medicine (Baltimore), 1998; Buhain et al, *Chest*, 1975; Pritzker et al, *Am J Med*, 1980.
[1]Pritzker et al, *Am. J. Med*, 1980.

Cardiac Manifestations



Autopsy specimen of Morquio A patient shows thickening of mitral valve cusps, tricuspid valve cusps, and chordae.[1]

- Valvular heart disease
- Myocardial hypertrophy
- Cardiomegaly
- Develops slowly over many years
- Unlikely to change in short term

Hendriksz et al, J Inherit Metab Dis, 2012; John et al, *Arch Dis Child*, 1990; Wipperman et al, *Eur J Pediatr*, 1995; Mohan et al, *Acta Paediatr*, 2002; Ireland and Rolands, *Br Heart J*, 1981.

[1]Ireland and Rolands, *Br Heart J*, 1981.

Reduced Endurance is Attributed to Multisystemic Complications of Morquio A

MUSCULOSKELETAL COMPLICATIONS

CARDIAC COMPLICATIONS

RESPIRATORY COMPLICATIONS

Reduced Endurance

Reduced Activities of Daily Living

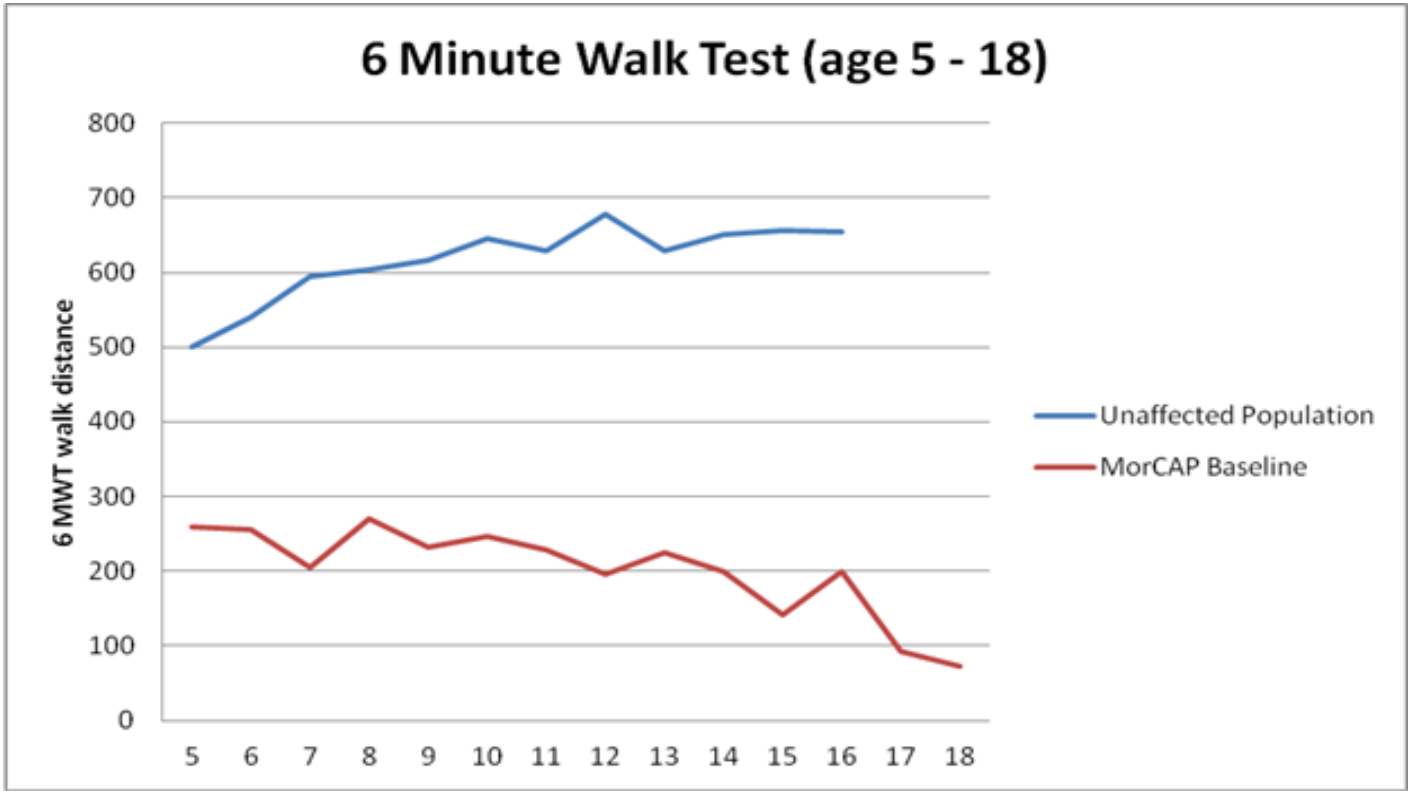
Chronic Fatigue

Decreased Quality of Life

Limited Mobility

Endurance (6MWT) is Severely Impaired in Morquio A Patients

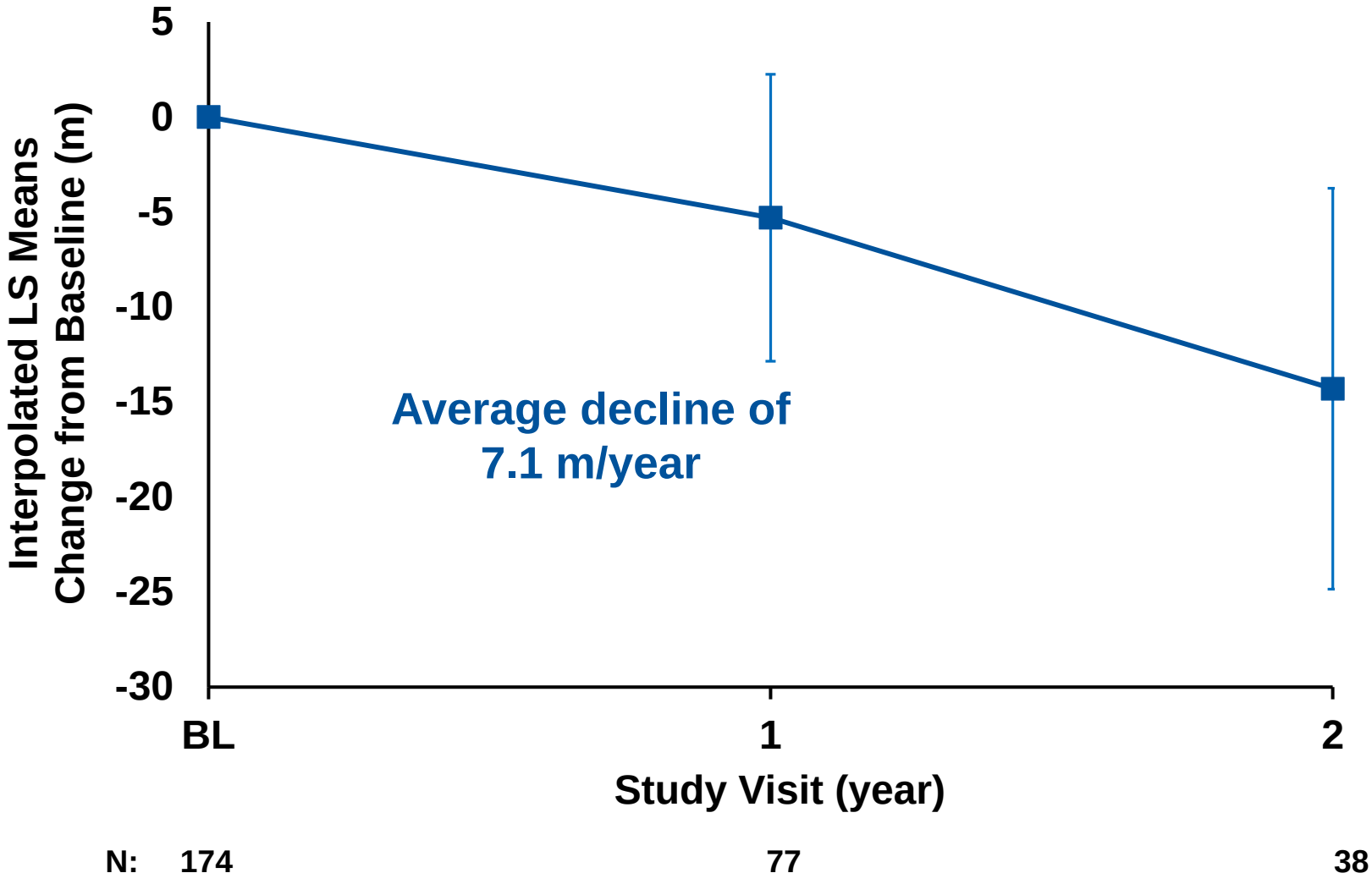
6MWT Distance in Untreated MPS IVA Patients and Age-matched Healthy Controls



Age (years)

Source: Silvia Ulrich et.al, Reference values for the 6-minute walk test in healthy children and adolescents in Switzerland, *BMC Pulmonary Medicine* 2013, 13:49.

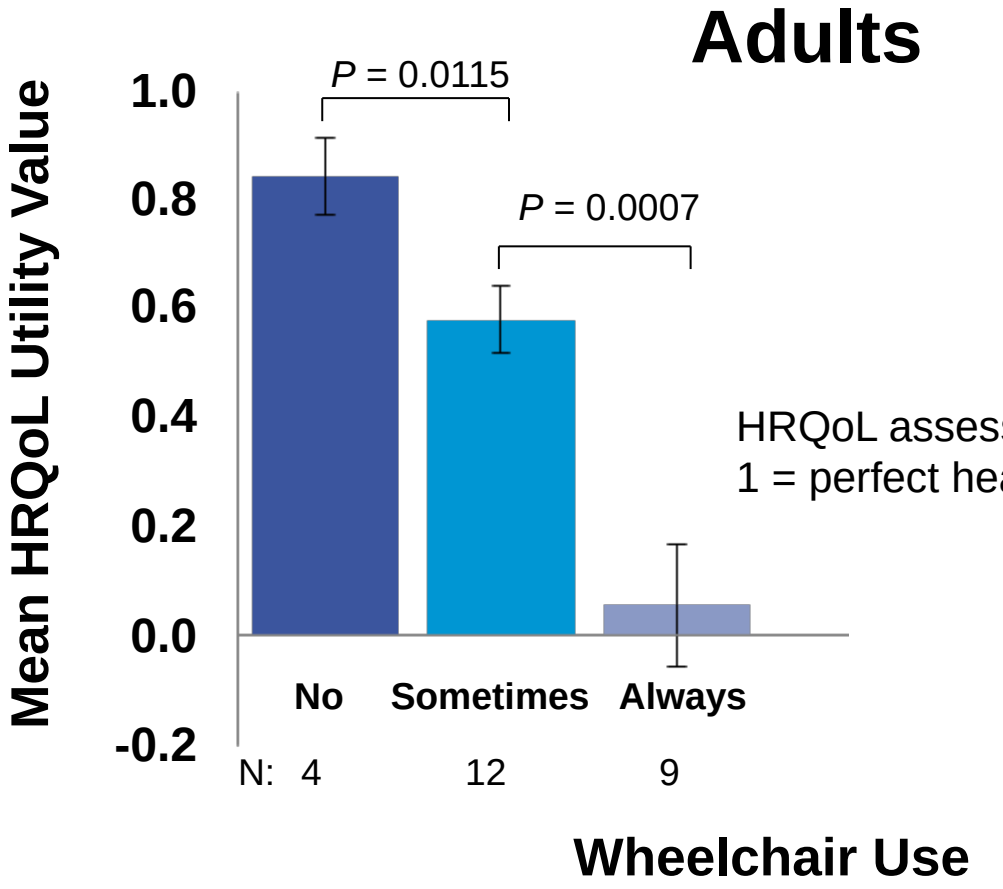
6MWT Distance Change (Meters) from Baseline (Age ≥5 and Baseline 6MWT is ≥30 and ≤325, MorCAP)



Case Illustration 6MWT

Case Illustration 3MSCT

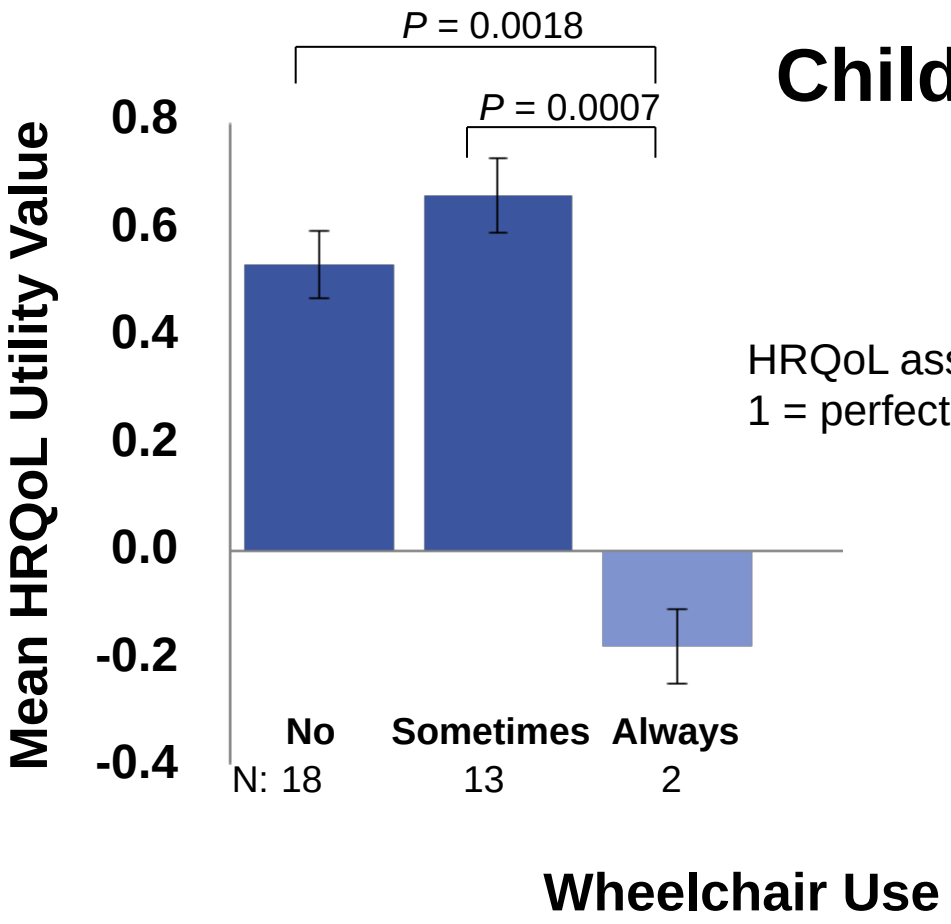
Ambulatory Patients Have Significantly Better QoL



HRQoL assessed using EQ-5D-5L[1]:
1 = perfect health; 0 = death

[1]http://www.euroqol.org/fileadmin/user_upload/Documenten/PDF/Folders_Flyers/UserGuide_EQ-5D-5L.pdf

Ambulatory Patients Have Significantly Better QoL



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[1]http://www.euroqol.org/fileadmin/user_upload/Documenten/PDF/Folders_Flyers/UserGuide_EQ-5D-5L.pdf.

Significant Unmet Medical Need

- Heterogeneous disease in severity and clinical manifestations – challenging to study
- No therapy except supportive care and surgery
- All patients experience progressive decline
- Maintaining mobility is critical
- High morbidity and early mortality

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Efficacy

Christine Haller, MD

Senior Group Medical Director

BioMarin Pharmaceutical, Inc.

Overview

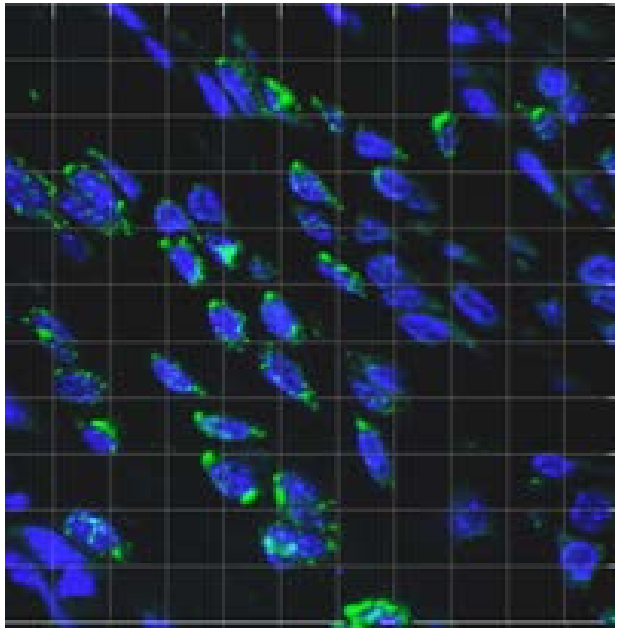
- Nonclinical
- Overview of clinical program
- Phase 1/2 study
- Phase 3 study
- Extension study

Nonclinical Overview

Elosulfase Alfa Tissue Distribution

- **Elosulfase alfa distributes to target tissues of the disease after IV administration in mice**

Chondrocytes



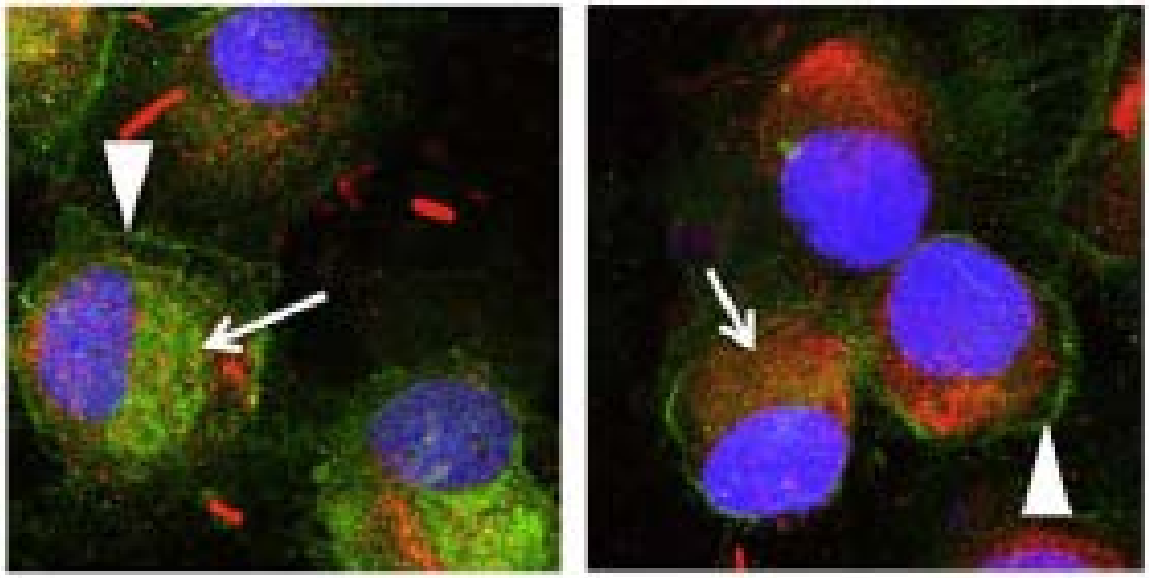
Nucleus Labeled Elosulfase alfa

Dvorak-Ewell et al, PLoS, 2010.

Elosulfase Alfa Cellular Uptake

- **CI-M6PR mediated uptake followed by translocation to the lysosomal compartment, the site of KS accumulation**
- **Elosulfase alfa K_{uptake} and intracellular half-life ($t_{1/2}$) were determined in human MPS IVA fibroblasts**
  - **K_{uptake} was ~ 138 ng/mL**
  - **Intracellular $t_{1/2}$ was ~ 5-7 days**

Elosulfase alfa Pharmacological Activity



Untreated 10 nM rhGALNS

- KS
- Lysosomes
- Co-localization
- Extracellular KS
- Intracellular KS
- Nucleus

- Elosulfase clears intracellular GAGs (KS) in MPS IVA chondrocytes
- Restores normal chondrocyte enzymatic function

Dvorak-Ewell et al, PLoS 2010.

Clinical Program

Clinical Program Objectives

- Conduct large, longitudinal observational study to characterize disease
- Investigate potential benefit of elosulfase alfa as ERT for patients with Morquio A syndrome
  - Evaluate safety, determine dose, assess clinical and pharmacodynamic responses (Ph 1/2)
  - Determine Risk:Benefit in diverse patient population (Ph 3)
- Understand how elosulfase alfa might benefit sub-groups of patients
  - Under 5 years old (MOR-007)
  - Limited ambulatory ability (MOR-006)
  - Less limited ambulation, cardiopulmonary testing (MOR-008)

Improving Outcomes in MPS IVA – 6MWT as the Primary Endpoint

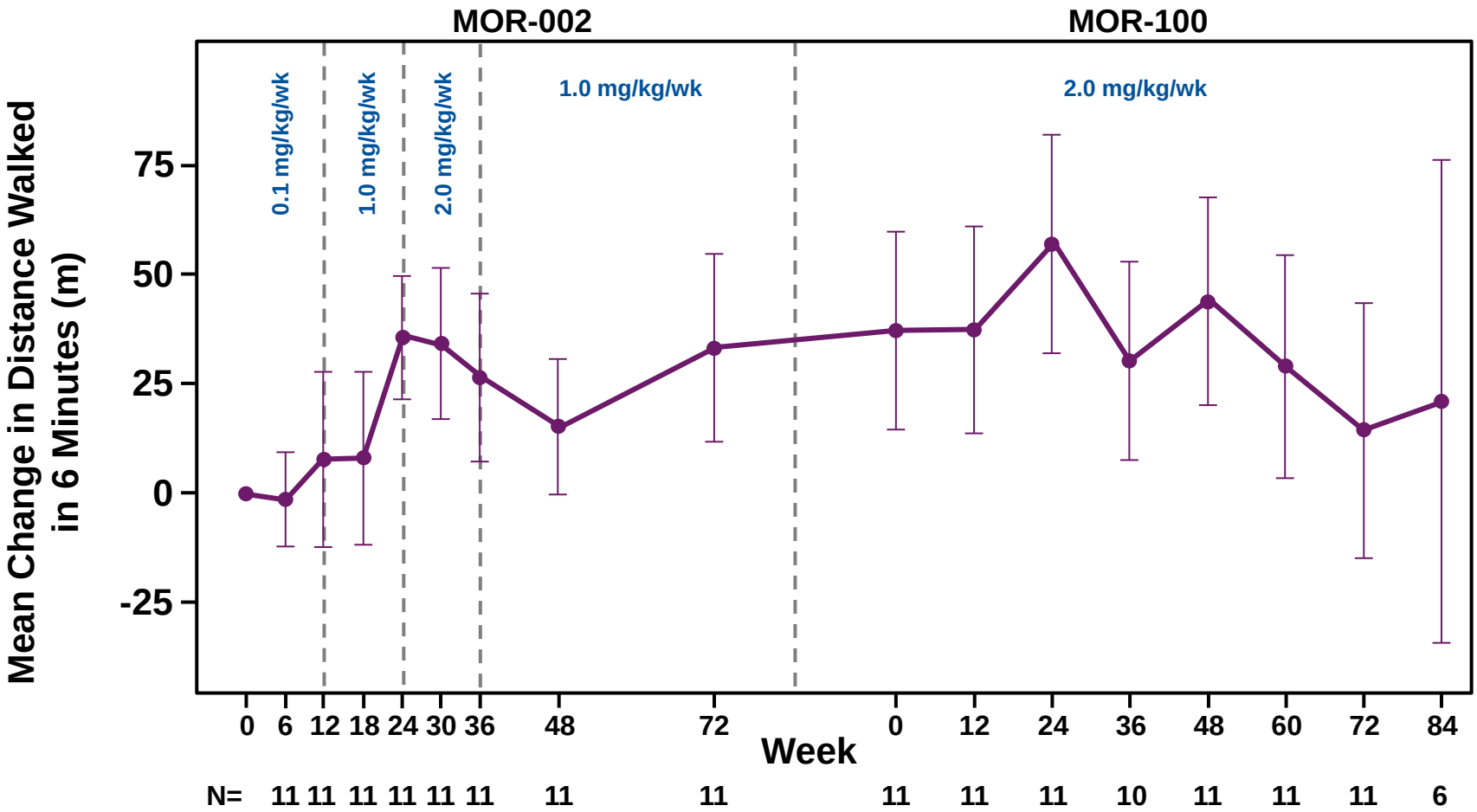
- **Significant skeletal abnormalities in MPS IVA presented challenge for endpoint selection**
- **Trial duration limited by need for frequent surgeries**
- **6MWT standardized, simple test of endurance, used in many studies of other diseases including other ERT trials**
- **Exploratory endpoints selected to address challenges in breathing, growth, activities of daily living, and other disease symptoms**

Morquio A Clinical Study Overview

Natural history study MorCAP initiated October 2008 (n=325)	MOR-001
Phase 1/2 clinical study initiated April 2009 (n=20) Long-term extension ongoing	MOR-002 MOR-100
Phase 3 placebo-controlled clinical study initiated January 2011 (n=176) Long-term extension ongoing	MOR-004 MOR-005
3 ancillary studies ongoing	MOR-006 MOR-007 MOR-008

Phase 1/2 – MOR-002/100
6 Minute Walk Test (6MWT)

Mean Change from Baseline in 6MWT vs. Study Week
(Evaluable Population with Baseline 6MWT ≤325 meters)

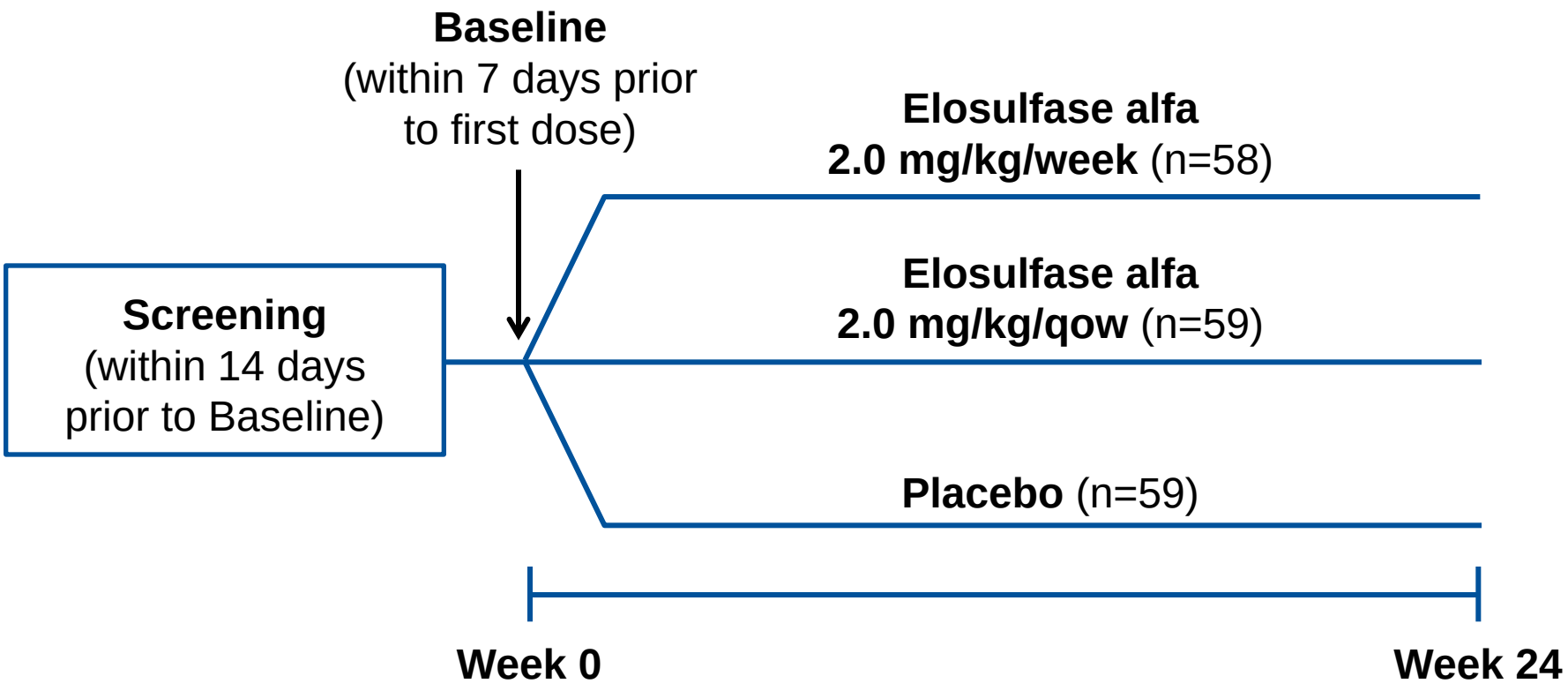


Error bar refers to standard error.

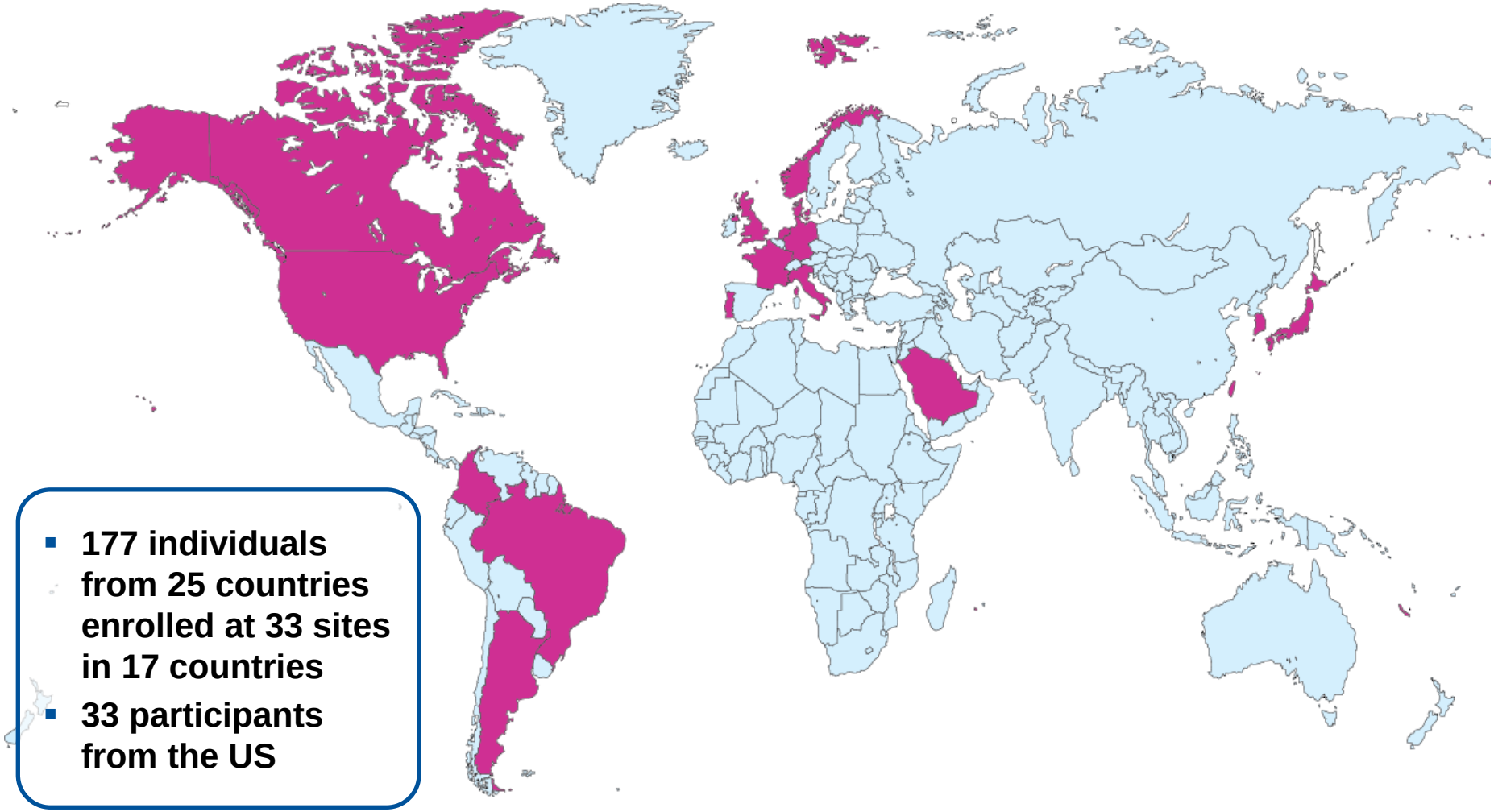
MOR-004
Pivotal Trial Overview

- **Randomized, double-blind, placebo-controlled study of elosulfase alfa administered for 24 weeks in patients with Morquio A Syndrome**
- **Primary endpoint: Change from baseline in 6MWT distance at Week 24**
- **Secondary endpoints: Change from baseline in 3MSC & uKS at 24 weeks**
- **Broadly Inclusive Study**
  - **Eligible: ≥5 years of age, 6MWD ≥30 m and ≤325 m at baseline**
  - **No major surgery within 3 months prior to study entry; nor planned major surgery during 24-week treatment period**

MOR-004
Trial Design

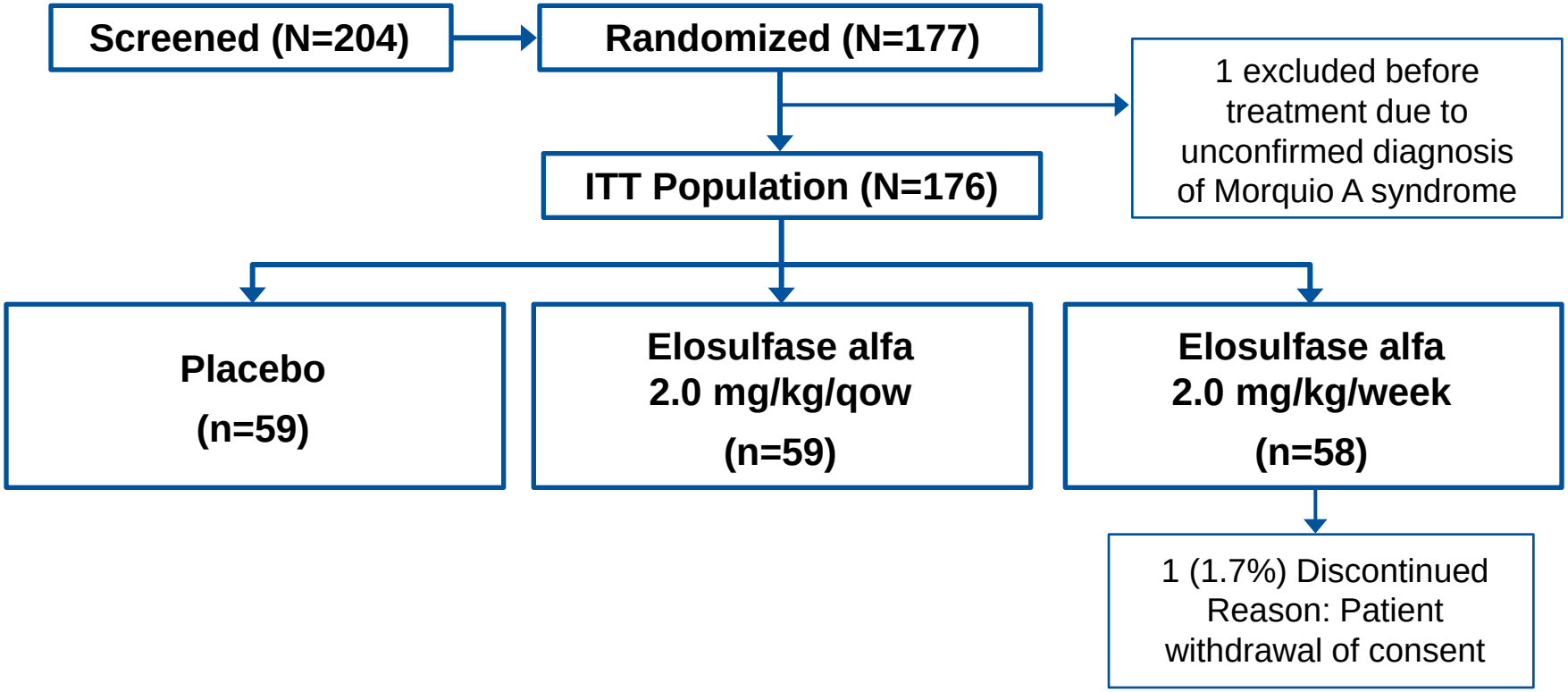


MOR-004
Study Sites



- 177 individuals from 25 countries enrolled at 33 sites in 17 countries
- 33 participants from the US

MOR-004
Subject Disposition



- **Dosing compliance exceeded 98%**
- **99% rate of study completion**

High Data Quality Maintained Throughout Study

- **Study quality measures implemented:**
  - **Verify patient eligibility**
  - **Duplicate 6MWTs**
  - **Maintain rigorous blinding**
- **High data quality achieved:**
  - **Few missing data points**
  - **High intra-class correlation coefficients**

MOR-004
Baseline Demographics

	Placebo n=59	Elosulfase alfa 2.0 mg/kg/qow n=59	Elosulfase alfa 2.0 mg/kg/week n=58
Age at Enrollment (years)			
Mean (SD)	15 (11)	15 (11)	13 (8)
Age Group (years)[a], n (%)			
5–11	30 (50.8)	31 (52.5)	32 (55.2)
12–18	15 (25.4)	16 (27.1)	16 (27.6)
≥19	14 (23.7)	12 (20.3)	10 (17.2)
Sex, n (%)			
Female	32 (54.2)	25 (42.4)	32 (55.2)
Race, n (%)			
Asian	11 (18.6)	15 (25.4)	14 (24.1)
Black or African American	0	2 (3.4)	2 (3.4)
White	44 (74.6)	35 (59.3)	36 (62.1)
Other	4 (6.8)	7 (11.9)	6 (10.3)
Ethnicity, n (%)			
Hispanic or Latino	13 (22.0)	16 (27.1)	9 (15.5)

[a]Stratification factor.

MOR-004
Baseline Characteristics

	Placebo n=59	Elosulfase alfa 2.0 mg/kg/qow n=59	Elosulfase alfa 2.0 mg/kg/week n=58
6-Minute Walk Test (meters)			
Mean (SD)	212 (70)	206 (81)	204 (76)
3-Minute Stair Climb Test (stairs/min)			
Mean (SD)	30 (14)	27 (16)	30 (16)
Normalized Urine KS (ug/mg)			
Mean (SD)	26 (15)	29 (21)	27 (14)
Walk Category[a], n (%)			
≤200m	23 (39.0)	24 (40.7)	23 (39.7)
>200m	36 (61.0)	35 (59.3)	35 (60.3)
Walking Aids Used[b]	11 (18.6)	16 (27.1)	9 (15.5)

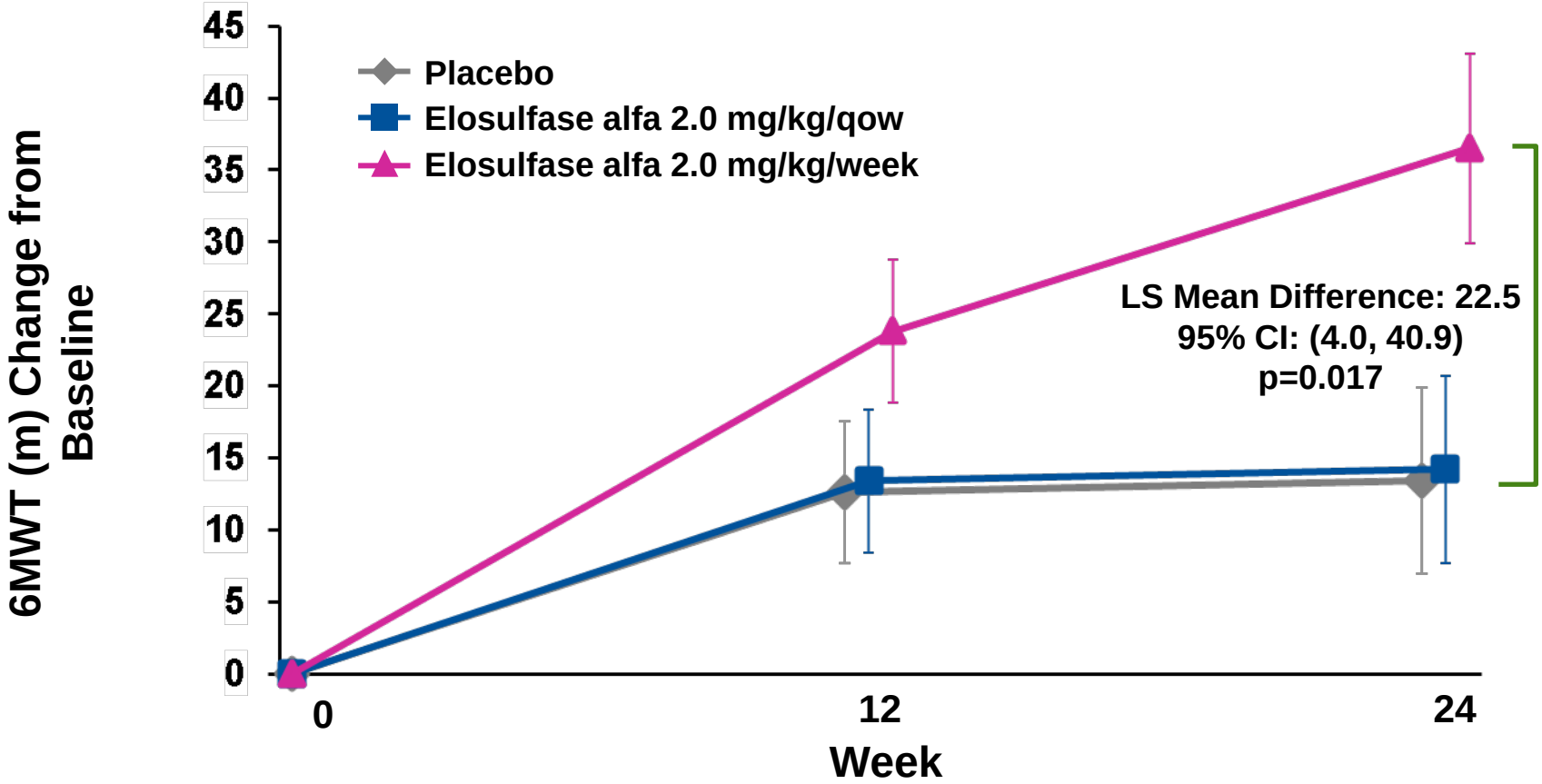
[a]Stratification factor.
[b]Walking aids used in 6MWT include crutches, walker/walking frame and cane/walking stick.

MOR-004
Statistical Methodology

- **ANCOVA model for 24 Week 6MWT change from baseline adjusting for:**
  - **Age (5–11, 12–18, ≥19 yrs)**
  - **6MWT (≤200 m and >200 m)**
- **Similar model for endpoints 3MSCT, uKS, RFTs (% change)**
- **QW & QOW comparisons to placebo with Hochberg multiplicity adjustment**

MOR-004
Primary Endpoint – 6MWT

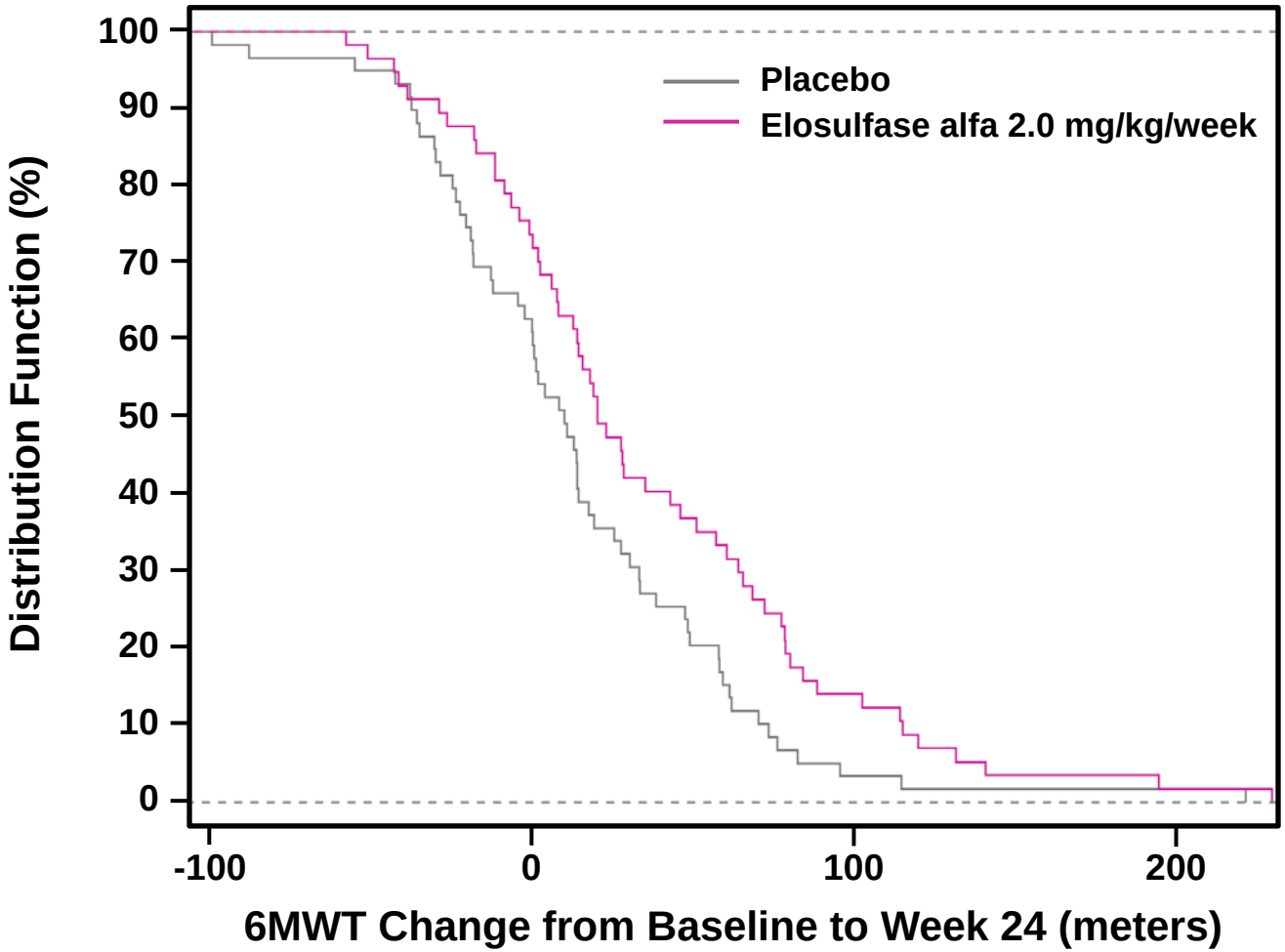
ANCOVA Mean Change in 6MWT (ITT Population)



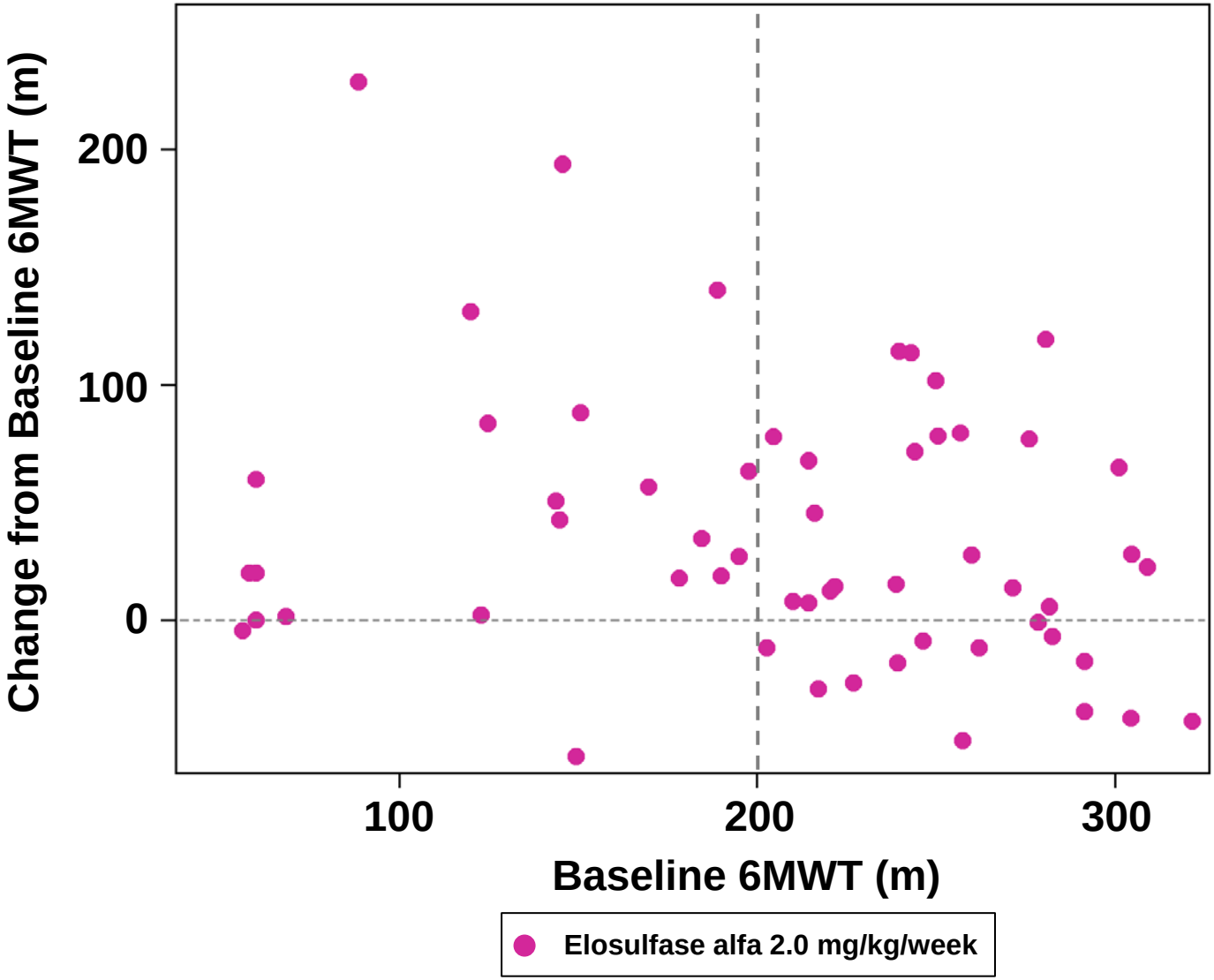
N:			
Placebo	59	59	59
Elosulfase 2.0 mg/kg/qow	59	59	58
Elosulfase 2.0 mg/kg/week	58	58	57

MOR-004
Responder Analysis of 6MWT

Cumulative Distribution for Change from Baseline to Week 24 (ITT Population)



MOR-004
Effect of Baseline 6MWT on Change in 6MWT

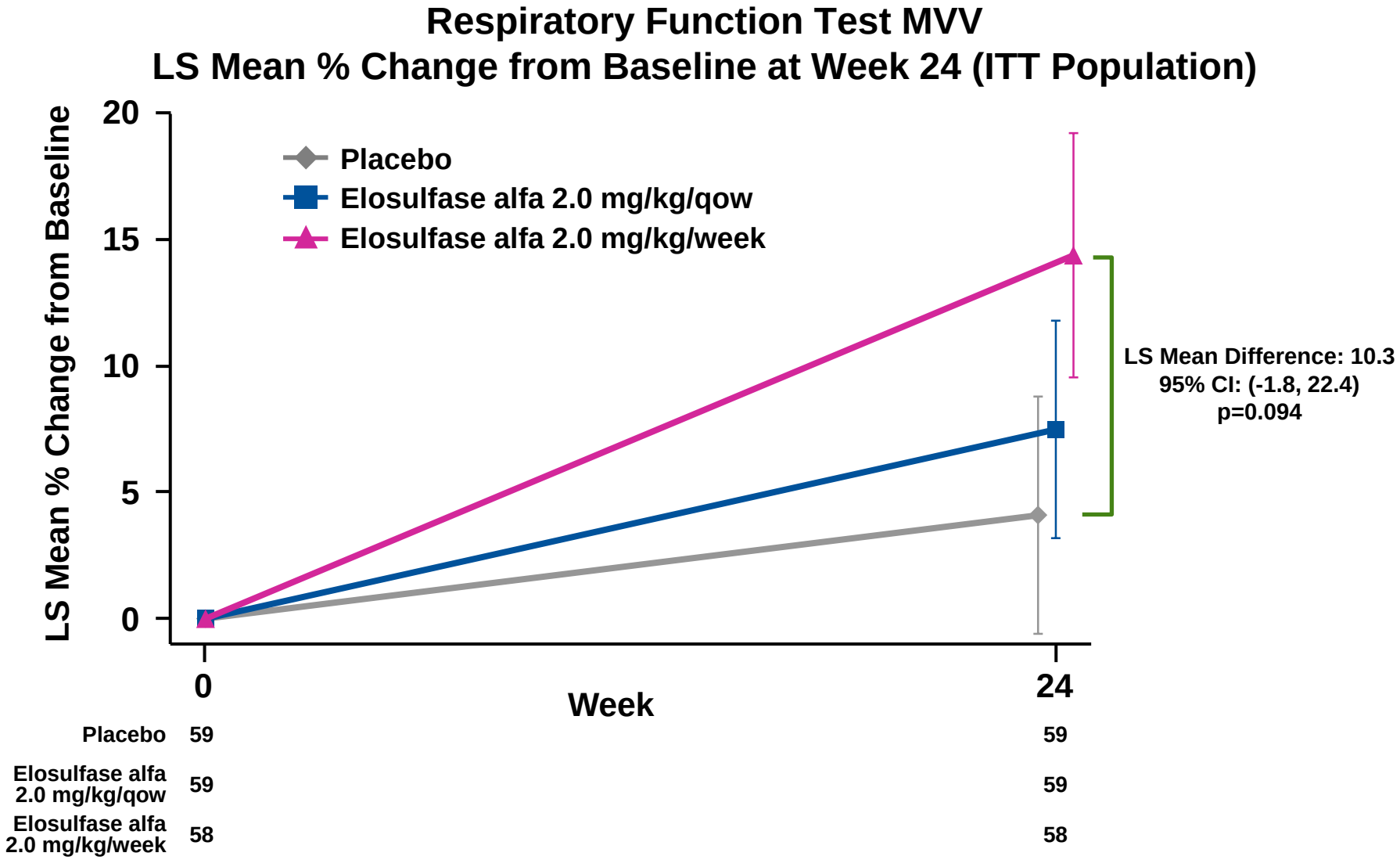


MOR-004
Secondary Endpoints

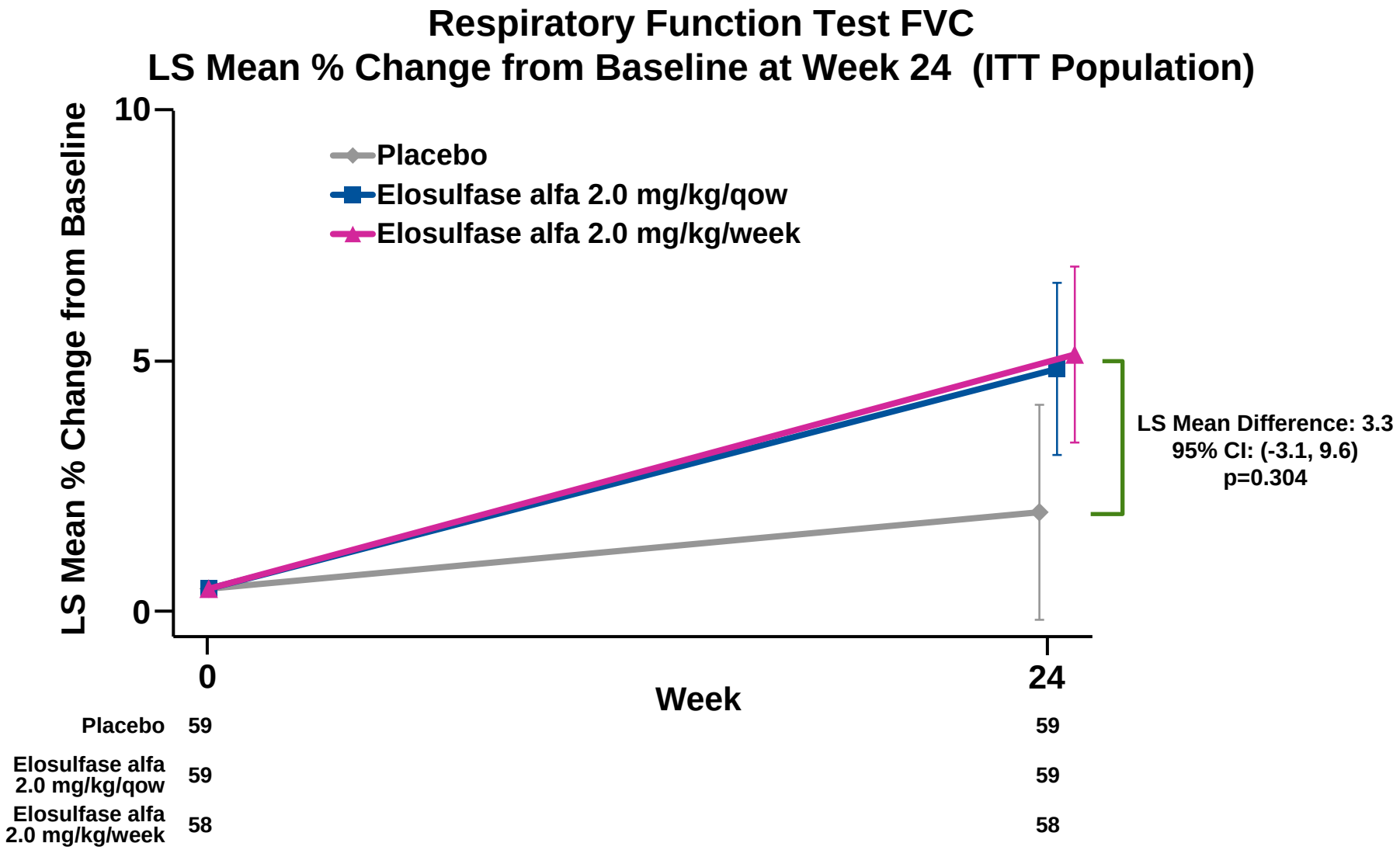
		Elosulfase alfa QW vs. Placebo[a]
3MSCT	Mean (stairs/min)	1.1
	95% CI	(-2.1, 4.4)
	p-value	0.494
uKS	Mean (%)	-40.7
	95% CI	(-49.0, -32.4)
	p-value	<0.0001

[a]Model-based mean of Elosulfase alfa minus Placebo, adjusted for baseline.

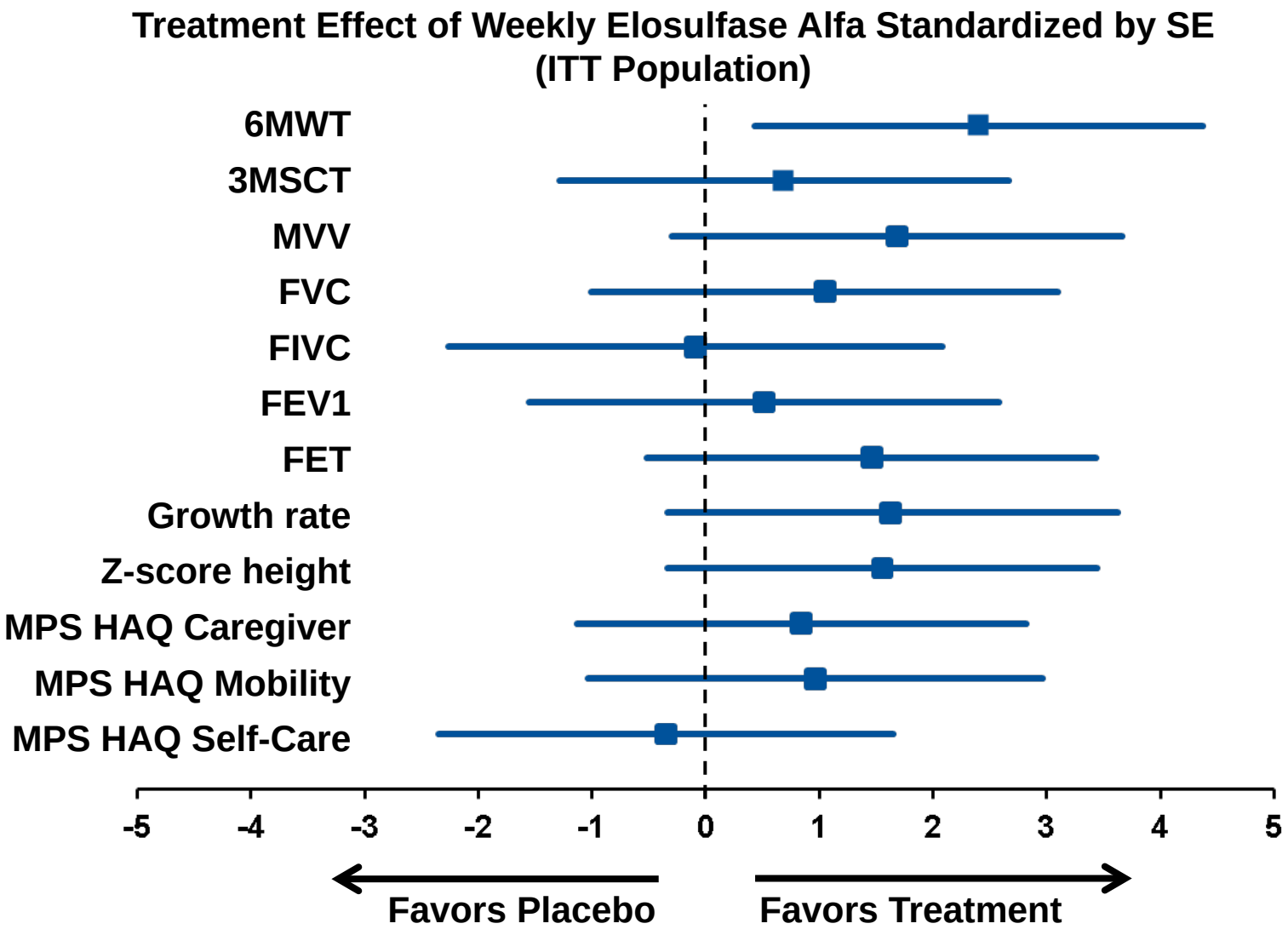
MOR-004
Exploratory Endpoint – MVV



MOR-004
Exploratory Endpoint – FVC



MOR-004
Summary of Efficacy Endpoints (QW Dose)

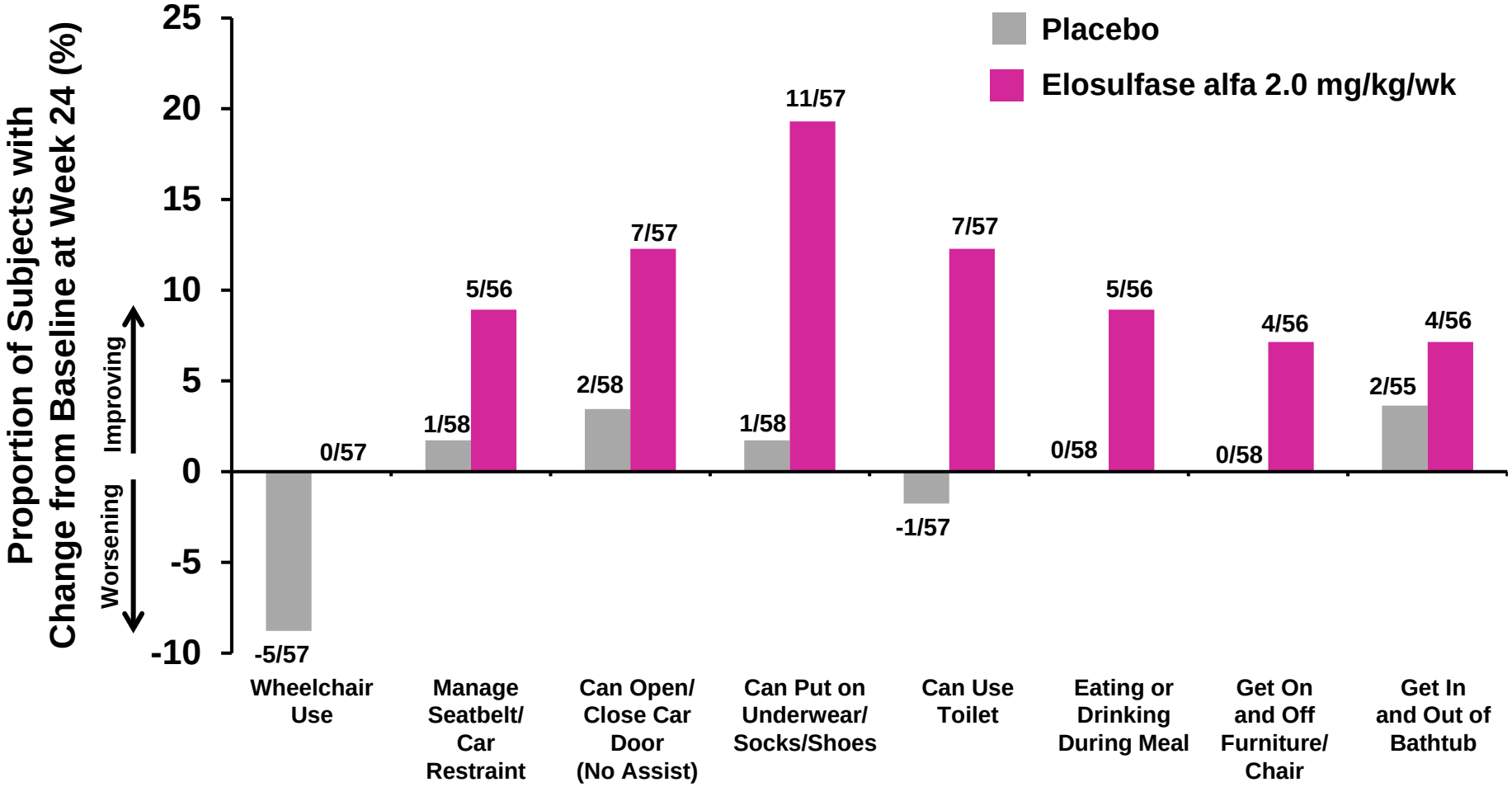


MOR-004
Summary of Other Exploratory Endpoints

- **Other efficacy endpoints that did not show clinically significant changes during MOR-004:**
  - **Cardiac EKGs/ECHOs**
  - **Lower extremity bone length**
  - **Inflammatory and bone and cartilage metabolism markers**
  - **Corneal clouding**
  - **Hearing**
- **Long-term treatment effects on these parameters will be examined in MOR-005 and patient registry**

MOR-004
Additional Analyses Related to Activities of Daily Living (MPS HAQ) – ITT Population

- **Of the 52 HAQ questions, responses to 36 questions favored weekly treatment, 12 favored placebo and 4 showed no difference**

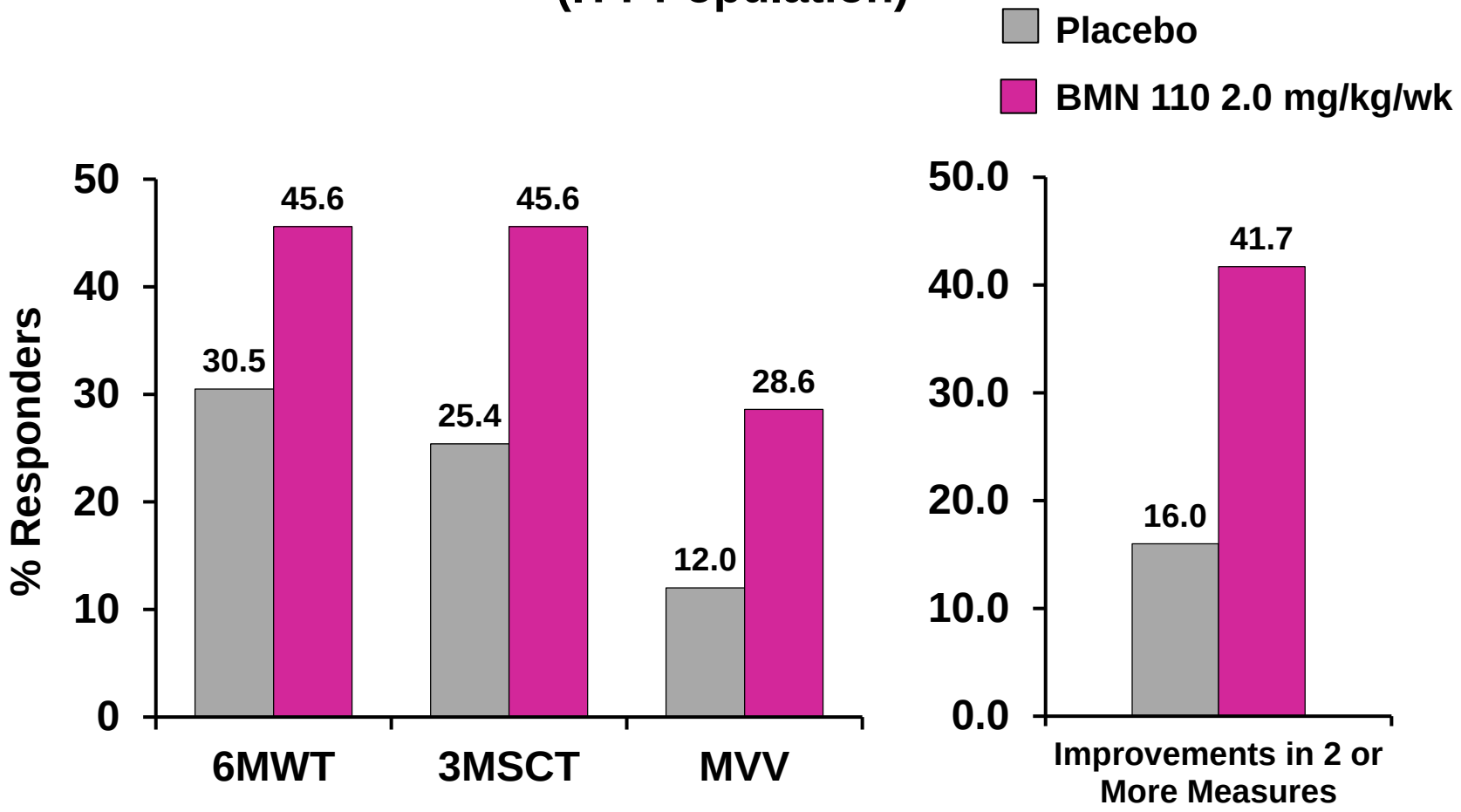


MOR-004
Responder Analyses Defined by Delphi

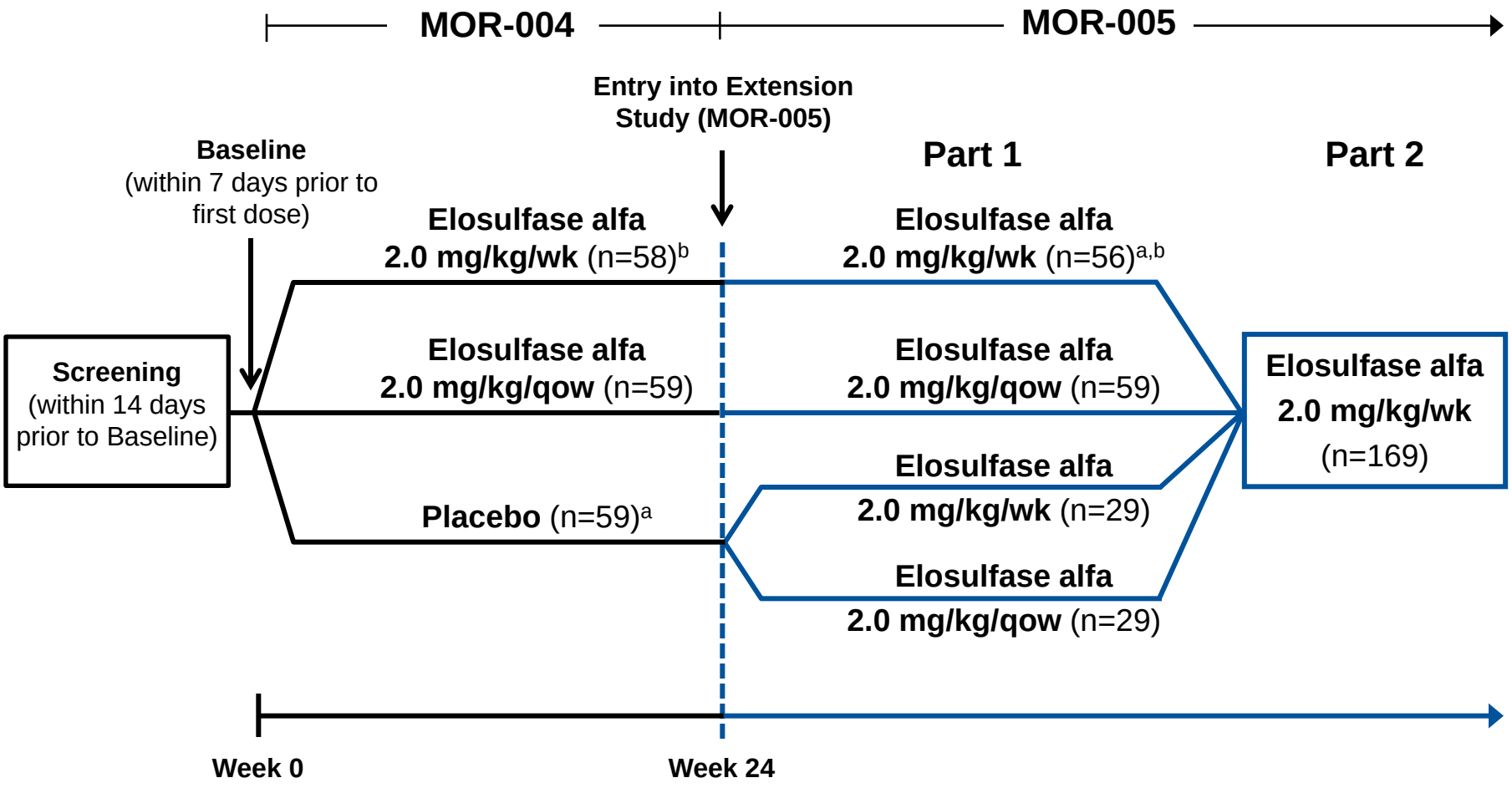
- **Delphi Panel consensus recommendations for a responder definition threshold, expressed as % change improvement from Baseline after 24 weeks of treatment:**
  - **15% change for the 6MWT**
  - **20% change for the 3MSCT**
  - **20% change for MVV**

MOR-004
Analyses Related to Delphi

Delphi Threshold Responder Analysis for 6MWT/3MSCT/MVV (ITT Population)



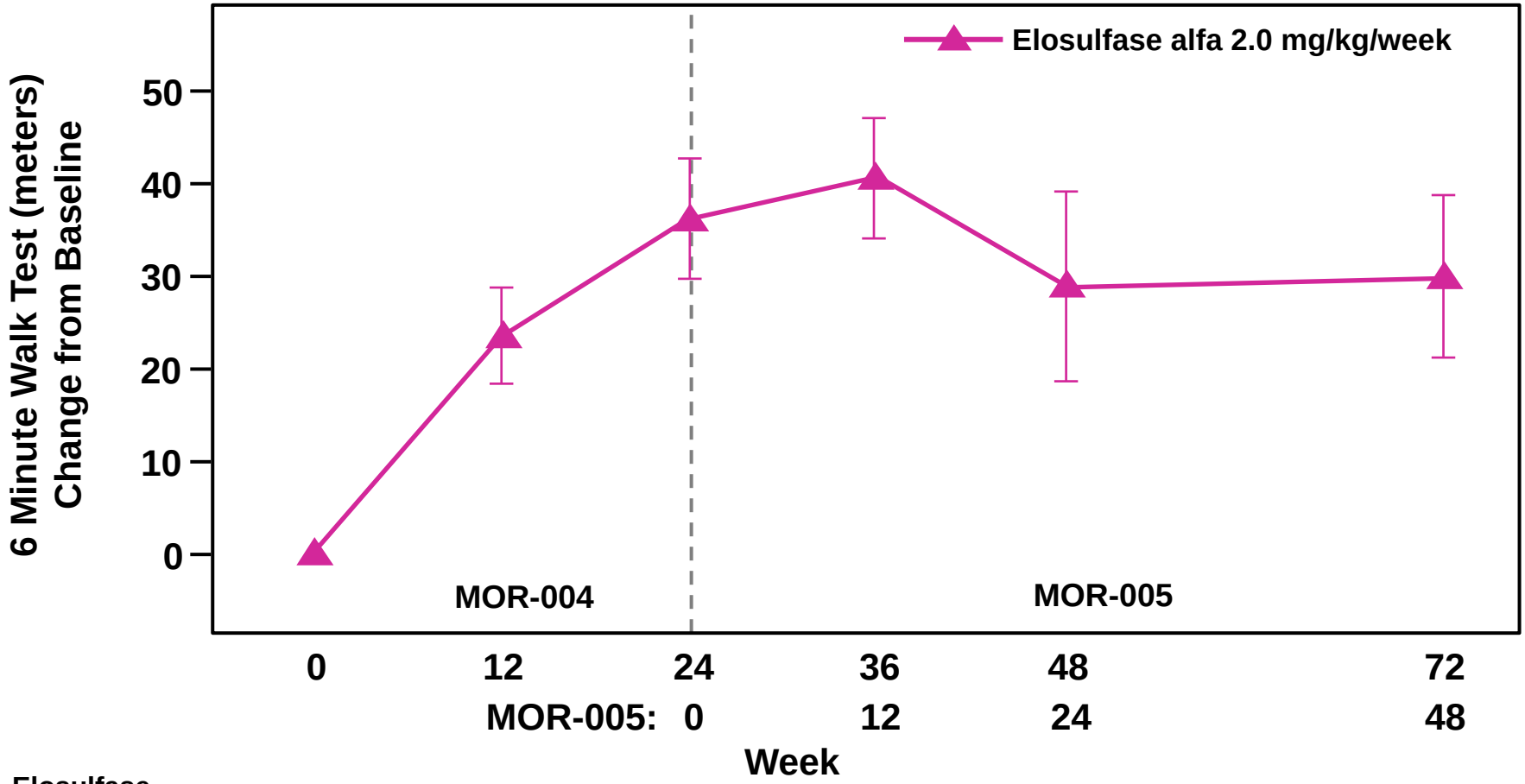
MOR-005 Study Design



[a]1 Subject did not enroll.
[b]1 subject withdrew consent.

MOR-005
6MWT

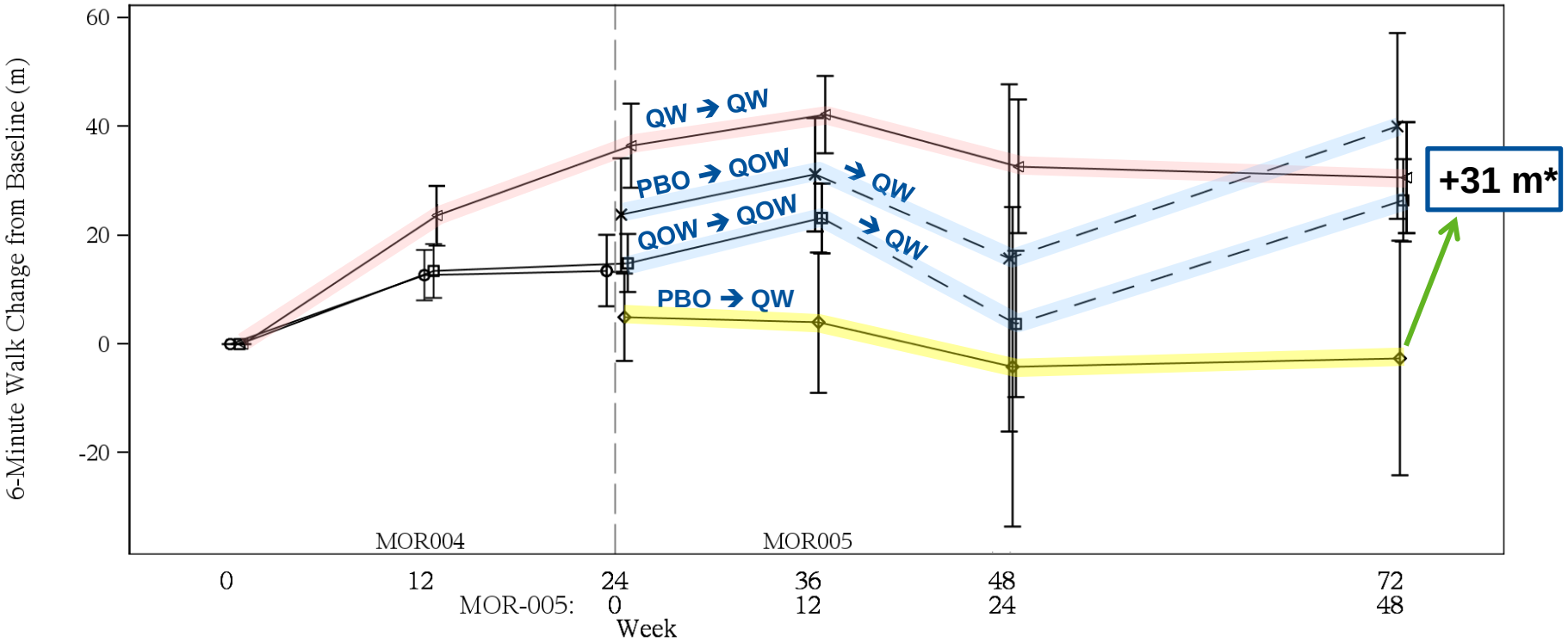
Repeated Measures Analysis: ITT Population (MOR-004/MOR-005)



Elosulfase 2.0 mg/kg/week	n=	58	58	57	54	27	54

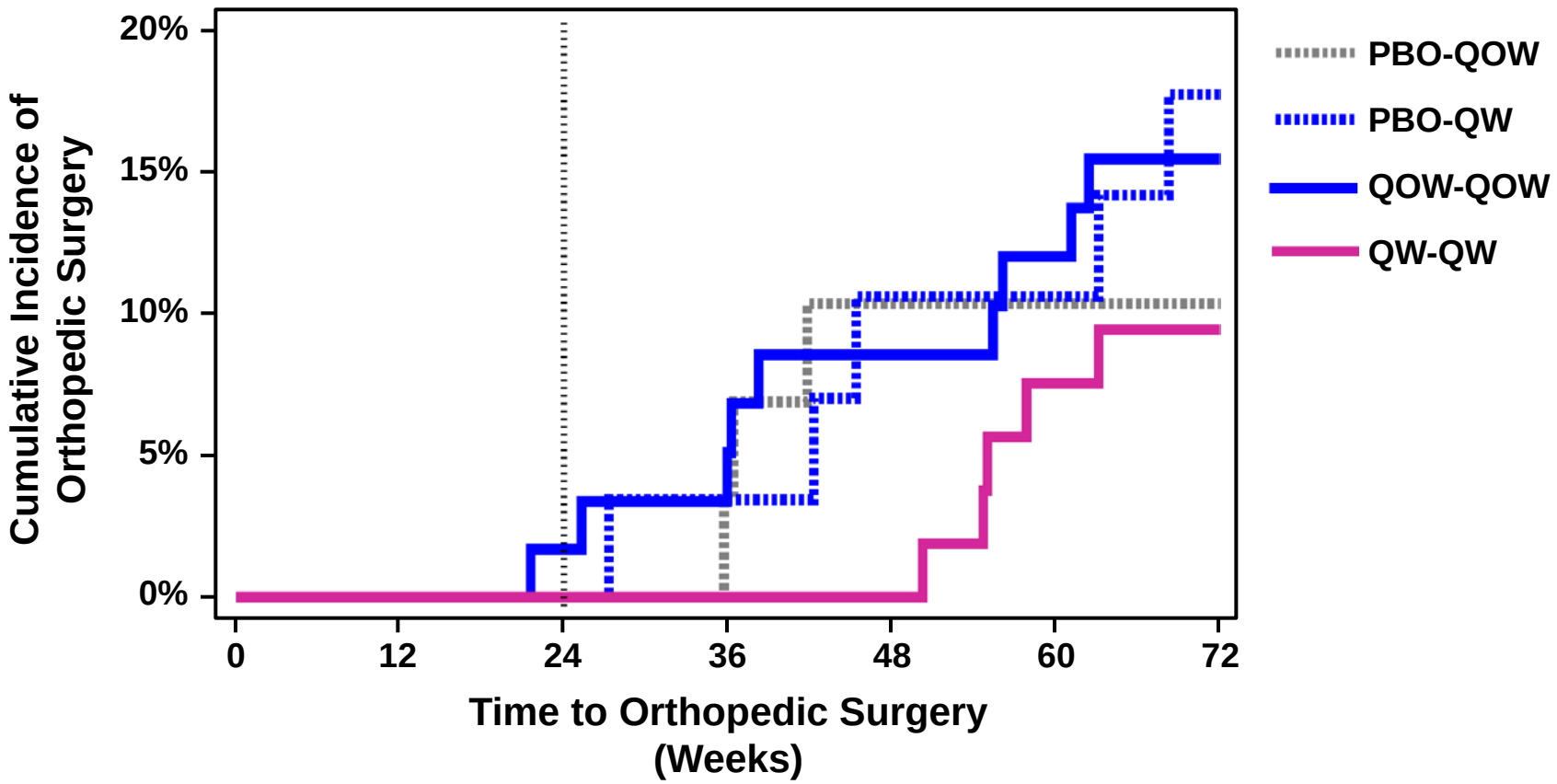
MOR-005
6MWT – All Treatment Groups

Mean Change in 6MWT from Baseline through Week 72 (ITT Population)



***PBO → QW: 5 subjects required orthopedic surgery; when censoring these subjects, the mean change from baseline at Week 72 is 31 m.**

MOR-004/005
Time to Orthopedic Surgery



- **Fewer orthopedic surgeries occurred in subjects receiving continuous weekly infusions of elosulfase alfa than QOW or placebo**

Clinical Efficacy Conclusions

- Pivotal Phase 3 study met primary endpoint of significant improvement from baseline in 6MWT distance at Week 24 for elosulfase alfa 2.0 mg/kg/week compared to placebo
- Totality of data including majority of exploratory endpoints directionally consistent with primary endpoint, supporting effectiveness of weekly dosing regimen
- Elosulfase alfa was efficacious across full spectrum of age, disease severity, and clinical manifestations in diverse patient population
- Long-term continuous treatment with elosulfase alfa generally maintained or improved efficacy measures
- Magnitude of observed effect is substantial in a disease characterized by progressive decline in mobility and endurance, resulting ultimately in need for life-long assistance with activities of daily living

Safety

Overview

- Exposure
- AEs and SAEs
- Severe allergic reactions
- Long-term safety
- Immunogenicity
- Safety assessments
  - Physical exam
  - Laboratory data
  - Concomitant meds
  - EKGs and ECHOs

Exposure to Elosulfase Alfa

- Total of 235 subjects treated with elosulfase alfa for periods ranging from 1 to 170 weeks
- Overall mean duration of exposure: 50.2 weeks
- 86 subjects exposed for more than 48 weeks
- More than 98% of infusions performed on schedule
  - Over 11,000 infusions administered
- Represents largest clinical safety database for a lysosomal storage disorder (LSD) at time of filing

120 day safety update:

- 244 subjects treated with elosulfase alfa
- Mean duration of exposure: 61.7 weeks
- 155 exposed for > 48 weeks

MOR-004
Common AEs >20%

Preferred Term, n (%)	Placebo n=59	elosulfase alfa 2.0 mg/kg/qow n=59	elosulfase alfa 2.0 mg/kg/week n=58
Subjects with at least 1 reported AE	57 (96.6)	59 (100.0)	56 (96.6)
Vomiting	21 (35.6)	21 (35.6)	26 (44.8)
Pyrexia	17 (28.8)	22 (37.3)	25 (43.1)
Headache	21 (35.6)	24 (40.7)	24 (41.4)
Nausea	12 (20.3)	14 (23.7)	18 (31.0)
Cough	21 (35.6)	17 (28.8)	16 (27.6)
Abdominal pain	5 (8.5)	8 (13.6)	14 (24.1)
Diarrhoea	7 (11.9)	12 (20.3)	12 (20.7)
Oropharyngeal pain	7 (11.9)	9 (15.3)	12 (20.7)
Arthralgia	17 (28.8)	9 (15.3)	10 (17.2)
Nasopharyngitis	9 (15.3)	12 (20.3)	10 (17.2)
Fatigue	15 (25.4)	8 (13.6)	9 (15.5)
Pain in extremity	9 (15.3)	14 (23.7)	9 (15.5)

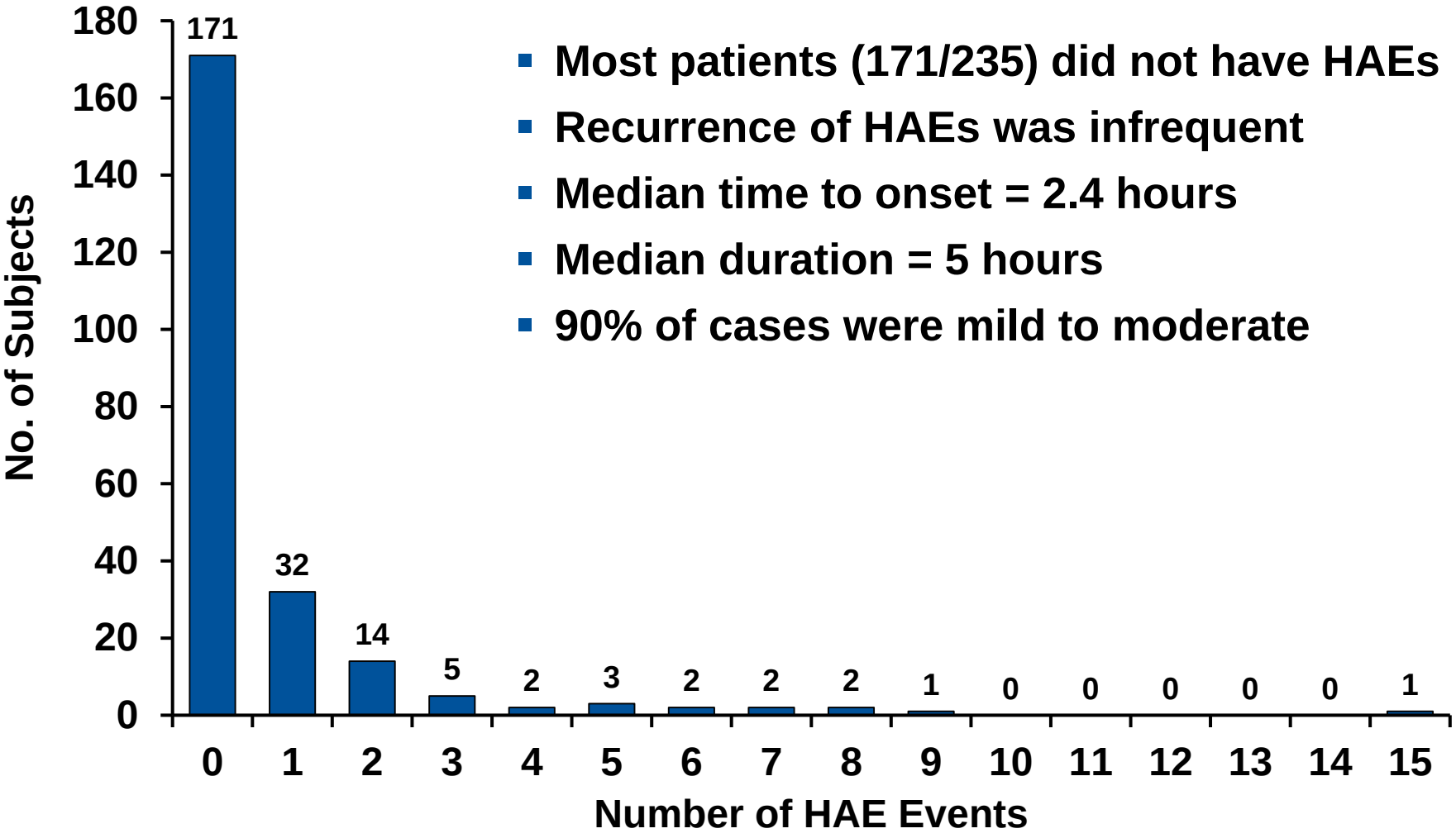
AEs coded by MedDRA version 15.0; Subjects who experienced more than one AE within a category were counted once within that category.

MOR-004 SAEs

Preferred Term, n (%)	Placebo n=59	elosulfase alfa 2.0 mg/kg/qow n=59	elosulfase alfa 2.0 mg/kg/week n=58
Subjects with at least 1 reported SAE	2 (3.4)	4 (6.8)	9 (15.5)
Pneumonia	0	0	2 (3.4)
Hypersensitivity	0	0	1 (1.7)
Infusion site pain	0	0	1 (1.7)
Lower respiratory tract infection	0	0	1 (1.7)
Otitis media	0	1 (1.7)	1 (1.7)
Urticaria	0	0	1 (1.7)
Viral upper respiratory tract infection	0	0	1 (1.7)
Vomiting	0	0	1 (1.7)
Anaphylactic reaction	0	1 (1.7)	0
Cervical cord compression	1 (1.7)	0	0
Deafness	1 (1.7)	0	0
Dengue fever	0	1 (1.7)	0
Suture removal	0	1 (1.7)	0

SAEs coded by MedDRA version 15.0; Subjects with more than one SAE within a MedDRA PT were counted once.
Includes only Treatment Emergent Serious Adverse Events.

Hypersensitivity AEs



- Most patients (171/235) did not have HAEs
- Recurrence of HAEs was infrequent
- Median time to onset = 2.4 hours
- Median duration = 5 hours
- 90% of cases were mild to moderate

Anaphylaxis Adverse Events

- HAEs across studies assessed against NIAID/FAAN 2006 criteria
- 18 (7.7%) subjects identified as having events that met criteria for potential anaphylaxis
- 26 events of anaphylaxis out of 11,239 infusions (0.2%)
  - All events resolved within 24 hours
  - Most treated with infusion rate adjustment and antihistamines
  - 4 events required epinephrine treatment
  - 2 events required hospitalization
  - No events of cardiac or respiratory arrest/no intubations
  - All but 3 subjects continued to receive infusions

Long-term Safety Summary All Exposed Population

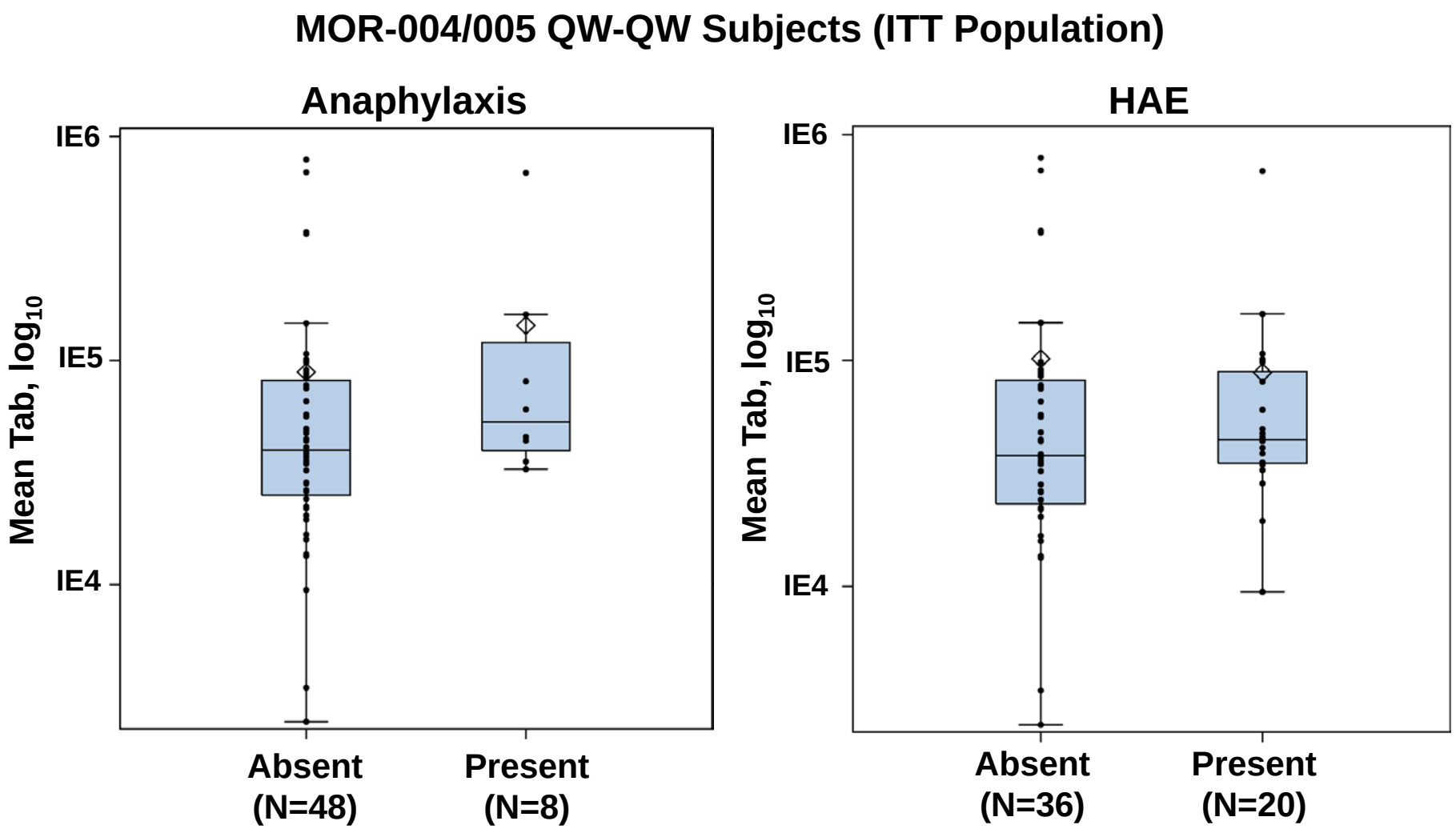
- Adverse events decreased in frequency with extended treatment duration
- Rate of SAEs remained low and constant over time
  - Serious respiratory infections decreased
- <1% of infusions were interrupted or discontinued due to an AE that required medical intervention
- Only 3 subjects permanently discontinued due to an AE
  - 2 in MOR-002 and 1 in MOR-005
- No deaths

Immunogenicity

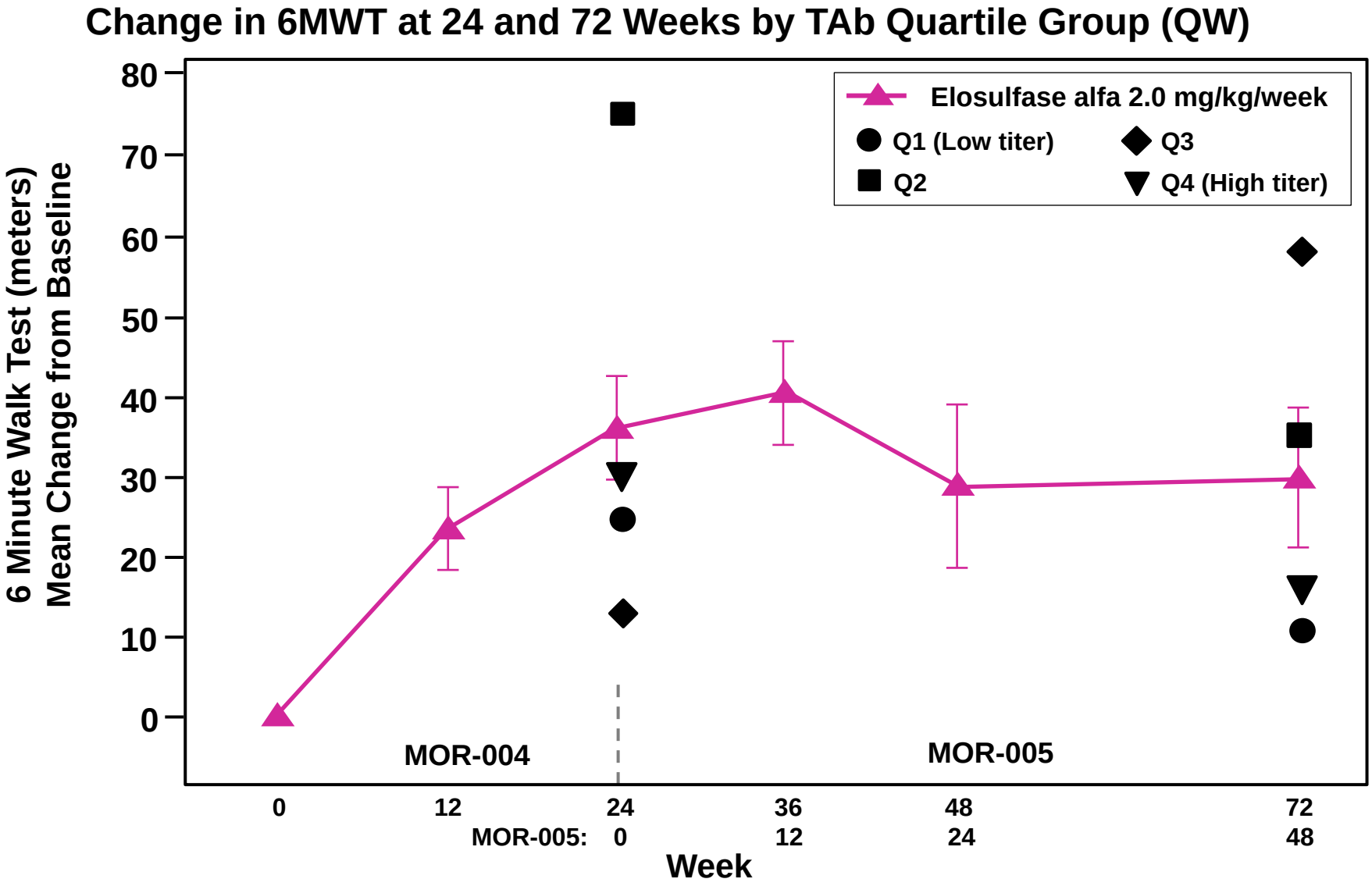
Immunogenicity Overview

- All treated subjects developed sustained anti-elosulfase alfa antibody titers
- Neutralizing antibodies were detected in a majority of subjects
- IgE was not consistently associated with anaphylaxis or increased incidence of HAE
- Comparable immunogenicity profile in long-term extension studies

MOR-004/005 – TAb Titers in Subjects with and without Anaphylaxis and HAE



MOR-004/005 TAb Titer and Change in 6MWT from Baseline to Weeks 24 and 72



Overall Safety/Immunogenicity Summary

- Most common side effects
  - Pyrexia, vomiting, headache, nausea, abdominal pain and fatigue
- Most important adverse reactions were acute reactions associated with infusion
  - 26 episodes in 18 patients met Sampson's criteria of anaphylaxis
  - Out of >11,000 infusions (0.2%)
  - Most events only occurred once
  - Most patients tolerated re-challenge, only 3 patients discontinued
- No deaths
- Anti-drug Abs frequent, but not associated with HAE or decreased efficacy

Post-marketing Surveillance Program

- Morquio A syndrome Global Disease Registry
  - 10 year registry to characterize and describe Morquio A syndrome population (variability, progression, and natural history)
  - Evaluate long-term effectiveness and safety of elosulfase alfa under standard care practices
- Continuous monitoring of elosulfase alfa safety profile will include signal detection, updating labeling and regular review of the risk-management plan

Agenda

Introduction	**Henry Fuchs, MD** Chief Medical Officer BioMarin Pharmaceutical Inc.
Description of Morquio A syndrome	**Christian Hendriksz, MB ChB, MSc, MRCP, FRCPCH** Birmingham Children's Hospital NHS Foundation Trust, United Kingdom Principal investigator, Phase 1/2, Phase 3 Trials
Clinical Trial Results	**Christine Haller, MD** Senior Group Medical Director BioMarin Pharmaceutical Inc.
Risk Benefit Assessment	**Christian Hendriksz, MB ChB, MSc, MRCP, FRCPCH**
Conclusion	**Henry Fuchs, MD**

Risk:Benefit

Christian Hendriksz, MB ChB, MSc, MRCP, FRCPCH

Birmingham Children's Hospital

NHS Foundation Trust, United Kingdom

Clinical Director- Acute Medicine Salford Royal NHS Foundation Trust

Favorable Risk:Benefit Profile

- **Enormously challenging disease with nothing but symptomatic supportive care at present**
- **Results demonstrate clinical benefit and acceptable safety profile of elosulfase alfa**
- **As with other ERTs in rare genetic diseases, initiating treatment as soon as possible after diagnosis is expected to provide maximal benefit**

Case Example from MOR-002

- Diagnosis age 14, just prior to spinal surgery
- Started MOR-002 age 16, wheelchair bound
- Totally caregiver dependent
- Length 101.7 cm, standing height 94.3 cm
- Sitting height 57 cm, weight 22.8 kg

- At week 60 in MOR-002 when video was taken:
  - No improvement in 6MWT and 3MSCT

Example of Patient Knee Walking

Patient Signing

Agenda

Introduction	**Henry Fuchs, MD** Chief Medical Officer BioMarin Pharmaceutical Inc.
Description of MPS IVA	**Christian Hendriksz, MB ChB, MSc, MRCP, FRCPCH** Birmingham Children's Hospital NHS Foundation Trust, United Kingdom Principal investigator, Phase 1/2, Phase 3 Trials
Clinical Trial Results	**Christine Haller, MD** Senior Group Medical Director BioMarin Pharmaceutical Inc.
Risk Benefit Assessment	**Christian Hendriksz, MB ChB, MSc, MRCP, FRCPCH**
Conclusion	**Henry Fuchs, MD**

Conclusion

Henry Fuchs, MD

Chief Medical Officer
BioMarin Pharmaceutical Inc.

Sponsor Perspective on Question 1 6MWT (1 of 2)

- No widely accepted method to assess treatment benefit in MPS IVA
- Strength of test
  - Fatigue, decreased endurance, joint pain are most bothersome symptoms
  - Improvement directly pertains to how a patient functions
- Limitations of test
  - Severely impaired in MPS IVA
  - Wide range of variability
  - Effort dependent

Sponsor Perspective on Question 1 6MWT (2 of 2)

Baseline 6MWT (m)			Improvement over Baseline 6MWT (m)			% Improvement over Baseline 6MWT		
1	Elaprase	392	1	Revatio	45	1	Revatio	13%
2	Adempas	363	2	Aldurazyme	38	2	Aldurazyme	12%
3	Tyvaso	359	3	Adempas	36	3	Elosulfase alfa	11%
4	Remodulin	345	4	Tracleer	35	4	Tracleer	11%
5	Adcirca	343	5	Elaprase	35	5	Adempas	10%
6	Revatio	343	6	Adcirca	33	6	Adcirca	10%
7	Letairis	340	7	Letairis	31	7	Letairis	9%
8	Lumizyme	332	8	Lumizyme	28	8	Elaprase	9%
9	Tracleer	326	9	Elosulfase alfa	23	9	Lumizyme	8%
10	Aldurazyme	319	10	Tyvaso	20	10	Tyvaso	6%
11	Elosulfase alfa	204	11	Remodulin	10	11	Remodulin	3%

Sponsor Perspective on Question 2 Other Measures of Treatment Benefit

- 3MSCT: small increase, not significant
- Urinary KS: measure of pharmacodynamics
- Pulmonary function: trend to improvement; has supported prior applications in similar diseases
- Height: modest numerical improvements
- Caregiver and Mobility QOL: modest numerical improvements but no improvement in self-care
- No apparent effects in hearing, echocardiogram, corneal clouding, lower extremity length
- Additional supportive analyses
  - Orthopedic procedures delayed
  - AEs of fatigue and joint pain improved

Sponsor Perspective on Question 3 Totality of Evidence (1 of 2)

- 6MWT improvement
- 3 MSCT: small, insignificant increase
- Exploratory analyses provide larger context of treatment benefit
  - Improvement >100 m in high performing patients
  - Reduced reliance on walking assistance (HAQ)
  - Improved mobility and caregiver assessments
  - Improved respiratory function
  - Improved growth
  - Reduced fatigue and joint pain
  - Delayed surgery
  - Delayed progressive impairment of mobility

Sponsor Perspective on Question 3 Totality of Evidence (2 of 2)

- In patients whose walk >200 m
  - There was improvement in walking
  - Underlying disease is progressive in nature
- Eight patients whose walk improved the most (>100 m)
  - Four had baseline walk >200 m
  - Four had baseline walk <200 m
  - No discerning characteristics
- Analysis was exploratory in nature

Sponsor Perspective on Question 4 Safety

- **Most common side effects**
  - **Pyrexia, vomiting, headache, nausea, abdominal pain and fatigue**
- **Most important adverse reactions were acute reactions associated with infusion**
  - **26 episodes in 18 patients met Sampson's criteria of anaphylaxis**
  - **Out of >11,000 infusions (0.2%)**
  - **Most events only occurred once**
  - **Most patients tolerated re-challenge, only 3 patients discontinued**
- **Pre-treatment with antihistamines with or without antipyretics is recommended prior to the start of infusion**
  - **Administered under supervision of a trained healthcare professional**

Sponsor Perspective on Question 5 Recommend Approval

- Enormously challenging disease to study
  - Extremely rare, debilitating, complicated
  - Limited to no outcome data at start of program
  - Widely variable disease in phenotype, state of progression
- Overcame obstacles to demonstrate favorable risk:benefit
  - Well-conducted Phase 3 trial, clinical endpoint widely used
  - Significant effect on challenging primary endpoint
  - Data in most other domains, but not all, supportive
  - Main important side effect infrequent and manageable
- Sponsor commitment to Morquio A continues as with MPS I, MPS VI
  - Post-approval registry
  - Post-approval risk management plan
  - Document long-term outcomes

Endocrinologic and Metabolic Drugs Advisory Committee (EMDAC) Meeting

Biologics License Application (BLA) 125460 for VIMIZIM (elosulfase alfa)

November 19, 2013