Life is Rare

Givinostat Update

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- Information concerning pharmaceuticals and medical devices (including those under development) contained herein is not intended as advertising or as medical advice. Givinostat is not currently approved in Japan, clinical data is for investor-information purposes only, this material does not constitute promotion of an unapproved product.

Italfarmaco S.p.A: Licensor of Givinostat

ITALFARMACO

Italfarmaco S.p.A

- Private global pharmaceutical company founded in 1938 (Milan, Italy)
- Development, manufacturing, marketing and sales of branded prescription & non-prescription products
- Proven success in many therapeutic areas including immuno-oncology, neurology, and cardiovascular disease
- Rare disease unit includes programs for Duchenne muscular dystrophy, ALS and polycythemia vera

Employees
>4000

Business
>90 countries

Manufacturing
6 sites
(GMP-compliant)

Gross sales
€ 1.1B
(2024)

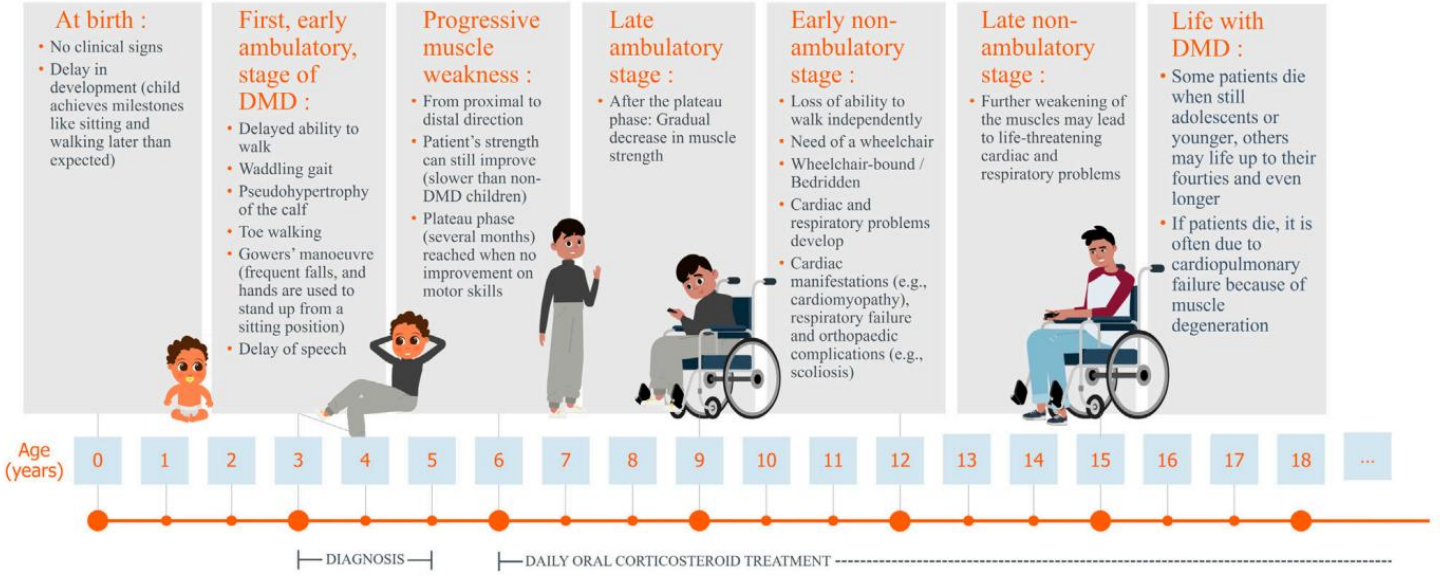
ALS, Amyotrophic lateral sclerosis; GMP, Good Manufacturing Practice

Overview: Duchenne Muscular Dystrophy (DMD)

【Etiology・Clinical course[1]】

- Caused by mutations in the dystrophin gene, leading to the absence of dystrophin protein
- Onset at 3–5 years of age, progressive motor decline; loss of ambulation around 10 years

【Life cycle of the patients with DMD[2]】

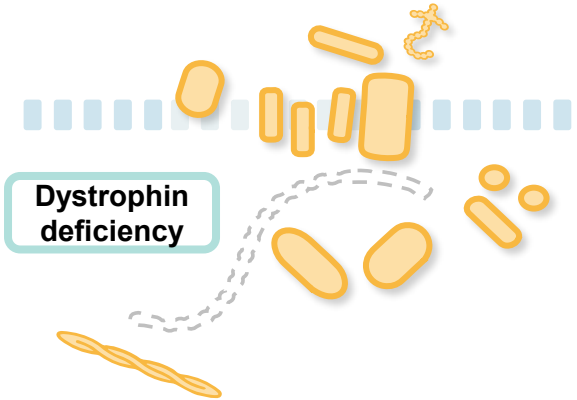


DMD, duchenne muscular dystrophy

1. Clinical practice guidelines for Duchenne Muscular Dystrophy 2014 (Japanese)
2. Desmet T, et al., *Front Pharmacol.* 2025; 16: 1662586.

Pathological Hallmarks of DMD

Dystrophin deficiency and disrupted HDAC activity **mediate the regulation of muscle homeostasis**[1-3]



Pathological events associated with HDAC upregulation[3]

HDAC upregulation

- Muscular atrophy[4-8]
- Activation of chronic inflammatory pathways[4,6,7]
- Impairment of muscle repair mechanisms[4,6,7]
- Fibrogenesis and adipogenesis[4,6,7]

DMD, Duchenne muscular dystrophy; HDAC, histone deacetylase.

1. Consalvi S, et al. *Mol Med.* 2011;17(5–6):457-465. **2.** Kodippili K, et al. *Front Physiol.* 2023;14:1180980. **3.** Sandonà M, et al. *Int J Mol Sci.* 2023;24(5):4306. **4.** Wilson DGS, et al. *Commun Biol.* 2022;5(1):1022. **5.** Campbell KP, et al. *Nature.* 1989;338(6212):259-262. **6.** Guiraud S, et al. *Exp Physiol.* 2015;100(12):1458-1467.**7.** Reid AL, Alexander MS. *Life.* 2021;11(7):648; **8.** Ervasti JM, et al. *J Cell Biol.* 1993;122(4):809-823.

Givinostat is a potent pan-HDAC inhibitor

Inhibition of the upregulated HDAC in DMD **redresses the imbalance in muscle homeostasis**, leading to[1,2]:

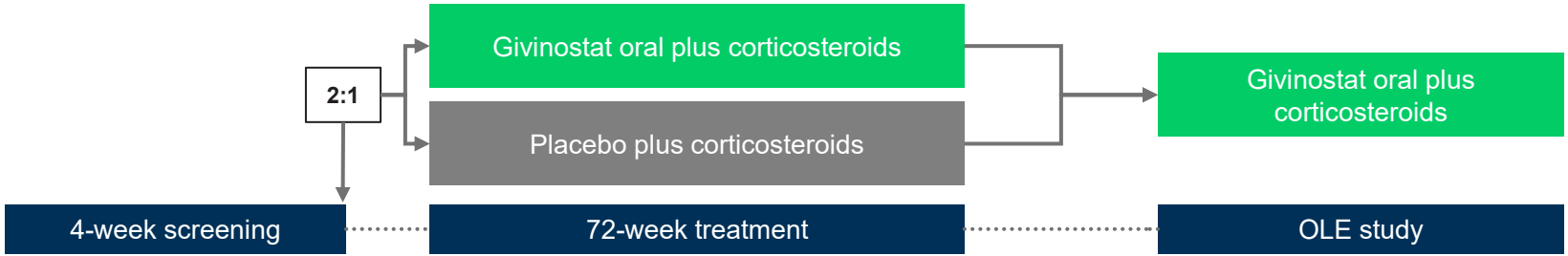
- **Increased** muscle repair and regeneration mechanisms[3,4]
- **Reduced** fibrosis and fat deposition[3]
- **Delayed** disease progression with preservation of functional capabilities[5,6]

DMD, Duchenne muscular dystrophy; HDAC, histone deacetylase.

1. Consalvi S et al. *Mol Med.* 2011;17(5-6):457-465. **2.** Kodippili K, Rudnicki MA. *Front Physiol.* 2023;14:1180980. **3.** Bettica P et al. *Neuromuscul Disord.* 2016;26(10):643-649. **4.** Sandonà M et al. *EMBO Rep.* 2020;21(9):e50863.
5. Mercuri E et al. *Lancet Neurol*. 2024;23(4):393-403. **6.** ClinicalTrials.gov. NCT02851797. Updated 2 February 2023. Available at https://clinicaltrials.gov/study/NCT02851797. Accessed August 1, 2024.

EPIDYS: Phase 3 Study Design[1-3]

- Randomized, double-blind, parallel-group, placebo-controlled study with a total of 179 ambulant boys randomized 2:1 (givinostat:placebo)
- Givinostat or placebo were administered in addition to corticosteroids

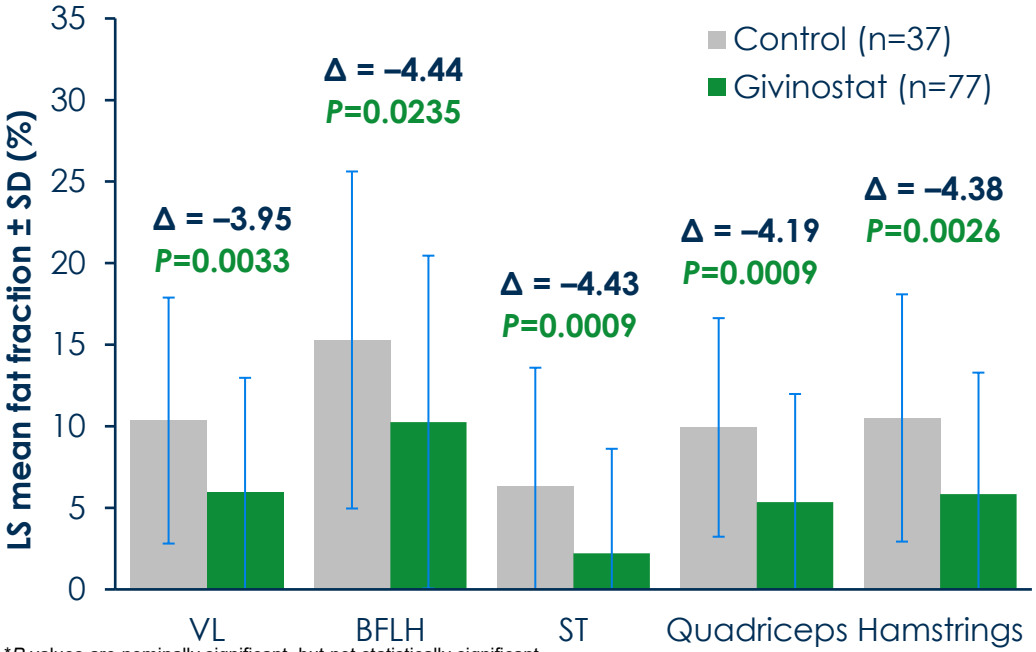


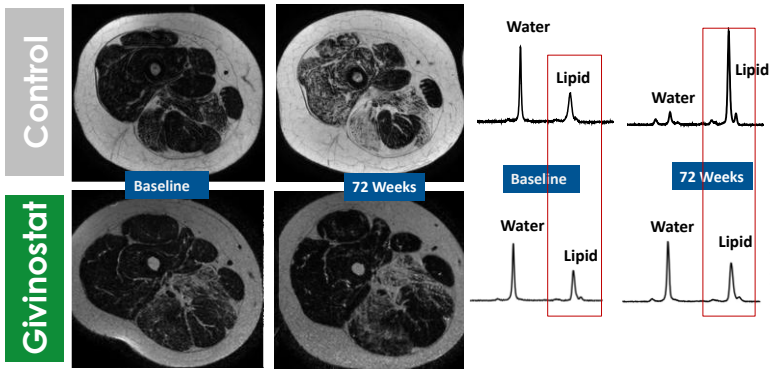
OLE, open-label extension.

1. Mercuri E et al. *Lancet Neurol*. 2024;23(4):393-403. **2**. ClinicalTrials.gov. NCT02851797. Updated February 2, 2023. Accessed May 9, 2024. https://clinicaltrials.gov/study/NCT02851797
3. Vandenborne K. Oral presentation at Muscular Dystrophy Association Clinical & Scientific Conference; March 19-22, 2023; Dallas, TX, USA.

Givinostat reduced fat fraction in 5 key muscles important for ambulation comprising the quadriceps and hamstrings groups compared with control at 72 weeks

Fat fraction in quadriceps and hamstrings muscles*





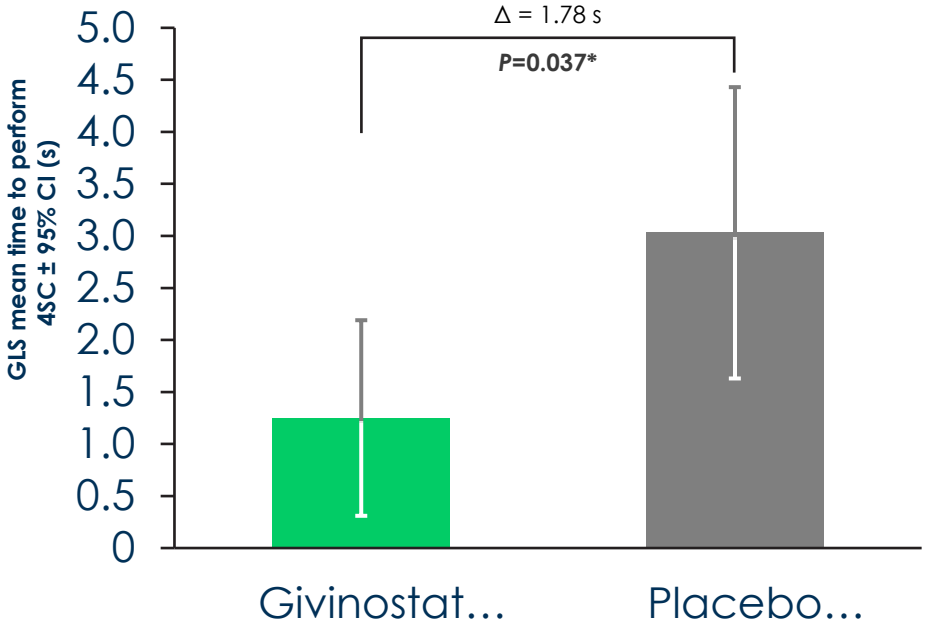
The images on the slide are from a single patient and may not be representative of all patients in EPIDYS.

*P-values are nominally significant, but not statistically significant.
BFLH, biceps femoris long head; LS, least squares; SD, standard deviation; ST, semitendinosus; VL, vastus lateralis.
Vandenborne K. Oral presentation at Muscular Dystrophy Association Clinical & Scientific Conference; March 19-22, 2023; Dallas, TX, USA.

EPIDYS Study: Primary Endpoint — 4SC at Week 72[1]

- At week 72, givinostat plus corticosteroids reduced the decline in time to perform the 4SC test by 1.78 s when compared with placebo plus corticosteroids

Mean change from baseline in time to perform the 4SC test at 72 weeks (non-log transformed)



*Data are means and 95% confidence intervals. The confidence intervals have not been adjusted for multiplicity and should not be used for hypothesis testing. Baseline mean values were 3.39 s and 3.48 s for the givinostat and placebo groups, respectively. All patients were also receiving systemic corticosteroids in a dose and regimen that was to remain unchanged over the follow-up period.
4SC, 4-stair climb; GLS, geometric least squares; s, seconds.

1. Mercuri E et al. *Lancet Neurol*. 2024;23(4):393-403.

Adverse Events (AEs) for Givinostat in the EPIDYS Study were Predictable, and Most of Them were Managed Through Dose Adjustment[1,2]

Gastrointestinal disturbances

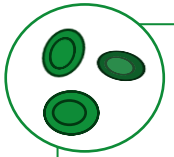
Gastrointestinal disturbances were the most common AEs in the EPIDYS study

- Diarrhoea (36%* vs 18%†)
- Vomiting (29%* vs 13%†)
- Abdominal pain (35%* vs 26%†)

Most cases were mild to moderate.

Diarrhoea usually occurred within the first few weeks of treatment.

Vomiting and nausea occurred within the first 2 months of treatment



Low platelet count

Low platelet counts occurred in 32% of patients treated with givinostat in EPIDYS vs none in the control group

The maximum decrease in platelets occurred within the first 2 months of therapy and remained low throughout the course of therapy.

In a few patients, thrombocytopenia was associated with bleeding events including epistaxis, hematoma or contusions.

Elevated triglycerides

Increased triglycerides occurred in 23% of patients treated with givinostat in EPIDYS vs 7% in the control group

High triglycerides (i.e., levels greater than 300 mg/dL) resulted in discontinuation and led to dosage modification in 2% and 8%, respectively, of patients treated with givinostat.

*Givinostat; †Placebo.
AE, adverse event.
1. Mercuri E, et al. Lancet Neurol. 2024;23(4):393–403; 2. Givinostat US PRESCRIBING INFORMATION Revised: 11/2024

Japan Development Plan

Based on discussions with the PMDA, we aim to achieve regulatory filing by the end of 2026 leveraging overseas clinical data

1 Development timeline

By end-2026 ODD, MAA

By end-2027 **Approval**
Commercial Launch

2 Clinical study in Japanese patients

- Evaluation of pharmacokinetics and safety
- **Conduct independently** of the Japanese regulatory filling and review process
- Initial CTN already submitted

Clinical Study Overview (Phase 2)	
Study Design	• Open-label, single-arm
Objective	• Collection of pharmacokinetic and safety data in Japanese patients with DMD
Target Enrollment	• 20 patients (10 ambulatory, 10 non-ambulatory)
Age Range	• ≧6 to <18 years
Treatment Duration	• 6 months

CTN, clinical trial notification; DMD, Duchenne muscular dystrophy; MAA, marketing authorization application; ODD, orphan drug designation; PMDA, Pharmaceuticals and Medical Devices Agency

Unmet Medical Needs in DMD Treatment

Only two therapies approved in Japan (excluding steroid therapy)

	Approval status			Target DMD Patients[1]
	Japan	US	EU	
Gene therapy	✓[2]	✓	—	Japan; Negative for anti-AAVrh74 antibodies Ambulatory patients 3 years to less than 8 years
Exon skipping	✓[2]	✓	—	Japan; Patients with specific genetic mutations[3]

Eligible patients remain limited by age and genetic mutation criteria, leaving substantial unmet medical needs in DMD

Givinostat	—	✓	✓[2]	**US;** **≥6 years** **EU;** **Ambulatory patients ≥6 years on concomitant steroid therapy**

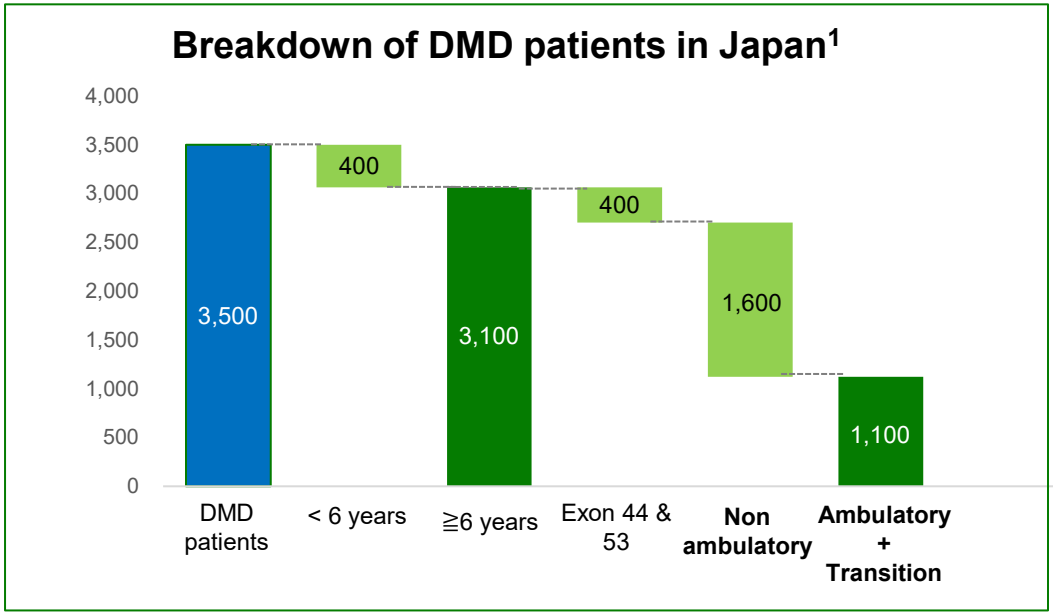
AAV, adeno associated virus; DMD, Duchenne muscular dystrophy

1. Based on labels for each product 2.Conditional approval 3. Patients who have a confirmed mutation of the DMD gene that is amenable to exon 53 skipping

Givinostat as a Key Driver of Revenue Growth

Givinostat

US; ≥6 years
EU; Ambulatory patients ≥6 years on concomitant steroid therapy



‘Ambulatory patients ≥6 years’
≧ 1,000 patients

Treatment cost; JPY 50 million/year[2]
Assuming 70% of eligible patients receive treatment

Estimated Revenue:
JPY 35 Billion

DMD, Duchenne muscular dystrophy; JPY, Japanese Yen
1. Company estimated based on ‘Kawai M. *No To Hattatsu*. (Japanese) 2013;45(Supple.):S324’, ‘Remudy (Registry of Muscular Dystrophy)’ and ‘Nakamura H et al. Orphanet J Rare Dis. 2013;8:60’
2. Estimated based on overseas treatment costs of givinostat (Company analysis)

Givinostat Update — Key Takeaways —

1 Obtain approval and launch givinostat in Japan in 2027

- Development plan determined following consultation with PMDA
- MAA will be filed in 2026, primarily using overseas clinical data

2 Expected to contribute to mid- to long-term earnings

- Givinostat can be used regardless of specific genetic mutations
  - Addresses a substantial unmet medical need
- Strong commercial potential in Japan

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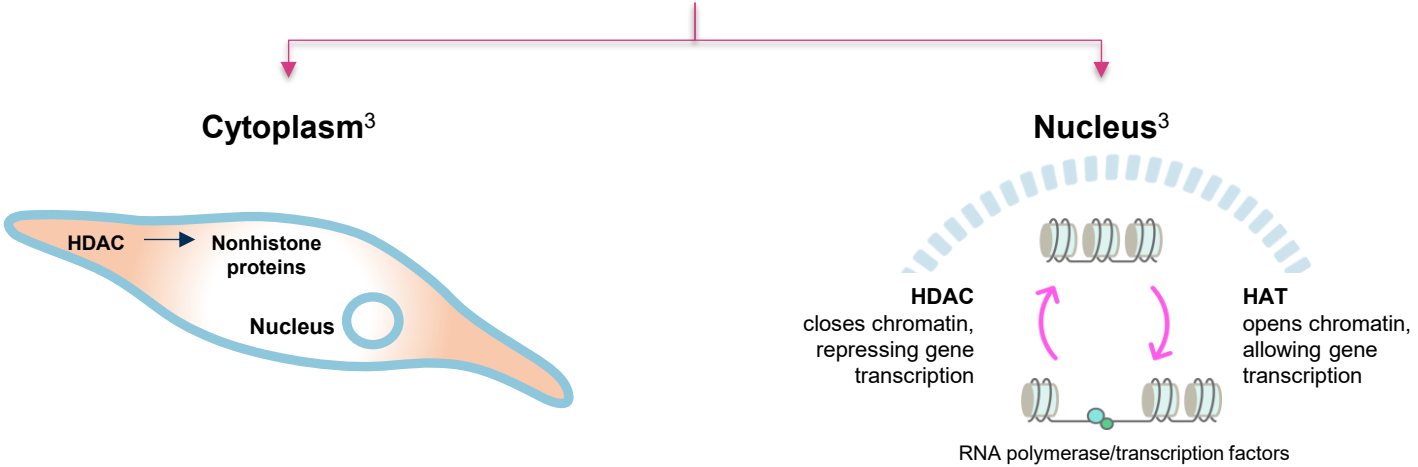
Appendix

Role of HDACs in Regulating Muscle Homeostasis

HDACs help mediate muscle homeostasis via **cytoplasmic** and **nuclear** activity[1,2]



HDACs regulate cellular homeostasis by acting on both histone and non-histone proteins[4]

- Reduces transcriptional accessibility[5]
- Regulates protein stability and localization, transcription factors, hormone receptors, mitochondrial proteins, enzymatic activity, mRNA stability[4]

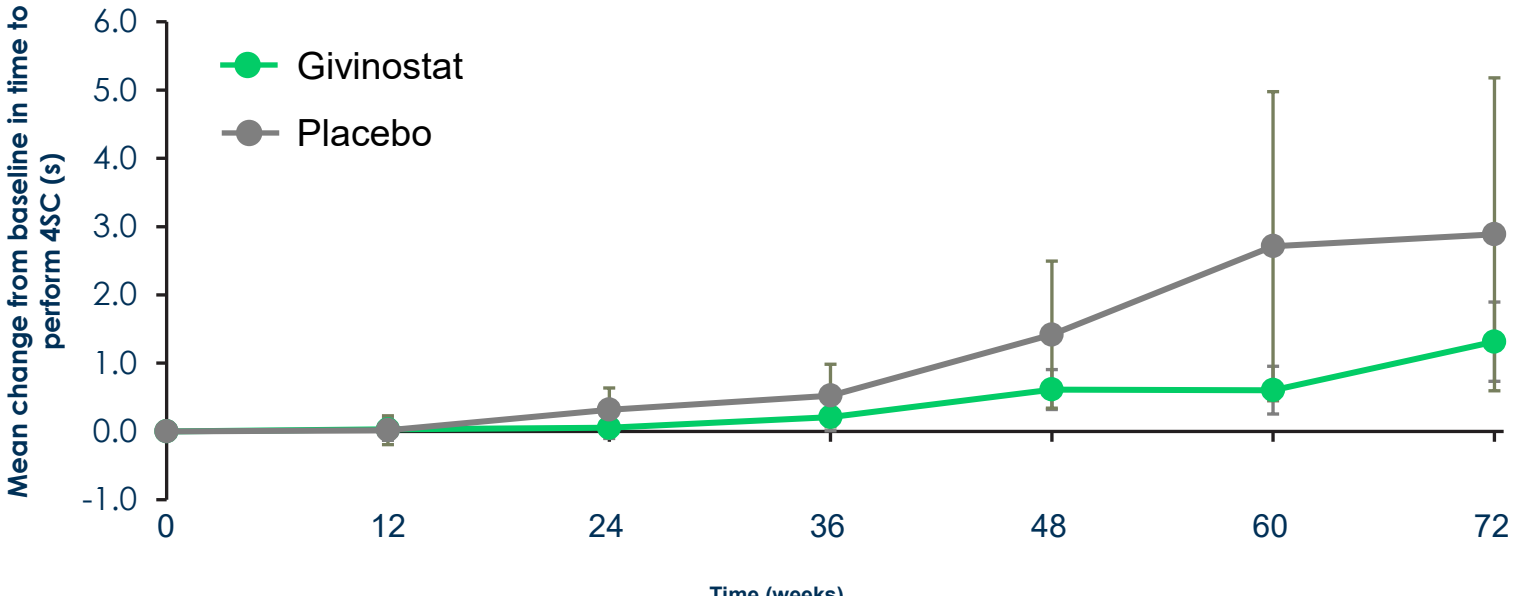
*HDAC and HAT work in balance to regulate the expression of muscle repair factors.

HAT, histone acetyltransferase; HDAC, histone deacetylase; mRNA, messenger ribonucleic acid; RNA, ribonucleic acid.

1. Consalvi S, et al. *Mol Med.* 2011;17(5-6):457-465. **2.** Kodippili K, et al. *Front Physiol.* 2023;14:1180980. **3.** Sandonà M, et al. *Int J Mol Sci.* 2023;24(5):4306. **4.** Milazzo G, et al. *Genes.* 2020;11(5):556. **5.** Ceccacci E, et al. *Br J Cancer.* 2016;114(6):605-11.

EPIDYS Study: 4SC From Baseline to Week 72[1]

Mean change from baseline over 72 weeks in the 4SC test*



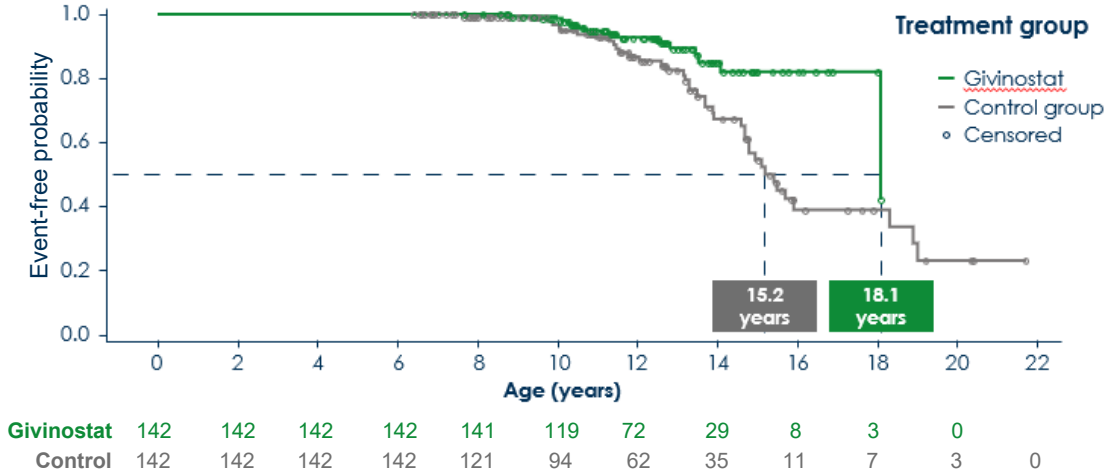
Mean change from baseline (95% CI), s						
Givinostat	0.03 (–0.13, 0.19)	0.05 (–0.10, 0.21)	0.21 (0.01, 0.41)	0.61 (0.32, 0.91)	0.60 (0.26, 0.95)	1.31 (0.73, 1.90)
Placebo	0.18 (–0.19, 0.23)	0.32 (–0.00, 0.64)	0.53 (0.07, 0.98)	1.42 (0.34, 2.49)	2.71 (0.45, 4.98)	2.89 (0.60, 5.18)

*Data are means and 95% confidence intervals. The confidence intervals have not been adjusted for multiplicity and should not be used for hypothesis testing. Baseline mean values were 3.39 s and 3.48 s for the givinostat and placebo groups, respectively. All patients were also receiving systemic corticosteroids in a dose and regimen that was to remain unchanged over the follow-up period.
4SC, 4-stair climb; s, seconds.

1. Mercuri E et al. *Lancet Neurol*. 2024;23(4):393-403.

Givinostat and Permanent Loss of Ambulation[1,2]

- Patients receiving givinostat plus corticosteroids (SoC) preserved their ability to walk for an additional 2.9 years (HR, 0.42; 95% CI, 0.23-0.76; *P*=0.004) compared with patients receiving SoC alone

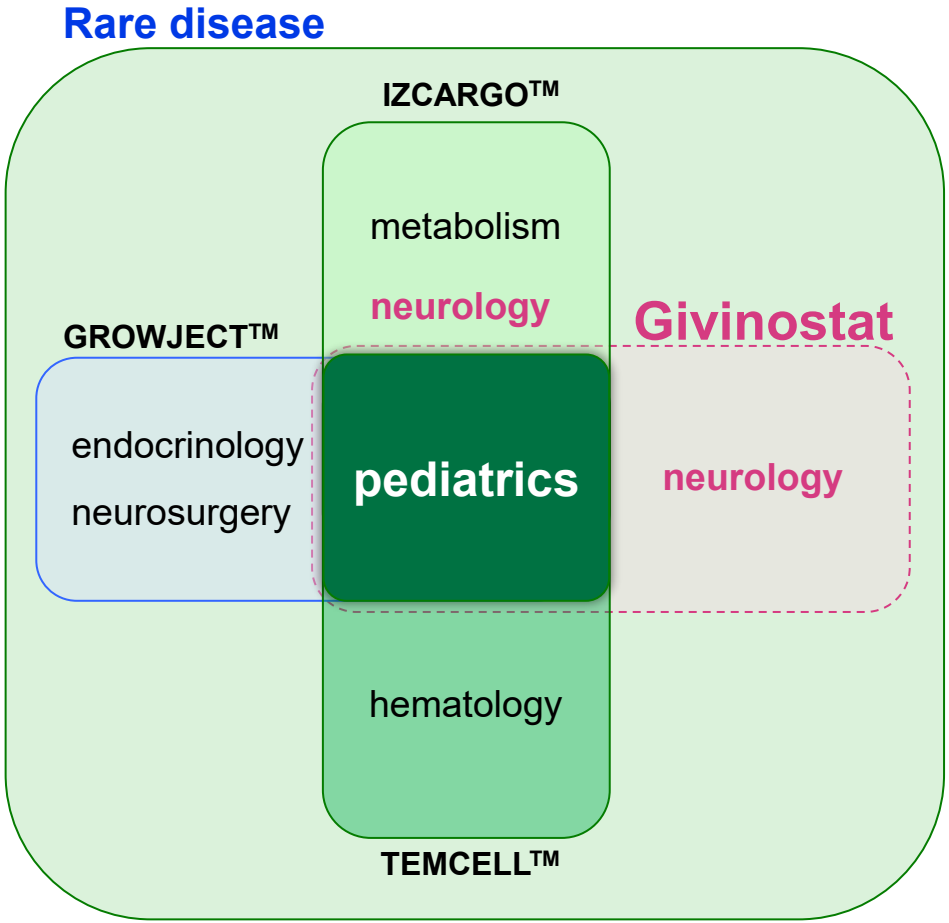


Parameter	Givinostat (n=142)	Control (n=142)
Patients, n (%)		
Assessed	142 (100)	142 (100)
Who lost ambulation	14 (9.9)	39 (27.5)
Censored	128 (90.1)	103 (72.5)
Age at loss of ambulation, years		
Median (95% CI)	18.1 (18.09, NE)	15.2 (14.70, 18.31)
P-value	0.004	
HR (95% CI)*	0.42 (0.23, 0.76)	

*HR and associated 95% CI and *P* value are obtained from a Cox proportional hazards model, including the treatment group as an independent classification factor.
HR, hazard ratio; NE, not estimable; SoC, standard of care.

1. McDonald CM, et al. *Ann Clin Transl Neurol*. Published online August 19, 2025. 2. Post hoc analysis comparing with natural history disease studies, using data that including the EPIDYS study

JCR's Competitive Strengths in Pediatric and Rare Disease Areas



- **Pediatric portfolio advantage**
  - Established presence in pediatrics
  - >60% coverage of DMD-treating institutions with existing products (internal data)
  - Clear marketing synergies
- **Extensive expertise in rare disease drug development**

DMD, duchenne muscular dystrophy