Givinostat Effect on Muscle Fat Fraction: Confirmatory Evidence in Duvyzat NDA Approval

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ITALFARMACO

Disclaimer

- Dr. Bettica is a full-time employee of Italfarmaco, the manufacturer of Givinostat
- Givinostat was recently approved by FDA and the MHRA for the treatment of Duchenne muscular dystrophy (DMD) in patients 6 years of age and older
- Givinostat is not approved in any other geography outside of the USA and the UK
- This presentation is intended for dissemination and discussion of scientific information only

Important Safety Information

Indication

DUVYZAT is a histone deacetylase inhibitor indicated for the treatment of Duchenne muscular dystrophy (DMD) in patients 6 years of age and older.

Important Safety Information

Warnings and precautions

- Hematological Changes: DUVYZAT can cause dose-related thrombocytopenia and other signs of myelosuppression, including anemia and neutropenia. Monitor platelets; dosage adjustment or discontinuation may be needed.
- Increased Triglycerides: An increase in triglycerides can occur; dosage modification may be needed. Discontinuation may be needed.
- Gastrointestinal Disturbances: Adjust dosage if moderate or severe diarrhea occurs. Antiemetics or antidiarrheal medications may be considered during treatment with DUVYZAT. Discontinue DUVYZAT if the symptoms persist.
- QTc Prolongation: Avoid use of DUVYZAT in patients who are at an increased risk for ventricular arrhythmias.

Recommended Evaluation and Testing Before Initiation of DUVYZAT:

Obtain and evaluate baseline platelet counts and triglycerides prior to initiation of DUVYZAT. Do not initiate DUVYZAT in patients with a platelet count less than 150 x 10^9/L. Monitor platelet counts and triglycerides as recommended during treatment to determine if dosage modifications are needed.

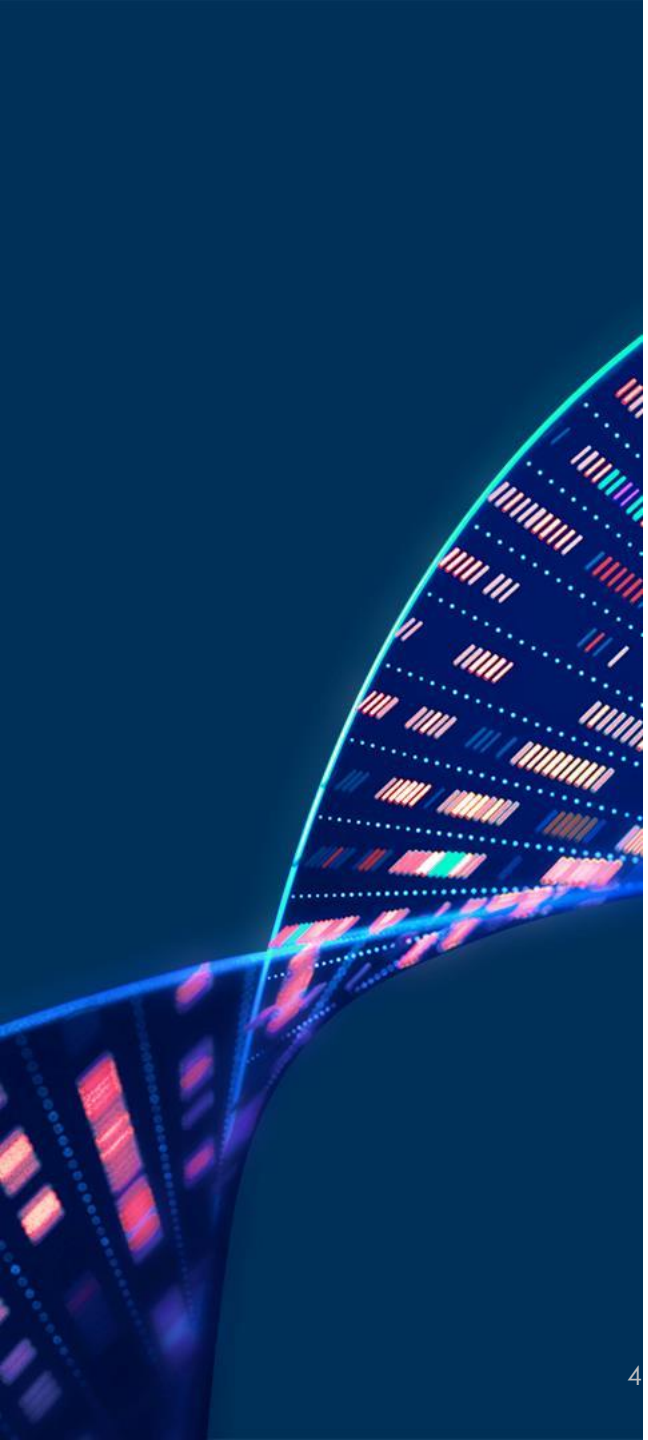
In addition, in patients with underlying cardiac disease or taking concomitant medications that cause QT prolongation, obtain ECGs when initiating treatment with DUVYZAT, during concomitant use, and as clinically indicated.

Most Common Adverse Reactions:

Most common adverse reactions (≥10% in DUVYZAT-treated patients) are diarrhea, abdominal pain, thrombocytopenia, nausea/vomiting, hypertriglyceridemia, and pyrexia.

To report SUSPECTED ADVERSE REACTIONS, contact ITF Therapeutics LLC. at 1-833-582-4312 or FDA at 1-800-FDA-1088 or www.fda.gov/medwatch.

Please see full Prescribing Information and Medication Guide.



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1) Introduction to Givinostat in DMD
2) Givinostat Clinical Development in DMD
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4) Concluding Remarks

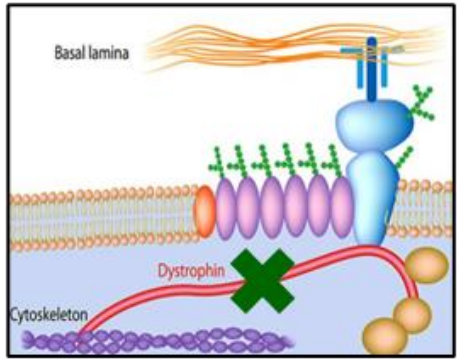
Duchenne muscular dystrophy: Etiopathogenesis
The sequence of events

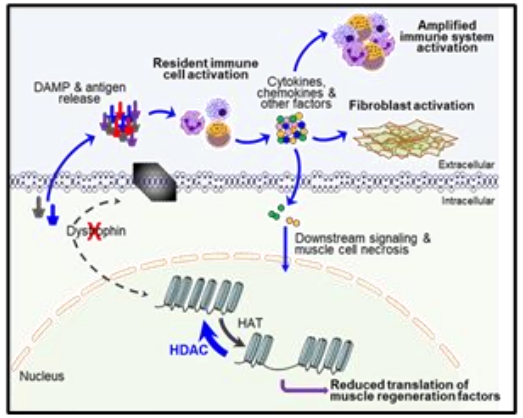
Genetic Defect → Lack of Dystrophin

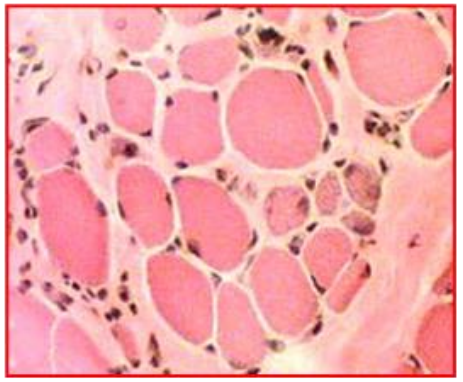
Muscle Damage, Necrosis, Inflammation, Impaired Repairing System

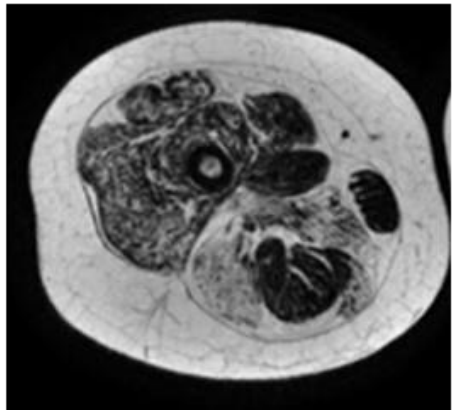
Fibro-Adipose Muscle Substitution

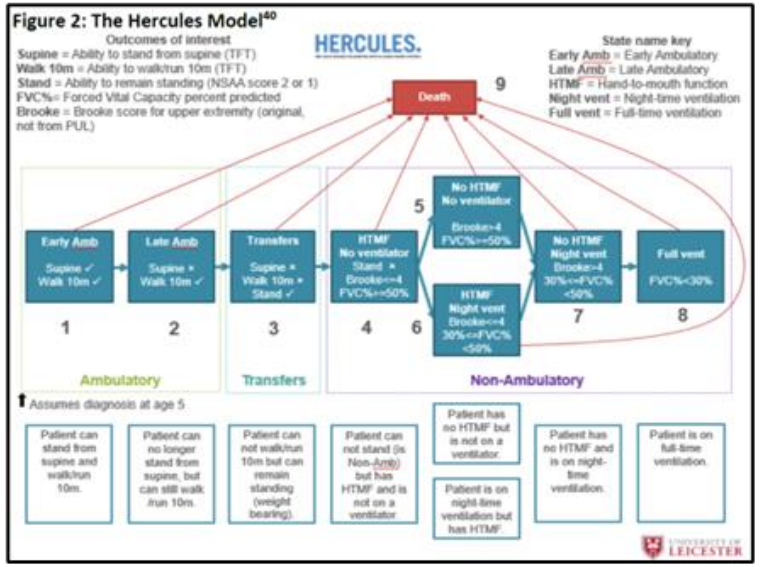
Progressive Muscle Function Insufficiency → Loss of Function → Death



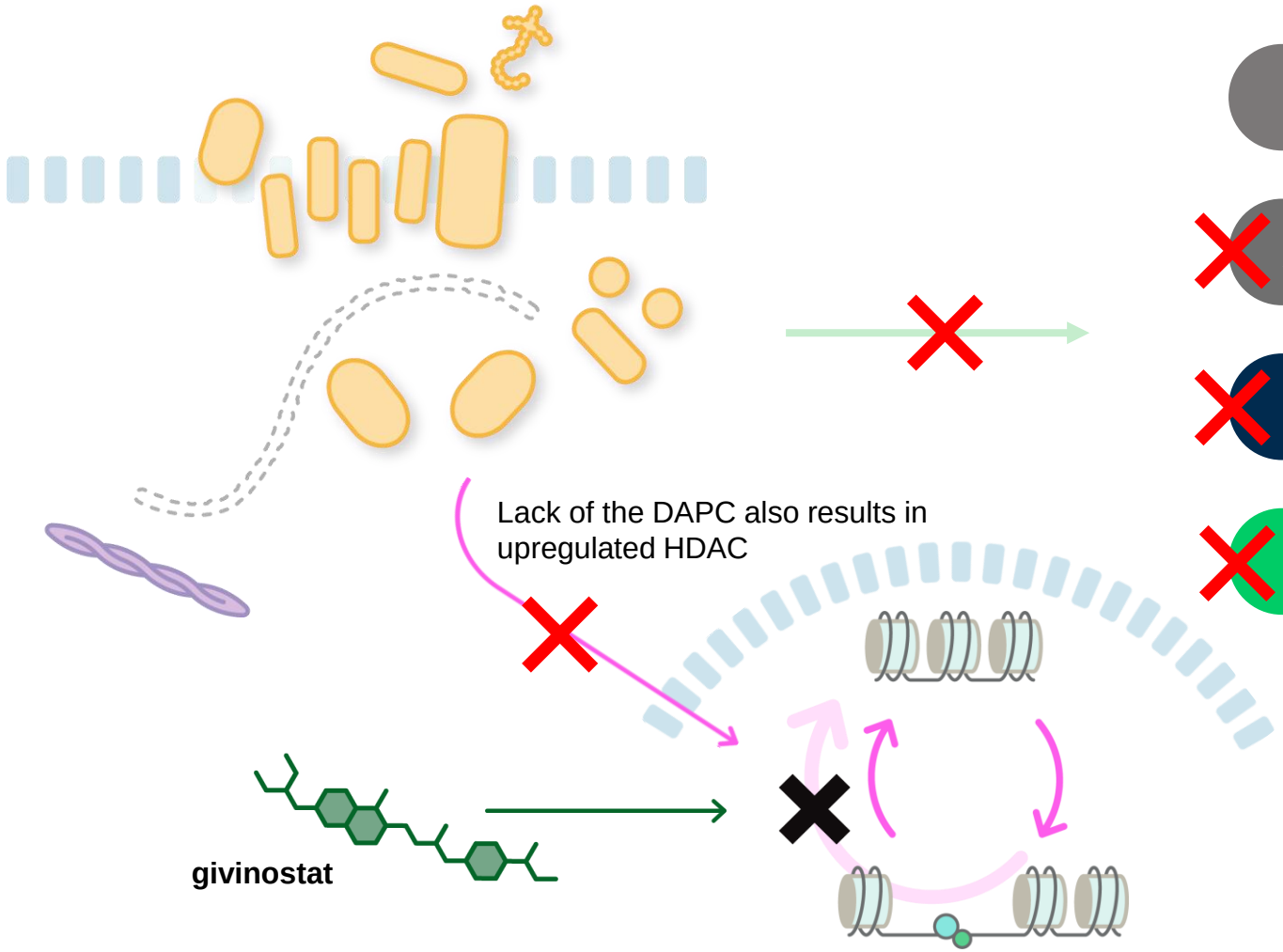








What happens when Givinostat is used?



Muscle fibre injury [6–9]

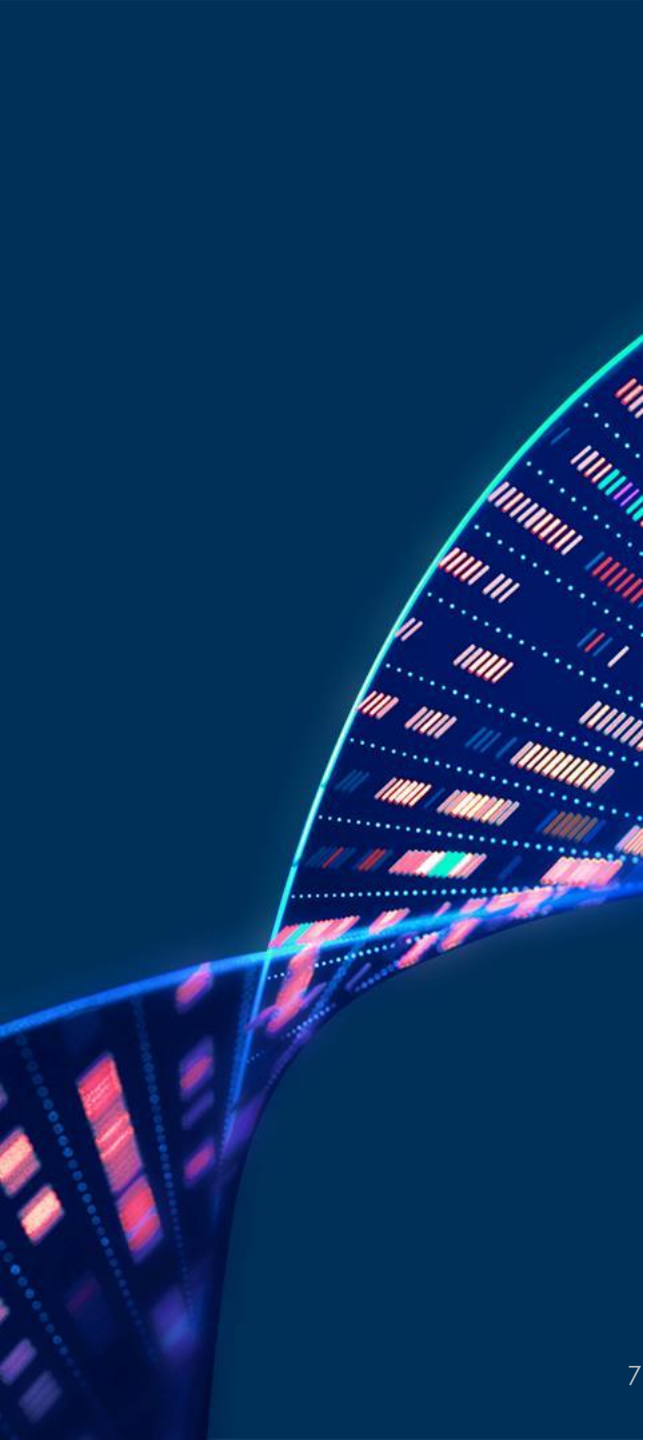
Activation of chronic inflammatory pathways[6,8,9]

Impairment of muscle regeneration mechanisms[6,8,9]

Fibrogenesis and adipogenesis[6,8–10]

DAPC, dystrophin-associated protein complex; 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. Mercuri E, et al. 2024. Manuscript submitted; 4. ClinicalTrials.gov. NCT02851797. Updated 2 February 2023. Available at https://clinicaltrials.gov/study/NCT02851797. Accessed December 2023; 5. Bettica P, et al. *Neuromuscul Disord.* 2016;26(10):643–649. Supplementary material; 6. Wilson DGS, et al. *Commun Biol.* 2022;5(1):1022; 7. Campbell KP, Kahl SD. *Nature.* 1989;338(6212):259–262; 8. Guiraud S, et al. *Exp Physiol.* 2015;100(12):1458–1467; 9. Reid AL, Alexander MS. *Life.* 2021;11(7):648; 10. Ervasti JM, Campbell KP. *J Cell Biol.* 1993;122(4):809–823..



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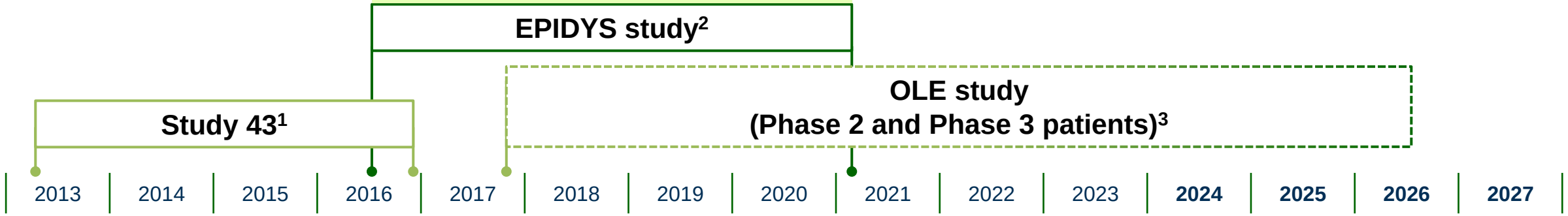
Givinostat Clinical Development Programme in Duchenne

- **Phase:** 3 in ambulant boys aged ≥6 years with DMD; duration 18 months
- **Sample:** N=179 (Givinostat n=118; control n=61)
- **Primary endpoint:** 4 Stairs Climb (4SC)
- **Secondary endpoints:** North Star Ambulatory Assessment (NSAA; total score and cumulative loss of function); Time To Rise (TTR) ; 6 Minute Walk Test (6MWT); knee extension; elbow flexion; Magnetic Resonance Spectroscopy (MRS) Vastus Lateralis Fat Fraction (MRS VLFF); Safety and acceptability/palatability.



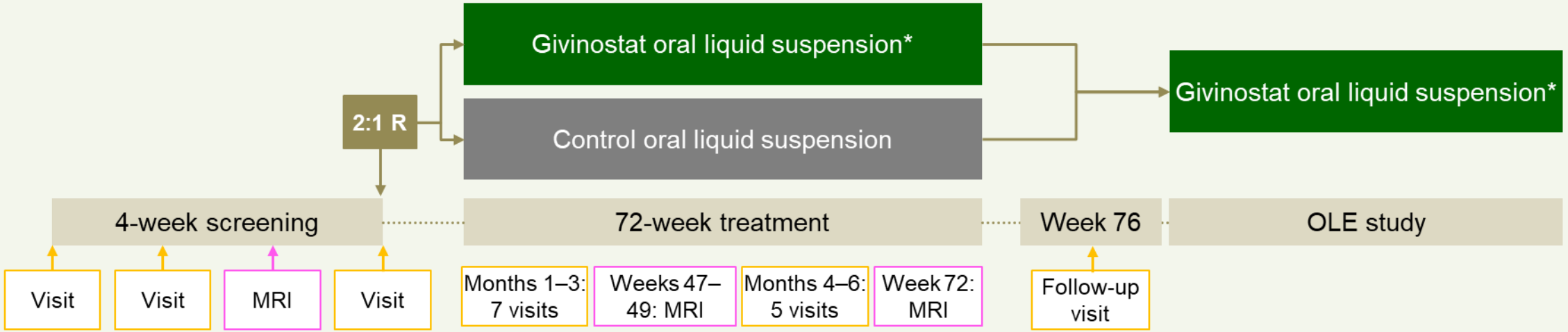
- **Phase:** 1/2; duration 12 months
- **Sample** N=20 ambulant boys aged 7 to <11 years with DMD
- **Primary endpoint:** muscle histology by biopsy
- **Secondary endpoints:** 6MWT; NSAA; PUL; Safety, tolerability and PK

- **Phase:** 2/3 N=208 DMD ambulant boys aged ≥6 years
- **Sample:** from Study 43 (N=18); EPIDYS (N=160) all previously treated with Givinostat; (N=30) naïve patients screened in Study 48, met all the Incl criteria for overall population but not randomized
- **Endpoints:** Safety, tolerability and efficacy

* Treatment duration until marketing authorization in respective country

EPIDYS: Phase 3 study design and eligibility criteria[1,2]

- Randomised, double-blind, parallel-group, controlled study with a total of 179 ambulant male participants randomised 2:1 (Givinostat: control)
- Givinostat and control were administered in addition to corticosteroid standard of care
- Conducted in USA, Canada, EU, UK, and Israel



*Dose adjustments permitted dependent on protocol version at randomisation.
CS, corticosteroids; MRI, magnetic resonance imaging; OLE, open-label extension; R, randomisation; SoC, standard of care.
1. Mercuri E, et al. 2024. Manuscript submitted; 2. ClinicalTrials.gov. NCT02851797. Updated 2 February 2023. Available at https://clinicaltrials.gov/study/NCT02851797. Accessed December 2023.

EPIDYS study: Significant Difference in Primary Endpoint between Givinostat and Control

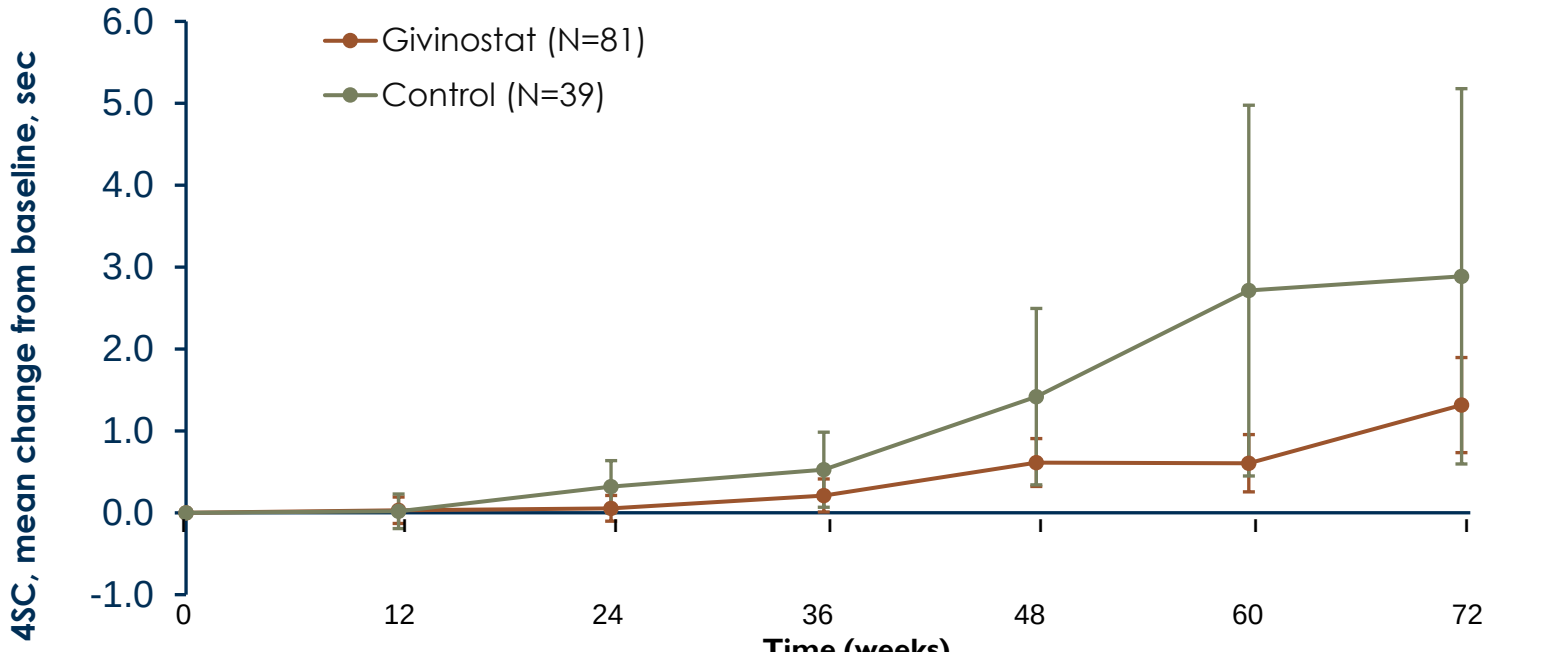
- Using non-log transformed data at week 72, givinostat added to corticosteroids significantly reduced the decline in time to perform the 4SC test by 1.78 s compared to control (CS plus placebo)


THE LANCET Neurology

Safety and efficacy of givinostat in boys with Duchenne muscular dystrophy (EPIDYS): a multicentre, randomised, double-blind, placebo-controlled, phase 3 trial

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

Mean change from baseline in time to perform the 4SC test*



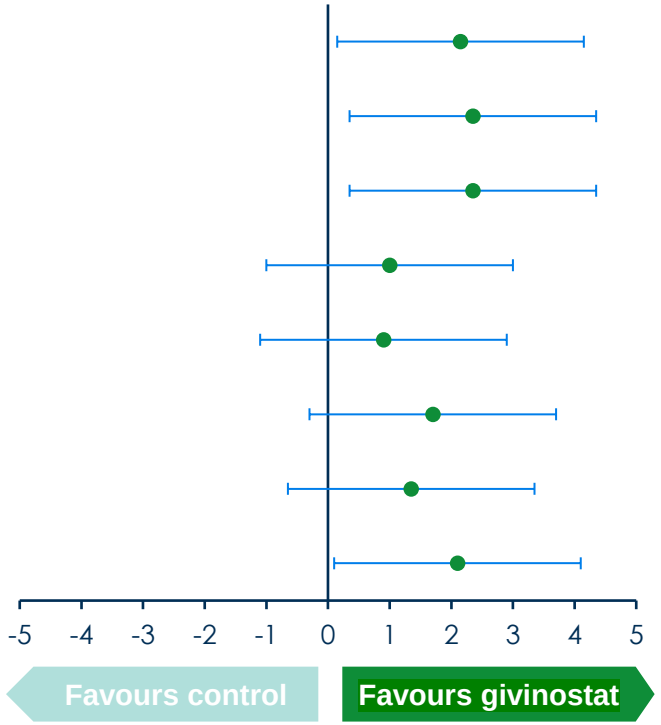
Mean change from baseline (95% CI), sec						
Givinostat	0·03 (–0·13, 0·19)	0·05 (–0·10, 0·21)	0·21 (0·01, 0·41)	0·61 (0·32, 0·91)	0·60 (0·26, 0·95)	1·31 (0·73, 1·90)
Control	0·18 (–0·19, 0·23)	0·32 (–0·00, 0·64)	0·53 (0·07, 0·98)	1·42 (0·34, 2·49)	2·71 (0·45, 4·98)	2·89 (0·60, 5·18)

*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 and 3.48 s for the givinostat and control groups, respectively.

The Effects of Givinostat on Key Secondary Endpoints Were Consistent with the Primary Endpoint

- Over time, givinostat consistently reduced decline in muscle function and strength as well as fatty infiltration

	Endpoint	Patients, n (%)		Standardised treatment effect (95% CI)	Mean difference (95% CI)
		givinostat (n=81)	Control (n=39)		
Function	Four-stair climb	81 (100)	39 (100)		0.86 (0.745, 0.989)
	Total NSAA score	81 (100)	39 (100)		1.91 (0.295, 3.533)
	Cum. loss of function (NSAA)	81 (100)	39 (100)		0.61 (0.408, 0.927)
	Time to rise from the floor	81 (100)	39 (100)		−3.28 (−9.573, 3.018)
	6-minute walk test	81 (100)	39 (100)		9.96 (−12.071, 31.893)
Strength	Overall knee extension	81 (100)	39 (100)		0.19 (−0.03, 0.401)
	Overall elbow flexion	81 (100)	39 (100)		0.09 (−0.041, 0.213)
MRS	Muscle fatty fraction	77 (95.1)	37 (94.9)		−2.92 (−53641, −0.204)



NSAA nominally significant but not statistically significant based on the prespecified multiplicity adjustment

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

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Confirmatory Evidence in Givinostat NDA Dossier

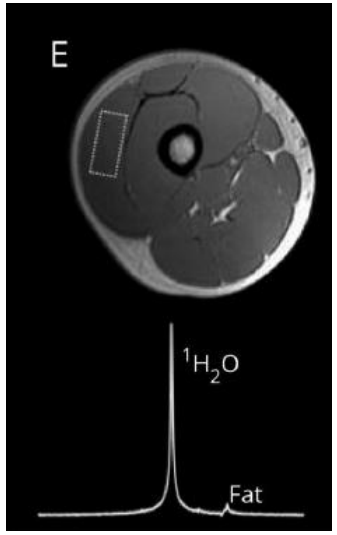
Givinostat benefit-risk assessment is based on:

- A single adequate and well-controlled positive study (EPIDYS Study)

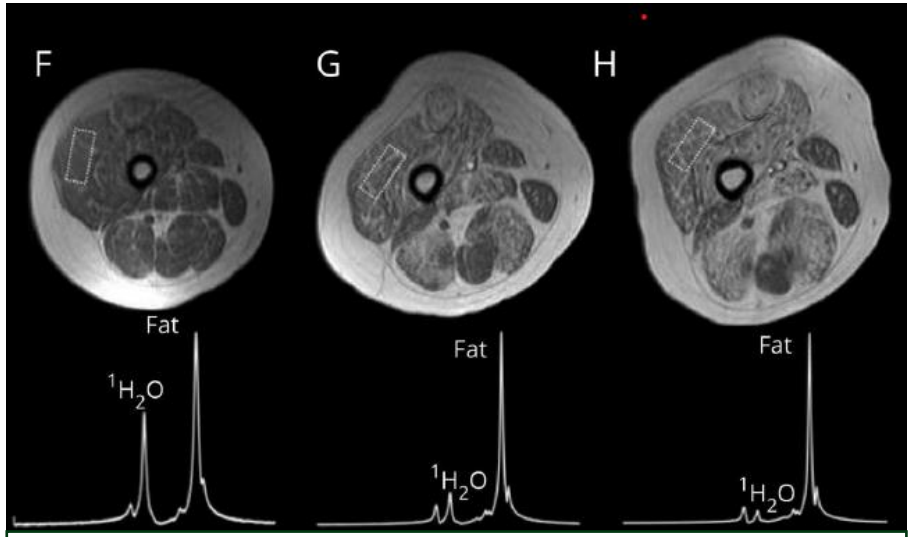
- Confirmatory Evidence:
  - Pharmacodynamic activity on the muscle (based on muscle biopsy histology and EPIDYS Magnetic Resonance Fat Fraction)
  - Long-term comparison to natural history demonstrating delayed loss of ambulation

DMD is Associated with Progressive Muscle Fat Infiltration

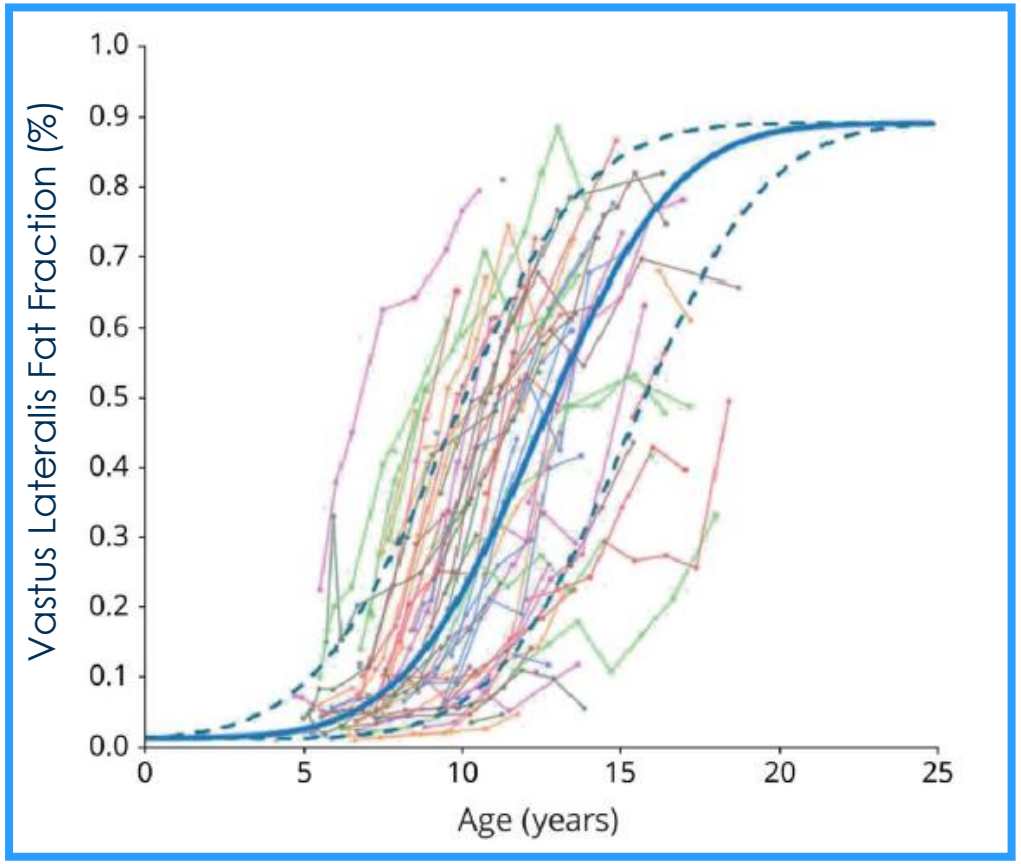
Unaffected Control



9 year-old DMD boy



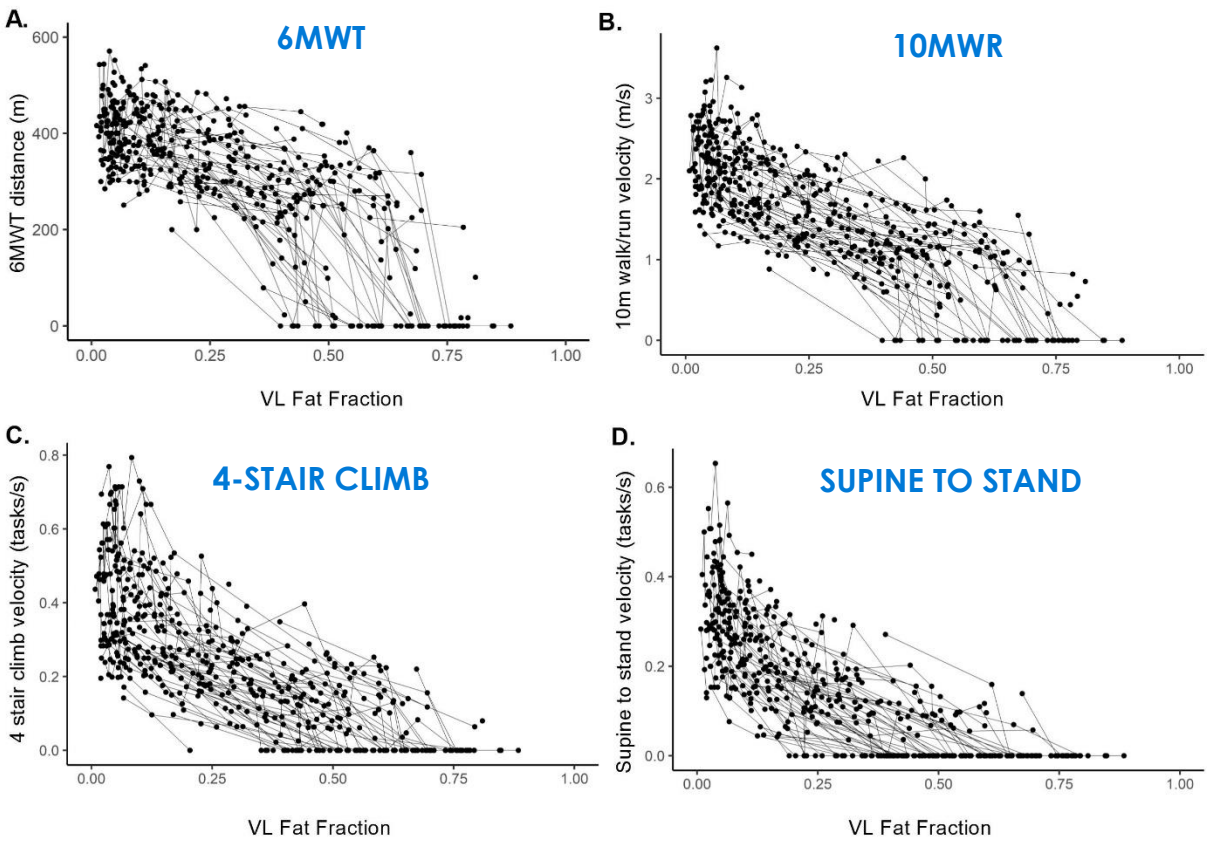
Baseline Year 1 Year 2



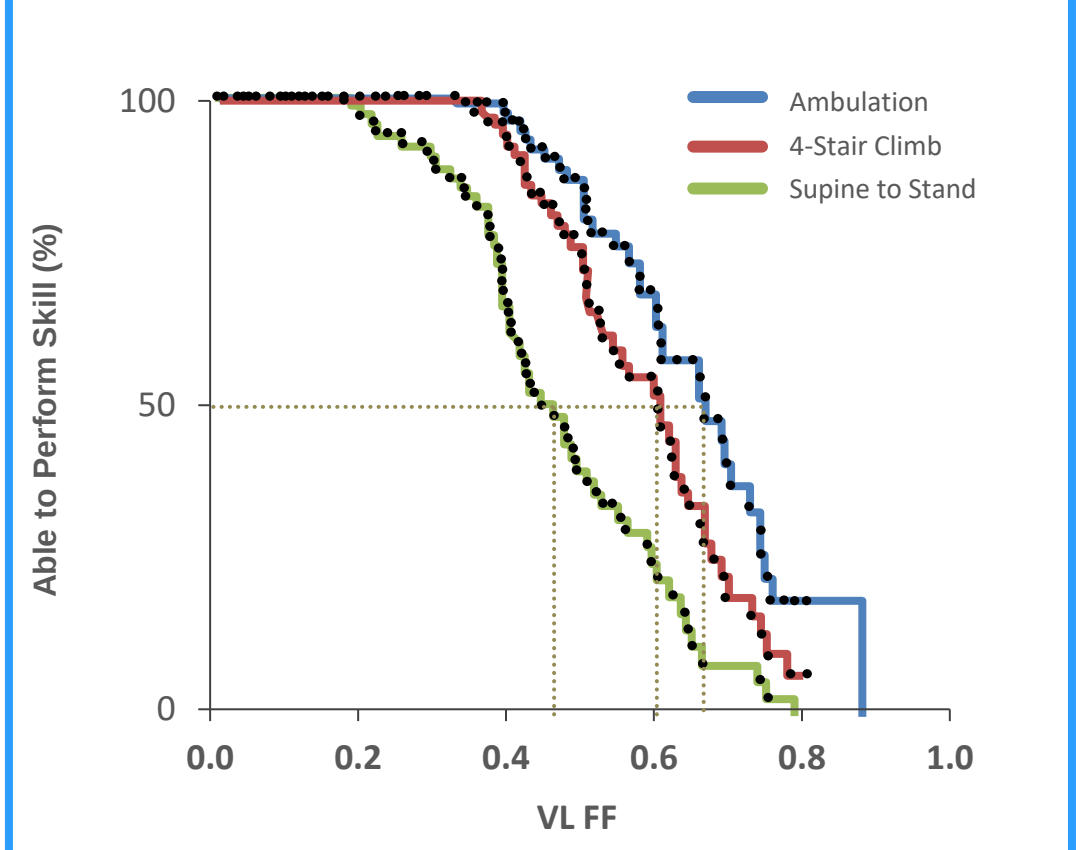
Muscle Fat Fraction Increases with Patients' Age

: Rooney WD, et al. Neurology. 2020;94:e1622-e1633

Muscle Fat Fraction Measured by Magnetic Resonance is Related to Meaningful Measures of Muscle Function



Muscle Fat Fraction significantly correlates with muscle function tests (correlation coefficient range: 0.58-0.78)

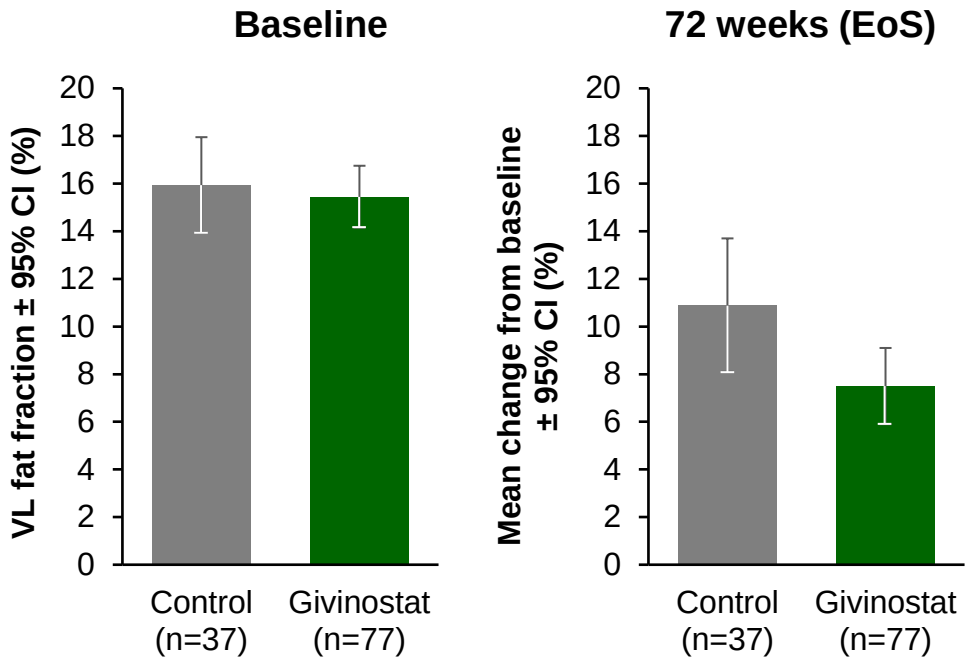


Muscle Fat Fraction predicts future loss of clinical function

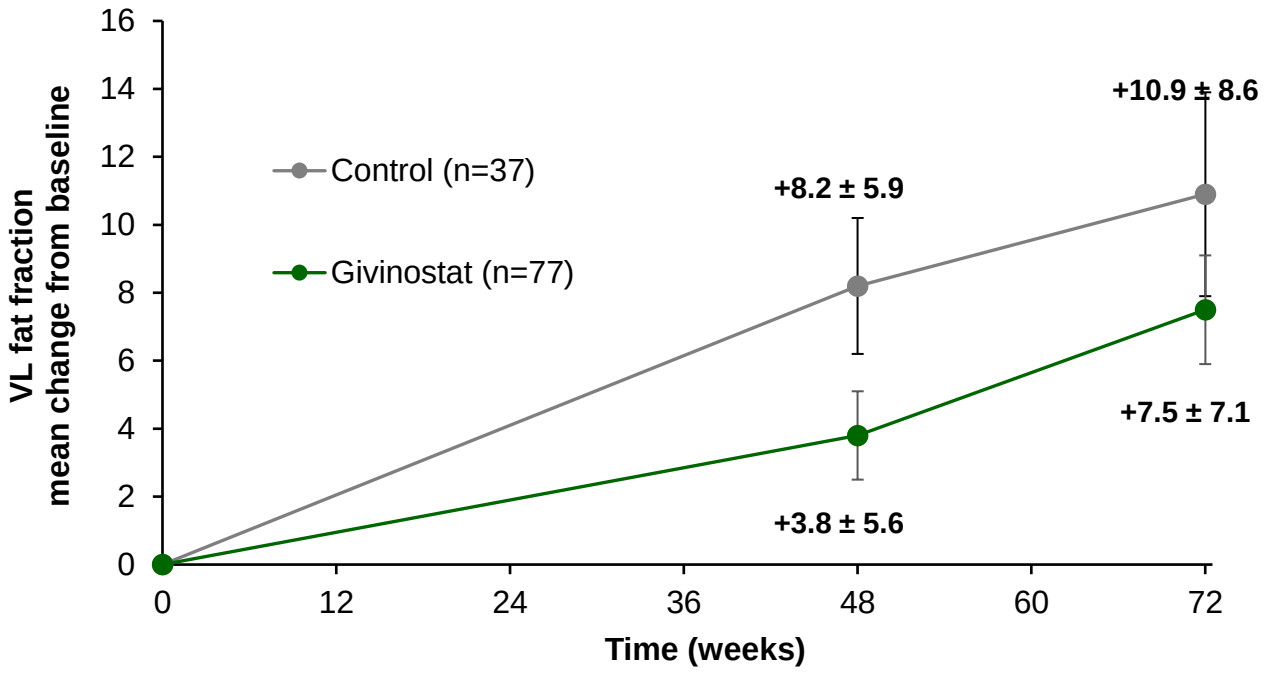
Ref: Barnard AM, et al. *Neurology*. 2020. PMID: 32024675

Givinostat Reduced New Muscle Fat Infiltration in the Vastus Lateralis by ~30%, as Measured by Magnetic Resonance Spectroscopy (EPIDYS Study)

VL fat fraction at baseline and 72 weeks (EoS)



Mean VL fat fraction change from baseline

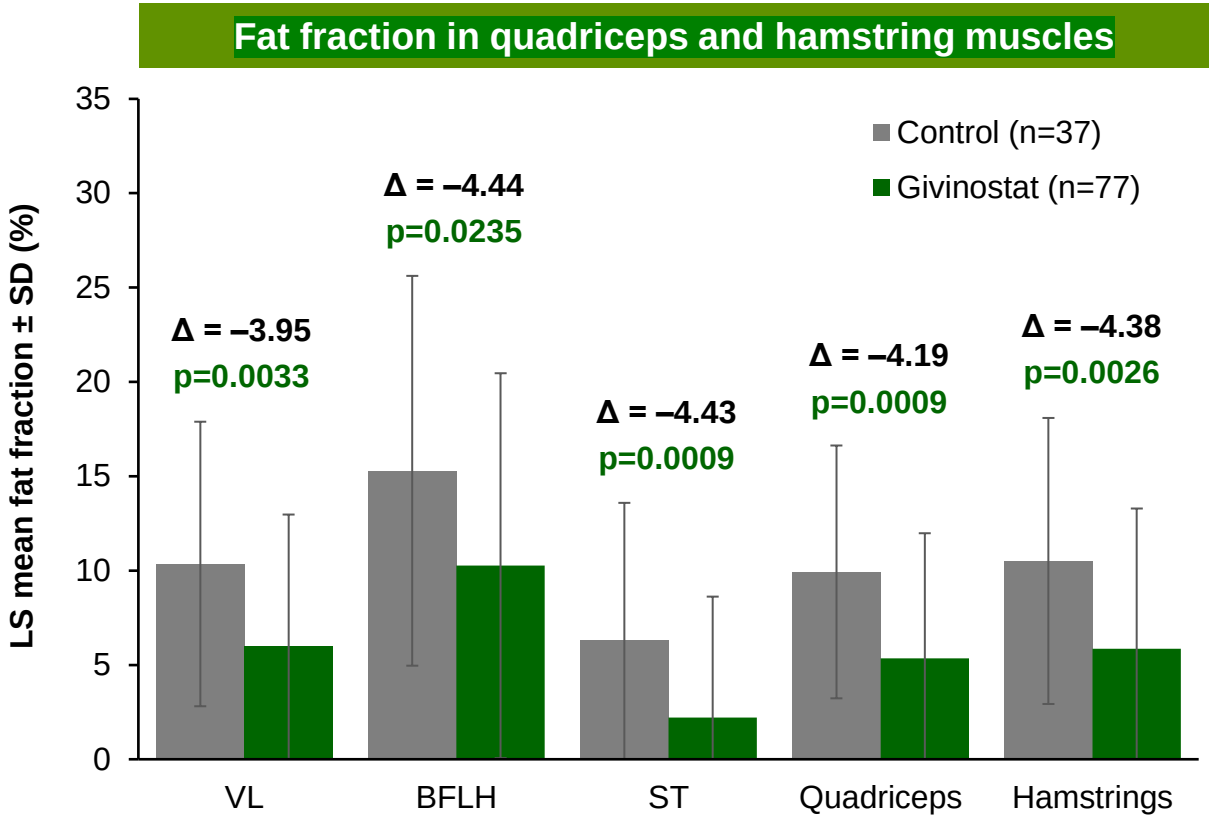


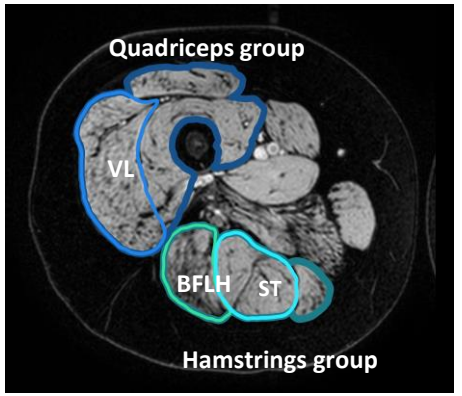
CI, confidence interval; EoS, end of study; MFF, muscle fat fraction; MRI, magnetic resonance imaging; VL, vastus lateralis.

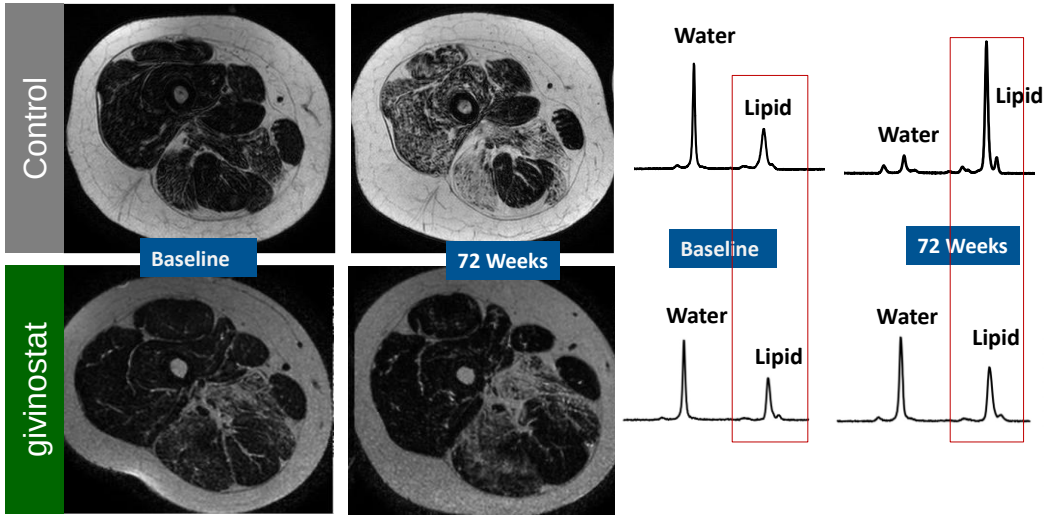
1. Mercuri E, et al. 2024. Manuscript submitted.

Givinostat Significantly Reduced New Fat Infiltration in All Muscles Key for Ambulation (EPIDYS Study)[1]

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







MRS of a single patient and may not be representative of general population

BFLH, biceps femoris long head; LS, least squares; SD, standard deviation; ST, semitendinosus; VL, vastus lateralis.

1. Vandenborne K, et al. Oral presentation at Muscular Dystrophy Association Clinical & Scientific Conference; 19–22 March 2023; Dallas, TX, USA.

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In Conclusion…

- Givinostat was the first nonsteroidal therapy approved in US and UK for the treatment of Duchenne Muscular Dystrophy in patients 6 years and older.
- The assessment of Givinostat benefit-risk was based on the results of a single adequate and well-controlled positive study (EPIDYS Study) and on confirmatory evidence.
- EPIDYS Study results:
  - Givinostat was found to provide a significant improvement vs Standard of Care in primary and 3 secondary endpoints, and favorable response across all secondary endpoints.
- Confirmatory Evidence:
  - Givinostat significantly reduced muscle fatty infiltration, a key feature of DMD pathogenesis and a predictor of loss of function.
  - Long-term comparison to natural history demonstrating delayed loss of ambulation.

To the children, families, advocates, and physicians who have been a part of our development program:

Thank you

patientadvocacy@italfarmacogroup.com

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