Long-Term Safety of Givinostat in Patients With Duchenne Muscular Dystrophy: Results From an Open-Label Extension Study

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BACKGROUND

- Duchenne muscular dystrophy (DMD) is characterized by mutations in the dystrophin gene, resulting in an absence of functional dystrophin[1]
- Givinostat, an oral histone deacetylase inhibitor, is a novel, nonsteroidal drug for DMD that can treat patients with all genetic variants underlying DMD[2]
- Givinostat is indicated for DMD treatment in patients aged ≥6 years[2-4] based on findings from EPIDYS (NCT02851797), a randomized, double-blind, placebo-controlled, phase 3 trial in ambulant patients[1]

OBJECTIVE

- To evaluate safety data from the ongoing, open-label, long-term safety, tolerability, and efficacy study of givinostat in boys who completed or were screened but not randomized in previous DMD givinostat studies and agreed to enter this study

METHODS

- As of the December 31, 2021, data cutoff, 194 patients have enrolled (**Figure 1**):
  - Givinostat throughout (n=110): randomized to givinostat in previous givinostat study 43 (NCT01761292)[5] and study 48 (NCT02851797 [EPIDYS])[1]
  - Placebo in prior study (n=54): randomized to placebo in previous givinostat study 48[1]
  - Not included in prior study (n=30): screened but not randomized in previous givinostat study 48 because enrollment was completed[1]
- All patients received givinostat at a flexible, weight-based dose and systemic corticosteroids during this study
- The starting dose of givinostat in this study was the same as the dose the patients received at the end of their previous givinostat study, regardless of whether they were in the givinostat throughout or placebo in prior study groups (**Table 1**)
- For givinostat-naïve patients (not included in prior study group), weight-based givinostat was initiated at an intermediate dose twice daily (**Table 1**)
- Safety data were evaluated for patients who received at least one givinostat administration

FIGURE 1. Study design

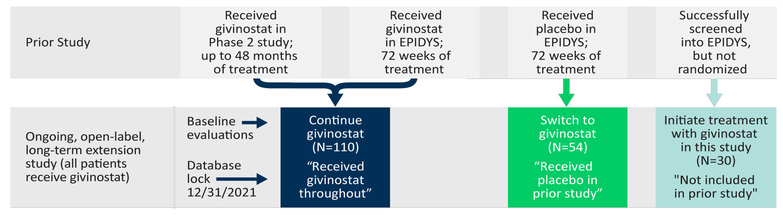


TABLE 1. Givinostat starting dose for patients from previous DMD givinostat studies

Dose level	Weight (kg)	≥10 and <12.5	≥12.5 and <20	≥20 and <25	≥25 and <30	≥30 and <40	≥40 and <50	≥50 and <60	≥60 and <70	≥70
A	Dose (mg) bid	20	25	30	35	40	50	55	60	70
	Oral suspension (mL) bid	2.0	2.5	3.0	3.5	4.0	5.0	5.5	6.0	7.0
B	Dose (mg) bid	13.3	16.7	20.0	23.3	26.7	33.3	36.7	40.0	46.7
	Oral suspension (mL) bid	1.3	1.7	2.0	2.3	2.7	3.3	3.7	4.0	4.7
C	Dose (mg) bid	10.6	13.4	16	18.6	21.4	26.6	29.4	32	37.4
	Oral suspension (mL) bid	1.1	1.3	1.6	1.9	2.1	2.7	2.9	3.2	3.7

For patients in the not included in prior study group, treatment was started on dose level B.
Givinostat hydrochloride monohydrate oral suspension (10 mg/ml) equates to 8.86 mg/ml of givinostat (USPI).
The weight bands are reduced in givinostat USPI compared with those used in clinical trials for ease of dosing administration.
BID, twice daily; DMD, Duchenne muscular dystrophy; USPI, US Prescribing Information.

RESULTS

- The mean (SD) ages of patients upon entry to the study were 11.6 (2.1), 11.4 (2.0), and 10.5 (2.2) years in the givinostat throughout, placebo in prior study, and not included in prior study groups, respectively (**Table 2**)
- Most patients were ambulant at screening, and the most common DMD mutation type was deletion (**Table 2**)
- The mean time since diagnosis was about 7 years in all groups, and all were receiving daily or intermittent corticosteroids (**Table 2**)

TABLE 2. Patient demographics and baseline clinical characteristics

	Received givinostat throughout n=110	Received placebo in prior study n=54	Not included in prior study n=30	Overall N=194
Age (y), mean (SD)	11.6 (2.1)	11.4 (2.0)	10.5 (2.2)	11.3 (2.1)
Race, n (%)				
African American or Black	4 (3.6)	0	1 (3.3)	5 (2.6)
Asian	2 (1.8)	2 (3.7)	2 (6.7)	6 (3.1)
White	100 (90.9)	50 (92.6)	22 (73.3)	172 (88.7)
Other	4 (3.6)	2 (3.7)	5 (16.7)	11 (5.7)
Weight (kg) at screening, mean (SD)	35.3 (10.6)	36.8 (11.7)	32.4 (9.6)	35.3 (10.8)
BMI (kg/m^2), mean (SD)	20.8 (4.7)	21.1 (5.1)	20.2 (4.1)	20.8 (4.7)
Ambulant at screening, n (%)	102 (92.7)	51 (94.4)	30 (100)	183 (94.3)
Time since DMD diagnosis (y), mean (SD)	7.5 (2.6)	7.2 (2.8)	6.9 (2.7)	7.3 (2.7)
DMD mutation, n (%)				
Deletion	71 (64.5)	36 (66.7)	17 (56.7)	124 (63.9)
Duplication	13 (11.8)	8 (14.8)	6 (20.0)	27 (13.9)
Point mutation	17 (15.5)	2 (3.7)	4 (13.3)	23 (11.9)
Other	8 (7.3)	8 (14.8)	3 (10.0)	19 (9.8)
Type of steroid, n (%)				
Prednisone	14 (12.7)	13 (24.1)	3 (10.0)	30 (15.5)
Deflazacort	91 (82.7)	39 (72.2)	27 (90.0)	157 (80.9)
Other	5 (4.5)	2 (3.7)	0	7 (3.6)
Steroid schedule, n (%)				
Daily	84 (76.4)	42 (77.8)	28 (93.3)	154 (79.4)
Intermittent	26 (23.6)	12 (22.2)	2 (6.7)	40 (20.6)

BMI, body mass index; DMD, Duchenne muscular dystrophy.

- The mean (SD) duration of givinostat exposure in this study was 616 (446), 506 (272), and 451 (116) days in the givinostat throughout, placebo in prior study, and not included in prior study groups, respectively
  - For patients in the givinostat throughout group, the overall maximum duration of exposure to givinostat exceeds 8 years, including 12 months in the original phase 2 study,[5] 3 extension periods of the phase 2 study totaling 48 months of treatment, and 72 weeks in study 48 (EPIDYS)[1]
- Overall, 87.1% of patients reported ≥1 treatment-emergent adverse event (TEAE), with similar incidence among the 3 groups (**Table 3**)
- Most TEAEs were mild to moderate in severity, and there were no life-threatening or fatal TEAEs
- The proportion of serious TEAEs was similar among all groups (**Table 3**)
- Discontinuation of the study treatment due to a TEAE and subsequent study withdrawal occurred in 2 patients in the placebo in prior study group (atrial fibrillation and increased blood triglycerides) and 1 patient in the givinostat throughout group (nausea)
- Among the most frequently reported TEAEs (≥10% of the overall population), incidences of vomiting and headache were most similar among the 3 groups (**Table 3**)
  - Diarrhea was reported more frequently by the placebo in prior study and not included in prior study groups compared with the givinostat throughout group
  - More falls were reported by the givinostat throughout group compared with the placebo in prior study and not included in prior study groups
  - More reports of thrombocytopenia were observed in the placebo in prior study group compared with the givinostat throughout and not included in prior study groups

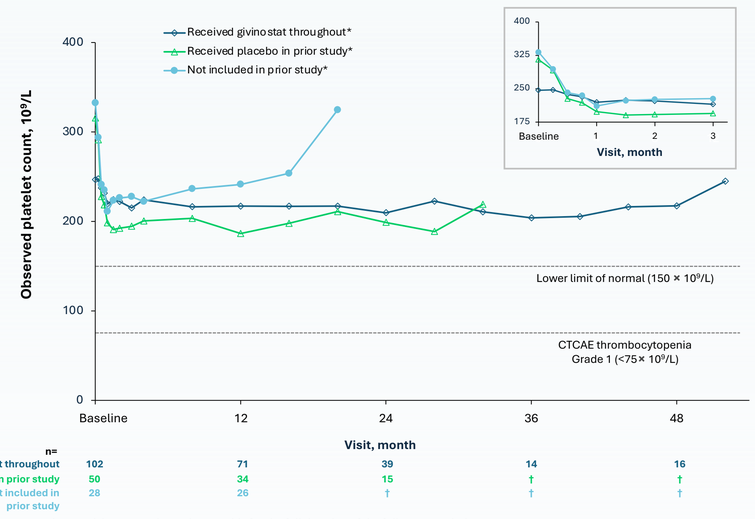
TABLE 3. TEAEs (most common preferred terms ≥10% overall; ≥5% for treatment-related; ≥2 patients for serious TEAEs)

Patients, n (%)	Received givinostat throughout n=110	Received placebo in prior study n=54	Not included in prior study n=30	Overall N=194
TEAEs	96 (87.3)	47 (87.0)	26 (86.7)	169 (87.1)
Diarrhea	20 (18.2)	15 (27.8)	11 (36.7)	46 (23.7)
Vomiting	16 (14.5)	8 (14.8)	5 (16.7)	29 (14.9)
Abdominal pain	12 (10.9)	9 (16.7)	1 (3.3)	22 (11.3)
Fall	22 (20.0)	5 (9.3)	4 (13.3)	31 (16.0)
Blood triglycerides increased	14 (12.7)	9 (16.7)	2 (6.7)	25 (12.9)
Platelet count decreased	10 (9.1)	8 (14.8)	2 (6.7)	20 (10.3)
Thrombocytopenia	10 (9.1)	11 (20.4)	3 (10.0)	24 (12.4)
Pyrexia	19 (17.3)	7 (13.0)	2 (6.7)	28 (14.4)
Headache	16 (14.5)	9 (16.7)	6 (20.0)	31 (16.0)
TEAEs considered related to treatment	60 (54.5)	36 (66.7)	18 (60.0)	114 (58.8)
Diarrhea	10 (9.1)	9 (16.7)	10 (33.3)	29 (14.9)
Abdominal pain	5 (4.5)	5 (9.3)	1 (3.3)	11 (5.7)
Blood triglycerides increased	12 (10.9)	8 (14.8)	2 (6.7)	22 (11.3)
Hypertriglyceridemia	9 (8.2)	2 (3.7)	0	11 (5.7)
Platelet count decreased	10 (9.1)	8 (14.8)	2 (6.7)	20 (10.3)
Thrombocytopenia	10 (9.1)	10 (18.5)	3 (10.0)	23 (11.9)
Serious TEAEs	12 (10.9)	8 (14.8)	3 (10.0)	23 (11.9)
Femur fracture	3 (2.7)	3 (5.6)	0	6 (3.1)
Back pain	1 (0.9)	1 (1.9)	0	2 (1.0)
Tendinous contracture	2 (1.8)	0	0	2 (1.0)
Dehydration	1 (0.9)	1 (1.9)	0	2 (1.0)
Serious TEAEs considered related to treatment	0	1 (1.9)	0	1 (1.9)

TEAE, treatment-emergent adverse event.

- Treatment dose was reduced in 16 (14.5%), 15 (27.8%), and 4 (13.3%) patients in the givinostat throughout, placebo in prior study, and not included in prior study groups, respectively
  - Dose reduction due to platelet count decrease occurred in 5, 4, and 1 patient in the givinostat throughout, placebo in prior study, and not included in prior study groups, respectively
  - Dose reduction due to triglyceride concentration increase occurred in 2 and 1 patient in the givinostat throughout and placebo in prior study groups, respectively
- Platelet counts and triglyceride concentration remained stable in the givinostat throughout group for the duration of the study (**Figures 2** and **3**)
- A decrease in mean platelet counts at about 2 weeks of treatment was observed in the placebo in prior study and not included in prior study groups; after 2 weeks of treatment, values were maintained for both groups (**Figure 2**)

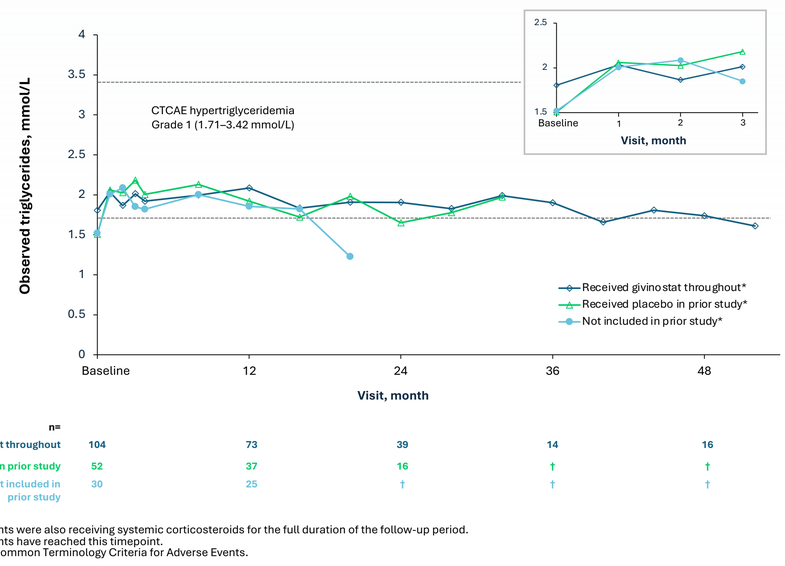
FIGURE 2. Mean observed values for platelet counts



*All patients were also receiving systemic corticosteroids for the full duration of the follow-up period.
†No patients have reached this timepoint.
CTCAE, Common Terminology Criteria for Adverse Events.

- Mean triglyceride concentration initially increased at about 4 weeks of treatment in the placebo in prior study and not included in prior study groups; after 4 weeks of treatment, values were stable for both groups (**Figure 3**)
- In patients with DMD, QTc prolongation was not observed with long-term givinostat treatment; mean value of QT did not increase in the study

FIGURE 3. Mean observed values for triglyceride concentrations



*All patients were also receiving systemic corticosteroids for the full duration of the follow-up period.
†No patients have reached this timepoint.
CTCAE, Common Terminology Criteria for Adverse Events.

CONCLUSIONS

- These results are consistent with the results of previous, shorter-duration studies
- The findings suggest that the safety profile of givinostat is also manageable in the long term, with most TEAEs being mild to moderate in severity
- Decreased platelets and increased triglycerides (first 2 to 4 weeks of treatment) followed by stabilization in the placebo in prior study and not included in prior study groups are consistent with givinostat treatment initiation[3]; levels remained stable for the givinostat throughout group
- No new safety signals were observed in patients continuing givinostat

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AUTHOR DISCLOSURES

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