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Safety and Tolerability of Givinostat: Evidence From Real-World and Clinical Practice

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ABSTRACT

Objective: The aim of our study was to establish the prevalence of adverse events in a real-world setting in boys living with Duchenne muscular dystrophy (DMD) treated with givinostat as part of an Expanded Access Program (EAP) in Italy.

Methods: The cohort included 90 ambulant boys, with age when treatment started between 6 and 23 years (mean 10.1 years, SD: 3.2 years) and with a follow up between 6.0 and 14.6 months (mean 10.6 months; SD 2.6 months).

Results: Platelets count decrease and triglyceride levels increase were the most common adverse events, followed by diarrhea. A dose reduction was needed in 38 of the 90 boys following thrombocytopenia ($n = 34$), diarrhea ($n = 2$), and hypertriglyceridemia ($n = 4$), with two of the boys presenting both thrombocytopenia and hypertriglyceridemia. Eleven of the 38 boys with initial dose reduction (10 with thrombocytopenia and 1 with hypertriglyceridemia) required an additional dose reduction for persistence of values outside the threshold, with one of them discontinuing treatment because of persistent hypertriglyceridemia even with the lowest dose.

Interpretation: Our results confirm the safety profile observed in the pivotal study providing further evidence of the management of the drug in a real-world setting. In our experience, treatment with givinostat was well managed by maintaining a strict monitoring. This was facilitated by allowing families to perform blood tests in local labs, reducing the stress and burden of frequent visits to the hospital.

Marika Pane, Anna Capasso and Chiara Arpaia equally contributed as first co-authors.

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1 | Introduction

Duchenne muscular dystrophy (DMD) is an X-linked recessive progressive disorder usually manifesting in young boys [1]. The availability of standards of care has produced significant improvements in survival and in slowing down disease progression [2, 3], but there are several unmet needs. In the last two decades there have been several clinical trials with therapeutic approaches targeting different steps of the mechanisms underlying DMD [4]. Most of the efforts have focused on dystrophin restoration, including gene therapy, exon skipping, or targeting nonsense mutations. Other efforts have been targeting the downstream effects of lack of dystrophin, such as inflammation and fibrosis that are responsible for progressive muscle damage [5].

One of these approaches uses givinostat, a histone deacetylase inhibitor, that has recently been approved worldwide for ambulant DMD boys aged ≥ 6 years, regardless of genetic mutation [6]. Preclinical study results [7–9] phase I–II [6], and more recently, a randomized double-blind placebo-controlled Phase III study (EPIDYS) [10] have provided evidence of significant improvements on motor functional scales mirrored by a reduction in the progression of muscle damage both on muscle biopsies and muscle imaging. In both trials, and in their long-term extensions, there was an overall satisfactory safety profile [11]. Decreased platelets count, increased triglycerides and diarrhea were frequent findings but could be easily managed with dose reduction. The phase III study initially used a high starting dose of givinostat (20–70 mg twice a day) with prespecified dose reductions (13.3–46.7 mg twice a day) in the presence of adverse events [6]. Because of the relatively high number of boys needing to reduce their dose, the protocol was amended in June 2018, with a new starting dose of 13.3–46.7 mg twice a day, and a prespecified reduced dose of 10.6–37.4 mg twice a day. In the EPYDIS study, a dose reduction due to decreased platelet count was reported in 33 of the 118 treated boys (28%). A lower percentage (38/194, 19.6%) has recently been reported in a larger cohort, also including the patients originally on placebo and subsequently treated with givinostat and others who were successfully screened but not randomized into EPIDYS [11].

In those studies, decreased platelet count and the other common adverse events mainly occurred in the first three months after the first dose, suggesting that this is the time when more careful and regular monitoring of these aspects should be performed.

Givinostat has been formally approved in several countries [12]. In Italy, after the approval from the European Medical Agency (EMA), while waiting for the final negotiations with the national authority, givinostat was made available as part of an Expanded Access Program (EAP) for use in ambulant patients from 6 years of age.

The aim of our study was to establish the prevalence of adverse events in a real-world setting in boys treated as part of the EAP who have been followed for at least 6 months after treatment started.

2 | Methods

As part of the EAP subjects were enrolled in the eight centers that had previously been involved in the givinostat clinical trials (Centro Clinico Nemo Roma, Fondazione Policlinico Universitario "Agostino Gemelli" IRCCS, Roma; Unità di malattie Neuromuscolari e Neurodegenerative, "Ospedale Pediatrico Bambino Gesù" IRCCS, Roma; Azienda Ospedale-Università Padova; Centro Clinico Nemo Milano, Unità di Neuroriabilitazione, Università di Milano, "ASST Grande Ospedale Metropolitano Niguarda", Milano; Azienda Ospedaliera Universitaria "G. Martino", Messina; Unità di Neurologia dello sviluppo, Fondazione IRCCS "Istituto Neurologico Carlo Besta", Milano; Centro di Miologia Traslazionale e Sperimentale, IRCCS Istituto "Giannina Gaslini; Policlinico di Milano "Ospedale Maggiore"—Fondazione IRCCS Ca′ Granda). The data collection was part of a larger study collecting longitudinal data in all DMD boys. The study was approved by the Ethics committee in each Centre. Written informed consent was obtained from all participants (or guardians of participants) in the study. In the first version of the EAP protocol, the inclusion criteria were similar to those used in the EPYDIS study (i.e., ambulant, able to get up from the floor within 10 s and no abnormal QT corrected (QTc), and exposure to a stable dose of corticosteroids in the past 6 months). After the approval from EMA in May 2025, a new protocol was released and the criteria were modified in line with the EMA label therefore excluding for example the need to get up from the floor within 10 s and with less stringent criteria in relation to previous therapies for DMD. Cut-off point to define hypertriglyceridemia was lowered from 500 mg/dL to 300 mg/dL.

The eight Centers agreed to have a common structured schedule of safety assessments. These included blood tests (complete blood count, fasting triglycerides, cholesterol, glucose, total and direct bilirubin, thyroid function test) and electrocardiogram (ECG) for assessing QT corrected (QTc) interval before starting treatment. The follow up assessments were scheduled with blood tests every two weeks, either performed at the hospital or locally and communicated to the referral center within 24 h. EKG was repeated at 6-month intervals. When appropriate, families were asked to repeat the blood tests one week after the abnormal results.

All patients started with the standard dose A (22.2–53.2 mg × 2/day).

Dose reduction to dose B (17.7–39.9 mg × 2/day) was applied in the presence of:

- Platelet count $< 150 \times 10^9$/L verified by two assessments 1 week apart, or
- Fasting triglycerides > 300 mg/dL (before May 2025 > 500 mg/dL) verified by two assessments 1 week apart, or
- Moderate or severe diarrhea (more than 4 stools per day).

If one or more of the above findings persisted after the dose reduction, a further reduction to dose C was applied (13.3–35.4 mg × 2/day).

If the abnormalities worsened despite dose modification, treatment was permanently discontinued.

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3 | Results

All the boys treated with givinostat as part of the EAP with at least 6-month follow-up were included in the study. The final cohort included 90 ambulant boys, with an age range between 6 and 23 years (mean 10.1 years, SD: 3.2 years). Three of 90 (3.33% of the total cohort) were older than 16 years. All of them had pathogenic variants (deletion exon 45; point mutation exon 70 c.10141 CT, p.Arg 3381X; and missense variant in exon 3, p.Leu53Pro), two of them had a muscle biopsy showing no dystrophin with the exception of traces of dystrophin on some revertant fibers. The follow-up after starting treatment ranged between 6.0 and 14.6 months (mean 10.6 months; SD 2.6 months). Table 1 shows the characteristic of the cohort.

3.1 | Platelet Count

Platelet count decrease ($<150\times10^9$/L) was found in 83/90 boys (92.2%) on at least one occasion, with a total number of 105 AEs. Thirty-four of those 83 (41.0%; 37.8 of the total cohort) had a confirmed platelet count decrease when retested after a week, leading to a dose reduction from dose A to dose B. The platelet count at the time of the switch ranged from 85×10^9/L to 148×10^9/L. Ten of the 34 boys on dose B (27% of the total cohort) had a further reduction to dose C due to a persisting platelet count decrease over two consecutive assessments; in these 10 boys on dose C, the platelet count at the time of the switch ranged from 147×10^9/L to 121×10^9/L. None required treatment discontinuation.

In the 34 boys with confirmed platelet count decrease, it occurred within one month in 7/34 (20.6%), in the second month in 13/34 (38.2%), in the third month in 9/34 (26.5%) and after the third month in 5/34 (14.7%) (one within the fourth; two within the sixth; one after the sixth and one after one year). (Figures 1 and 2 show details of the sub-cohort who needed dose reduction).

TABLE 1 | Characteristics of the cohort.

Patients	90
Age at start; mean (SD)	10.1 (3.2)
Weight at start of treatment (kg); mean (SD)	30.1 (11.2)
Treatment duration (months); mean (SD)	10.6 (2.6)
Number of AEs	236
Platelet count decrease (%)	105 (44.5%)
Hypertriglyceridemia (%)	125 (53.0%)
Diarrhea (%)	4 (1.7%)
Other (%)	2 (0.8%)
Number of AEs bringing to a dose reduction	55
Number of AEs bringing to a dose reduction (from A to B)	40[a]/90 (44.4%)
Platelet count decrease (%)	34[a]/90 (37.7%)
Hypertriglyceridemia (%)	4[a]/90 (4.4%)
Diarrhea (%)	2/90 (2.2%)
Number of AEs bringing to a dose reduction (from B to C)	11/90 (12.2%)
Platelet count decrease (%)	10/90 (11.1%)
Hypertriglyceridemia (%)	1/90 (1.1%)
Total of patients dose A (%)	50/90 (55.6%)
Total of patients dose B (%)	29/90 (32.2%)
Total of patients dose C (%)	10/90 (11.1%)
Total of patients withdrawal (%)	1/90 (1.1%)

Abbreviations: AE, Adverse Event; SD, standard deviation.
[a]The same patient reported two adverse events (AEs) at the same time, one for platelet count decrease and the other for hypertriglyceridemia. Both events led to a dose reduction from Dose A to Dose B.

3.2 | Hypertriglyceridemia

Forty-nine of the 90 (54.4%) had increased triglyceride levels ≥150 mg/dL with a total number of 125 AEs. Thirty-six of those 49 (73.5%; 40% of the total cohort) presented increased triglyceride levels between 150 mg/dL and 300 mg/dL while the other 13/49 (26.5%; 14.4% of the total cohort) had triglyceride levels ≥300 mg/dL. According to the EAP protocol, the cut-off points for hypertriglyceridemia levels requiring dose reduction when repeated after a week were ≥500 mg/dL in the first version and ≥300 mg/dL after the amendment.

None of the boys at the time of the first version of the protocol required a dose reduction due to a confirmed hypertriglyceridemia ≥500 mg/dL. After the amendment, four boys (4.4% of the total cohort) had a confirmed hypertriglyceridemia ≥300 mg/dL at the one-week retest, leading to a dose reduction to dose B. One of this 4 (25%) had persistent hypertriglyceridemia with a further reduction to dose C within the third month of treatment. This patient was discontinued due to persistent hypertriglyceridemia in the following weeks. In the remaining three, the values returned below the cut-off.

3.3 | Diarrhea

Four of the 90 (4.1%) had an increase of stools/day over baseline. Two of them (2.2% of the total cohort) had ≥4 stools/day leading to a dose reduction from A to B. In both, there was no persistence of diarrhea with no need for reduction to dose C or for treatment discontinuation.

Figure 3 summarizes the dose modification due to the AEs.

3.4 | Electrocardiogram QTc Interval Prolonged

None of the 90 boys included in the study had Electrocardiogram QTc interval prolonged (>450 ms). None of the boys reduced the dose or discontinued.

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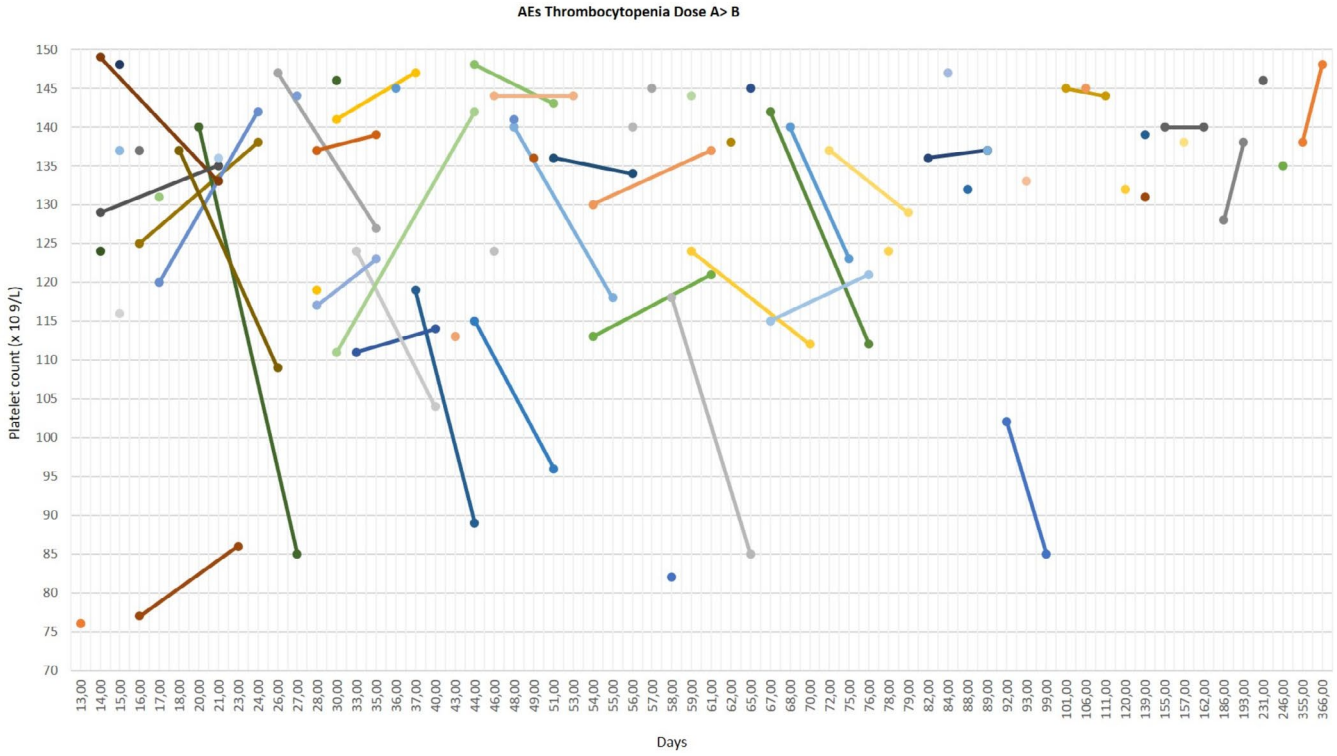

FIGURE 1 | Details of platelet count in the 31 DMD boys with dose modification from A to B.

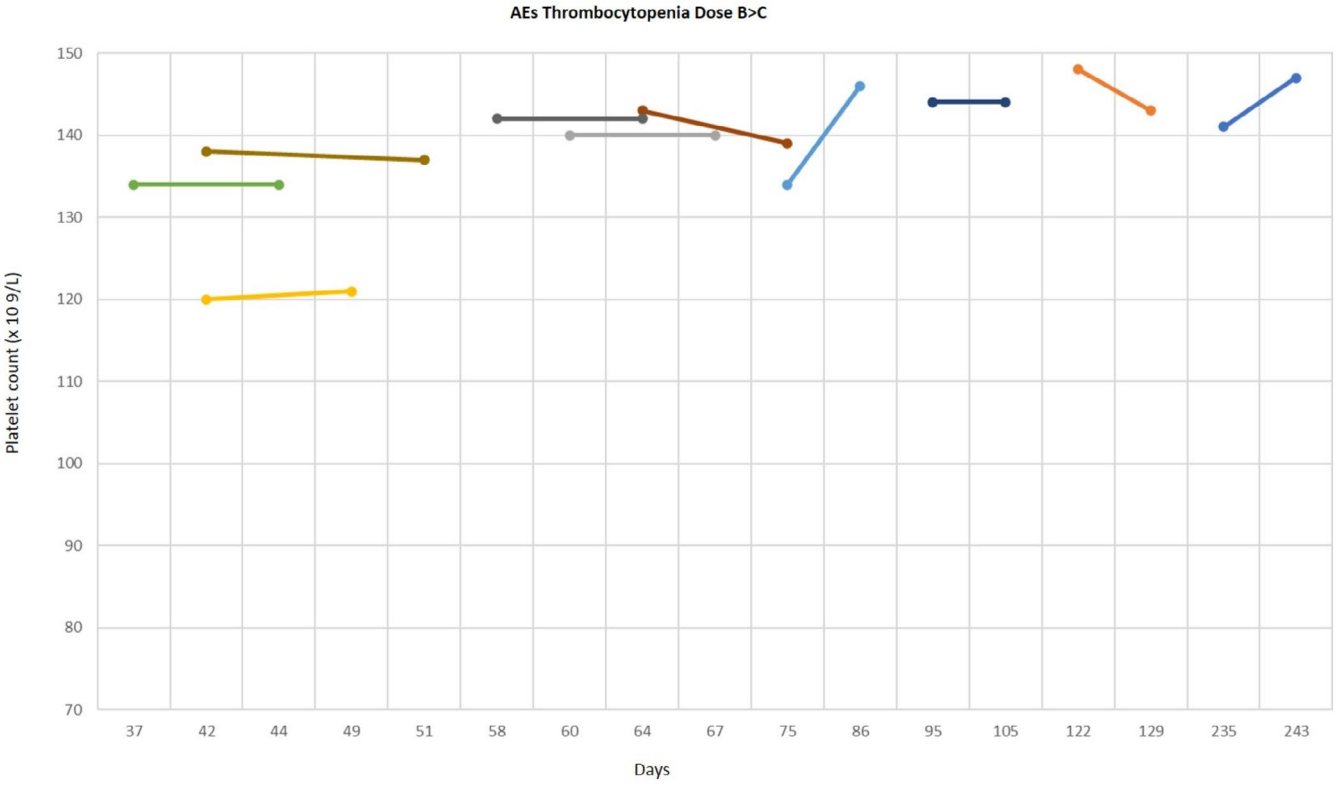

FIGURE 2 | Details of platelet count in the 9 DMD boys with dose modification from B to C.

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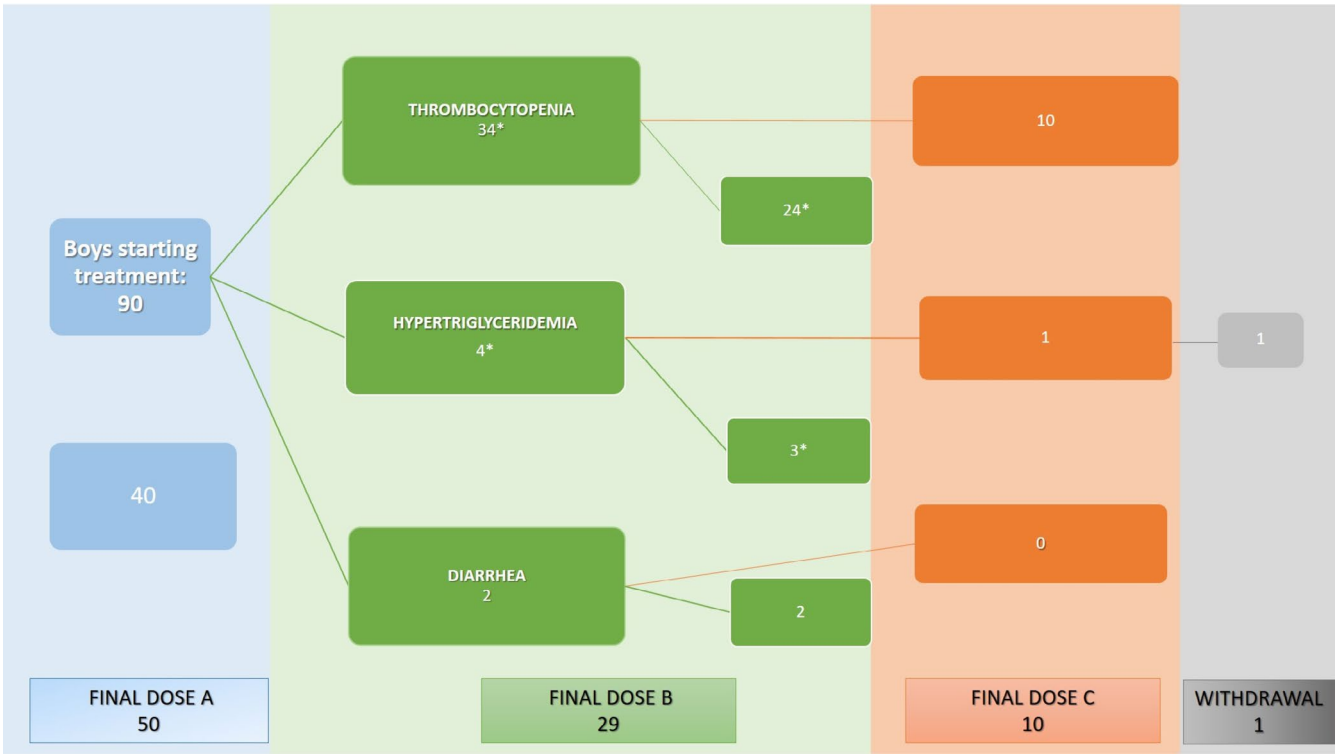

FIGURE 3 | Dose modification due to the AEs.

3.5 | Other Observed AEs

Four of 90 (4.4%) had reduced appetite with weight loss. None of the boys reduced the dose or discontinued due to other observed AEs.

4 | Discussion

The aim of our study was to evaluate the short-term safety and tolerability of givinostat in patients treated as part of the EAP in Italy and followed up for at least six months. The rationale behind the choice of 6-month follow-up was that in previous clinical trials the most frequent drug-related adverse events, such as blood triglyceride increases, platelet count decreases, and diarrhea were observed in the first 6 months after treatment started [6, 10]. These data were confirmed by recent reports on long-term data from extension study, confirming the absence of new safety signals after the first months [11].

In our cohort, we confirmed that platelet count decrease and triglyceride levels increase were the most common adverse events, followed by diarrhea.

The number of boys who had platelet count below 150×10^9/L on at least one occasion was 83/90 (92.2%), but only in 34/90 (37.8%) was it confirmed by a subsequent evaluation requiring a dose reduction. It is of interest that even when below 150×10^9/L, the values were often above 120×10^9/L, only 10.8% had values below 100×10^9/L, and none of them were associated with any clinical signs. Our results confirmed that platelet count decrease was more often observed in the first three months, but in a more limited number of cases (18.1%) these occurred after three months of treatment. These findings further highlighted the importance of regular assessments after the first three months of treatment.

Reduction to dose B was generally associated with normalization of platelet levels except for 10 cases in whom the dose had to be further modified for persistently platelet count decrease. Interestingly, this was not always associated with the lowest values found at the time of the first reduction.

Although increased triglyceride levels (> 150 mg/dL) were the most common AE in our cohort, the need for dose modification was much less frequent even when the cut-off point for reducing the dose was lowered from 500 mg/dL to 300 mg/dL (4/90%–4.4%). Dose reduction was generally associated with values returning below the threshold in all but one subject, in whom givinostat had to be withdrawn for persistent hypertriglyceridemia even after the second dose reduction.

Dose reduction due to diarrhea was also uncommon (2/90%–2.2%).

As also observed in the clinical trial [10] some boys reported nausea and decreased appetite, resulting in weight loss in 4/90, even though this did not lead to dose modification or discontinuation.

In our experience, treatment with givinostat could be managed by maintaining strict monitoring and paying attention to possible concomitant factors. Instructing the families and providing written schedules on how and when to perform blood tests in local labs close to their residence was very effective, reducing the stress and burden of frequent visits to the hospital and decreasing the risk of missing visits. A careful dietary counseling also helped to reduce the risk of increased blood triglyceride levels. We also found that collecting a detailed past history of

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tendency to easily develop hematomas or bruises was important as this was present in some boys. When present, a detailed coagulation assessment was performed before starting treatment to exclude possible concomitant risk factors.

Our results compared with the recently published data on long-term evaluation of givinostat in DMD [11] report a greater number of platelet count decreases (44.5% vs. 22.2%) and triglyceride levels increase/hypertriglyceridemia (53.0% vs. 18.5%). These differences could at least partially be explained by the fact that all the boys in our cohort started from the highest dose regime available. In contrast, a significantly lower number of diarrhea (1.7% vs. 23.7%) was reported in our cohort, maybe due to a lack of reports from the families outside the set of the clinical trials in cases with only minimal variations from baseline.

Although there has been recent concern about possible cardiac involvement with QTc interval prolongation [13], we did not find any evidence of it in our cohort. A more detailed protocol has recently been implemented [13] to provide a more accurate assessment of possible signs.

In conclusion, our paper provides further evidence of the tolerability of givinostat at the dose indicated in the label. The EAP protocol was initially designed with the same criteria of the EPYDIS trial but recently this was amended to include less able and often older ambulant patients who were unable to perform the time to rise from the floor within 10 s; our data therefore partially widen the age and functional range of patients in the trial [10]. Longer follow-up will help to further confirm the long-term safety of givinostat in a larger cohort with wider inclusion criteria.

Author Contributions

M.P., A.C., C.A., E.M. contributed to the conception and design of the study. M.P., A.C., C.A., A.D., E.A., R.M., L.B., R.V., C.B., S.M., G.C., E.P., V.A.S., E.M. contributed to drafting the text or preparing the figures. M.P., A.C., C.A., F.T., M.S., F.M., C.D., E.M. participated in the acquisition and analysis of data.

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The authors have nothing to report.

Conflicts of Interest

M.P. participated to Advisory Board for ROCHE, Sarepta, PTC, Italfarmaco, Pfizer and Dyne; C.B. and G.C. participated to Advisory Board for ROCHE; V.A.S. participated to Advisory Board for ROCHE, PTC, and Dyne; L.B. participated to Advisory Board for PTC, Pfizer, ROCHE, and Edgewise Therapeutics; E.P. participated to Advisory Board for Alexion, Sanofi, and UCB Biopharma; R.M. participated to Advisory Board for PTC, Pfizer, and ROCHE; E.M. participated to Advisory Board for ROCHE, Sarepta, PTC, Italfarmaco, Pfizer, Dyne, NS Pharma, Santhera, Edgewise, Entrada, and Solid. The remaining authors have nothing to disclose.

Data Availability Statement

Data available on request.

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