Givinostat Study in DMD: supportive results

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INTRODUCTION

Duchenne muscular dystrophy (DMD) is a lethal X-linked disorder that leads to muscle wasting.

Givinostat is a histone deacetylase inhibitor that counteracts the pathogenic events downstream of the dystrophin deficiency[1].

In a previous Phase II study in DMD, givinostat administered on top of corticosteroids, increased muscle fraction and reduced fibrotic tissue in brachial biceps biopsies, and reduced tissue necrosis and fatty replacement[2]

OBJECTIVES

The aim of this poster is to present a supportive post-hoc analysis using the ITT population.

METHODS / DESIGN

Epidys Study:

Phase 3 randomized, double blind, parallel group, placebo-controlled study in ambulant DMD boys, on stable corticosteroids for ≥ 6 months, to demonstrate that givinostat preserves muscle mass and slows down disease progression . The Study was conducted in USA, Canada, European countries and Israel (NCT02851797).

Main Inclusion criteria:

- ambulant DMD boys from 6 years of age
- on stable corticosteroid for at least 6 months prior to start the treatment,
- able to perform the 4 stairs climb in no more than 8 seconds and time to stand up in ≥ 3 and less than 10 seconds,

Population: Boys recruited in two groups:

- Group A - target population (BL VLMFF by MRS >5–30%)
- Group B - off-target population (BL VLMFF by MRS ≤5% or >30%)

Primary Endpoint:

- Mean 4-stair climb (4SC) time change from baseline to 18

Key secondary Endpoints:

- Mean change in NSAA total score
- Cumulative loss of function on the NSAA
- Mean change in time to rise from floor
- Mean change in 6MWT
- Mean change in muscle strength evaluated by knee extension, elbow flexion as measured by HHM
- Mean change in vastus lateralis muscles fat fraction (VLMFF) by MRS

Safety Endpoints: TEAE, Serious AE, discontinuation due to AE

The primary endpoint was analysed using an analysis of covariance (ANCOVA). As prespecified in the Statistical Analysis Plan, blinded 4SC data were found to lack normality, and so were log-transformed prior to analysis. Key secondary endpoints were analysed using a similar ANCOVA (without log-transformation), except cumulative loss-of-function, which was analysed using negative binomial regression.

The ITT, Group A Population was used for the prespecified efficacy analyses; supportive analyses were also performed post-hoc in the overall ITT population

The safety population (i.e., all randomised boys who received at least one dose of study drug), was used for safety evaluations.

RESULTS

Subjects disposition and baseline characteristics

- 359 boys were screened and 179 boys were enrolled, and 120 of them were enrooled in Group A - Target population. Subjects disposition is shown in Figure 1 .
- Baseline demographics and disease characteristics were similar in the two treatment groups, both overall and in the target population as shown in Figure 2.

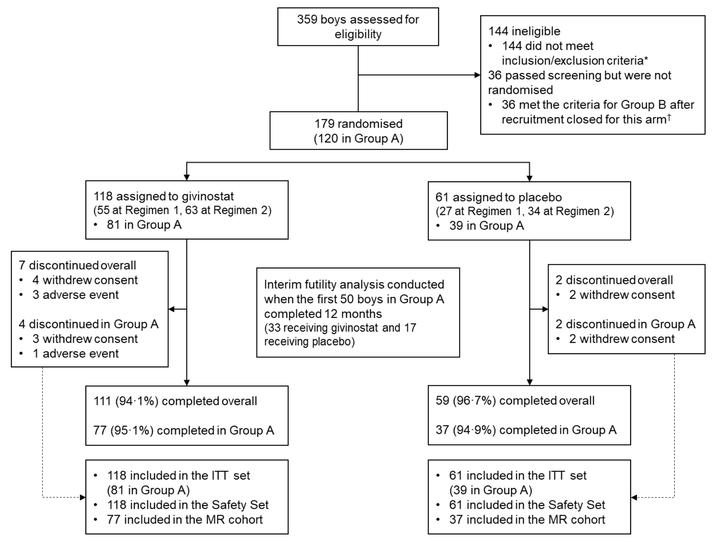

Figure 1 – Patient Disposition.

Parameter	Overall population		Target Population	
	Givinostat (N=118)	Placebo (N=61)	Givinostat (N=81)	Placebo (N=39)
Age (years), mean (SD); range	9.8 (2.02); 6.3 to 15.9	10.0 (2.08); 6.1 to 14.4	9.6 (1.88); 6.3 to 14.2	9.8 (2.10); 6.1 to 13.5
Race, n (%)				
White	106 (89.8)	57 (93.4)	74 (91.4)	36 (92.3)
BMI (kg/m^2), mean (SD); range	19.7 (4.10); 12.4 to 30.6	19.9 (4.40); 13.3 to 31.4	19.5 (3.83); 12.4 to 30.6	20.1 (4.52); 13.3 to 31.3
Time since diagnosis (years), mean (SD); range	5.5 (2.60); 0.1 to 11.4	5.6 (2.72); 0.5 to 12.3	5.7 (2.52); 0.4 to 10.6	5.6 (2.89); 0.5 to 12.3
Steroid regimen, n (%)				
Deflazacort daily regimen	84 (71.2)	39 (63.9)	60 (74.1)	25 (64.1)
Deflazacort intermittent regimen	7 (5.9)	6 (9.8)	6 (7.4)	4 (10.3)
Other steroid daily regimen	15 (12.7)	9 (14.8)	9 (11.1)	6 (15.4)
Other steroid intermittent regimen	12 (10.2)	7 (11.5)	6 (7.4)	4 (10.3)

Figure 2 – Baseline characteristics .

Efficay Results – Group A – target population (Figure 3)

- Over the 18-month follow-up period, 4SC decline was significantly slower with givinostat than placebo (GLSmean ratio [SD] = 0.86 [0.071]; p=0.0345) [3].
- Overall, treatment effect estimates relating to the key secondary endpoints consistently favored givinostat over placebo supporting the primary endpoint result (p<0.0001).

Efficacy Results – Overall ITT population (Figure 4)

- Over the 18-month follow-up period, 4SC decline was significantly slower with givinostat than placebo (GLSmean ratio [SD] = 0.84 [0.069]; p=0.0116).
- Overall, treatment effect estimates relating to the key secondary endpoints consistently favored givinostat over control supporting the primary endpoint result.
- Givinostat treatment was associated with less decline in NSAA Total Score (Mean difference: 1.50 points; nominal p=0.035)

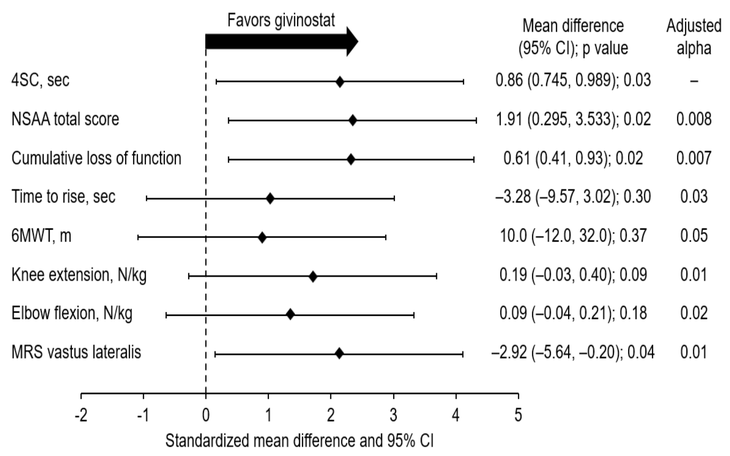

Figure 3 - Forest Plot of primary and key secondary endpoints at Month 18 (Group A, ITT set)

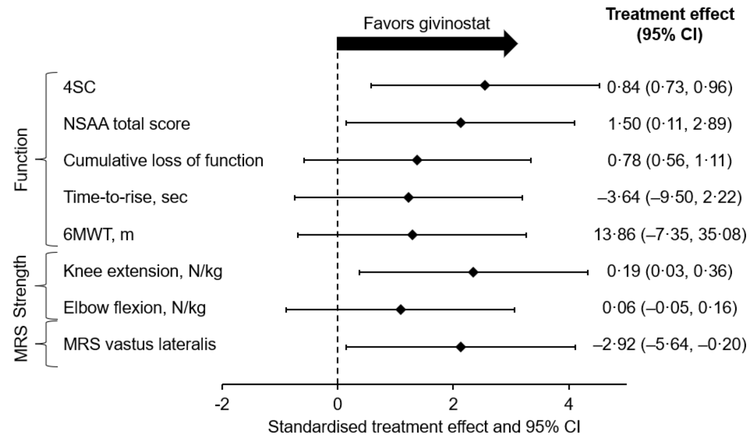

Figure 4 – Forest Plot of primary and key secondary endpoints at Month 18 (Overall Population, ITT set) .

Safety Results

- Similar proportions of boys had AEs with both treatments (95% vs 93%) (Figure 5) [3] .
- The most common AEs with givinostat were diarrhoea and vomiting (both in more than twice as many boys than placebo), nasopharyngitis, headache, and abdominal pain (Figure 5).
- 3.4% of subjects who received givinostat experienced TEAE leading to permanent discontinuation of the study drug

Patients (%)	Overall population	
	Givinostat (N=118)	Placebo (N=61)
Adverse event	112 (95)	57 (93)
Diarrhoea	43 (36)	11 (18)
Vomiting	34 (29)	8 (13)
Nasopharyngitis	31 (26)	19 (31)
Headache	28 (24)	14 (23)
Abdominal pain	25 (21)	9 (15)
Platelet count decreased or thrombocytopaenia	38 (32)	0
Abdominal pain upper	17 (14)	7 (11)
Fall	15 (13)	13 (21)
Pyrexia	15 (13)	5 (8)
Blood triglycerides increased or hypertriglyceridaemia	27 (23)	4 (7)
Cough	13 (11)	9 (15)
Pain in extremity	8 (7)	7 (11)
Upper respiratory tract infection	7 (6)	8 (13)
Back pain	6 (5)	8 (13)
Rhinitis	6 (5)	7 (11)

Figure 5 – Most common adverse events (≥10% boys in either group for adverse events)- (Overall Population, Safety set).

KEY POINTS

- Givinostat significantly reduced the decline in 4SC by ~40% (primary endpoint), in both Group A (target population) and overall ITT population
- Consistently reduced decline in muscle function and strength over time (secondary endpoints)

CONCLUSIONS

- Epidys study successfully met its primary endpoint with consistent results in the key secondary endpoints.
- The post-hoc analysis of the overall ITT population were consistent with the prespecified analyses.
- Givinostat tolerability profile in Epidys study was in line with results in previous studies in DMD and in other diseases.

REFERENCES & ACKNOWLEDGEMENTS

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