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Drisapersen treatment for Duchenne muscular dystrophy: results of a 96-week follow-up of an open-label extension study following two placebo-controlled trials

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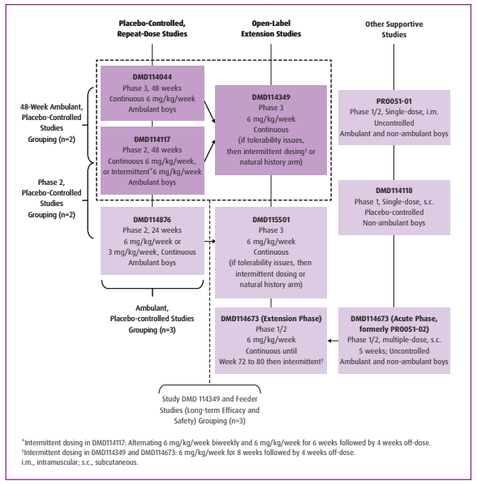
Background

- Duchenne muscular dystrophy (DMD) is a severely debilitating and ultimately fatal childhood disease that affects 1 in 3500–5000 newborn boys[1,2] and which is characterized by a progressive decrease in muscle function,[3] leading to loss of ambulation, respiratory failure, and cardiomyopathy.
- DMD is caused by mutations in the dystrophin *DMD* gene, resulting in disruption of the open-reading frame, which cause dystrophin deficiency and muscle fiber degeneration.[4]
- Drisapersen is a 2′-*O*-methyl-phosphorothioate antisense oligonucleotide that induces skipping of exon 51 in the dystrophin pre-mRNA, to correct mutations occurring in approximately 13% of boys with DMD.[5]
- A comprehensive clinical trial program to assess the safety and efficacy of drisapersen in DMD has been conducted, including two Phase 2 and one Phase 3 reported, randomized, placebo-controlled studies (total N=290), and two open-label extension studies (data currently available for N=200) (**Figure 1**).
  - The Phase 2 studies (DMD114117 and DMD114876) enrolled similar populations with earlier stages of disease (mean baseline 6-minute walking distance [6MWD] ~400 m).
  - The Phase 3 study (DMD114044) (mean baseline 6MWD <350 m) enrolled a more heterogeneous population, including some patients with more advanced DMD than those enrolled in DMD114117.
  - In the first open-label extension study (DMD114673), 12 boys (average age of 12.9 years for the 10 boys who completed the 6MWD at extension baseline) were evaluated up to 188 weeks (3.4 years).
- We present results up to Week 48 from the second open-label extension study of drisapersen treatment in boys with DMD (DMD114349), who had previously completed a 48-week, double-blind, placebo-controlled treatment phase in one of two feeder studies discussed above (DMD114117 and DMD114044).

Figure 1. Overview of the drisapersen clinical trial program.



*Intermittent dosing in DMD114117: Alternating 6 mg/kg/week biweekly and 6 mg/kg/week for 6 weeks followed by 4 weeks off-dose.
†Intermittent dosing in DMD114349 and DMD114673: 6 mg/kg/week for 8 weeks followed by 4 weeks off-dose.
i.m., intramuscular; s.c., subcutaneous.

Objectives

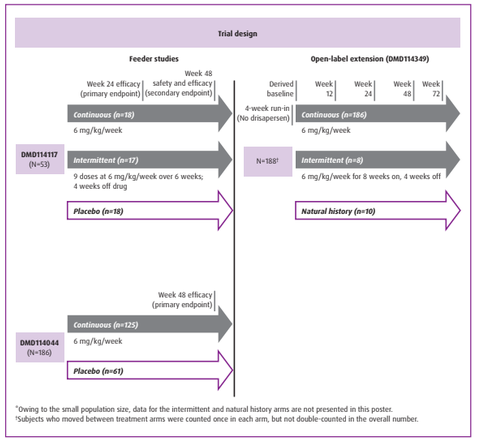
- The primary objective of study DMD114349 was to assess the long-term safety, tolerability, and efficacy of drisapersen administered at a dose of 6 mg/kg once weekly.
- The additional objective of the retrospective analyses also presented in this poster is to compare the efficacy results from boys from each of the feeder studies in this open-label extension study.

Methods

DMD114349 study design and subject population

- An open-label, multicenter, uncontrolled extension study (DMD114349; NCT01480245) in subjects with DMD who had completed the 48-week double-blind treatment phase in either the DMD114117 (NCT01153932) or the DMD114044 (NCT01254019) feeder studies.
  - Subjects who had to withdraw from either of the feeder studies owing to safety or tolerability issues may have been able to enroll in DMD114349 after consultation with the medical monitor.
- The study design for both feeder studies and the open-label extension is shown in **Figure 2**.
- The study included a 4-week run-in period with no drug or assessments, unless subjects had already been off drisapersen for at least 4 weeks.
- This study was performed in compliance with Good Clinical Practices. Written informed consent was obtained from each subject and their parent/guardian prior to any study-specific procedures.

Figure 2. Study design of DMD114349.*



*Owing to the small population size, data for the intermittent and natural history arms are not presented in this poster.
†Subjects who moved between treatment arms were counted once in each arm, but not double-counted in the overall number.

DMD114117 and DMD114044 feeder studies

- DMD114117 (N=53) was a Phase 2, double-blind, exploratory, parallel group, placebo-controlled study conducted at 13 sites in nine countries to assess two dosing regimens of drisapersen for efficacy, safety, tolerability, and pharmacokinetics in ambulant subjects with DMD.
  - At Week 25, 6MWD was assessed and a statistically significant and clinically meaningful treatment difference of 35 m (p=0.014) shown for 6 mg/kg/week of drisapersen treatment versus placebo. This treatment difference was maintained to Week 49 (36 m; p=0.051). The improvement in percent-predicted 6MWD was 6% at both time points (p=0.010 and 0.049, respectively).
- DMD114044 (N=186) was a Phase 3, randomized, double-blind, placebo-controlled clinical study conducted at 47 sites in 20 countries to assess the efficacy and safety of drisapersen in subjects with DMD.
  - At Week 48, no statistically significant or clinically meaningful treatment difference (10.3 m; p=0.42) was observed for 6 mg/kg/week of continuous drisapersen treatment versus placebo.
- On average, boys in study DMD114044 were older with a longer time since first diagnosis and treatment than those in study DMD114117 (**Table 1**).
- Study populations also differed with respect to disease severity at baseline (**Table 1**).
  - Boys from DMD114044 had lower mean baseline 6MWD, and slower mean rise from floor time, 10 m walk/run time, and 4 stairs climb-ascent/descent than boys from DMD114117.

Table 1. Baseline characteristics of boys at beginning of feeder studies DMD114117 and DMD114044.

	DMD114117 (N=53)		DMD114044 (N=186)	
	Drisapersen 6 mg/kg/week	Placebo	Drisapersen 6 mg/kg/week	Placebo
Mean (SD), range age, years	7.2 (1.7), 5–11	6.9 (1.2), 5–9	8.0 (2.4), 5–16	8.3 (2.4), 5–16
Mean (SD) time since first symptoms, months	61 (25)	64 (24)	72 (32)	67 (31)
Mean (SD) time since diagnosis, months	45 (28)	44 (22)	58 (35)	54 (33)
6MWD, m	428	403	337	348
10 m walk/run time, s	4.98	4.96	6.49*	6.37*
4 stairs climb-ascent time, s	3.14	3.50	4.65*	4.55*
4 stairs climb-descent time, s	2.98	2.81	3.92*	4.08*
Rise from floor time, s	4.83	4.67	12.34	13.41
Muscle strength, lbs	124.29	122.01	102.49	98.55

*Seconds estimated from velocity summary statistics.
6MWD, 6-minute walking distance; SD, standard deviation.

Assessments

- Analyses of DMD114349 data alone (including the primary endpoint and safety data) are based on a cut of the data taken on June 6, 2013. The integrated analyses are based on a cut of the data taken on October 14, 2013.
- The primary endpoint in DMD114349 was the change from study DMD114349 baseline in 6MWD at Week 104; however, no subjects had reached Week 104 at the time of the data cut and, therefore, results from Weeks 24 and 48 are presented here. Additionally, within this poster, results of the integrated data (DMD114349 and the feeder studies) are presented, demonstrating the change from the original (feeder study) baseline in 6MWD.
- The 6MWD was performed as described previously[6] and percent-predicted 6MWD was calculated using the Geiger equation as described by Henricson and colleagues.[7]
- The mean change (95% confidence interval) from original baseline in the 6MWD was calculated retrospectively by age group (≤7 and >7 years) at each visit within the feeder study and within DMD114349, up to DMD114349 Week 48, for subjects receiving either regimen of drisapersen in study DMD114349. Only subjects reaching Week 48 of DMD114349 are included in these figures.
- Safety endpoints included all on-treatment adverse events (AEs).
  - AEs of special interest included those resulting from any of the laboratory safety parameter stopping criteria for hepatic or renal toxicity, thrombocyte count, inflammation, and coagulation abnormalities, and any AEs resulting from injection-site reactions.
- Changes from DMD114349 baseline in the primary efficacy endpoint, 6MWD, were analyzed using mixed models for repeated measures, including fixed terms for visit and country grouping. Data from the integrated database are summarized.
- The modified safety population was defined as all subjects who received at least one dose of study medication or entered the natural history arm at the start of study DMD114349 and, as such, did not take any study medication. This is the primary population for evaluation of safety parameters.
- The modified ambulant intent-to-treat (ITT) population is defined as all subjects in the modified safety population who had at least one post-baseline efficacy assessment and who were ambulant at the baseline visit of study DMD114349. This is the primary population for evaluation of efficacy parameters, relevant to only the ambulant population, eg, the 6MWD.
- Comparisons between treatment arms within DMD114349 cannot be made as changes in treatment were made (in response to safety/tolerability concerns) resulting in different populations on different treatment arms.

Results

Treatment arms and subject baseline characteristics

- A total of 188 subjects were enrolled and assigned to a treatment group as of June 6, 2013.
- A total of 171 subjects were treated continuously, two subjects were treated intermittently, five subjects began continuous treatment and later moved across to the intermittent treatment arm, one subject began with continuous treatment, moved to the intermittent treatment arm, and ultimately stopped treatment and formed part of the natural history arm, nine subjects began continuous treatment but stopped treatment and moved to the natural history arm, and one subject had not been assigned treatment at the time of the data cut (data not shown).
- The study was terminated and last subject last visit was achieved on March 17, 2014.
- Patient baseline characteristics are shown in **Table 2**.

Table 2. Patient baseline characteristics (modified safety population; June 6, 2013 data cut) for DMD114349.

	Continuous drisapersen 6 mg/kg (N=186)
Age, years	8.8 (2.06)
Time since first symptoms, months	80.0 (29.87)
Time since diagnosis, months	67.1 (33.53)
Time since first corticosteroids, months	43.4 (25.28)
Corticosteroid regimen, n (%)	
Continuous	103 (55)
Intermittent	83 (45)

All values are mean (SD) unless stated otherwise.
SD, standard deviation.

Efficacy

Change in 6MWD from study DMD114349 baseline

- At derived baseline of study DMD114349, the adjusted mean (standard error) 6MWD for all subjects (n=168) in the continuous 6 mg/kg/week drisapersen group was 362.6 (9.2) m.
  - The difference versus baseline at Week 12 was −20.7 m (n=155), which increased to −35.2 m at Week 24 (n=137) and −78.3 m at Week 48 (n=67) (decrease statistically significant, p<0.001 at each time point).

Change in 6MWD from feeder study baseline

- At Week 48 of the extension study (96 weeks after the original baseline of both feeder studies), the treatment difference in 6MWD for subjects receiving drisapersen throughout versus those who received placebo in the feeder studies and started drisapersen at extension baseline was 46.1 m (**Figure 3a**).
  - The mean change from the original baseline was −66.8 m for the continuous drisapersen treatment group and −112.9 m for the placebo/delayed drisapersen treatment group.
- For subjects from only the DMD114117 feeder study, the treatment difference at Week 48 of the extension study in 6MWD for subjects receiving drisapersen throughout versus those who received placebo in the feeder study and started drisapersen at extension baseline was 52.0 m (**Figure 3b**).
  - The mean change from the original baseline was −5.1 m for the continuous drisapersen treatment group and −57.1 m for the placebo/delayed drisapersen treatment group.
- For subjects from only the DMD114044 feeder study, the treatment difference at Week 48 of the extension study in 6MWD for subjects receiving drisapersen throughout versus those who received placebo in the feeder studies and started drisapersen at extension baseline was 49.2 m (**Figure 3c**).
  - The mean change from the original baseline was −87.0 m for the continuous drisapersen treatment group and −136.2 m for the placebo/delayed drisapersen treatment group.

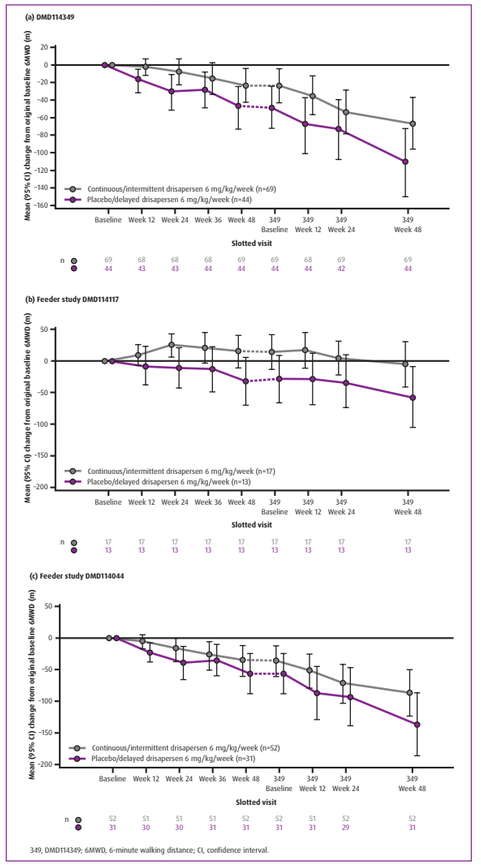
6MWD subset analysis by age

- At Week 48 of the extension study (Week 96 after the original baseline of both feeder studies), the 6MWD for subjects ≤7 years of age (n=52) being treated with drisapersen throughout increased by 8.4 m from baseline versus a decrease of −28.7 m for those who received placebo in the feeder studies and started drisapersen at extension baseline. The treatment difference was 37.1 m (**Figure 4a**).
  - For subjects >7 years of age (n=61), both groups declined; by −128.1 m in the continuous drisapersen group compared with −189.7 m in the delayed group. The treatment difference was 61.6 m (**Figure 4b**).

Safety and tolerability

- The most common AEs during study DMD114349 for the continuous treatment arms are shown in **Table 3**.
- The majority of subjects (n=163/186; 88%) experienced an on-treatment AE.
  - For 145 (78%) subjects, these AEs were related to the study drug.
- A total of 149 subjects (80%) receiving continuous drisapersen had AEs of special interest, including injection-site reactions (n=113; 61%), renal abnormality (n=112; 60%), inflammation (n=53; 28%), coagulation (n=14; 8%), thrombocytopenia (n=11; 6%), and hepatic abnormality (n=9; 5%).
  - In total, 8% of subjects reported a serious AE, most commonly thrombocytopenia.
- Of all subjects who reported AEs, only seven (4%) subjects had to withdraw or permanently discontinue the study drug: five (3%) had thrombocytopenia and one (<1%) each had asthenia and proteinuria.
  - One subject had elevated alanine aminotransferase 43 days after the first dose of drisapersen but continued treatment with drisapersen in the continuous dosing arm.

Figure 3. Mean change from original baseline in the 6MWD for (a) subjects from both feeder studies, (b) subjects from study DMD114117, and (c) subjects from study DMD114044.



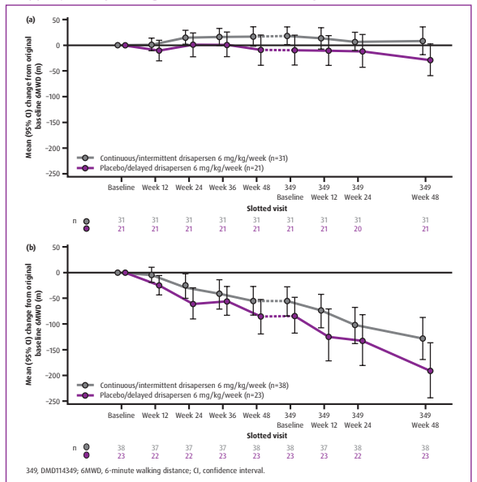
349, DMD114349; 6MWD, 6-minute walking distance; CI, confidence interval.

Table 3. Most common AEs with continuous drisapersen treatment (modified safety population; June 6, 2013 data cut).

Events, n (%)	Continuous drisapersen 6 mg/kg/week (N=186)
Any event	163 (88)
Proteinuria	60 (32)
Injection-site erythema	51 (27)
Vomiting	49 (26)
Headache	48 (26)
Nasopharyngitis	47 (25)
Fall	43 (23)
Pyrexia	43 (23)
Injection-site discoloration	37 (20)
Diarrhea	36 (19)
Abdominal pain	27 (15)
Protein urine present	28 (15)
Pain in extremity	24 (13)
Cough	26 (14)
Upper respiratory tract infection	25 (13)
Contusion	23 (12)
Hematuria	23 (12)
Injection-site induration	24 (13)
Injection-site reaction	24 (13)
Red blood cells urine positive	22 (12)
Epistaxis	17 (9)

Eight patients were treated in the intermittent arm but data are not reported here owing to small numbers.

Figure 4. Mean change from the original baseline in 6MWD for (a) subjects ≤7 years of age, and (b) subjects >7 years of age at the start of the feeder study.



349, DMD114349; 6MWD, 6-minute walking distance; CI, confidence interval.

Conclusions

- A comprehensive clinical trial program has been conducted to assess the safety and efficacy of drisapersen in DMD, comprising both placebo-controlled and open-label extension studies.
- In this long-term study, drisapersen was generally well tolerated. Overall, the safety profile was generally consistent with that seen in other drisapersen studies with the most frequent AEs associated with injection-site reactions and renal effects (subclinical proteinuria). Moderate-to-severe thrombocytopenia, which resolved on permanent discontinuation of drisapersen therapy, was seen in approximately 3% of the overall drisapersen-treated population in the clinical program as a whole.
- Although an overall decline in 6MWD compared with DMD114349 baseline was observed for all treatment groups, the results from the open-label extension study demonstrate that a clinically meaningful treatment difference in 6MWD of 46 m can be seen for subjects receiving continuous drisapersen 6 mg/kg/week (or intermittently in DMD114349) versus those who received placebo in the feeder studies and started drisapersen at extension baseline.
- Boys with less progressed disease declined less or even improved from baseline with 2-year continuous drisapersen therapy, suggesting a treatment difference from those initially on placebo.
  - Boys from the DMD114117 study decline by −5 m over 96 weeks on continuous drisapersen compared with −57 m with delayed treatment.
  - Boys aged ≤7 years in study DMD114349 improve from original baseline by 8.4 m with continuous drisapersen treatment compared with −28.7 m from those with delayed treatment.
  - For subjects >7 years of age (n=61), both groups declined; by −128.1 m in the drisapersen group compared with −189.7 m in the delayed group. The treatment difference was 61.6 m.
- This extension study suggests maintenance of benefit in a subpopulation of boys with less severe disease, and a clinically meaningful benefit slower to emerge in a subpopulation that is, on average, more severely affected.

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NG has served on clinical steering committees and/or as a consultant and received compensation from Shire, PTC Therapeutics, Eli Lilly, Italfarmaco, and UCB. TV is an SAB member of Prosensa Holding NV. CMcD has served on the scientific advisory committee and received compensation for consulting from PTC Therapeutics, has served as a consultant and received compensation from Sarepta, Novartis, Halo Therapeutics, Pfizer, Italfarmaco, GlaxoSmithKline, and Prosensa, and has served on a clinical trial steering committee and received compensation for consulting from Eli Lilly. CW, JK, KR, JN, and BJ are employees of GlaxoSmithKline. CW and KR have shares in GlaxoSmithKline. RW is a consultant for Prosensa Holding NV. GC is an employee of Prosensa Holding NV.