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Pharmacokinetics and safety of single doses of drisapersen in non-ambulant subjects with Duchenne muscular dystrophy: Results of a double-blind randomized clinical trial ☆

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Abstract

Duchenne muscular dystrophy (DMD) is a progressive, lethal neuromuscular disorder caused by the absence of dystrophin protein due to mutations of the dystrophin gene. Drisapersen is a 2′-*O*-methyl-phosphorothioate oligonucleotide designed to skip exon 51 in dystrophin pre-mRNA to restore the reading frame of the mRNA. This study assessed safety, tolerability, and pharmacokinetics of drisapersen after a single subcutaneous administration in non-ambulatory subjects. Eligible subjects were non-ambulant boys aged $\geqslant$9 years, in wheelchairs for $\geqslant$1 to $\leqslant$4 years, with a diagnosis of DMD resulting from a mutation correctable by drisapersen treatment. Four dose cohorts were planned (3, 6, 9 and 12 mg/kg), but study objectives were met with the 9 mg/kg dose. Less than proportional increase in exposure was demonstrated over the 3–9 mg/kg dose range, though post hoc analysis showed dose proportionality was more feasible over the 3–6 mg/kg range. Single doses of drisapersen at 3 and 6 mg/kg did not result in significant safety or tolerability concerns; however, at the 9 mg/kg dose, pyrexia and transient elevations in inflammatory parameters were seen. The maximum tolerated dose of 6 mg/kg drisapersen was identified for further characterization in multiple dose studies in the non-ambulant DMD population.

Keywords: Drisapersen; Duchenne muscular dystrophy; DMD; Dystrophin; Exon 51; Non-ambulant; Oligonucleotide, Pharmacokinetics; Safety

1. Introduction

Duchenne muscular dystrophy (DMD) is an inheritable, X chromosome-linked lethal childhood disease with an incidence of approximately 1 in 3500 newborn boys [1]. DMD is caused by mutations in the gene coding for the protein dystrophin resulting in little or no dystrophin being produced. Dystrophin is essential for the integrity

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and functioning of muscle fibers [2,3]. Absence of dystrophin leads to progressive muscle weakness, with DMD patients typically wheelchair-bound before the age of 12. As the disease progresses, respiratory and cardiac muscles are affected, orthopedic complications occur, and, in the absence of intervention, death occurs at approximately age 19 [4]. Current supportive treatments include physiotherapy, mechanical supports, orthopedic surgery, assisted ventilation, disease management (e.g., for respiratory infections, cardiomyopathy) and glucocorticosteroids. This multidisciplinary approach to treatment has prolonged life expectancy, with some patients surviving into the fourth decade and beyond [4,5].

In DMD, genetic mutations, such as a deletion of one or more exons, result in an out-of-frame transcription product and subsequent disrupted dystrophin protein synthesis [6]. The aim of oligonucleotide-based therapy is to manipulate the post-transcriptional splicing process of the pre-mRNA in such a way that the reading frame of the resulting mRNA is restored. This would result in the production of a shortened yet partially functional dystrophin protein, analogous to that seen in the less severe Becker muscular dystrophy (BMD). Such treatment could potentially delay disease progression and improve function in the remaining muscle [7].

Drisapersen (formerly GSK2402968 and PRO051) is a 20mer chemically-modified (2′-*O*-methyl-phosphorothioate) oligonucleotide with a sequence optimized to skip exon 51 in the human dystrophin pre-mRNA. Mutations thought to be correctable by skipping exon 51 account for approximately 13% of all DMD patients [8]. Drisapersen has been shown to induce novel dystrophin production after both local injection [9] and systemic administration [10], and weekly subcutaneous drisapersen treatment (6 mg/kg/week) has shown encouraging results on functional endpoints, including the 6 Minute Walk Distance (6MWD) test [10].

The efficacy and safety of drisapersen is currently being studied in ambulant boys with DMD in several clinical trials worldwide [11–15]; however, there has been limited experience in non-ambulant boys with DMD. Since muscle potentially accounts for a large proportion of uptake of drisapersen, there is the potential that the pharmacokinetics of drisapersen may be different in the non-ambulant DMD population due to reduced lean muscle mass relative to ambulant boys. The purpose of the current study (DMD114118; ClinicalTrials.gov Identifier: NCT01128855) was to assess the safety, tolerability, and pharmacokinetics of drisapersen after a single subcutaneous administration at different dose levels in non-ambulant subjects with DMD.

2. Patients and methods

Eligible subjects were non-ambulant boys aged $\geqslant 9$ years, in wheelchair for at least one year but no more than 4 years, and with a diagnosis of DMD resulting from a mutation correctable by treatment with drisapersen. Patients with additional mutations not correctable by drisapersen, with a history of renal or hepatic disease, or with symptomatic cardiomyopathy were excluded. Treatment with glucocorticosteroids was allowed, but these had to be started at least 6 months and have been dosed with a stable regimen for at least 3 months before the anticipated first administration of study medication. Use of anticoagulants, antithrombotics or antiplatelet agents, previous treatment with investigational drugs within 6 months of the first administration of study medication, and use of idebenone or other forms of Coenzyme Q10 within 1 month of study medication was prohibited.

Following a screening period of up to 2 weeks, subjects were randomized to receive a single subcutaneous dose of drisapersen or dose-matched placebo. Subjects were assigned to study treatment in accordance with a central randomization schedule. In each cohort, subjects were randomized to a single dose level of drisapersen or dose-matched placebo, in a ratio of 3:1. Drisapersen was supplied as a solution for subcutaneous injection, 200 mg/mL. The precise amount administered was titrated against body weight in accordance with the protocol instructions. The study was designed to enroll up to 32 subjects within 4 cohorts, with the final 2 cohorts being divided into 2 sub-groups (1, 2, 3a/3b, 4a/4b). Each planned cohort was comprised of 8 subjects (6 active and 2 placebo) not to exceed the following levels:

- Cohort 1: 3 mg/kg drisapersen or placebo;
- Cohort 2: 6 mg/kg drisapersen or placebo;
- Cohort 3: 9 mg/kg drisapersen or placebo;
- Cohort 4: 12 mg/kg drisapersen or placebo

Cohorts 3 and 4 were divided into sub-groups 3a/3b and 4a/4b, with 4 subjects in each sub-group. All subjects in Cohort 3 (3a and 3b) were planned to receive up to 9 mg/kg, and all subjects in Cohort 4 (4a and 4b) were planned to receive up to 12 mg/kg. There was planned to be at least 14 days between treating the last subject of sub-group a and treating the first subject in sub-group b, with safety parameters reviewed prior to moving to subgroup b.

The study allowed dose levels in subsequent cohorts to be modified downwards or repeated at the same dose of the previous cohort following review of data by a Safety Review Team. Subjects had a 1 month active study period and a 5 month post-dose follow-up period.

The primary pharmacokinetic (PK) endpoints included: area under the plasma concentration–time curve (AUC) from time 0 to 24 h post-dose ($AUC_{0–24h}$), and time 0 to 7 days post-dose ($AUC_{0–7d}$); the observed maximum plasma concentration post-dose (C_{max}); and the time of maximum plasma concentration post-dose (T_{max}). The primary safety and tolerability endpoints included: adverse event (AE) monitoring; 12-lead ECG; vital signs; laboratory safety tests (biochemistry, hematology, urinalysis and coagulation parameters); and local