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Long-term Safety and Efficacy of Golodirsen in Male Patients With Duchenne Muscular Dystrophy Amenable to Exon 53 Skipping

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BACKGROUND

- Duchenne muscular dystrophy (DMD) is a fatal, X-linked neuromuscular disease caused by mutations in the dystrophin gene[1]
- Mutations leading to deletions flanking exon 53 account for 8% of all DMD patients[2]; natural history studies demonstrate disparate disease trajectories for patients with different mutations[3]
- Patients between the ages of 4–7 are expected to gain motor skills and function, but those >7 years of age tend to exhibit progressive deterioration and declining ambulatory function[3-6]
- Golodirsen binds to dystrophin pre-mRNA to allow skipping of exon 53, restoring the mRNA reading frame and allowing translation of a truncated dystrophin protein[7]
- Study 4053-101 (NCT02310906) is a first-in-human, Phase 1/2, 2-part clinical trial designed to assess safety, tolerability, and efficacy of golodirsen in patients with mutations amenable to exon 53 skipping who have progressive deterioration and declining ambulatory function[7]

OBJECTIVE

- To report efficacy and safety of long-term golodirsen treatment in study 4053-101

METHODS

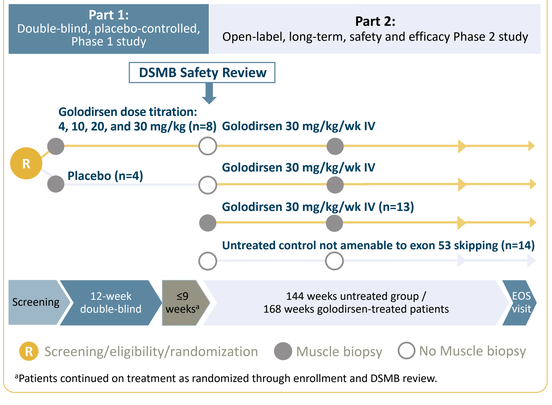
Study Population

- Boys, 6–15 years of age, diagnosed with genotype-confirmed DMD amenable to exon 53 skipping
- Received stable dose of oral corticosteroids for ≥24 weeks prior to Week 1
- Mean 6-minute walk test (6MWT) distance of ≥250 m at both screening and baseline
- North Star Ambulatory Assessment total score >17 and/or rise time <7 s (Gowers' sign)

Study Design and Treatment

- Study 4053-101 is a 2-part, multicenter study (**Figure 1**)[7]
  - Part 1 (12 weeks): 12 patients were randomized to receive double-blind treatment of dose-titrated, IV golodirsen (n=8) or placebo (n=4)
  - Part 2: patients from Part 1 plus 13 additional patients received open-label golodirsen (30 mg/kg/wk; 168 weeks); an untreated group (n=14) was used to evaluate natural history for patients not amenable to exon 53 skipping (144 weeks)

Figure 1. Study 4053-101 Design



[a]Patients continued on treatment as randomized through enrollment and DSMB review.

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METHODS

Endpoints

- Part 1
  - Primary: safety
- Part 2
  - Primary efficacy: 6MWT at Week 144
  - Secondary efficacy: percent predicted forced vital capacity (FVC%p)
  - Primary biologic: dystrophin protein levels at Week 48
  - Secondary biologic: percent dystrophin-positive fibers, exon 53 skipping

Statistical Analyses

- Adverse events (AEs) were analyzed using descriptive statistics
- Changes in dystrophin expression were analyzed using a 1-sample permutation t-test; in a post hoc analysis, correlation of exon 53 skipping and dystrophin expression was analyzed using Spearman correlation
- Ambulation data were compared post hoc with matched exon 53 skipping–amenable natural history external controls aged ≥6 years, with steroid use and able to rise at baseline, identified from a longitudinal multicenter cohort study in Italy, Belgium, and the UK[3]
- For all hypothesis testing, 2-sided significance level was 0.05 with no formal adjustment for multiplicity

RESULTS

Untreated Arm Results

- The untreated arm was intended to evaluate the natural history of the disease and exploratory biomarkers
- Per protocol, it was not considered as a control group for golodirsen-treated patients because these patients had genetic mutations not amenable to exon 53 skipping, including a wider range of deletions and genotypes associated with milder clinical course
- Results for the untreated arm are shown in **Table 1**

Table 1. Untreated Arm Efficacy Results

Endpoints	Baseline	Year 3
6MWT distance, m	n=13	n=6
Mean (SD)	455.1 (51.1)	278.7 (188.9)
Range	351–539	0–525
FVC%p	n=13	n=5
Mean (SD)	97.9 (18.3)	77.5 (18.6)
Range	60.85–120.51	53.86–99.96

Baseline Characteristics

- Efficacy comparisons were instead made using a matched exon 53 skipping–amenable external natural history control cohort[3]
  - 28 patients in the natural history cohort had mutations amenable to exon 53 skipping; 19 were selected by applying matching criteria (at baseline: age ≥6 years, steroid use, 6MWT ≥250 m, able to rise)
- Baseline characteristics of all golodirsen-treated study patients and matched exon 53 skipping–amenable controls were similar (**Table 2**)

Table 2. Baseline Characteristics

Characteristic	Golodirsen (N=25)	Matched Exon 53 Skipping–Amenable Natural History Control (N=19)
Age, years	8.4 (2.2)	9.1 (1.7)
Range	6–13	6.0–11.6
Height, cm	120.5 (10.1)	N/A
Weight, kg	28.4 (9.0)	N/A
BMI, kg/m^2	19.1 (3.7)	N/A
6MWT distance, m	405.8 (55.1)	382.1 (55.9)
Range	290–512	300–489
Time to rise, s	5.9 (3.5)	6.2 (3.1)
Range	2.3–18.6	3.0–14.9
Time since DMD diagnosis, months	55.8 (24.8)	N/A
Duration of corticosteroid use, months	35.3 (24.4)	N/A

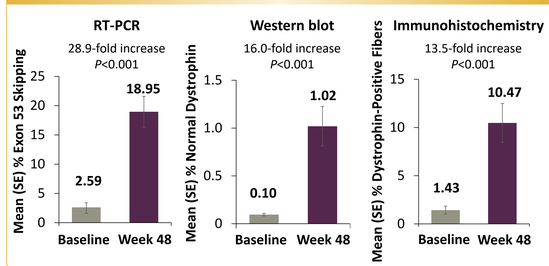
BMI=body mass index; N/A=not available. Values are mean (SD) unless noted otherwise.

RESULTS

Dystrophin Expression

- Exon 53 skipping measured by RT-PCR and dystrophin protein expression measured by Western blot and immunohistochemistry increased significantly from baseline to Week 48 (**Figure 2**)[7]
- Exon 53 skipping and dystrophin production by Western blot were significantly correlated (Spearman correlation coefficient = 0.50; P=0.011)[7]

Figure 2. Increased Exon 53 Skipping and Dystrophin Expression After 48 Weeks With Golodirsen Treatment[7]



Ambulatory and Pulmonary Function

- Compared with matched exon 53 skipping–amenable natural history controls, golodirsen treatment attenuated ambulatory function loss based on 6MWT (**Figure 3**) and prolonged ambulatory status based on loss of ambulation (LOA) (**Figure 4**) over 3 years
- FVC%p declined 8.4% over 144 weeks in golodirsen patients (**Table 3**)

Figure 3. Golodirsen-Treated Patients Had Attenuation of Ambulatory Decline Compared With Matched Exon 53 Skipping–Amenable Natural History Controls

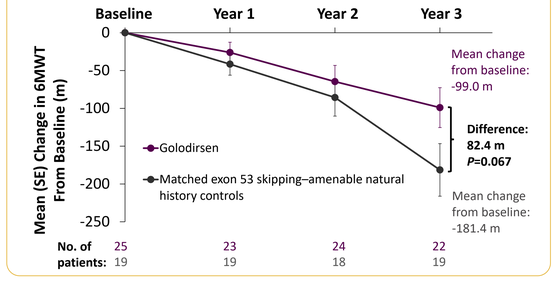


Figure 4. Golodirsen Prolonged Ambulatory Status Compared With Matched Exon 53 Skipping–Amenable Natural History Controls

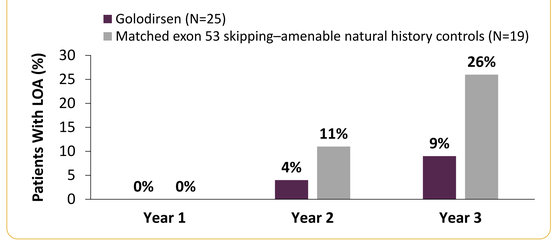


Table 3. Pulmonary Function in Golodirsen-Treated Patients

FVC%p	Baseline[a] (n=25)	Week 48 (n=24)	Week 96 (n=23)	Week 144 (n=23)
Mean (SD)	92.7 (23.95)	92.5 (18.71)	93.9 (17.55)	83.8 (23.22)
Range	16.43–137.84	41.88–129.91	37.41–124.89	7.83–121.14

[a]Baseline FVC%p for placebo patients was defined as Part 2 baseline FVC%p, and inclusion criteria (FVC%p >50%) for screening was not applied at that time.

RESULTS

Safety

- Safety was assessed up to 189 weeks (mean 167 weeks)
- The majority of AEs reported were mild, nonserious, and assessed as unrelated to golodirsen, and are common events in the general pediatric population or DMD population (**Table 4**)
- No anaphylaxis or serious hypersensitivity events were reported
- Cardiac events possibly related to golodirsen were reported in 2 patients (tachycardia and syncope); both were nonserious and mild
- There was no evidence of renal toxicity
  - 2 patients had mild renal AEs that were transient and nonserious, and resolved spontaneously
- No patient discontinued treatment due to an AE and there were no deaths

Table 4. Adverse Events Overview

	Part 1		Combined Parts 1 and 2
	Placebo (n=4)	Golodirsen (n=8)	Total Golodirsen Group (N=25)
Patients with ≥1 AE, n (%)	4 (100)	8 (100)	25 (100)
Related to treatment	2 (50.0)	5 (62.5)	9 (36.0)
Serious	0	0	4 (16.0)[a]
Leading to treatment discontinuation	0	0	0
Total AEs by severity, n	23	69	860
Mild	22	68	831
Moderate	1	1	24
Severe	0	0	5[b]

[a]4 (16%) patients had 7 serious AEs (vomiting, pyrexia, hypocalcemia, hematemesis, gastroenteritis viral, convulsion, tonsillar hypertrophy), all deemed not related to golodirsen treatment. [b]5 AEs were severe (5 events of fracture or abasia), all nonserious.

CONCLUSIONS

- Golodirsen demonstrated a significant increase in exon 53 skipping and dystrophin protein expression (all P<0.001)
- Functional benefits in a declining DMD population were obtained by comparing a matched untreated external cohort of patients with golodirsen-treated patients
  - Ambulatory assessments suggest benefit from golodirsen treatment as seen in post hoc 6MWT and LOA comparisons vs matched exon 53 skipping–amenable natural history controls
  - Cumulative FVC%p decline of 8.4% over 3 years (144 weeks) favorably compares with published DMD natural history decline of ~5% annually[8,9]
- During long-term treatment with golodirsen, AEs were generally mild, nonserious, and unrelated to golodirsen, and there were no discontinuations due to safety
  - Overall, there was no suggestion of a significant risk of renal abnormality or toxicity
- The clinical benefit of golodirsen is currently being assessed in an ongoing Phase 3 study (NCT02500381)

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