M162

Six-Year Long-Term Safety and Efficacy of Golodirsen in Patients With DMD vs Mutation-Matched External Controls

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Background

- Duchenne muscular dystrophy (DMD) is a fatal, X-linked neuromuscular disease caused by mutations in the dystrophin (*DMD*) gene, resulting in the lack of dystrophin protein[1]
- Patients with DMD aged ≤7 years treated with corticosteroids may have improved functional tests due to the effect of physiologic growth and development, whereas those aged >7 years tend to exhibit progressive deterioration and declining ambulatory function, with loss of ambulation (LOA) occurring at age ~13 years[1–4]
- Mutations leading to deletions flanking exon 53 account for up to 8% of all patients with DMD[5]; natural history studies demonstrate disparate disease trajectories for patients with different mutations[6]
- Golodirsen binds to dystrophin pre-mRNA to allow skipping of exon 53, which restores the mRNA reading frame and allows for production of an internally shortened functional dystrophin protein[7]
- Study 4053-101, a first-in-human, phase 1/2, 2-part clinical trial, provided evidence for long-term safety of golodirsen and suggested functional benefit vs matched external controls (ECs) in patients with mutations amenable to exon 53 skipping who have progressive deterioration and declining ambulatory function[8]

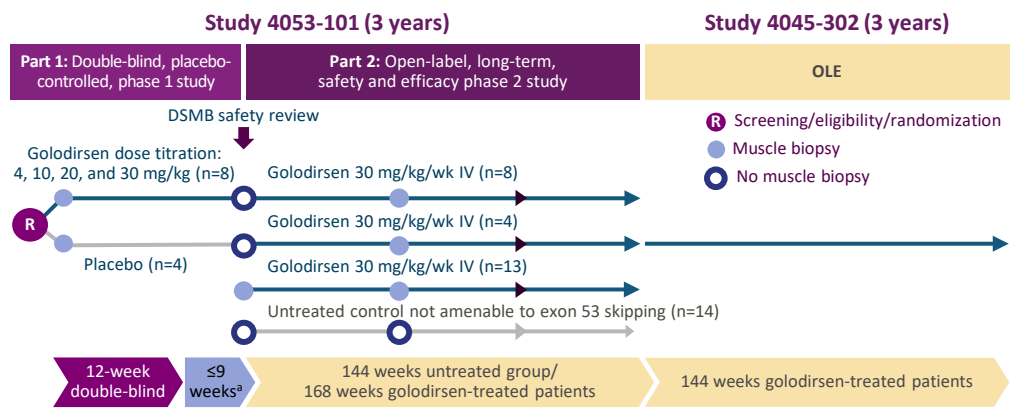
Objective

To describe results from post hoc analyses of patients enrolled in Study 4053-101 (NCT02310906) who continued into the open-label extension (OLE), Study 4045-302 (NCT03532542), evaluating the safety and efficacy of golodirsen treatment up to 6 years in patients amenable to exon 53 skipping with progressive disease deterioration

Study Design

- Study 4045-302 is a 3-year multicenter, OLE study evaluating the long-term safety and efficacy of golodirsen 30 mg/kg in patients with DMD amenable to skipping of exon 53 (**F1**)
- Patients from Study 4053-101 were eligible to transfer into the 3-year OLE

F1 *Study Design*



[a]Patients continued on treatment as randomized through enrollment and DSMB review. DSMB=Data and Safety Monitoring Board; IV=intravenous; OLE=open-label extension; R=randomization.

Assessments

- Incidence of serious adverse events (AEs)
- Ambulatory function over 6 years by LOA
  - LOA was defined as meeting at least one of the following criteria: **1)** 2 consecutive visits of either North Star Ambulatory Assessment (NSAA) walk score 0, or inability to complete 10-meter walk run (10MWR) test, or a 10MWR time >30 seconds, or **2)** continuous wheelchair use or other documented information indicating age at LOA
  - This expanded definition of LOA was used because frequent NSAA administration was not available for the matched EC patients due to a sparse visit schedule or lack of NSAA assessment
- Pulmonary function by percent predicted forced vital capacity (FVC%p)

Post hoc analyses

(Scan QR code for full study details)

- Golodirsen-treated patients were compared with matched EC patients (for age, mutation, steroid use, ambulation at baseline) for ambulatory function or with matched EC patients (for age, mutation, steroid use, FVC%p at baseline) for pulmonary function
- Aside from ambulation status, baseline functional parameters were not available for all the mutation-matched EC patients; however, since LOA is a time-to-event milestone, it is less influenced by bias compared with intermediate functional trajectory analyses

Results

Safety

- At the last assessment before prior golodirsen initiation, 25 patients received treatment at a mean (SD) age of 8.4 (2.2) years; 18/25 (72%) completed the OLE up to 338.6 weeks (6.49 years) (**Scan QR code for full study details**)
- Over 6 years, golodirsen was well tolerated: treatment-emergent adverse events (TEAEs) were generally mild, nonserious, and unrelated to treatment (**T1**)
  - Most common TEAEs by incidence were diarrhea (18/25; 72%), vomiting (18/25; 72%), cough (16/25; 64%), rhinitis (16/25; 64%), nasopharyngitis (15/25; 60%), and pyrexia (15/25; 60%)
- No evidence of kidney toxicity and no TEAEs leading to treatment discontinuations or deaths up to 6 years
- Among 8 patients with implanted ports; no port-related infections occurred during the OLE
- TEAEs and TEAEs possibly related to treatment decreased in the OLE (4–6 years) compared with the parent study (0–3 years)
- 8/25 (32%) patients experienced 11 severe TEAEs, including fractures (n=4), LOA (n=6), and scoliosis (n=1); none were considered related to treatment
- 8/25 (32%) patients experienced 17 serious AEs, including fractures (n=4), pyrexia (n=1), and convulsion (n=1); none were considered related to treatment

Golodirsen prolonged ambulation compared with matched exon 53 skip-amenable EC patients

- Over 3 years, LOA occurred in 4/25 (16.0%) of golodirsen-treated patients compared with 12/54 (22.2%) of matched EC patients, representing a 91.1% risk reduction (hazard ratio [HR], 0.089; *P*=0.022) (**T2, F2a**)
  - Median time to LOA was not reached for both golodirsen-treated and matched EC patients since there were not enough events observed during the duration of follow-up for this analysis to reach 50% of patients with LOA
- Over 6 years, 15 golodirsen-treated patients experienced LOA (10.7–19.5 years old), with 7 patients still ambulant at OLE completion (12.4–20.3 years old)
- Compared with matched EC patients (n=19), golodirsen-treated patients experienced a median delay in time to LOA of ~2.4 years, suggesting a 47.4% risk reduction (HR, 0.526; *P*=0.149) (**T2, F2b**)
  - Due to unavailability of follow-up for matched EC patients up to 6 years, this analysis may need to be interpreted with caution

Golodirsen treatment attenuated pulmonary decline compared with mutation-matched EC patients

- Golodirsen-treated patients (≥10 years) experienced a statistically significant and clinically meaningful attenuation in annual FVC%p decline compared with matched EC patients (2.9% vs 6.67%, respectively; *P*<0.01) (**see poster M161 for full details of pulmonary analysis**)

T1 *Adverse Events Overview*

	Golodirsen (0–3 years)[8] (N=25)	Golodirsen (4–6 years) (N=25)	Golodirsen (0–6 years) (N=25)
Patients with ≥1 TEAE, n (%)	25 (100)	19 (76)	25 (100)
Possibly related to study drug	9 (36)	6 (24)	15 (60)[a]
Serious	4 (16)	5 (20)	8 (32)[b]
Total TEAEs by severity, n	860	408	1268
Mild	831	360	1191
Moderate	24	42	66
Severe	5	6	11

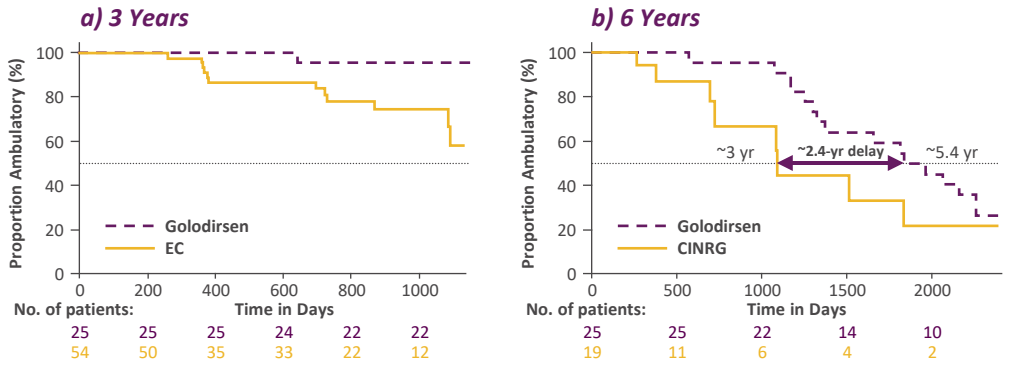
[a]No cases confirmed related to study drug. [b]One patient had serious AEs in both the parent and the OLE study so was not counted twice in the total. AE=adverse event; OLE=open-label extension; TEAE=treatment-emergent adverse event.

T2 *Baseline Characteristics to Show Matching Comparability*

	Golodirsen (N=25)	CINRG[9]+PRO-DMD[10] (for 3-year time to LOA analysis) (N=54)	CINRG[9] (for 6-year time to LOA analysis) (N=19)
Age, years	8.8 (2.15)[a]	8.8 (2.46)	8.4 (2.14)
Race, n (%)			
White	23 (92.0)	47 (87.0)	15 (78.9)
Black	—	1 (1.9)	—
Asian	—	5 (9.3)	4 (21.1)
Other	2 (8.0)	1 (1.9)	—
Weight, kg	28.4 (9.01)	28.7 (12.25)	28.1 (10.03)
Height, cm	120.6 (10.38)	122.2 (12.66)	120.2 (10.06)
BMI, kg/m²	18.9 (3.79)	18.6 (4.13)	19.0 (4.38)
Total time on treatment during study, days[b]	1162.0 (181.64)	933.8 (640.27)	1243.6 (963.03)
Corticosteroid regimen, n (%)			
Prednisone or prednisolone (daily)	10 (40.0)	12 (22.2)	6 (31.6)
Deflazacort (daily)	9 (36.0)	22 (40.7)	6 (31.6)
Prednisone/prednisolone (intermittent)	3 (12.0)	11 (20.4)	5 (26.3)
Others[c]	3 (12.0)	8 (14.8)	1 (5.3)

Values are mean (SD) unless otherwise stated. [a]Baseline age at the time of golodirsen initiation. [b]Treatment refers to SOC (steroid) for EC patients and to total time on golodirsen during the study for the golodirsen-treated patients. [c]Others: deflazacort (2 days/week; intermittent; weekends only; other dosing); methylprednisolone (continuous). BMI=body mass index; CINRG=Cooperative International Neuromuscular Research Group; EC=external control; LOA=loss of ambulation; SOC=standard of care.

F2 *Time to LOA in Golodirsen-Treated Patients vs Matched External Controls*



At 3 years, there was a 91.1% risk reduction (HR, 0.089; *P*=0.022) in time to LOA with golodirsen

At 6 years, there was ~2.4-year delay in time to LOA with golodirsen (*P*=0.149), representing a 47.4% risk reduction

Median time to LOA for golodirsen-treated vs matched EC patients: 1968 days (~5.4 years) vs 1092 days (~3 years)

CINRG=Cooperative International Neuromuscular Research Group; EC=external control; HR=hazard ratio; LOA=loss of ambulation; yr=year.

Key Findings

In the longest follow-up of a declining DMD population treated with golodirsen, results demonstrated functional benefit and a favorable safety profile

Conclusions

Golodirsen treatment for up to 6 years demonstrates a favorable, consistent safety profile, and post hoc analyses support its long-term efficacy vs matched EC patients

- Safety was consistent with previous clinical and real-world experience
- Time to LOA suggests benefit in ambulation from golodirsen treatment, although the analysis is limited due to unavailability of follow-up for the matched EC patients
- Pulmonary decline based on FVC%p function was associated with significant attenuation

These data provide the longest follow-up to date of safety and functional outcomes of golodirsen in a declining DMD population of patients with mutations amenable to exon 53 skipping

Acknowledgments & Disclosures

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Disclosures: FM: Received consultant fees and speaker honoraria from Sarepta Therapeutics, Inc. **AMS, MG, LS:** Received speaker honoraria and research collaboration from Sarepta Therapeutics, Inc. **VS**: Participated in advisory boards, received speaker honoraria, and has a research collaboration with Sarepta Therapeutics, Inc. **EW-D, XN, PG, MH, JI, LH, IS, LO:** Employees of Sarepta Therapeutics, Inc, and may own stock/options in the company. **EM:** Received consultant fees from Sarepta Therapeutics, Inc. Previously presented at the 28th International Annual Congress of the World Muscle Society, October 3–7, 2023, Charleston, SC.

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Methods

Study population (Study 4053-101 and Study 4045-302)

- Boys aged 6–15 years 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 distance of ≥250 meters at both screening and baseline
- NSAA total score >17 and/or rise time <7 seconds (Gowers' sign)

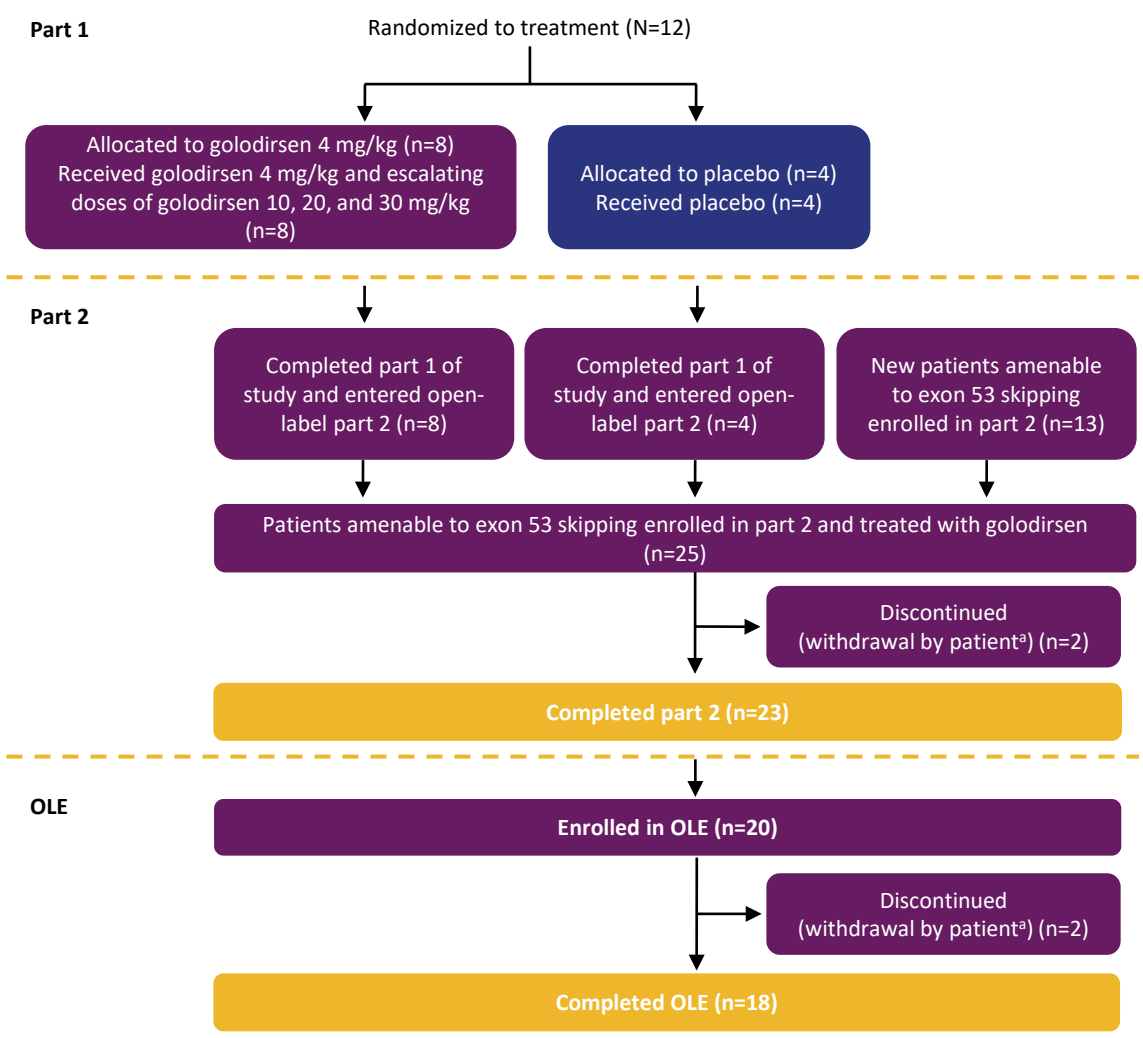
Statistical analyses

- Adverse events were analyzed using descriptive statistics
- Ambulation data were compared post hoc with mutation-matched EC patients aged ≥6 years, with steroid use and able to rise at baseline, identified from CINRG-DNHS (NCT00468832)[8] and PRO-DMD-01 (NCT01753804)[9]
- Pulmonary data were compared post hoc with mutation-matched EC patients aged ≥10 years, with at least 1 FVC%p assessment at age 10–12 years followed by at least 1 additional valid FVC%p assessment, identified from CINRG-DNHS (NCT00468832),[9] PRO-DMD-01 (NCT01753804),[10] or Study 301 (NCT02255552)[11]
- The impact of golodirsen treatment on FVC%p compared with mutation-matched EC was evaluated using mixed models with repeated measures framework (response variable: FVC%p; fixed effects: treatment group, age at visit, and treatment group by age interaction; random effect: patient)

Results (cont)

- 18/25 (72%) of patients completed the OLE up to 6.49 years (**F3**)
- Baseline characteristics from Study 4053-101 are shown in **T3**
- A total of 54 ECs matched for age, ambulation at baseline, steroid use, and mutation were included in the LOA analysis from CINRG and PRO-DMD (**F4**)

F3 *Patient Disposition*



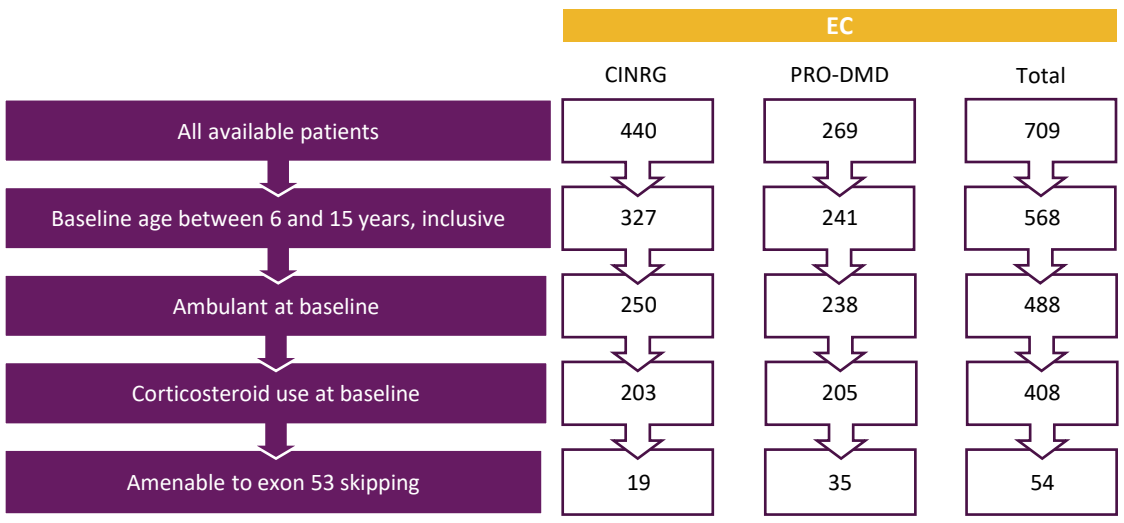
[a]Reasons for withdrawal were unrelated to treatment. OLE=open-label extension.

T3 *Baseline Characteristics of Golodirsen-Treated Patients (Study 4035-101)*

Baseline Characteristic[a]	Golodirsen-Treated Patients (n=25)
Age, years	8.4 (2.2; range, 6–13)
Height, cm	120.5 (10.1)
Weight, kg	28.4 (9.0)
BMI, kg/m²	19.1 (3.7)
Mutation, n (%)	
45–52	8 (32.0)
48–52	5 (20.0)
49–52	5 (20.0)
50–52	4 (16.0)
52	3 (12.0)
NSAA	23.6 (5.0; range, 13–33)
6MWT distance, m	405.8 (55.1; range, 290–512)
Time to rise from floor, s	5.9 (3.5; range, 2.3–18.6)
FVC%p	92.7 (24.0; range, 16.4–137.8)
Time since DMD diagnosis, mo	55.8 (24.8; range, 16.1–122.9)
Duration of corticosteroid use, mo	35.3 (24.4; range, 8.9–97.7)
Frequency of corticosteroid administration, n (%)	
Continuous	19 (76.0)
Intermittent	6 (24.0)
Corticosteroid type, n (%)	
Deflazacort	12 (48.0)
Prednisone	13 (52.0)

Data are mean (SD) unless otherwise stated. [a]For golodirsen-treated patients, baseline was defined as the last assessment prior to golodirsen initiation. 6MWT=6-minute walk test; BMI=body mass index; DMD=Duchenne muscular dystrophy; FVC%p=percent predicted forced vital capacity; NSAA=North Star Ambulatory Assessment.

F4 *LOA Analysis Population Selection Flowchart*



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