



# Delay in Duchenne Muscular Dystrophy Progression With Eteplirsen: Longer Time to Loss of Ambulation Versus Standard of Care

Joel Iff,<sup>1</sup> George Bungey,<sup>2</sup> Abby Paine,<sup>2</sup> Baoguang Han,<sup>1</sup> Heather Gordish-Dressman,<sup>3</sup> Erik Henricson,<sup>4</sup> Craig McDonald,<sup>4</sup> and the Eteplirsen and CINRG Duchenne Natural History Study Investigators

<sup>1</sup>Sarepta Therapeutics Inc, Cambridge, MA, USA; <sup>2</sup>DRG Abacus, Part of Clarivate, London, UK; <sup>3</sup>Children's National Hospital, George Washington University School of Medicine and Health Sciences, Washington DC, USA; <sup>4</sup>University of California, Davis, CA, USA

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## Objective

To estimate the treatment benefit of eteplirsen vs standard of care (SOC) for time to loss of ambulation (LOA) in patients with Duchenne muscular dystrophy (DMD) using a post hoc analysis of individual patient-level data

## Key Takeaway

LOA is significantly delayed in patients treated with eteplirsen vs SOC



## CONCLUSIONS

- Eteplirsen treatment was associated with increased median age at loss of ambulation by 2.7 years (15.7 vs 13.0 years for eteplirsen vs SOC)
- Eteplirsen treatment was associated with a statistically significant 47% risk-reduction of LOA vs SOC across the lifespan
- Median age at LOA in the SOC group was similar to the 13.40 years identified in a broader population of patients from CINRG<sup>1</sup>
- Results are robust to the inclusion of all genotyped CINRG patients who were ambulatory at baseline in SOC group



## RESULTS

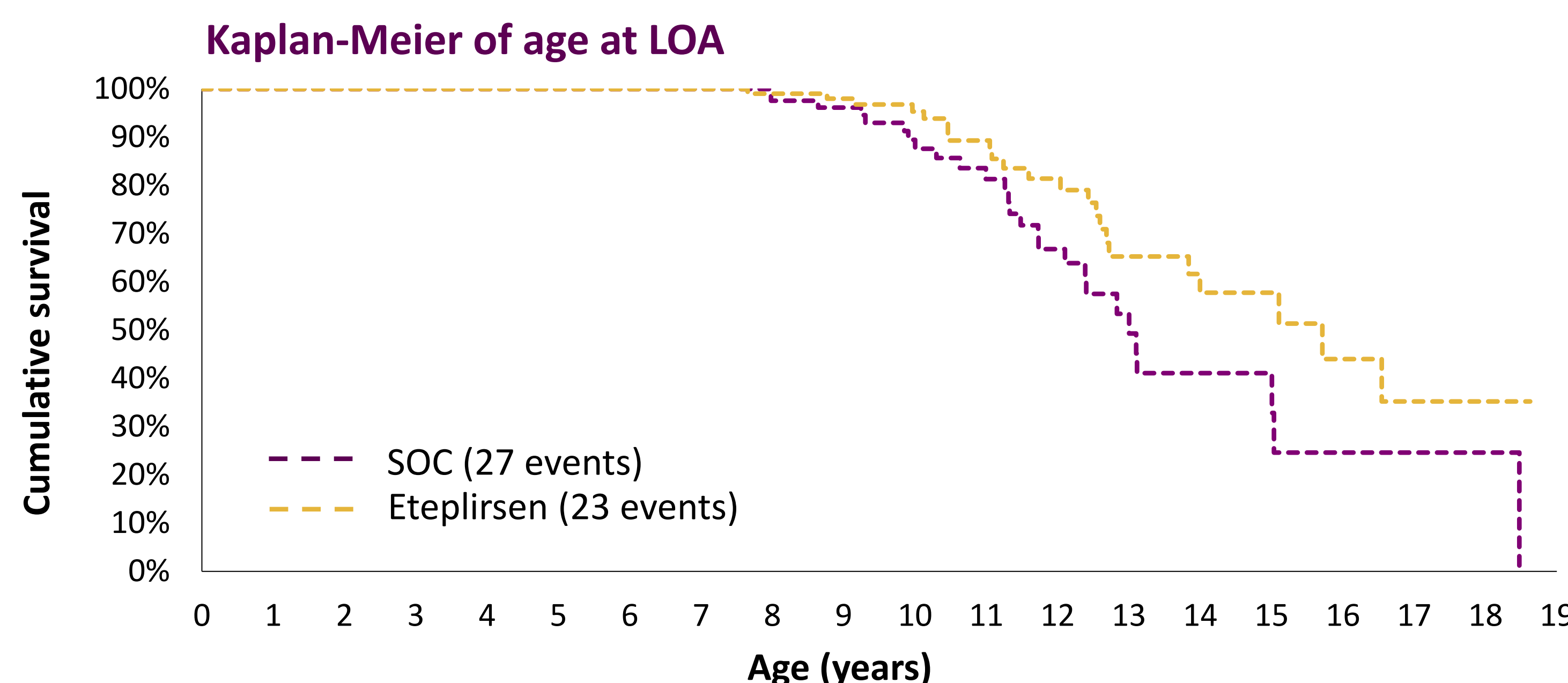
### Baseline characteristics at study entry: Base case analysis

- Eteplirsen patients were significantly older than SOC at the start and end of study
- Overall, corticosteroid use was similar between the treatment groups

Characteristic	Eteplirsen (n=118)	SOC/Placebo (n=113)
Race, n (%)		
White	100 (84.7)	69 (61.1)
Black or African American	3 (2.5)	1 (0.9)
Pacific Islander	2 (1.7)	0
Asian	9 (7.6)	16 (14.2)
Other	4 (3.4)	3 (2.7)
Unknown	0	24 (21.2) <sup>a</sup>
Baseline age, years	8.68 (2.42)	7.85 (2.30)
Age at last study visit, years	10.73 (2.74)	9.73 (2.57)
Total time on treatment during study, days	748 (440)	687 (589)
Corticosteroid regimen, n (%)		
Prednisone or prednisolone (daily)	53 (44.9)	18 (15.9)
Deflazacort (daily)	28 (23.7)	47 (41.6)
Prednisone or prednisolone (intermittent)	13 (11.0)	17 (15.0)
All others (including unknown)	24 (20.3)	31 (27.4)
Treatment exposure, patient years	241.8	0

All values are mean (SD) unless otherwise noted. <sup>a</sup>Race data were not available for any patients in the Leuven and Telethon SOC studies.

### Age at LOA: Base case analysis



#### Patients at risk over time:

	0	1	2	3	4	5	6	7	8	9	10	11	12	13	14	15	16	17	18	19
SOC	113	113	113	113	113	112	110	96	79	63	48	35	21	11	6	5	3	1	1	0
Eteplirsen	118	118	118	118	118	118	116	109	98	88	65	48	34	21	16	10	5	3	2	0

- Maximum study follow-up times were 8.1 years for eteplirsen and 8.9 years for SOC
- Median study follow-up times were 1.8 years for eteplirsen and 1.1 years for SOC

### Median age at LOA and Cox model results

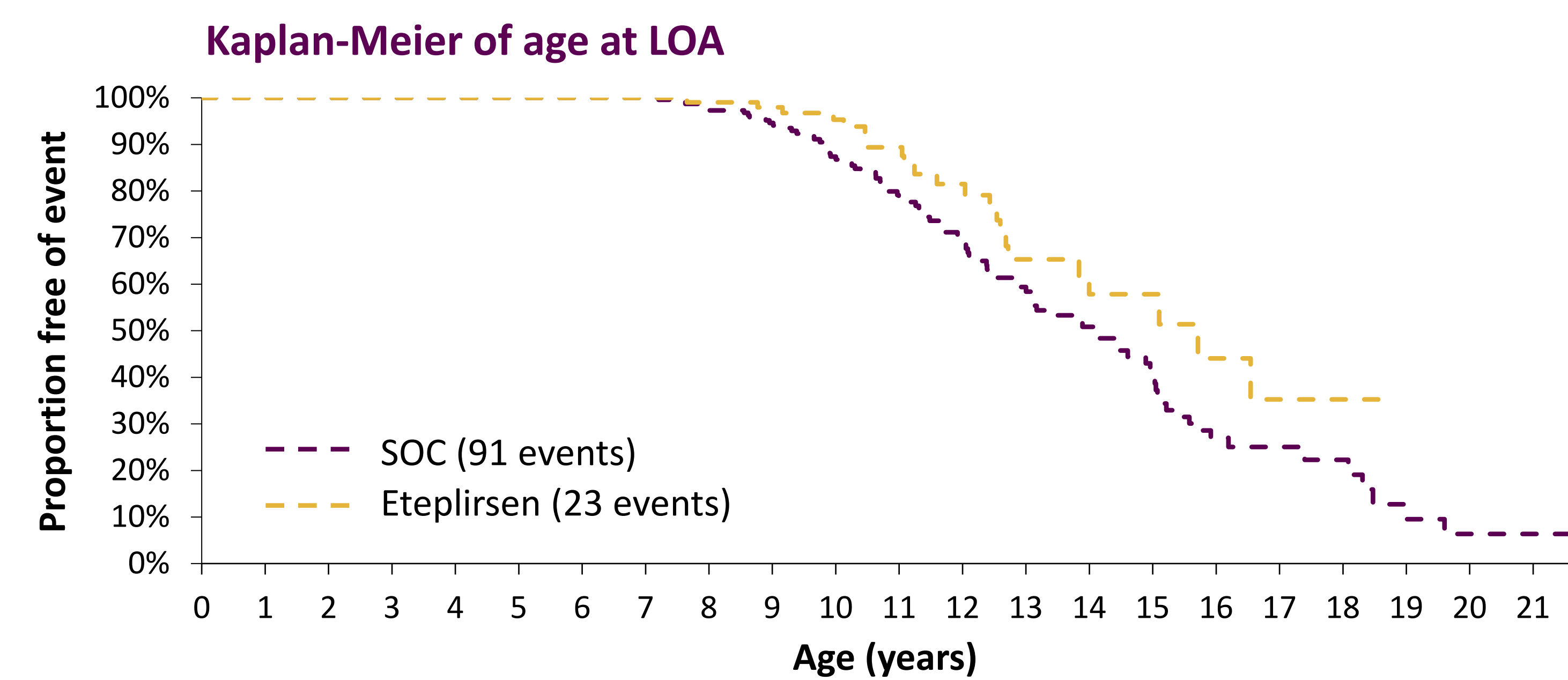
Treatment	Median age at LOA (K-M estimate), years (95% CI)	Cox model HR	95% CI	P value
Eteplirsen	15.7 (12.7–NE)	0.53	0.30–0.93	0.027
SOC	13.0 (12.1–15)			

CI=confidence interval; HR=hazard ratio; K-M=Kaplan-Meier; NE=not evaluable

Eteplirsen treatment was associated with a statistically significant 47% risk reduction of LOA vs SOC across the lifespan, translating to ~21% longer in ambulation

- Time to LOA was significantly longer in the eteplirsen treatment group
- Tests of proportion hazards assumption suggest assumption is valid (e.g.,  $P=0.86$  for Schoenfeld residual)
- Median age at LOA in SOC group was similar to the 13.40 years identified in a broader population of patients from CINRG<sup>1</sup>

### Age at LOA: Sensitivity analysis



#### Patients at risk over time:

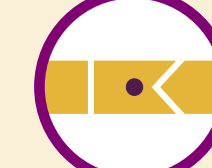
	0	1	2	3	4	5	6	7	8	9	10	11	12	13	14	15	16	17	18	19	20	21	22
SOC	278	278	278	278	278	277	268	245	208	171	138	103	79	59	41	29	16	10	7	4	1	1	0
Eteplirsen	118	118	118	118	118	118	116	109	98	88	65	48	34	21	16	10	5	3	2	0	0	0	0

### Median age at LOA and Cox model results

Treatment	Median age at LOA (K-M estimate), years (95% CI)	Cox model HR	95% CI	P value
Eteplirsen	15.7 (12.7–NE)	0.62	0.39–0.99	0.045
SOC	14.1 (13.0–15.0)			

CI=confidence interval; HR=hazard ratio; K-M=Kaplan-Meier; NE=not evaluable

- Time to LOA was significantly longer in the eteplirsen treatment group
- Tests of proportion hazards assumption suggest assumption is valid (e.g.,  $P=0.66$  for Schoenfeld residual)
- Median age at LOA in SOC group was similar to the 13.40 years identified in a broader population of patients from CINRG<sup>1</sup>



## METHODS

### Data sources

- Eteplirsen clinical trials: Studies 201/202/405, Study 203, Study 204, and Study 301/PROMOVI
- SOC: Placebo arm of the DEMAND III trial, Leuven Neuromuscular Reference Center Registry, Telethon Italian DMD Registry, and the Cooperative International Neuromuscular Research Group Duchenne Natural History (CINRG DNH)

### Inclusion criteria

- Amenable to exon 51 skipping
- Receiving treatment with eteplirsen or SOC/placebo
- Receiving steroids for  $\geq 30\%$  of the study
- Ambulatory at baseline visit

### Analyses

- Base case analysis: SOC group includes only exon 51 skip-amenable patients
- Sensitivity analysis: SOC group includes all genotyped CINRG patients who were ambulatory at baseline, excluding skip exon-44 and del\_3-7

### Definition of LOA

- LOA was defined according to a combination of 10-meter walk/run time  $\geq 30$  s and 6-minute walk distance = 0 m, or inability to complete the tests

Please scan QR code for additional study details

## REFERENCES

- McDonald C, et al. *Lancet*. 2018; 391:451-461.
- Mendell JR, et al. *Ann Neurol*. 2016;79(2):257-271.
- Mendell JR, et al. *J Neuromuscular Dis*. 2021;doi:10.3233/JND-200548.

## ACKNOWLEDGMENTS & DISCLOSURES

The authors and Sarepta Therapeutics, Inc., thank the patients and their families for their participation in the studies. This study was funded by Sarepta Therapeutics, Inc. Editorial support was provided by Kristin M. Allan, PhD, and was funded by Sarepta Therapeutics, Inc. Disclosures: JJ and BH are employees of Sarepta Therapeutics, Inc. and may own stock/options in the company. GB was an employee of DRG Abacus at the time of the study. AP is an employee of Zedediah Consulting and partner of DRG Abacus. HG-D is the co-founder of TRINDS, LLC. EH reports consulting fees (Sarepta Therapeutics, Inc.). CM reports consulting (Astellas/Mitobridge, Bristol Myers Squibb, Capricor, Catabasis Pharmaceuticals, Edgewise Therapeutics, Eli Lilly, Epirium Bio [formerly Cardero Therapeutics], Gilead, Halo Therapeutics, Italfarmaco, Novartis, Pfizer, Prosenza, PTC Pharmaceuticals, Santhera Pharmaceuticals, and Sarepta Therapeutics, Inc.), research funding, principal investigator, and speaking fees (Sarepta Therapeutics, Inc.). Presented previously at the 2021 Muscular Dystrophy Association Virtual Clinical & Scientific Conference, March 15–18, 2021.



## BACKGROUND

- Eteplirsen is indicated to treat Duchenne muscular dystrophy (DMD) in patients with genetic mutations amenable to exon 51 skipping
- Previous analyses have shown that eteplirsen is associated with significant and clinically meaningful delays in time to loss of ambulation (LOA)<sup>2,3</sup>
- Additional data now allow for a more comprehensive analysis of a larger number of eteplirsen-treated patients

## DEFINITION OF LOA

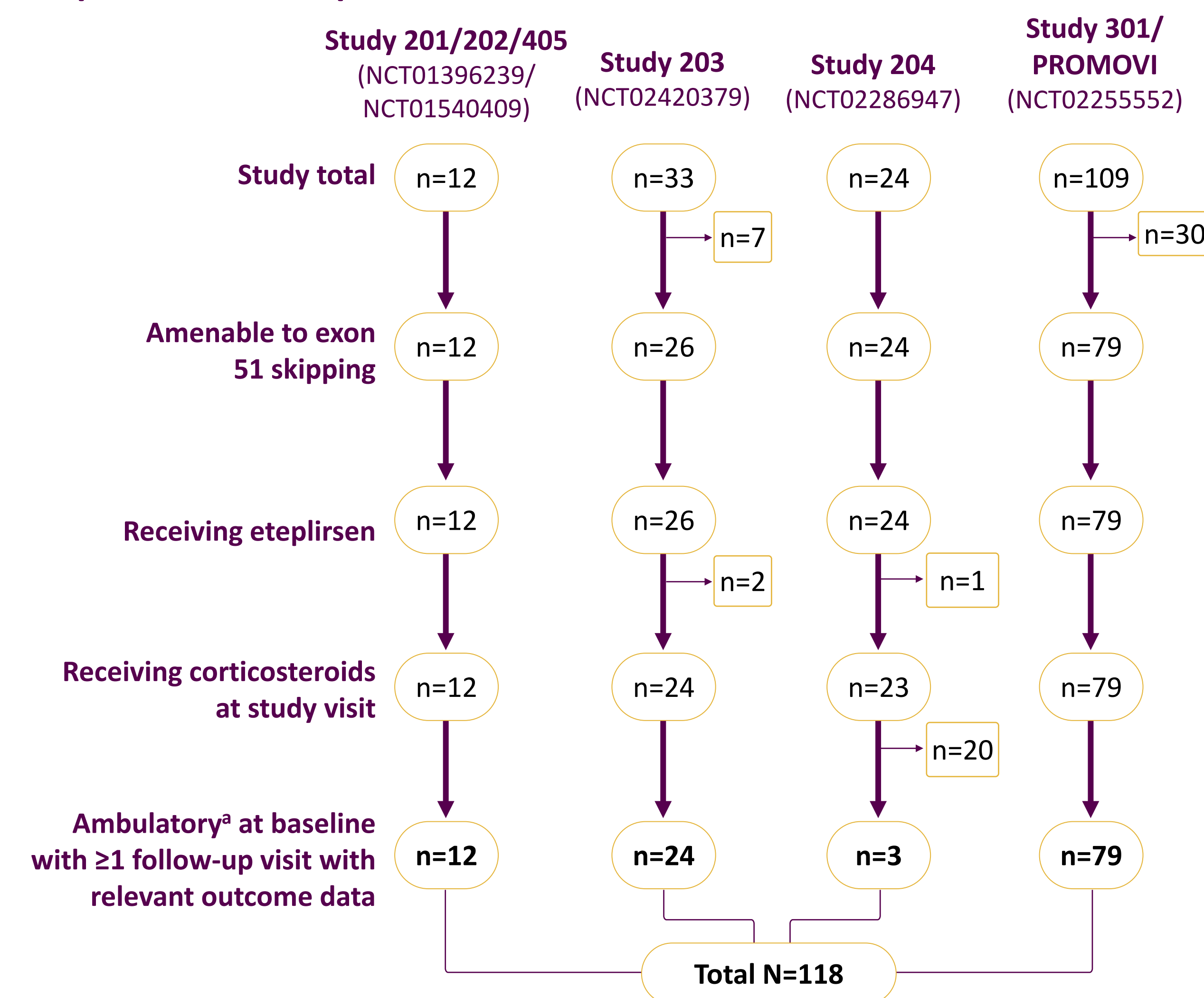
- Loss of ambulation (LOA) was defined according to a combination of 10-meter walk/run time  $\geq 30$  s and 6-minute walk distance = 0 m (or inability to complete the tests)
  - For patients with both outcomes available, both outcomes had to be satisfied to indicate LOA
  - In the eteplirsen trial datasets, a rate-limiting cell value of 30 s was recorded by clinicians if the patient failed the test
  - In the CINRG dataset LOA was confirmed by ensuring the variable measuring velocity to complete 10m walk run = 0 m/s
- Time to wheelchair use was used for Study 405, as 10-meter walk/run time was not available
  - Time to LOA based on this definition aligned with time to LOA based on 10-meter walk/run time for the 2 patients in Study 405 who had lost ambulation during the 201/202 study
- Outcomes were checked at prior and subsequent visits to LOA event to prevent confounding of missing data/fractures

## STATISTICAL ANALYSIS

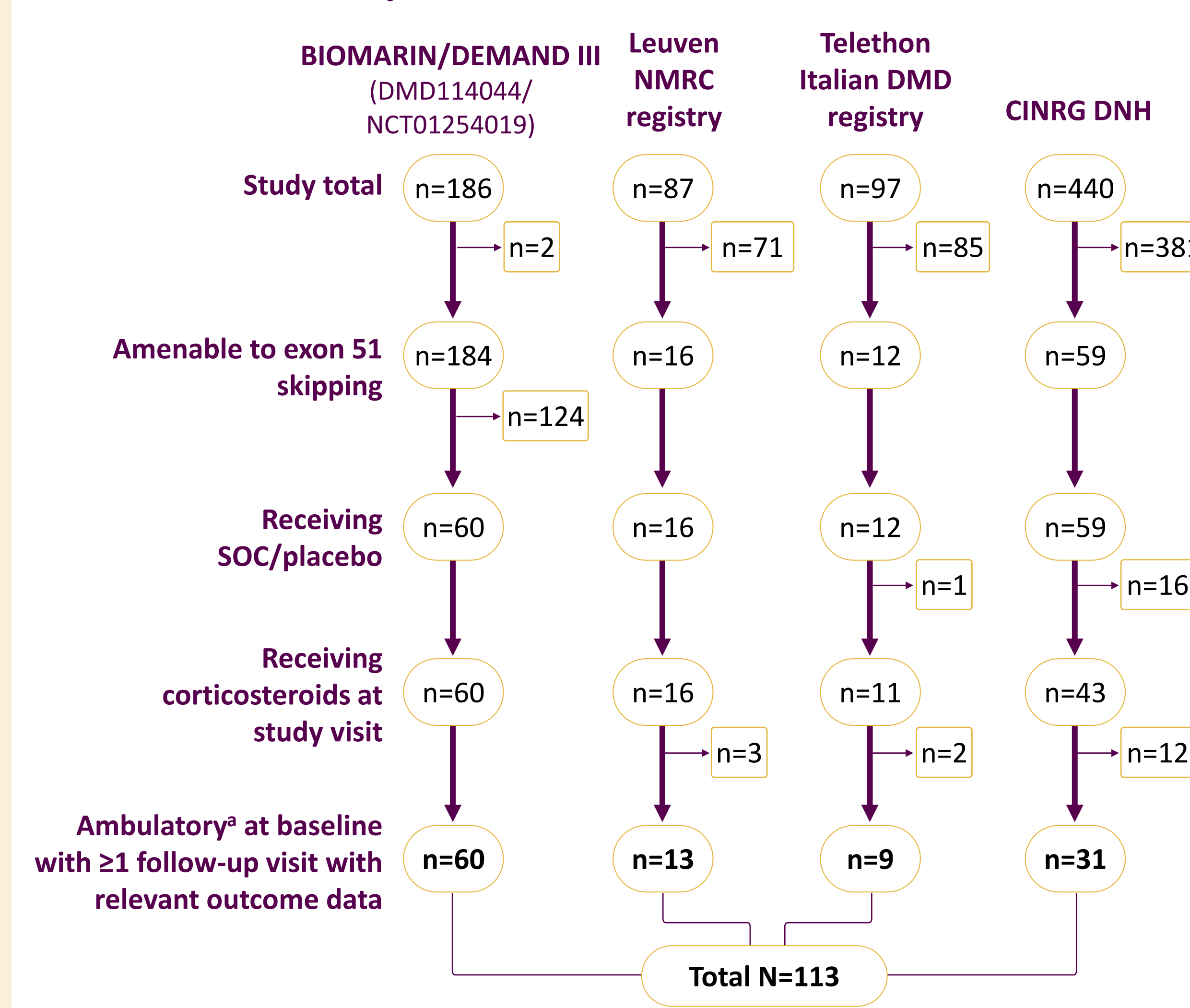
- Kaplan-Meier curves were constructed from the patient data sets to provide a visual representation of the proportion of patients who experienced LOA or were censored over time (i.e., did not experience an event before the end of the study, were lost to follow-up, or withdrew)
- A Cox proportional hazards model was used to calculate a hazard ratio to compare the difference in treatment effect between eteplirsen and SOC over time

## PATIENT SELECTION

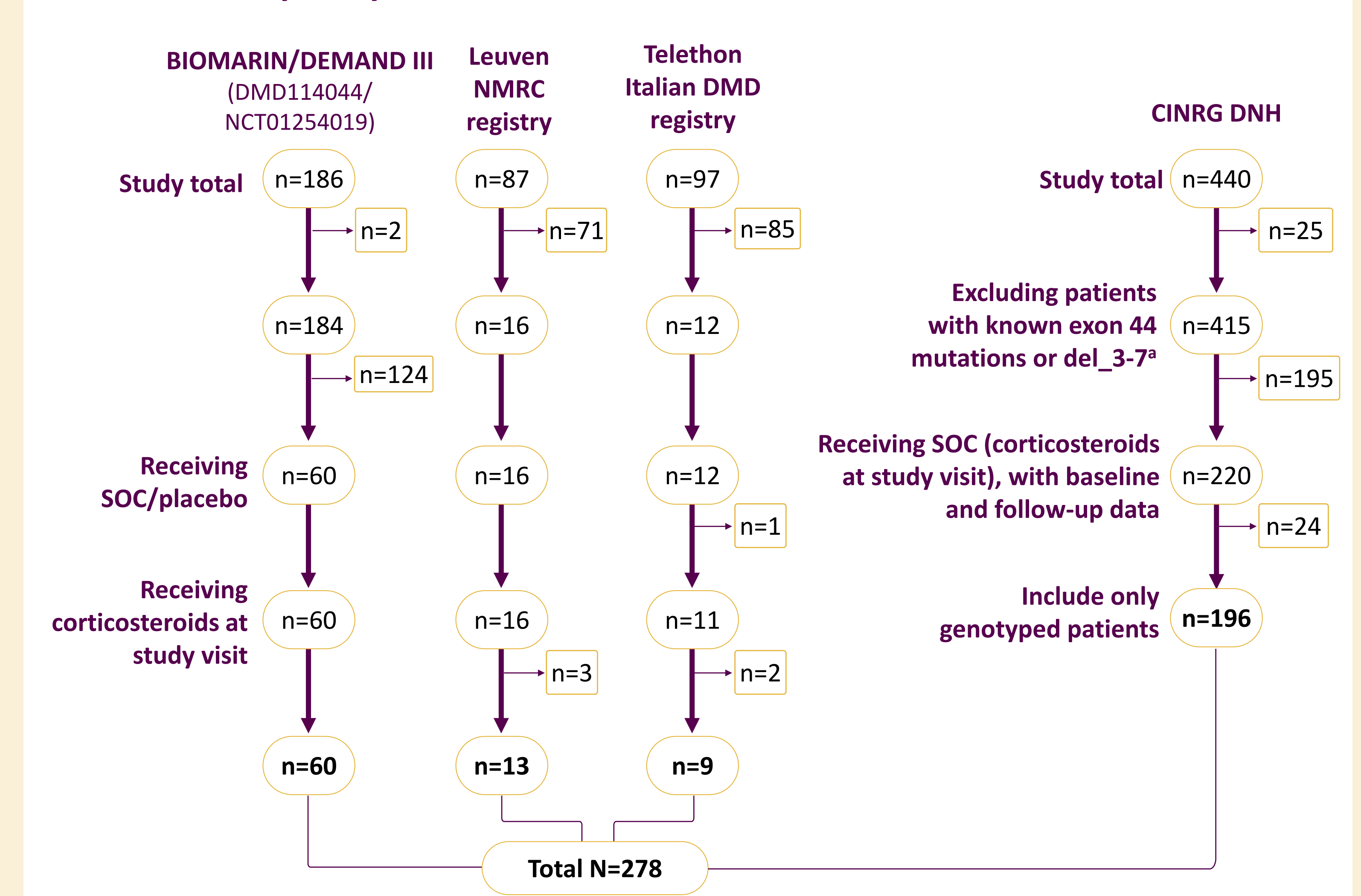
### Eteplirsen-treated patients



### SOC – Base case analysis



### SOC – Sensitivity analysis



<sup>a</sup>Ambulatory defined as 10-meter walk-run time <30 secs / 6-minute walk distance > 0. CINRG DNH=The Cooperative International Neuromuscular Research Group Duchenne Natural History; NMRC=Neuromuscular Reference Center.