Delay of Loss of Ambulation with Eteplirsen Versus Standard of Care in Duchenne Muscular Dystrophy

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DISCLOSURES

- J. Iff is an employee of Sarepta Therapeutics, Inc. and may own stock/options in the company
- G. Bungey at the time of the study was an employee of DRG Abacus
- A. Paine is an employee of Zedediah Consulting and partner of DRG Abacus
- B. Han is an employee of Sarepta Therapeutics, Inc. and may own stock/options in the company
- H. Gordish-Dressman is the co-founder of TRiNDS, LLC
- E. Henricson reports consulting fees (Sarepta Therapeutics, Inc.)
- C. McDonald 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, Prosensa, PTC Pharmaceuticals, Santhera Pharmaceuticals, and Sarepta Therapeutics, Inc.); research funding, principal investigator, and speaking fees (Sarepta Therapeutics, Inc.).
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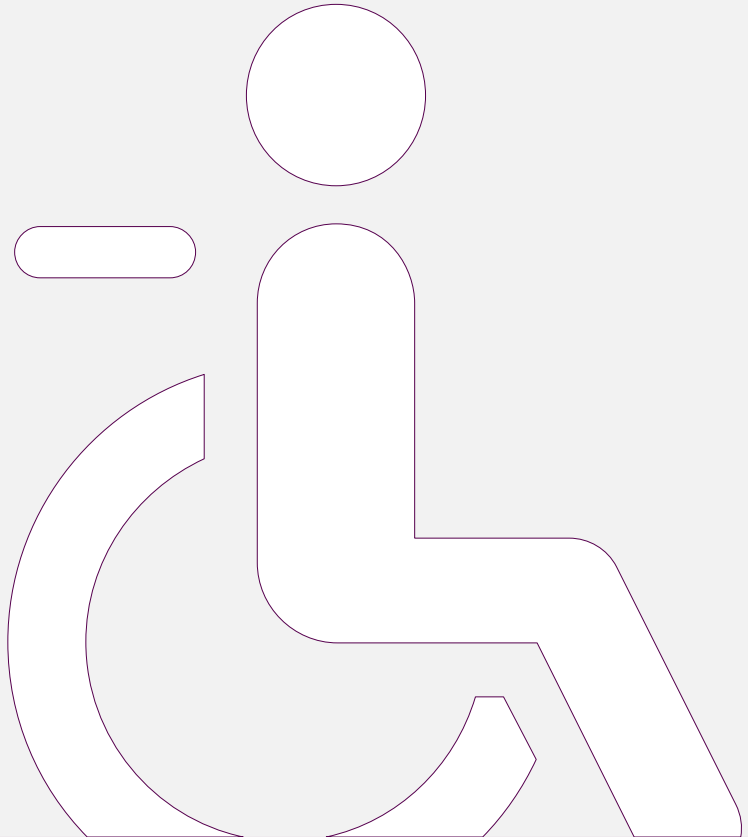
SAREPTA THERAPEUTICS

AGE AT LOSS OF AMBULATION

FOR PATIENTS TREATED WITH ETEPLIRSEN VS SOC



OBJECTIVE

To estimate the treatment benefit of eteplirsen vs SOC for time to loss of ambulation using a post-hoc analysis of individual patient level data

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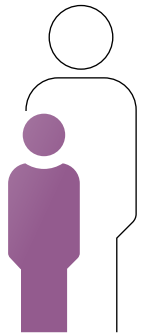
Abbreviations: SOC, standard of care

METHODOLOGY

Inclusion criteria

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



Sensitivity analysis

SOC group includes all *genotyped* CINRG patients who were ambulatory at baseline, excluding skip exon-44 and del_3-7

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 / 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. A Cox model is a widely used, standard statistical approach for analysing survival time data, e.g. time to LOA.

Definition of LOA

- Loss of ambulation (LOA) was defined according to a combination of 10m walk/run time ≥30s and 6MWD = 0m (or inability to complete the tests)
  - For patients with both outcomes available, both outcomes had to be satisfied to indicate loss of ambulation
  - In the eteplirsen trial datasets, a rate limiting cell value of 30s 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 the 405 chart review data, as 10m walk/run time was not available
  - Time to LOA based on this definition aligned with time to LOA based on 10m walk/run time for the 2 patients in the 405 chart review 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

Abbreviations: LOA, loss of ambulation; SOC, standard of care; 6MWD, six-minute walk distance

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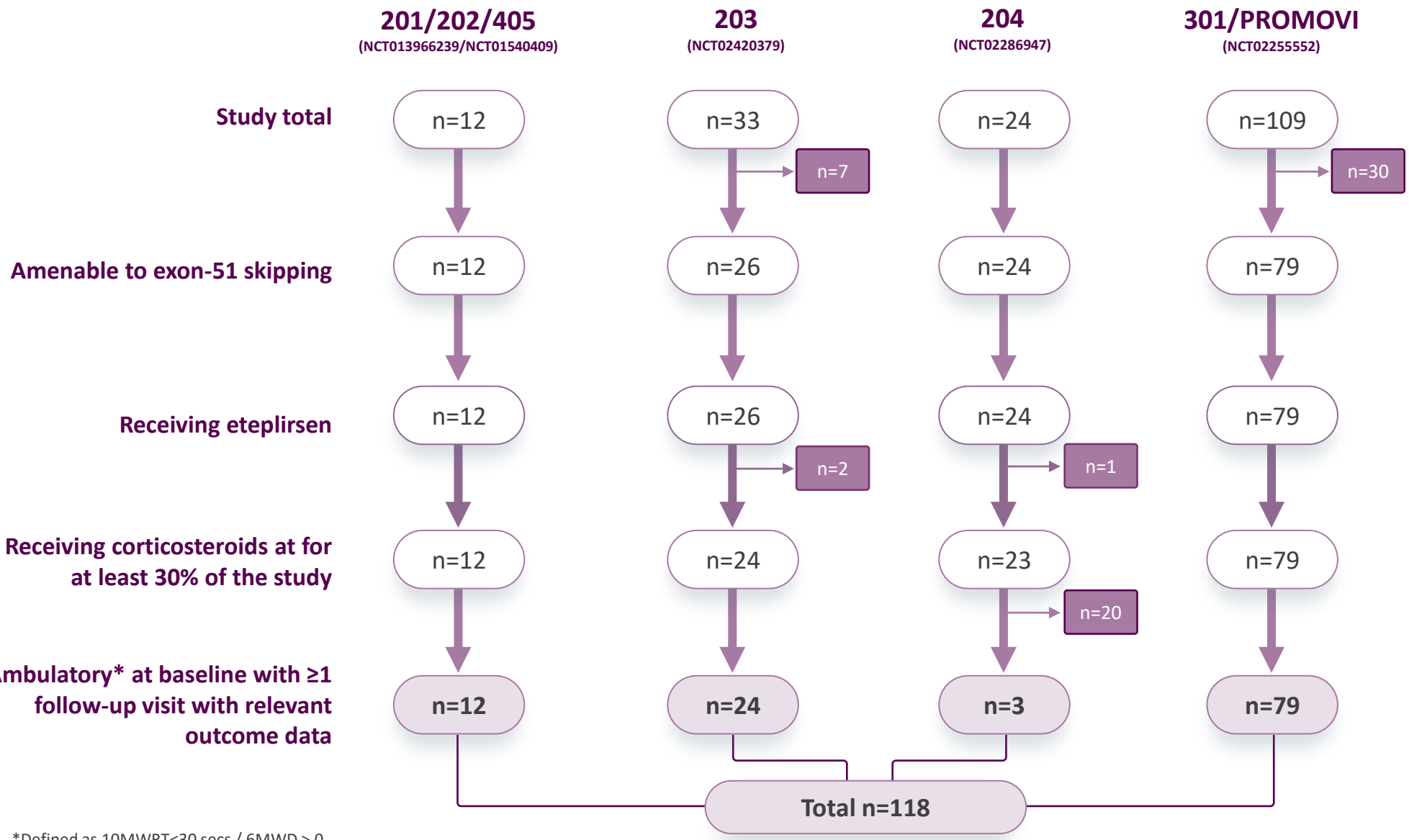
PATIENT SELECTION – ETEPLIRSEN-TREATED PATIENTS



*Defined as 10MWRT<30 secs / 6MWD > 0

Abbreviations: 6MWD, six-minute walk distance; 10MWRT, ten-metre walk/run time

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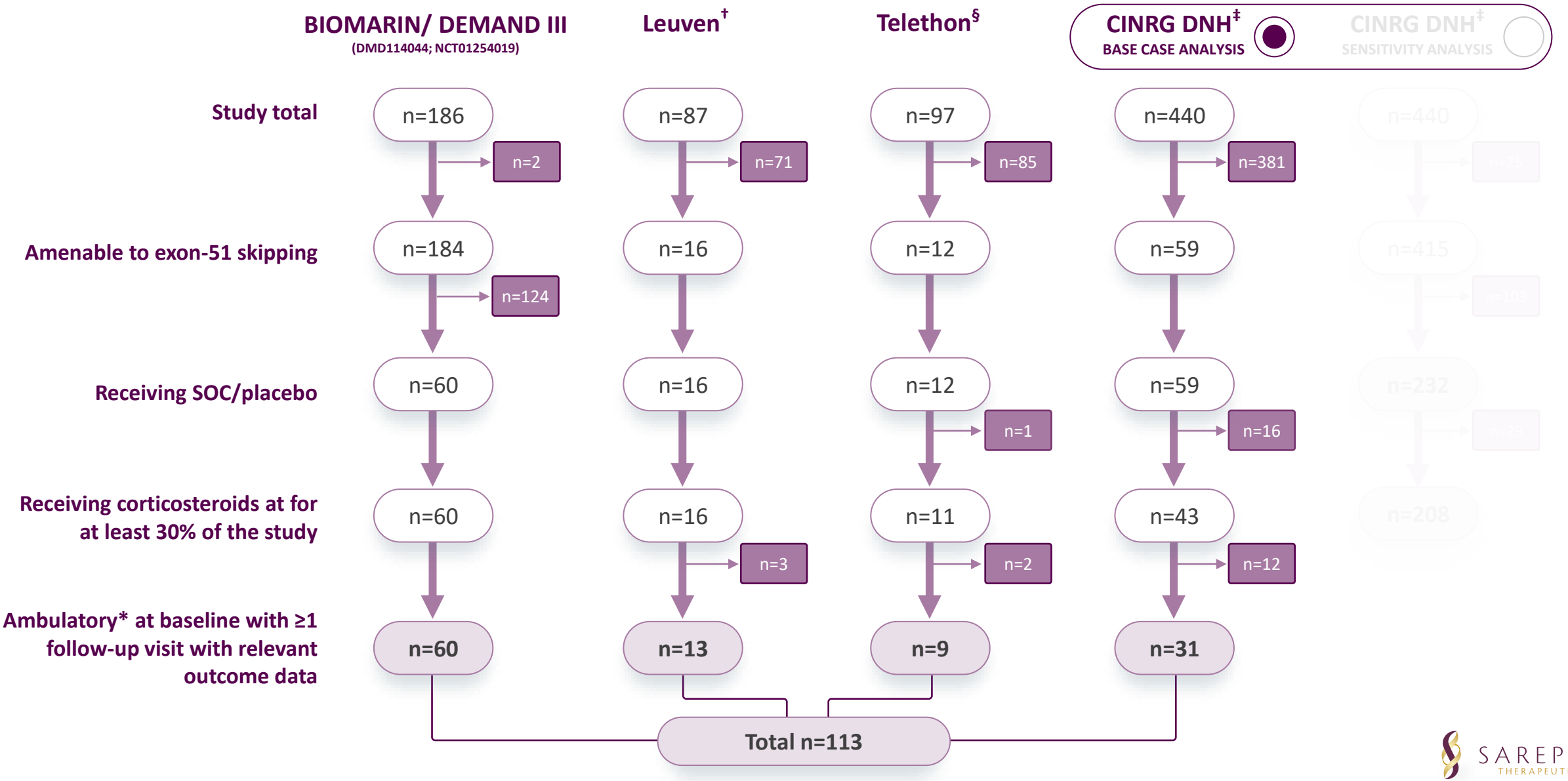
PATIENT SELECTION – SOC



*Defined as 10MWRT<30 secs / 6MWD > 0; †Leuven NMRC Registry; §Italian DMD Registry; ‡CINRG DNH, The Cooperative International Neuromuscular Research Group Duchenne Natural History)

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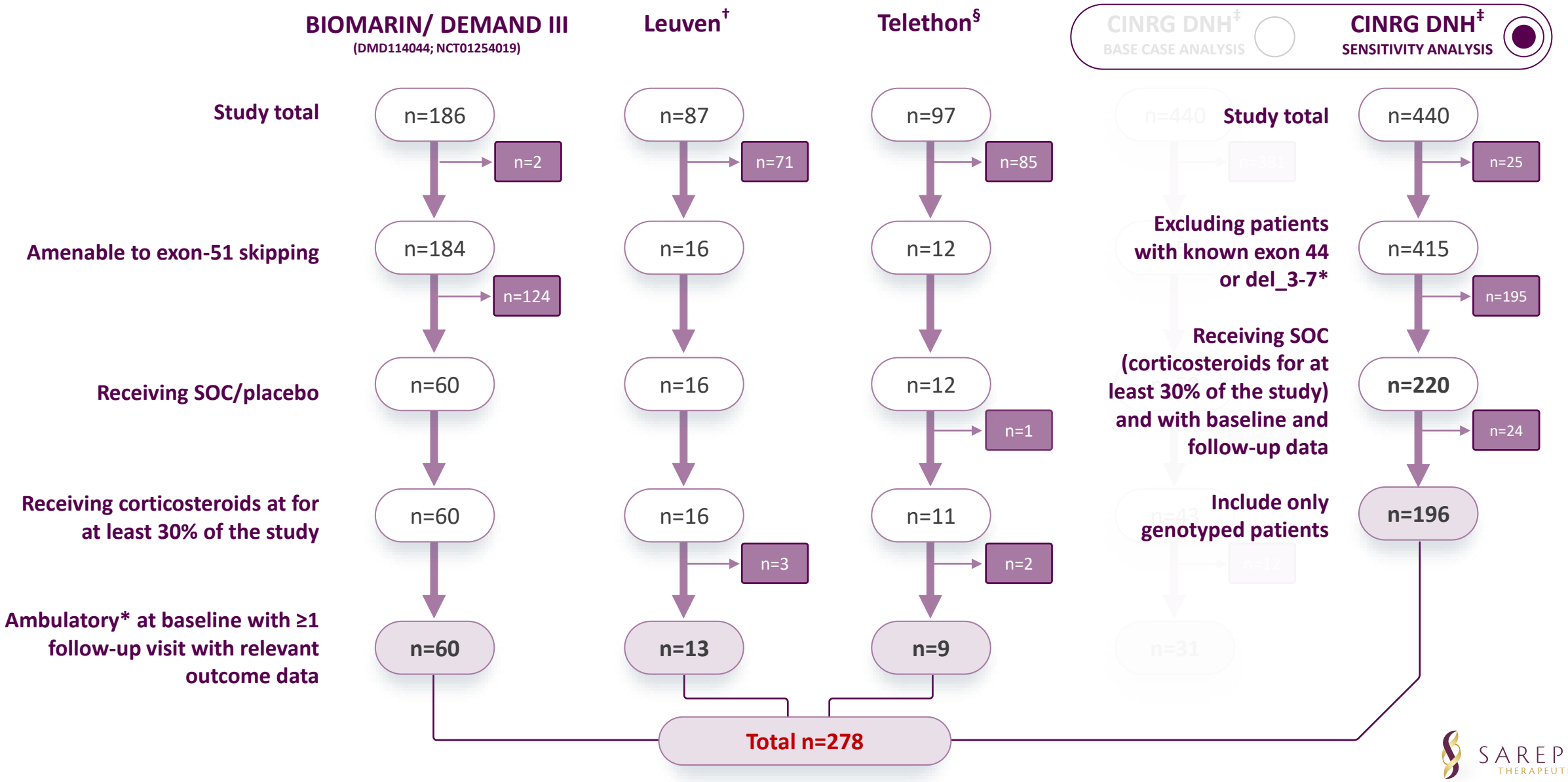
PATIENT SELECTION – SOC



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COMPARISON OF BASELINE CHARACTERISTICS
AT STUDY ENTRY (BASE CASE ANALYSIS)

Outcome		Eteplirsen n=118	SOC/Placebo n=113
Race, n (% of eligible patients)	White	**100** (84.7%)	**69** (61.1%)
	Black of African American	**3** (2.5%)	**1** (0.9%)
	Pacific Islander	**2** (1.7%)	**0** (0%)
	Asian	**9** (7.6%)	**16** (14.2%)
	Other	**4** (3.4%)	**3** (2.7%)
	Unknown	**0** (0%)	**24** (21.2%)*
Baseline age, years	Mean (SD)	**8.68** (2.42)	**7.85** (2.30)
	Median [IQR]	**8.61** [2.88]	**7.49** [3.10]
Age at last study visit, years	Mean (SD)	**10.73** (2.74)	**9.73** (2.57)
	Median [IQR]	**10.52** [3.40]	**9.60** [3.93]
Ambulatory status at initial visit	Ambulatory	**118** (100%)	**113** (100%)
	Non-ambulatory	**0** (0%)	**0** (0%)
Total time on treatment during study, days	Mean (SD)	**748** (440)	**687** (589)
	Median [range]	**665** [160-2956]	**336** [84-2879]
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	Eteplirsen	**241.8**	**0**

Eteplirsen patients were significantly older than SOC at start and end of study

Overall, corticosteroid use was similar between the treatment groups

*Note that race data was not available for any patients in the Leuven and TELETHON SOC studies

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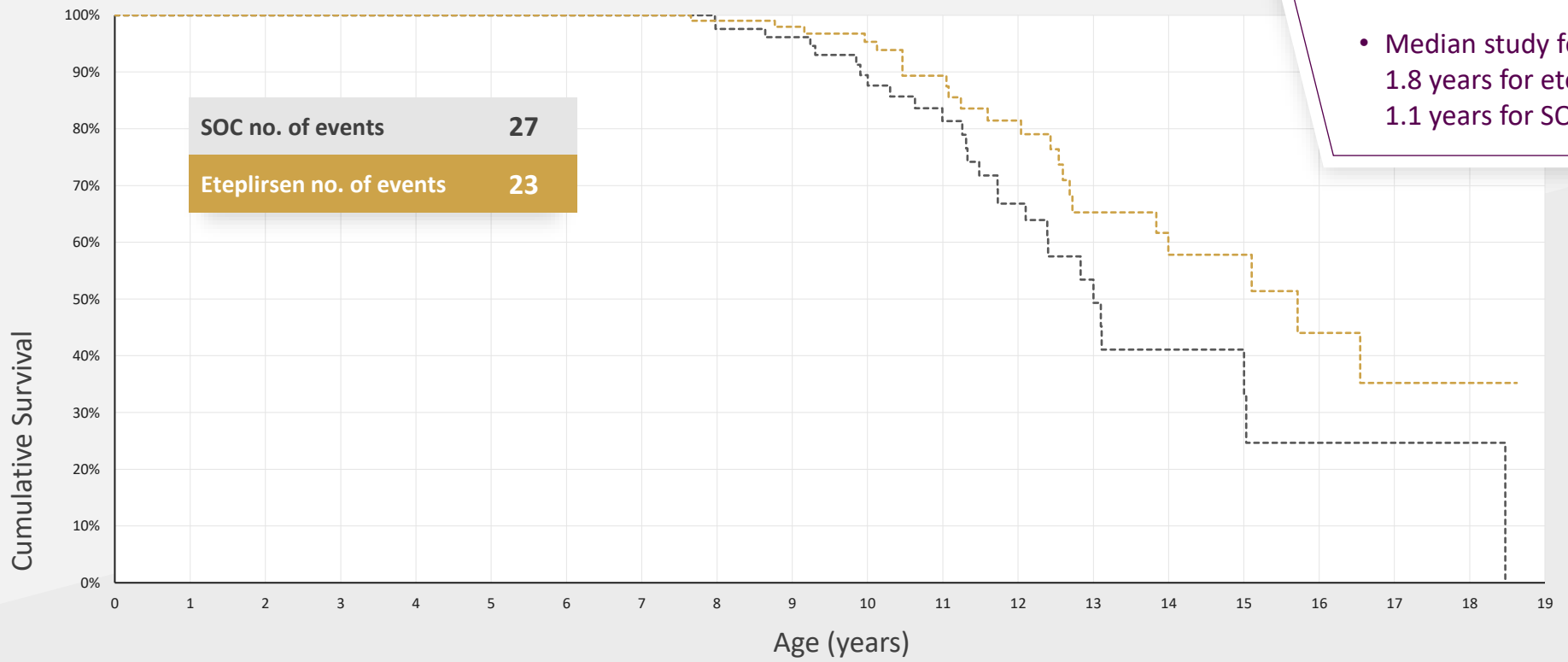
AGE AT LOA – BASE CASE ANALYSIS
KAPLAN-MEIER CURVES

- 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



Patients at risk over time:

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

Eteplirsen SOC

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AGE AT LOA – BASE CASE ANALYSIS
MEDIAN AGE AT LOA AND COX MODEL RESULTS

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

- Time to LOA was significantly longer in the eteplirsen treatment group
- Tests of proportion hazards assumption suggest assumption is valid
  (e.g. p-value=0.86 for Schoenfeld residual)
- Median age at event in SOC group was similar to the 13.40 years identified in a broader population of patients from CINRG[1]

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

Abbreviations: CI, confidence interval; HR, hazard ratio; K-M, Kaplan-Meier; NE, not evaluable; SOC, standard of care

References: 1. McDonald et al. Lancet 2018; 391:451-461

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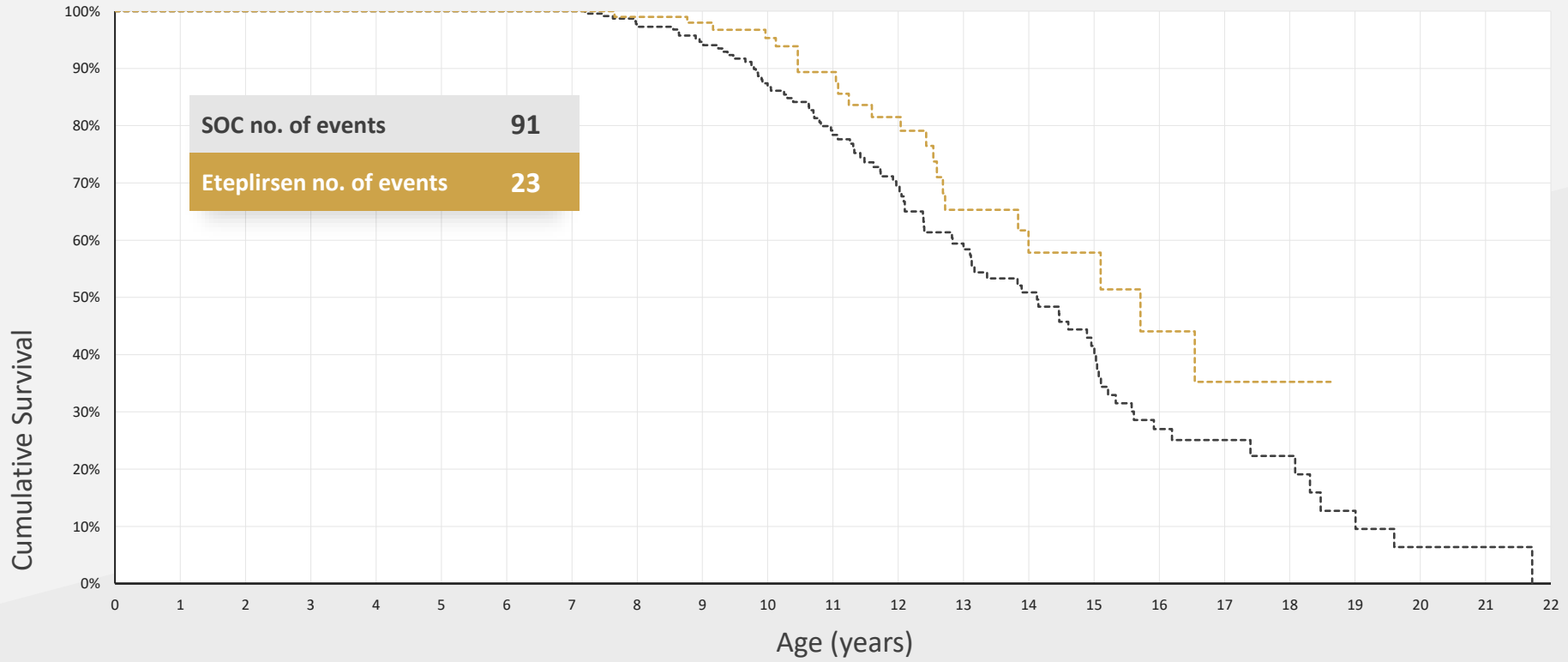
AGE AT LOA – SENSITIVITY ANALYSIS
KAPLAN-MEIER CURVES



Patients at risk over time:

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

Eteplirsen SOC

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AGE AT LOA – SENSITIVITY ANALYSIS
MEDIAN AGE AT LOA AND COX MODEL RESULTS

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

- Time to LOA was significantly longer in the eteplirsen treatment group
- Tests of proportion hazards assumption suggest assumption is valid
  (e.g. p-value=0.66 for Schoenfeld residual)
- Median age at event in SOC group was similar to the 13.40 years identified in a broader population of patients from CINRG (McDonald 2018; Lancet 2018; 391:451-461)

CI, confidence interval; HR, hazard ratio; K-M, Kaplan-Meier; NE, not evaluable; SOC, standard of care

DISCUSSION

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 loss of ambulation in SOC group was similar to the 13.40 years identified in a broader population of patients from CINRG[1]

Results are robust to the inclusion of all *genotyped* CINRG patients who were ambulatory at baseline in SOC group

CONCLUSION

LOA is significantly delayed in patients treated with eteplirsen vs SOC

References: **1.** McDonald 2018; Lancet 2018; 391:451-461

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QUESTIONS