

Survival outcomes by baseline disease burden in participants with infantile-onset Niemann-Pick disease type C treated with adrabetadex

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BACKGROUND

- Niemann–Pick disease type C (NPC) is a lethal, rare, progressive, neurodegenerative disorder caused by impaired cholesterol trafficking, resulting in cholesterol accumulation and downstream cellular dysfunction.^{1,2}
- Disease severity and progression are strongly influenced by age of neurological onset, with infantile-onset (I-NPC; neurological onset <6 years of age) representing the most severe neurological phenotype.^{1,2}
- Mean age of death is 5.6 years in early I-NPC (neurological onset <2 years of age) and 13.4 years in late I-NPC (2 to <6 years of age), consistent with more rapid disease progression in earlier-onset disease.³
- Adrabetadex is an investigational intrathecal therapy for I-NPC and the only therapy designed to directly target accumulated intracellular cholesterol in the central nervous system, the central pathogenic driver of NPC, by restoring cholesterol trafficking.
- No therapies have been approved by the FDA to improve survival in NPC.^{4–10}
- Adrabetadex improved survival in both early and late I-NPC (overall survival in I-NPC compared with matched external controls, hazard ratio [95% confidence interval]: 0.289 [0.141, 0.593]; p<0.0001).¹⁰
- Because cholesterol accumulation drives progressive neuronal cell loss and neurodegeneration,^{11,12} baseline disease burden at treatment initiation may influence long-term outcomes. Earlier removal of accumulated cholesterol and restoration of cholesterol trafficking may reduce the rate of neurological decline and improve long-term survival.
- This analysis evaluated overall survival in adrabetadex-treated participants with I-NPC stratified by baseline disease burden using a rescored 4-domain NPC Clinical Severity Scale (R4DNPCSS).

OBJECTIVES

To evaluate overall survival among individuals with I-NPC treated with adrabetadex and an untreated cohort, stratified by baseline disease burden.

RESULTS

Figure 1. Survival by Baseline R4DNPCSS Score (quartile) – Adrabetadex-Treated

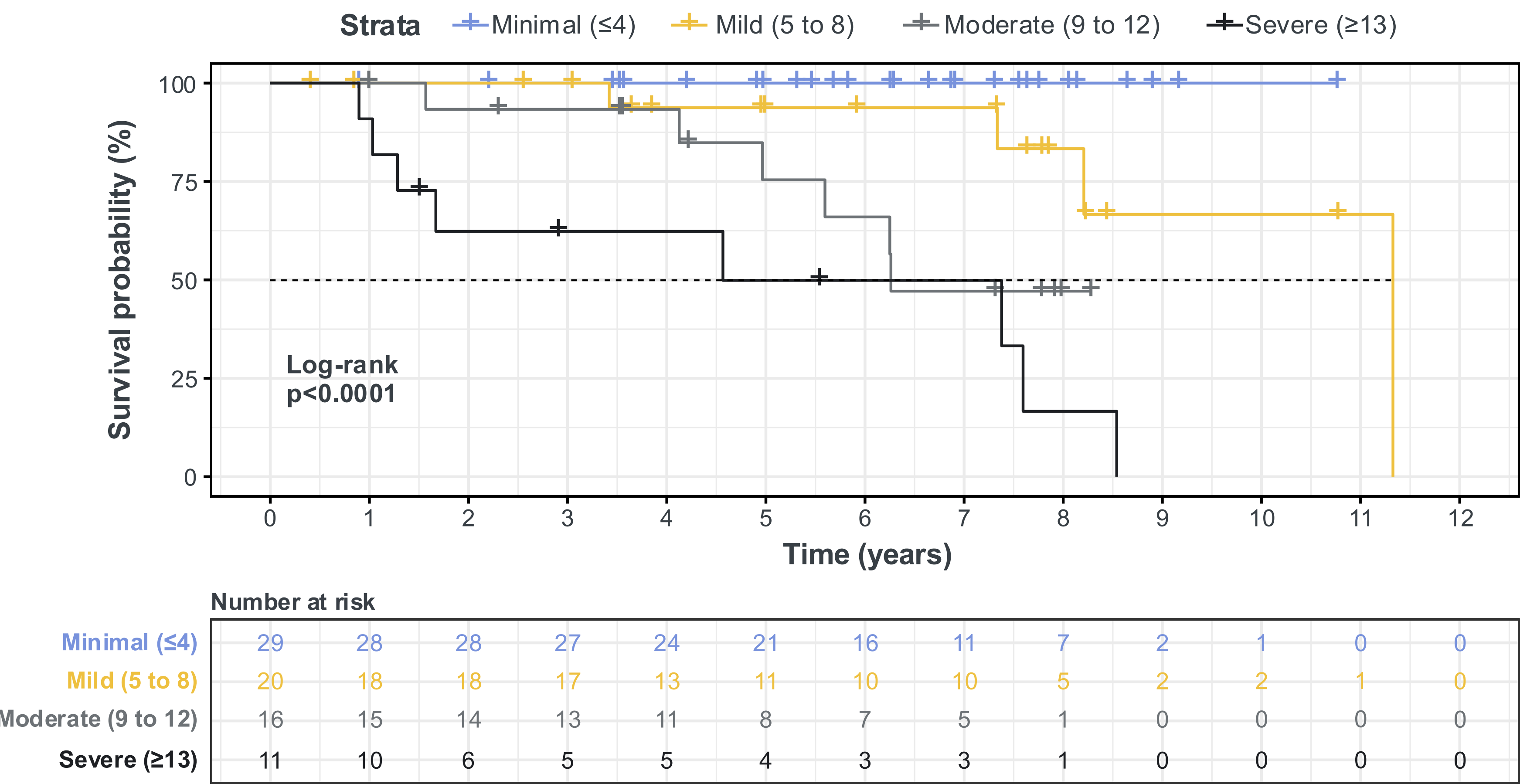
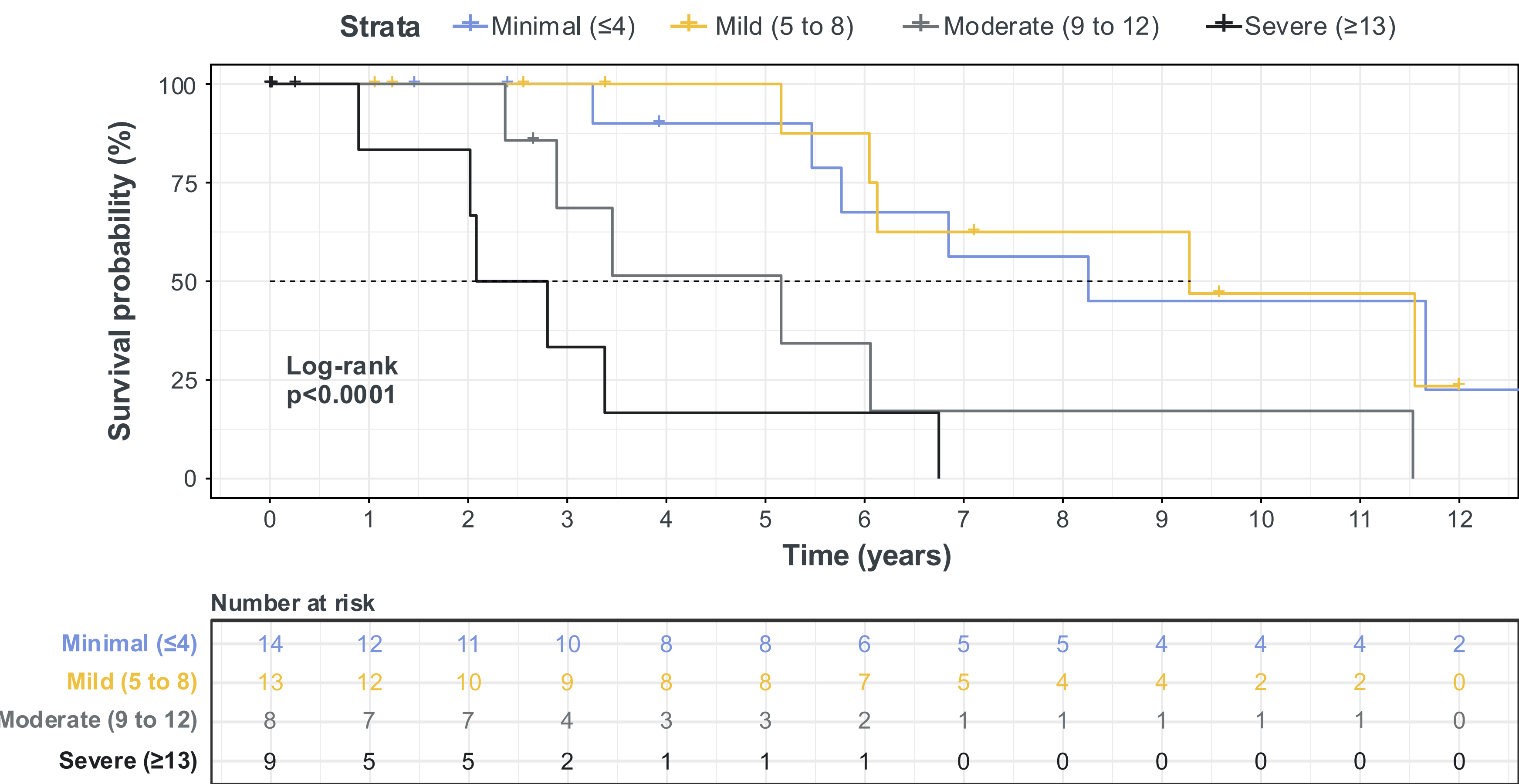


Figure 2. Survival by Baseline R4DNPCSS Score (quartile) - Untreated NIH Cohort



METHODS

Baseline Characteristics and Disease Burden Stratification

- Summaries were carried out for adrabetadex-treated participants with I-NPC (neurological onset <6 years) in clinical studies or the Expanded Access Program (N=80; Supplementary Table 1) and for the untreated cohort (N=44; Supplementary Table 2).
 - Baseline was defined as the last available observation before the first adrabetadex dose date for the pooled adrabetadex-treated participants and the first available observation for participants in the untreated cohort.
 - Baseline R4DNPCSS scores (0–20 composite score; higher scores indicate greater impairment) were used to stratify participants into disease burden groups defined by quartiles (minimal [≤4], mild [5 to 8], moderate [9 to 12], severe [≥13]).
 - The R4DNPCSS is a modified version of the 5-domain NPCCSS, which includes the domains most relevant to patients, caregivers, and clinicians: ambulation, swallowing, cognition, speech, and fine-motor.⁷
 - The R4DNPCSS eliminates the cognitive domain and adds an improved swallow scoring algorithm.⁷
 - This analysis was updated from tertiles to quartiles to better reflect NPC disease characteristics.
- Overall Survival**
- Overall survival was estimated using the Kaplan–Meier (KM) method for the adrabetadex-treated participants and for an untreated cohort from the National Institutes of Health (NIH) natural history study of NPC.
 - For the adrabetadex-treated participants, baseline was defined as the date of the initial dose of adrabetadex, and for the untreated cohort as the date of the first available record for a participant.
 - Within each cohort, estimates of survival across quartiles at baseline were compared using a Mantel–Haenszel log-rank test for trend.
 - The untreated cohort data are provided for context. However, caution should be used when evaluating these two cohorts side-by-side, as no matching procedure was performed between treated and untreated participants.

Baseline characteristics (Supplementary Tables 1-2)

- Seventy-six treated participants were included in the analysis stratified by minimal (n=29, 38.2%), mild (n=20, 26.3%), moderate (n=16, 21.1%), and severe (n=11, 14.5%) baseline R4DNPCSS scores.
 - A total of 4 participants did not have a baseline R4DNPCSS score and were excluded from the analysis.
- Forty-four untreated participants were included in the analysis stratified by minimal (n=14, 31.8%), mild (n=13, 29.5%), moderate (n=8, 18.2%), and severe (n=9, 20.5%) baseline R4DNPCSS scores.
- The age at neurological symptom onset was generally comparable across quartiles in both cohorts.

Survival (Figures 1-2, Table 1)

- Participants received adrabetadex treatment for up to 11.325 years.
- Among the adrabetadex-treated participants with minimal disease burden at baseline, no deaths were recorded.
- Survival probability was markedly improved across the lower quartiles in both the adrabetadex-treated participants and the untreated cohort with adrabetadex-treated participants surviving longer in each quartile.

Table 1. Survival by Baseline R4DNPCSS Score (quartile)

	Minimal Quartile (R4DNPCSS ≤4)	Mild Quartile (R4DNPCSS 5 to 8)	Moderate Quartile (R4DNPCSS 9 to 12)	Severe Quartile (R4DNPCSS ≥13)
Median Survival Time, months				
Median OS (95% CI)				
Adrabetadex-treated participants	NE (NE, NE)	136 (88, NE)	75 (60, NE)	55 (12, NE)
Untreated cohort	99 (39, 192)	111 (62, NE)	62 (28, NE)	29 (11, NE)

CI, confidence interval; NE, not estimated; OS, overall survival; R4DNPCSS, Composite Outcome (Ambulation, Speech, Fine Motor, Rescored Swallowing). Median survival time is presented in months.

CONCLUSIONS

- Given the rapid progression, high unmet need, and limited treatment options in the patients with I-NPC, these findings support the importance of early diagnosis and intervention in I-NPC.
- No deaths were observed among 29 adrabetadex-treated participants with minimal baseline disease burden (R4DNPCSS ≤4) during up to 11.3 years of treatment, consistent with earlier intervention before irreversible neurodegeneration.
- The median KM-estimated overall survival was numerically higher for adrabetadex-treated participants than for the untreated cohort in all the quartiles; in the severe quartile, the 5-year KM-estimated survival was 50% compared to 17%.
- Findings are consistent with the hypothesis that earlier restoration of cholesterol trafficking, before substantial neurological disease burden accumulates, may improve long-term outcomes.
- Some caution is warranted when interpreting results between the two cohorts, considering the variations in group size, as well as the absence of a matching procedure between the two cohorts.

References

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Acknowledgments

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SUPPLEMENTARY RESULTS

Baseline characteristics (Supplementary Table 1)

- Seventy-six treated participants were included in the analysis stratified by minimal (n=29, 38.2%), mild (n=20, 26.3%), moderate (n=16, 21.1%), and severe (n=11, 14.5%) baseline R4DNPCCSS scores.
 - A total of 4 participants did not have a baseline R4DNPCCSS score and were excluded from the analysis.
- The age at neurological symptom onset and the distribution of early and late infantile-onset participants were generally comparable across quartiles.

Supplementary Table 1. Baseline Demographics and Disease Characteristics – Adrabetadex-Treated

Baseline Characteristics	Minimal Quartile (R4DNPCCSS ≤4) (n=29)	Mild Quartile (R4DNPCCSS 5 to 8) (n=20)	Moderate Quartile (R4DNPCCSS 9 to 12) (n=16)	Severe Quartile (R4DNPCCSS ≥13) (n=11)	Overall (N=76)
Age at neurological symptom onset category, n (%)					
<2 years old	11 (37.9)	10 (50.0)	4 (25.0)	8 (72.7)	33 (43.4)
2 - <6 years old	18 (62.1)	10 (50.0)	12 (75.0)	3 (27.3)	43 (56.6)
Age at neurological symptom onset, years					
Mean (SD)	2.5 (1.54)	2.5 (1.61)	2.7 (1.54)	2.3 (1.75)	2.5 (1.56)
Median (Q1, Q3)	2.1 (1.1, 4.0)	1.8 (1.2, 4.0)	2.5 (1.5, 3.7)	1.6 (1.0, 4.7)	2.0 (1.1, 4.0)
Age at adrabetadex treatment start, years					
Mean (SD)	5.7 (4.55)	9.2 (6.20)	8.2 (4.48)	9.4 (7.14)	7.7 (5.56)
Median (Q1, Q3)	4.7 (3.0, 6.6)	8.5 (4.5, 12.8)	8.6 (4.7, 10.8)	9.3 (3.0, 13.7)	6.2 (3.2, 10.8)
Sex, n (%)					
Male	20 (69.0)	10 (50.0)	6 (37.5)	5 (45.5)	41 (53.9)
Female	9 (31.0)	10 (50.0)	10 (62.5)	6 (54.5)	35 (46.1)
Race					
Asian	0 (0.0)	2 (10.0)	0 (0.0)	1 (9.1)	3 (3.9)
White	28 (96.6)	18 (90.0)	13 (81.3)	7 (63.6)	66 (86.8)
Multiple	0 (0.0)	0 (0.0)	1 (6.3)	0 (0.0)	1 (1.3)
Other	0 (0.0)	0 (0.0)	2 (12.5)	3 (27.3)	5 (6.6)
Not Reported	1 (3.4)	0 (0.0)	0 (0.0)	0 (0.0)	1 (1.3)
Miglustat use at baseline ^a					
Yes	15 (51.7)	13 (65.0)	7 (43.8)	6 (54.5)	41 (53.9)
No	14 (48.3)	7 (35.0)	9 (56.3)	5 (45.5)	35 (46.1)
R4DNPCCSS baseline value ^b					
Mean (SD)	2.3 (1.28)	6.5 (1.10)	10.6 (1.20)	16.2 (2.27)	7.2 (5.06)
Median (Q1, Q3)	2.0 (1.0, 3.0)	7.0 (5.0, 7.0)	10.0 (10.0, 12.0)	17.0 (14.0, 18.0)	7.0 (3.0, 10.0)

Percentages are based on the total number of patients (n).
Q1, first quartile; Q3, third quartile; R4DNPCCSS, rescored 4-domain Niemann-Pick disease type C clinical severity scale (composite outcome [ambulation, speech, fine motor, rescored swallowing]); SD, standard deviation.
^aMiglustat use at baseline is derived from concomitant medications. Miglustat use was derived as Yes if there was a record of miglustat use in the concomitant medications at or prior to the first dose of study medication. Otherwise, miglustat use is No.
^bFour patients out of 80 were missing baseline R4DNPCCSS score. They are excluded from the analysis.

Supplementary Table 2. Baseline Demographics and Disease Characteristics – NIH Infantile-onset Participants

Baseline Characteristics	Minimal Quartile (R4DNPCCSS ≤4) (n=14)	Mild Quartile (R4DNPCCSS 5 to 8) (n=13)	Moderate Quartile (R4DNPCCSS 9 to 12) (n=8)	Severe Quartile (R4DNPCCSS ≥13) (n=9)	Overall (n=44)
Age at neurological symptom onset category, n (%)					
<2 years old	6 (42.9)	5 (38.5)	5 (62.5)	5 (55.6)	21 (47.7)
2 - <6 years old	8 (57.1)	8 (61.5)	3 (37.5)	4 (44.4)	23 (52.3)
Age at neurological symptom onset, years					
Mean (SD)	2.2 (1.13)	2.3 (1.19)	2.2 (1.83)	2.4 (1.53)	2.3 (1.33)
Median (Q1, Q3)	2.0 (1.4, 3.0)	2.0 (1.5, 3.0)	1.4 (0.9, 3.8)	1.7 (1.5, 2.0)	2.0 (1.4, 3.0)
Sex, n (%)					
Male	8 (57.1)	6 (46.2)	4 (50.0)	4 (44.4)	22 (50.0)
Female	6 (42.9)	7 (53.8)	4 (50.0)	5 (55.6)	22 (50.0)
Race					
African American	0 (0.0)	1 (7.7)	1 (12.5)	1 (11.1)	3 (6.8)
Asian	0 (0.0)	0 (0.0)	0 (0.0)	1 (11.1)	1 (2.3)
Caucasian	12 (85.7)	12 (92.3)	6 (75.0)	6 (66.7)	36 (81.8)
Caucasian, American Indian	1 (7.1)	0 (0.0)	0 (0.0)	0 (0.0)	1 (2.3)
Hispanic or Latino	1 (7.1)	0 (0.0)	1 (12.5)	1 (11.1)	3 (6.8)
Overall miglustat use					
Yes	9 (64.3)	11 (84.6)	4 (50.0)	3 (33.3)	27 (61.4)
No	5 (35.7)	2 (15.4)	4 (50.0)	6 (66.7)	17 (38.6)
R4DNPCCSS baseline value					
Mean (SD)	1.9 (1.49)	6.2 (1.09)	10.9 (1.13)	16.2 (1.92)	7.8 (5.52)
Median (Q1, Q3)	2.0 (1.0, 3.0)	6.0 (5.0, 7.0)	11.0 (10.0, 12.0)	16.0 (15.0, 17.0)	6.5 (3.0, 12.0)

Percentages are based on the total number of patients (n).
Q1, first quartile; Q3, third quartile; R4DNPCCSS, rescored 4-domain Niemann-Pick disease type C clinical severity scale (composite outcome [ambulation, speech, fine motor, rescored swallowing]); SD, standard deviation.

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