

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 genetic 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 phenotype.^{1,2}
- Mean age of death has been reported as 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 CNS, the central pathogenic driver of NPC, by restoring cholesterol trafficking.
- Adrabetadex is the only therapy studied in I-NPC and shown to improve survival in both early and late I-NPC (overall survival in I-NPC compared with matched external controls, HR [95% CI]: 0.289 [0.141, 0.593]; p<0.0001).⁴
- Because cholesterol accumulation drives progressive neuronal cell loss and neurodegeneration,^{5,6} baseline disease burden at treatment initiation may influence long-term survival 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; ambulation, fine motor skills, speech, rescored swallowing).

OBJECTIVES

To evaluate overall survival among individuals with I-NPC treated with adrabetadex, stratified by baseline disease burden as assessed using a rescored 4-domain NPC Clinical Severity Scale.

METHODS

Disease Burden Stratification

- Individuals with I-NPC (neurological onset <6 years) treated with adrabetadex in clinical studies or the Expanded Access Program were included.
- Baseline R4DNPCSS scores (0–20 composite score; higher scores indicate greater impairment) were used to stratify participants into disease burden groups defined by tertiles: low (≤ 4), medium (5 to 9), high (10 and above).
 - The R4DNPCSS is a modified version of the 5 domain NPCSS, 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

Overall Survival

- Overall survival was estimated using Kaplan-Meier (KM) method.
- Estimates of survival across score tertiles at baseline were compared using a log-rank test for trend.

References

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RESULTS

Baseline characteristics (Table 1)

- Seventy-six treated participants were included in the analysis stratified by low (n=29, 38.2%), medium (n=23, 30.3%), and high (n=24, 31.6%) baseline R4DNPCSS scores.
- The age at neurological symptom onset and the distribution of early and late infantile-onset participants are generally comparable across tertiles.
- The low tertile has a lower median age at start of adrabetadex treatment than the medium and high tertiles.
- There are no apparent differences in baseline miglustat use between tertiles.

Table 1. Baseline Demographics and Disease Characteristics

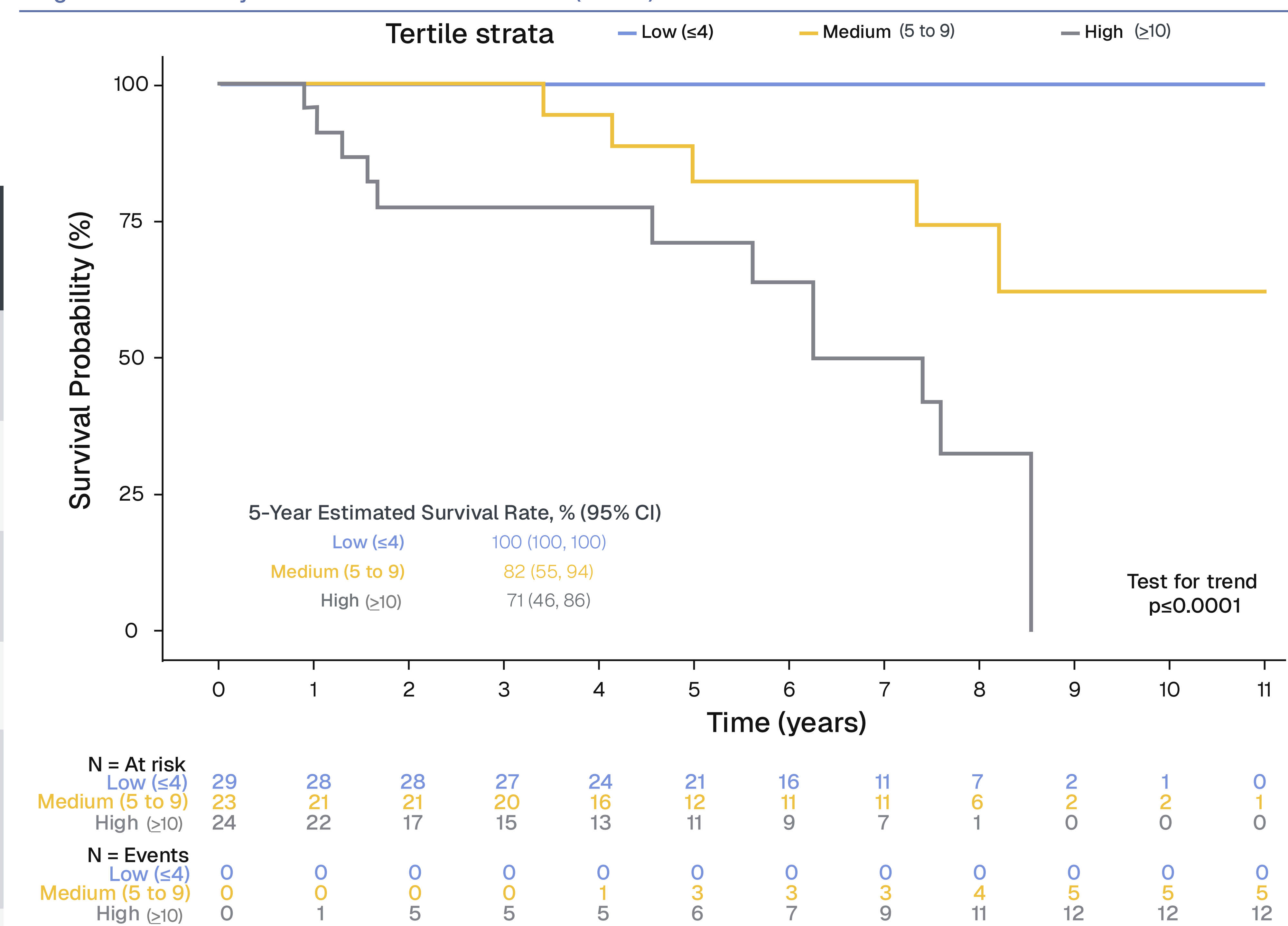
Baseline Characteristics	Low Tertile (R4DNPCSS ≤ 4) (n=29)	Medium Tertile (R4DNPCSS 5 to 9) (n=23)	High Tertile (R4DNPCSS 10 and above) (n=24)	Overall (n=76)
Age at symptom onset category, n (%)				
<2 years old	11 (37.9)	11 (47.8)	11 (45.8)	33 (43.4)
2–6 years old	18 (62.1)	12 (52.2)	13 (54.2)	43 (56.6)
Age at neurological symptom onset, years	n=29	n=23	n=24	n=76
Mean (SD)	2.5 (1.54)	2.5 (1.71)	2.5 (1.51)	2.5 (1.56)
Median (Q1, Q3)	2.1 (1.1, 4.0)	2.0 (1.2, 4.0)	2.1 (1.3, 3.7)	2.0 (1.1, 4.0)
Age at adrabetadex treatment start, years				
Mean (SD)	5.7 (4.55)	9.0 (5.95)	8.7 (5.79)	7.7 (5.56)
Median (Q1, Q3)	4.7 (3.0, 6.6)	8.8 (4.5, 12.7)	8.6 (3.4, 11.3)	6.2 (3.2, 10.8)
Sex, n (%)				
Male	20 (69.0)	11 (47.8)	10 (41.7)	41 (53.9)
Female	9 (31.0)	12 (52.2)	14 (58.3)	35 (46.1)
Race				
Asian	0	2 (8.7)	1 (4.2)	3 (3.9)
White	28 (96.6)	21 (91.3)	17 (70.8)	66 (86.8)
Multiple	0	0	1 (4.2)	1 (1.3)
Other	0	0	5 (20.8)	5 (6.6)
Not Reported	1 (3.4)	0	0	1 (1.3)
Miglustat use at baseline^a				
Yes	15 (51.7)	15 (65.2)	11 (45.8)	41 (53.9)
No	14 (48.3)	8 (34.8)	13 (54.2)	35 (46.1)
R4DNPCSS baseline value^b				
Mean (SD)	2.3 (1.28)	6.8 (1.35)	13.4 (3.12)	7.2 (5.06)
Median (Q1, Q3)	2.0 (1.0, 3.0)	7.0 (5.0, 8.0)	12.0 (10.5, 16.0)	7.0 (3.0, 10.0)

Percentages are based on the total number of patients (n). Q1, first quartile; Q3, third quartile; R4DNPCSS, 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 R4DNPCSS score. They are excluded from the analysis. Max, maximum; Min, minimum; Q1, first quartile; Q3, third quartile; R4DNPCSS, rescored 4-domain Niemann-Pick disease type C clinical severity scale; SD, standard deviation.

Survival

- Participants received adrabetadex treatment for up to 11.325 years. At 5 years, KM-estimated overall survival was 100% (95% CI: 100%, 100%) in the low R4DNPCSS group, 82% (95% CI: 55%, 94%) in the medium group, and 71% (95% CI: 46%, 86%) in the high group (Figure 1).

Figure 1. Survival by Baseline R4DNPCSS Score (tertile)



CONCLUSIONS

- Adrabetadex-treated participants with the lowest baseline disease burden (R4DNPCSS ≤ 4) demonstrated the longest observed survival, including 100% survival at 5 years in the lowest severity group, consistent with earlier intervention before irreversible neurodegeneration.
- Five-year survival exceeded 70% across all disease burden tertiles and was numerically higher than previously reported survival in matched external control populations (42%).⁴
- Findings are consistent with the hypothesis that earlier restoration of cholesterol trafficking may improve long-term outcomes when initiated before advanced neurodegeneration.
- Given the rapid progression, high unmet need, and limited treatment options in the youngest patients with I-NPC, these findings support the importance of early diagnosis and prompt initiation of adrabetadex as foundational therapy.

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