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Original Article

# Efficacy and safety of efavirenz in Niemann-Pick disease type C

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ABSTRACT

*Introduction:* In search of disease-modifying treatments for the Niemann-Pick disease type C (NPC), this Phase II single-arm clinical trial evaluated the safety and efficacy of efavirenz, a reverse transcriptase inhibitor that potentially ameliorates neuronal cholesterol turnover, typically impaired in this rare lysosomal storage disorder.
*Material and methods:* Patients 14 years of age or older with genetically confirmed NPC received efavirenz 25 mg/day (Weeks 1–26) or 100 mg/day (Weeks 27–52) orally on top of standard care including miglustat. The primary endpoint was the proportion of response, defined as lack of deterioration in a composite outcome of cognitive performance. Secondary endpoints included the quantitative scores of several clinical neuropsychological assessment tools, some relevant neurological signs and symptoms, and imaging and biological specimen-based biomarkers. Measures were taken repeatedly over time and were analyzed using generalized linear mixed models.
*Results:* Sixteen patients 15–60 years of age were enrolled. All (100.0 %, 95 % exact confidence interval: 79.4–100.0 %) met the primary endpoint response criterion at Week 52. Quantitative neuropsychological assessments yielded more nuanced results, with relative preservation of learning, memory and executive control, and subtle impairments of verbal fluency, selective and divided attention, and cognitive inhibition. Some patients had better responses than others, allowing us to set two well-differentiated subgroups that differed essentially in the time since symptoms onset. No efavirenz-related or serious adverse events were reported.

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*Conclusion:* Efavirenz appears to be a safe, easy-to-use, new targeted therapeutic option which slows the rate of NPC progression. The benefits of efavirenz are greater if started earlier.
*Trial Registration:* Registered on the European Union Clinical Trials Register (EurdraCT) on December 20th, 2019 under the number: 2019-004498-18 (https://www.clinicaltrialsregister.eu/ctr-search/trial/2019-004498-18/ES/). The first patient was enrolled on May 25th, 2022.

## Introduction

Niemann-Pick disease type C (NPC) is a rare autosomal recessive lysosomal storage disorder linked to abnormal intracellular lipid trafficking [1]. It is caused by mutations in either the *Npc1* or *Npc2* genes—the latter being mutated in only 5 % of patients [2–4]. NPC1 and NPC2 are ubiquitous lysosomal membrane and luminal proteins involved in intracellular cholesterol transportation [5–7]. Therefore, the endgame of defective NPC1/NPC2 proteins is the intracellular accumulation of unesterified cholesterol and glycosphingolipids within the late endolysosomal compartment, a biochemical hallmark of NPC (Supplemental Material, Fig. S1) [7,8].

NPC has an overall estimated incidence of 1:100,000 live births, although late-onset phenotypes may have higher incidence [9]. Disease onset can occur anywhere throughout the lifespan [3], and features a highly heterogeneous phenotypic spectrum. Although classically described as a neurovisceral condition (each component following independent clinical courses) [2,10], the systemic component (liver, spleen, and sometimes lungs) is often less clinically significant—except in a small subset of newborns dying within the first 6 months after birth from hepatic or respiratory failure [2,11]. In turn, neurodegenerative involvement—with vertical supranuclear saccadic palsy, progressive cerebellar ataxia, dysarthria, dysphagia and dementia, is the main feature in 90 % of cases, aside from this subset of neonatal patients and a few anecdotal adult cases [2,11].

Although current pathophysiological knowledge of lipid dynamics within the central nervous system (CNS) in NPC disease is limited, we already have important insights. The abundance of NPC1 in axon terminals and synaptosomes [12,13], where appropriate cholesterol distribution and elimination is essential for the correct development of long-term potentiation (LTP)—a major event in synaptic plasticity [14], suggests that neurons may be particularly vulnerable to NPC1/NPC2 loss-of-function. Furthermore, since neurons have high cholesterol requirements to keep membrane and synaptic functions, defective NPC1/NPC2 proteins may ultimately lead to neurodegeneration by undermining the ability of the late endosome/lysosome system to supply cholesterol [15,16].

Notably, although NPC occurs throughout the CNS, certain regions are more prone to early and severe injury and give rise to some disease hallmarks [1], particularly ataxia, dysarthria, and dysphagia (due to cerebellar Purkinje cell loss) [1,2,17], dementia and seizures (caused by brain cortical lesions) [1,2,17], and the characteristic vertical supranuclear gaze palsy (VSGP, resulting from severe cell loss in the rostral interstitial nucleus of the medial longitudinal fasciculus) [1,18]. Although the basis for this selective neuronal vulnerability remains unclear, the absence of redundant neural circuitry might be a partial explanation [17,19].

Although a number of molecules have been investigated over the last decades as potential treatments for NPC [20], the inhibitor of glucosylceramide synthase miglustat is the only drug registered for clinical use [21]. Efavirenz is a non-nucleoside reverse transcriptase inhibitor (NNRTI) holding a market authorization for anti-human immunodeficiency virus (HIV) therapy for up to 25 years [22]. Efavirenz is known to interact with different components of the cytochrome P450 enzyme system [23], including the CYP46A1 (*i.e.*, cholesterol 24-hydroxylase), a CNS- specialized enzyme responsible for neuronal cholesterol turnover [24]. Disturbances in levels of 24-hydroxycholesterol have been detected in NPC mice and human patients [25]. Interestingly, animal studies have suggested that 24-hydroxycholesterol cerebrospinal fluid (CSF) and plasma levels are potential biomarkers of several neurodegenerative diseases [26], which improve after potentiating CYP46A1 activity [27–31]. Efavirenz was shown to enhance CYP46A1 activity at typically low-doses [32], which normalized the *in vivo* synaptic cholesterol levels, LTP, and cognitive abilities in *NPC1*$^{nmf164}$ mice (a late-onset NPC disease model), while extending their lifespan by 30 % [33]. In turn, a recently published pilot clinical trial demonstrated the ability of repeated low doses of efavirenz to enhance CYP46A1 activity in patients with early Alzheimer's disease [34].

Considering this pathophysiological knowledge and the promising results, we hypothesized that efavirenz's potentiation of CYP46A1 activity could compensate for NPC1 deficiency and improve synaptic function, therefore counteracting or even ameliorating the characteristic cognitive and psychiatric alterations of the CNS disease of NPC patients. The present clinical trial was conducted to assess the efficacy and safety of efavirenz in late-juvenile/adult-onset NPC patients over 52 weeks of treatment, in addition to standard care treatment, using a complete set of neuropsychological, neurological and biological outcomes.

## Materials and Methods

### *Trial design and oversight*

The study consisted of a single-center, phase II, single-arm clinical trial of efavirenz on top of standard care treatment over 52 (±2) weeks for late-juvenile/adult-onset NPC patients (EudraCT: 2019-004498-18). The trial was performed at the Bellvitge University Hospital and was sponsored by the Bellvitge University Hospital and the Severo Ochoa Molecular Biology Center, both non-commercial. Patients were recruited in 2022, between May 25th and December 14th. Funding was provided by the not-for-profit Spanish Niemann-Pick Foundation. All investigators and the trial site were bound by confidentiality agreements according to current Spanish and European legislations.

The study protocol, available in the Supplemental Material, received Institutional Review Board approval, and all patients and/or their legal representatives provided written informed consent before enrollment. This trial was conducted in accordance with the terms of the Declaration of Helsinki, Good Clinical Practice guidelines, and all applicable regulatory requirements. All authors had access to the trial data and vouch for its accuracy and completeness and for the fidelity of the trial to the protocol—the full text can be found at the Supplemental Material, and a dedicated publication is available elsewhere [35].

### *Patients*

Eligible patients had to be 14 years of age or older, of either sex, with a genetically confirmed diagnosis of late-juvenile/adult-onset (onset of symptoms—see below— at or after 14 years of age) NPC and a global Clinical Dementia Rating (CDR) score of between 0.5 and 2 or a CDR-Sum of Boxes (SB) ≤12 (*i.e.*, mild to moderate cognitive impairment), at least 8 years of schooling, and under treatment with miglustat. Patients with chronic liver disease or unstable epilepsy were excluded. See the Supplemental Material (Table S1) for the full list of eligibility criteria and prohibited concomitant medications during the trial.

*Trial procedures*

All included participants started receiving efavirenz 25 mg/day orally for 52 weeks in addition to standard care treatment, including miglustat. The trial featured a baseline screening visit (V1), conducted 30–60 days before treatment start (V2). Participants' sociodemographic characteristics and medical history were collected at this visit. These included the time since the onset of symptoms, which was mostly based on patients' or patient relatives' recall of the moment when first difficulties arose. A first follow-up visit (V2.1) was performed at 4 weeks (±3 days), and subsequent follow-up visits (V3, V4, V5, and V6) were performed at 13-week intervals after V2. The study's main procedures are summarized and displayed in the Supplemental Material (Fig. S2); lumbar punctures were not mandatory for trial participation and an additional written informed consent was required for this procedure.

Efavirenz dose selection was based on preclinical studies [32,33] and on an ongoing (at the time of writing the protocol) clinical trial with efavirenz for Alzheimer's dementia (NCT03706885). Of note, the starting dose of efavirenz is 6-fold lower than that recommended for anti-HIV therapy, and was increased to 100 mg/day at V4, approximately 6 months from the start, to maximize efficacy. Additional details on the trial design, methods, rationale for dose selection, and objectives can be found elsewhere [35].

*Outcomes*

Given the relevance of cognitive disturbances in adult-onset NPC, we based the primary efficacy outcome on cognitive performance. We used a composite qualitative measure to assess the change from baseline in 3 domains (*i.e.*, dementia severity, verbal memory, and executive functioning). Patients were considered responders if they lacked deterioration in at least 2 of these domains.

Dementia severity was quantified by the CDR-SB (scores range from 0 to 18, with higher scores indicating greater impairment); dementia progression was defined as a ≥2-point CDR-SB increase. Verbal memory assessment was carried out with the Free and Cued Selective Reminding Test (FCSRT), and a decrease ≥1 standard deviation (SD) was used to define verbal memory deterioration.

Because of the complexity and multidimensionality of executive functioning assessment, different test components were used: (i) the digit span subtests of the revised Barcelona Test (r-BT); (ii) the mental control subtests of the r-BT; (iii) the semantic and phonemic tasks of the Verbal Fluency Test (VFT); (iv) the Trail Making Test (TMT) A and B; and (v) the Stroop Color-Word Interference Test (SCWT). They together provide a comprehensive functional assessment including selective (mainly via the TMT A and r-BT) and divided attention (TMT B), working memory (r-BT and VFT), executive control (Phonemic VFT), mental flexibility (TMT), information processing speed, cognitive flexibility, and cognitive inhibition (TMT B, SCWT). Executive functioning deterioration was assessed using both, a soft criterion—a ≥1-SD worsening in 2 or more of these five executive functioning component tests—and a strict criterion—a ≥1-SD reduction in 2 or more individual executive functioning tests scores (*i.e.*, r-BT, semantic task, TMT A, TMT B, SCWT). Detailed descriptions of each neuropsychological assessment can be found in the Supplemental Material (Supplemental Methods).

Secondary efficacy outcomes were divided in neuropsychological, neurological, and biological. Secondary neuropsychological outcomes included the individual scores of each neuropsychological instrument used in the composite primary outcome and the following scores: (i) global CDR; (ii) Boston naming test (BNT); (iii) judgment of line orientation (JLO) test; (iv) dysexecutive questionnaire (DEX); (v) neuropsychiatric inventory questionnaire (NPI); (vi) apathy evaluation scale (AES); (vii) Beck depression inventory (BDI).

Secondary neurological outcomes consisted of changes from baseline through week 52 in the total score on 4 different scales: (i) the Scale for the Assessment and Rating of Ataxia (SARA); (ii) the Eating Assessment Tool for dysphagia (EAT-10); (iii) the Pineda Disability Scale (PDS); and (iv) the block design and symbol search subtests of the Wechsler Adult Intelligence Scale III (WAIS-III). Higher scores in these scales indicate greater ataxia, dysphagia, disability, and higher cognitive abilities, respectively.

Secondary biological outcomes included, among others, brain imaging, CSF proteins, and plasma 24-hydroxycholesterol levels.

Safety outcomes included the cumulative incidence and seriousness of adverse events.

*Statistical analysis*

All collected data were described using appropriate descriptive statistics, including means (SD) and medians (ranges) for continuous variables, as well as numbers and frequencies for categorical variables. Except for the global CDR and the CDR-SB, all neuropsychological tests had their scores mapped into norms-based scaled scores (mean = 10, SD = 3) for the healthy Spanish population, with higher scores invariably reflecting better clinical states (see the references provided in the Supplemental Material).

Notably, some patients had better responses to efavirenz than others, allowing us to set 2 well-differentiated subgroups of patients, namely a favorable response (FR) subgroup featuring improvements in most of the assessments and an unfavorable response (UR) one (*i.e.*, with worsening/unchanged results despite efavirenz). For that purpose, we used a semi-automated discriminant analysis to classify patients into these two subgroups before proceeding with the remaining analyses (Supplemental Material, Fig. S3).

The primary outcome was analyzed as a Binomial proportion, for which exact Binomial 95 % confidence intervals (CI) were calculated. Adjusted means of scale scores and their 95 % CI were calculated at each study visit using generalized linear mixed models for repeated measures with a Gamma distribution for errors and a logarithmic link function. Note that these models are a general case of the analyses of covariance foreseen in the study protocol [35], and may be a valid framework for imputing missing data. These models were also used to explore factors associated with response, including the SARA and PDS scores as dynamic (*i.e.*, changing over time) fixed factors, and age, subgroup, and time from symptom onset as static (baseline) fixed factors. We also performed a *post-hoc* analysis of the sensitivity to change of the component tests of the primary efficacy outcome by calculating some effect size measures (Cohen's *d* and Guyatt indices, and standardized mean responses) to ascertain those most sensitive to changes in disease status throughout treatment.

Since NPC is quite an uncommon condition, we were able to recruit most subjects from the target population since the study site is a reference center of the Spanish National Health System for NPC adult patients. For this reason, we did not perform formal sample size calculations, but rather based the planned number of 14 participants on pragmatic grounds. Because this sample exceeds half the size of the target population (to date, only 27 adult patients have been diagnosed with NPC in Spain), uncertainty measures (such as confidence intervals) do not have the inferential role emanating from sampling theory but should rather be viewed as credibility margins. Although Bayesian credible intervals would fit such a role more appropriately, their calculation was outside the scope of this study, and we deem that the confidence intervals are a conservative (*i.e.*, wider) replacement.

All statistical analyses were performed using SAS version 9.4 (SAS Institute Inc., Cary, NC).

## Results

*Patients*

In total, 17 patients were screened for eligibility. One (5.9 %) patient failed NPC diagnosis confirmation based on genetic testing and was

excluded; ultimately, a total of 16 (94.1 %), who attended all study visits, were analyzed (Fig. 1). The median (range) age was 41.5 (15.0–60.0) years and 11 (68.8 %) of them were males. The median (range) age at diagnosis was 29.5 (8.0–41.0) years, which was similar in both subgroups. The time since symptom onset (median: 21 years, range: 5–54 years) was shorter in the FR subgroup than in the UR subgroup (Table 1). Noteworthy, most patients of the FR subgroup had disease durations of under 10 years (third quartile: 12 years), but these were considerably longer in patients of the UR subgroup (first quartile: 24 years). All patients completed the trial; their demographic and baseline characteristics are shown in Table 1.

Overall, they had mild cognitive impairment at baseline, poor memory performance and moderate executive functioning deficits. All patients met the most restrictive genetic inclusion criterion of showing at least 2 NPC-related mutations; all but one (93.8 %) had cerebral and thalamic hypometabolism, and all had cerebellar hypometabolism at baseline; however, only 4 (25.0 %) and 6 (37.5 %) showed brain and cerebellar atrophy, respectively. Splenomegaly was evidenced in 11 (68.8 %) patients.

*Primary efficacy outcome*

All 16 (100.0 %, exact 95 % CI: 79.4–100.0 %) patients responded to efavirenz at week 52 (V6), meeting both strict and soft response criteria (Fig. 2). Of these, 15 (93.7 %, exact 95 % CI: 69.8–99.8 %) had already responded at V4, sustaining such a response at V6 for both criteria. The remaining patient presented deterioration of all cognitive performance domains at V4; however, these improved at V6 and, herewith, became a responder.

*Secondary efficacy outcomes*

Results for the secondary efficacy outcomes are presented for the whole sample and for the FR and UR subgroups.

*Secondary neuropsychological outcomes*

The FR subgroup featured a downward trend (toward improvement) in the global CDR score (Fig. 3A), while the CDR-SB showed no apparent changes (Fig. 3B). Conversely, the UR subgroup had upward (worsening) trends in both the CRD and CDR-SB scores. There were significant differences between subgroups that persisted even after adjusting for the time since symptom onset.

Verbal memory improved in the FR subgroup; both the free recall (Fig. 3C) and cued recall (Fig. 3D) adjusted mean scores reached the reference band contained within ±1 SD of the mean population scaled score. On the other hand, the UR subgroup showed a mild free recall improvement at V6 while presenting a slight progressive decline in its cued recall. There were significant differences between subgroups that persisted even after adjusting for the time since symptom onset.

Results varied among the different components making up the executive functioning assessment. The FR subgroup presented better adjusted mean scores at V6 on both r-BT digit span components (Fig. 3E and F); however, it remained unchanged for the r-BT mental control component—despite the remarkable improvement at V4 that produced an inverted V-shaped curve (Fig. 3G)—and progressively deteriorated for the time to complete the mental control component (Fig. 3H). In turn, the UR subgroup presented progressive declines in both r-BT digit span subtests, whilst the time component of the mental control subtest showed a V-shaped curve (Fig. 3G). The differences between subgroups were not significant, except for the time trajectories of the latter (Fig. 3G).

All components of the VFT (Fig. 3I and J), TMT A (Fig. 3K), and TMT B (Fig. 3L) showed poor scores at baseline and worsening trends during the study. Notably, both subgroups presented improvements in the semantic task of the VFT and the TMT A at V4. Still, they had subsequent declines at V6, thus presenting similar trajectories in both tests (Fig. 3I and K). There were significant differences between subgroups in verbal fluency scores that persisted after adjusting for the time since symptom onset.

Except for the Interference scores (Fig. 3P) SCWT scores were in general poor at all study assessments (Fig. 3M–P). The FR subgroup had slightly better scores at the Word-Color and Interference components than the UR subgroup, and this difference even increased a little during the study. Conversely, Interference scores worsened between V4 and V6 in the UR subgroup. Word-Color and Interference scores differed significantly between subgroups even after adjusting for the time since symptom onset.

As a corollary, improvements and deteriorations were observed in 5 and 7 patients, respectively, for dementia scores, 7 and 3 patients, respectively, for verbal memory scores, and 5 and 8 patients, respectively, for executive functioning scores (Supplemental Material, Fig. S3), all constituting the primary efficacy outcome.

Last, the FR subgroup presented slight improvements in all remaining neuropsychological tests performed, with higher BNT (naming and fluency components) and JLO mean scores and lower DEX (particularly in the self-assessed version), NPI, AES, and BDI mean scores at V6 (Supplemental Material, Fig. S4). On the other hand, the UR subgroup presented improvements in the BNT naming component, NPI and AES, but not in the remaining tests.

Individual trajectories are available in the Supplemental Material (Fig. S5).

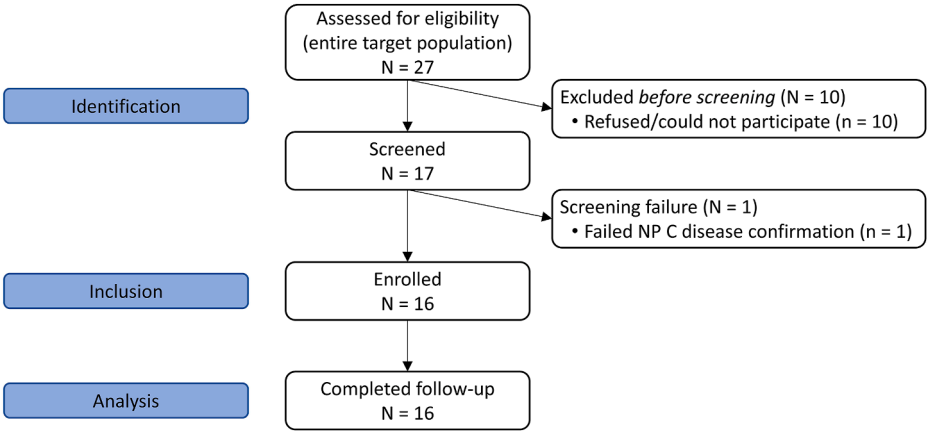


**Fig. 1.** STROBE flow diagram.

**Table 1**
Demographics and baseline characteristics.

| Characteristic | Favorable Response | Unfavorable Response | Total |
|---|---|---|---|
| | n = 7 | n = 9 | n = 16 |
| Age (years), median (range) | 40 (22–48) | 43 (15–60) | 41.5 (15–60) |
| Sex, n (%) | | | |
| Male | 4 (57.1) | 7 (77.8) | 11 (68.9) |
| Female | 3 (42.9) | 2 (22.2) | 5 (31.3) |
| Age at diagnosis (years), median (range) | 30.0 (17.0–41.0) | 29.0 (8.0–39.0) | 29.5 (8.0–41.0) |
| Time since symptom onset (years), median (range)[b] | 8 (6–34) | 27 (5–54) | 21 (5–54) |
| Education (years completed), median (range) | 12 (9–20) | 11 (8–14) | 11.5 (8–20) |
| Body weight (Kg), median (range) | 62.0 (56.0–72.3) | 66.0 (53.0–80.0) | 65.0 (53.0–80.0) |
| Height (cm), median (range) | 170 (158–180) | 171 (156–178) | 171 (156–180) |
| Right brain dominance, n (%) | 0 (0)[a] | 6 (75.0)[a] | 6 (46.2) |
| Harmful habits, n (%) | | | |
| Smoking (active) | 2 (28.6) | 0 (0) | 2 (12.5) |
| Alcohol intake | 0 (0) | 0 (0) | 0 (0) |
| Past medical history, n (%) | | | |
| Dyslipidemia | 0 (0) | 1 (11.1) | 1 (6.3) |
| Psychiatric disorders | 0 (0) | 1 (11.1) | 1 (6.3) |
| Neonatal jaundice | 0 (0) | 4 (44.4) | 4 (25.0) |
| Family history of neurodegenerative disorders, n (%) | 4 (57.1) | 3 (33.3) | 7 (43.8) |
| Family history of metabolic disorders, n (%) | 2 (28.6) | 1 (11.1) | 3 (18.8) |
| Motor delay, n (%) | 4 (57.1) | 7 (77.8) | 11 (68.8) |
| Cognitive impairment, n (%) | 5 (71.4) | 9 (100.0) | 14 (87.5) |

[a] Two patients (28.6 %) in the Favorable Response and one (11.1 %) in the Unfavorable Response group had missing values. Percentages in the table are calculated over the total number of patients with available results.
[b] Based on patients' or patient relatives' recall of the moment when first difficulties arose.

*Post hoc analysis*

The effect size measures showed that both r-BT digit span subtests (forward and backward, measuring selective attention and working memory) are particularly sensitive to deterioration while the TMT B and the SCWT Interference subtest (measuring cognitive flexibility and inhibition) are more sensitive to both improvement and deterioration (Table 2 and Table S2).

*Secondary neurological outcomes*

Ataxia and disability scores remained quite stable throughout the study (Fig. 4A and C); yet, they were better in the FR subgroup than in the UR subgroup. On the other hand, dysphagia improved in both subgroups (Fig. 4B); however, this improvement was remarkably more pronounced in the UR subgroup. Both WAIS-III subtests (symbol search and block design) improved in both subgroups (Fig. 4D and E). Individual trajectories are available in the Supplemental Material (Fig. S5).

*Secondary biological outcomes*

At V6, all patients had evidence of brain and cerebellar hypometabolism, and all but one in the UR subgroup (88.9 %), thalamic hypometabolism. Brain atrophy was found in 6 (100.0 %) and cerebellar atrophy in 5 (83.3 %) patients of the FR subgroup; one patient had missing values for these outcomes. In turn, in the UR subgroup, brain and cerebellar atrophy were evidenced in 3 (33.3 %) and 5 (55.6 %) patients, respectively (Supplemental Fig. S6).

As for splenomegaly, 4 (57.1 %) patients in the FR and 6 (66.7 %) in the UR subgroup had sonography-evidenced splenomegaly at V6.

Both subgroups had upsurges in their mean CSF levels of amyloid beta protein at V6; however, the relative change was less pronounced in the UR subgroup (Supplemental Fig. S7A). Mean CSF tau protein levels remained stable (Supplemental Fig. S7B and S7C).

*Safety outcomes*

Only 3 adverse events occurred during the trial—all in the same patient—and consisted of traumatic brain injury and grade IV (American Association for the Surgery of Trauma) splenic laceration, both due to an accidental fall related to his/her ataxia, and stage IV myelocytic leukemia; the cumulative incidence of adverse events was 6.3 %. All adverse events were deemed unrelated to efavirenz.

## Discussion

In this phase II single-arm trial, all included NPC patients responded to efavirenz on top of standard care treatment at 52 weeks—that is, lacked deterioration in at least 2 out of 3 cognitive performance

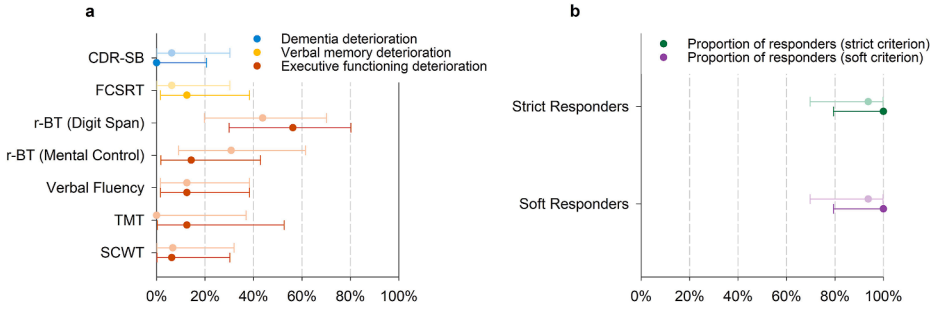


**Fig. 2.** Proportion of patients presenting deterioration in each neuropsychological milestone and proportion of responders to efavirenz. CDR-SB, Clinical Dementia Rating scale – Sum of Boxes; FCSRT, Free and Cued Selective Reminding Test; r-BT, revised Barcelona Test; TMT, Trail Making Test; SCWT, Stroop Color-Word Interference Test. (A) Percentage (exact 95 % CI) of patients presenting deterioration in each cognitive performance domain at visits 4 (lighter colors) and 6 (darker colors). (B) Percentage (exact 95 % CI) of responders at visits 4 (lighter colors) and 6 (darker colors).

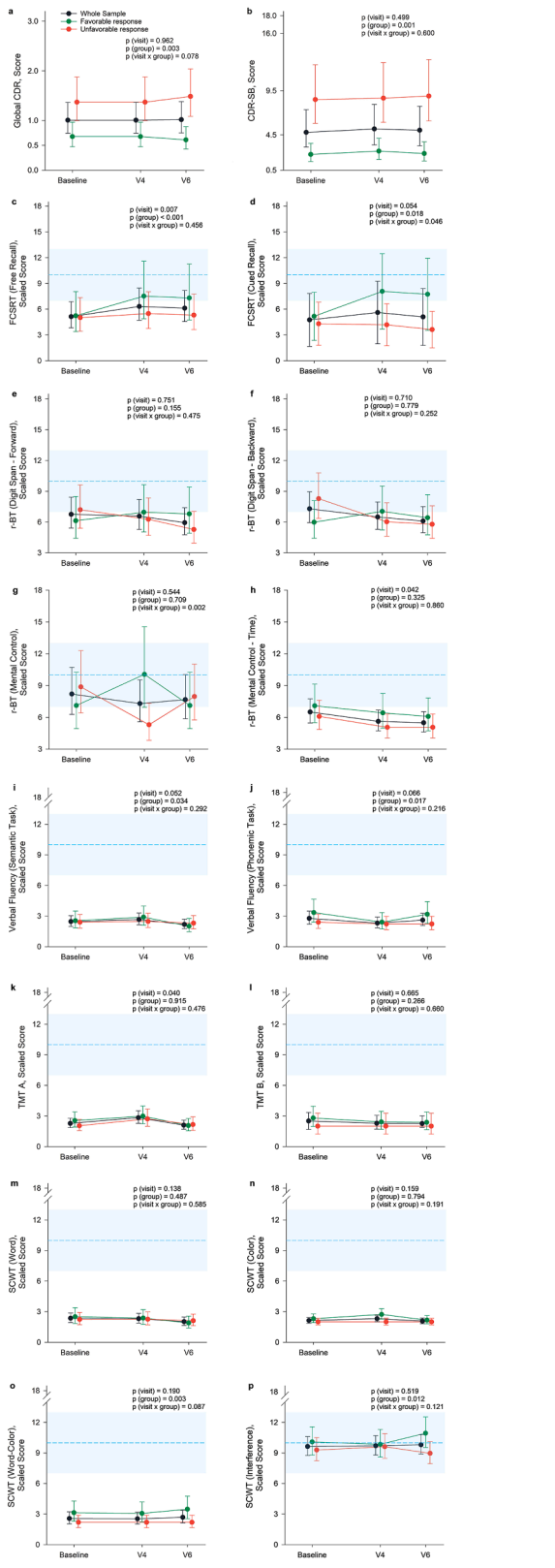


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**Fig. 3.** Evolution of adjusted (least square) mean scores (95 % CI) of the components of the composite primary outcome throughout the trial. CDR, Clinical Dementia Rating scale; CDR-SB, Clinical Dementia Rating scale – Sum of Boxes; FCSRT, Free and Cued Selective Reminding Test; r-BT, revised Barcelona Test; TMT, Trail Making Test; SCWT, Stroop Color-Word Interference Test; V4, visit 4; V6, visit 6. The blue band within each scaled score indicates the mean and ±1 standard deviation for the scaled scores (mean = 10, SD = 3). Of note, due to the non-proportional relationship between raw and scaled scores, the 95 % CI limits do not necessarily reflect the actual (sample) distribution of the scaled scores; however, this distortion does not affect the adjusted means (point estimates). P values come from adjusted analyses (for age, time from symptom onset, ataxia and disability scores) and reflect the effects of changes over time in both subgroups combined (visit factor), sustained differences between subgroups (group factor), and differences in time trajectories between subgroups (visit × group factor).

**Table 2**
Effect size measures (Cohen's *d* index) of the primary outcome components.

| Neuropsychological Assessment | Favorable Response | Unfavorable Response |
|---|---|---|
| CDR | −0.21[a] | 0.08 |
| CDR-SB | −0.06 | 0.08 |
| FCSRT (free recall) | 0.28[a] | 0.13 |
| FCSRT (cued recall) | 0.25[a] | −0.08 |
| r-BT (digit span – forward) | 0.13 | −0.82[c] |
| r-BT (digit span – backward) | 0.00 | −0.65[b] |
| r-BT (mental control) | −0.24[a] | 0.00 |
| r-BT (mental control – time) | −0.29[a] | −0.37[a] |
| Verbal fluency (semantic task) | −0.53[b] | −0.03 |
| Verbal fluency (phonemic task) | −0.08 | 0.09 |
| TMT A | 0.11 | −0.57[b] |
| TMT B | −0.40[a] | 0.91[c] |
| SCWT (word) | −0.33[a] | −0.10 |
| SCWT (color) | −0.10 | 0.17 |
| SCWT (word-color) | 0.26[a] | −0.19 |
| SCWT (interference) | 0.60[b] | −0.34[a] |

CDR, Clinical Dementia Rating scale; CDR-SB, Clinical Dementia Rating scale – Sum of Boxes; FCSRT, Free and Cued Selective Reminding Test; r-BT, revised Barcelona Test; TMT, Trail Making Test; SCWT, Stroop Color-Word Interference Test.

Relationship with recommended cutoff values for Cohen's *d* [50] have been marked with superscripts.

[a] Small absolute values $0.20 \leq |d| < 0.50$.

[b] Moderate absolute values: $0.50 \leq |d| < 0.80$.

[c] Large absolute values: $|d| \geq 0.80$.

domains. Remarkably, some patients even showed slight improvements in some neuropsychological and neurological outcomes. Beyond this encouraging general picture, some nuances deserve attention. First, although no patient met the criteria for progression (simultaneous deterioration of several outcomes) the trajectories of individual scores allowed us to distinguish two distinct subgroups in which improvements and decays predominated. Second, these two subgroups differed essentially in the duration of the disease, which somewhat contradicts the reported linear rate of progression of adult-onset NPC once the neurological disease appears [36,37]. Third, in line with this, despite the baseline status of neurological endpoints such as ataxia, dysphagia or disability scores being consistently worse among those with longer diseases, the neuropsychological outcomes differed more from each other within subgroups than between subgroups. The onset of efavirenz therapy at the beginning of follow-up could partially explain the deviation from linear progression (first and second issues), but not the differences of neuropsychological outcomes at baseline (third issue).

Although results from previous research efforts are somewhat contradictory regarding the cognitive correlates of neurological disease stages, with some reports stating that motor deficits precede cognitive deficits, and others the opposite [38–42], they can shed light on the results of the present study. Regardless of the time since symptom onset, verbal fluency, selective and divided attention, and cognitive inhibition were clearly impaired at baseline, whilst learning, memory and executive control were relatively preserved. In turn, memory tests (r-BT digit span) detected worsening courses particularly well, whilst divided attention (TMT B) and cognitive inhibition (SCWT interference) were particularly sensitive to changes in either direction (worsening or improvement). Within the context of the aforementioned research, these findings suggest that the patients from this study were still at an early, albeit not initial, stage of the disease, in which impairments of verbal fluency, coordination and divided attention predominate, and memory, constructional praxis and visuospatial organizational abilities are relatively preserved [39,40,42]. In this vein, we did not observe the particular sensitivity of VFTs for detecting early difficulties that others have reported [39], probably because the patients had already passed this point in their disease stages.

Efavirenz, which allegedly potentiates synaptic function by activating CYP46A1 to compensate for NPC1 deficiency, appeared to be beneficial in this setting of not very advanced disease. Because LTP is a major event for synaptic plasticity, involved in processes like memory, learning, and emotional responses, it seems reasonable to speculate that efavirenz could also help patients in more advanced stages. In fact, the statistical models showed benefits even when adjusted for the time since symptom onset, suggesting that efavirenz effects were relatively

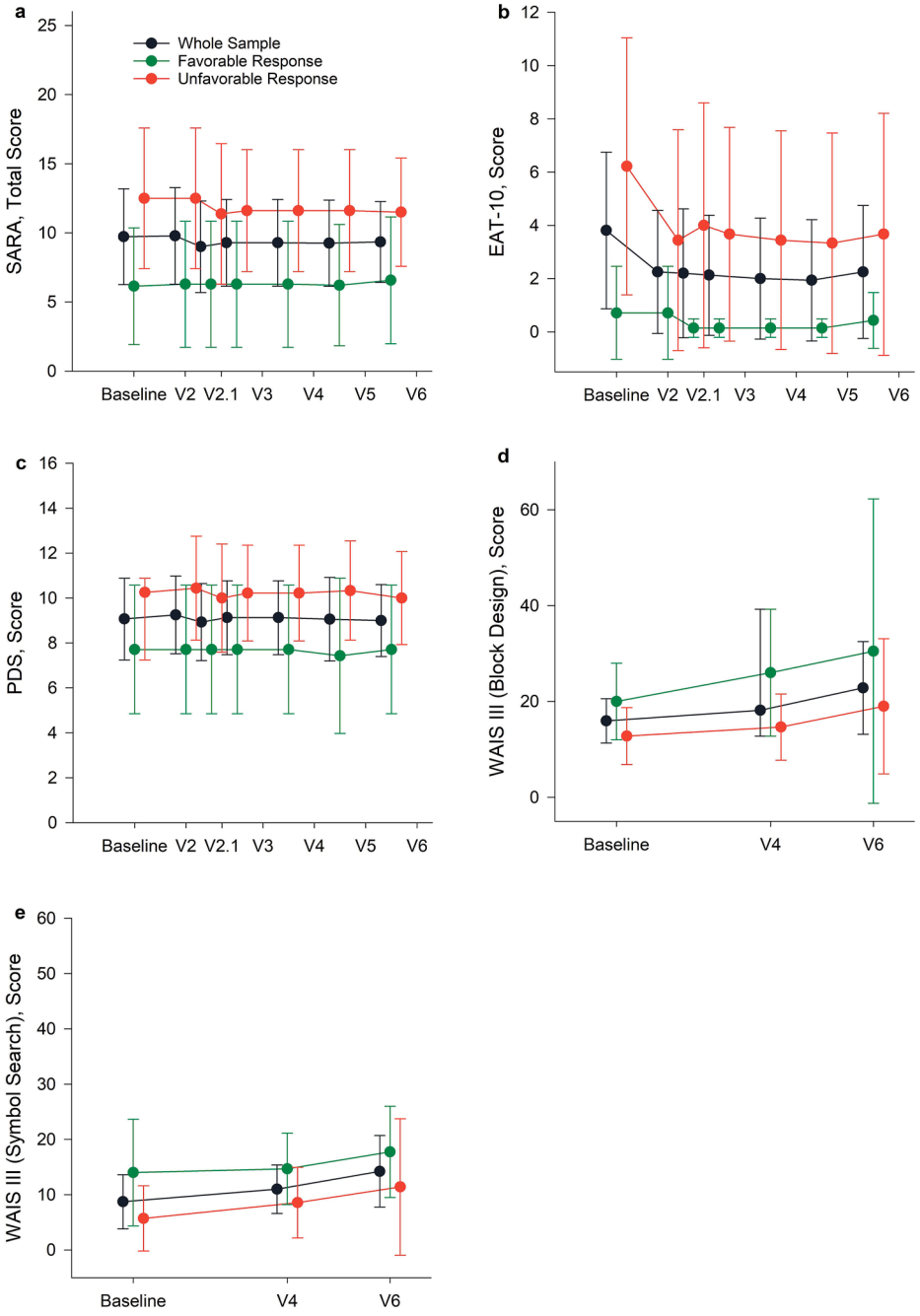


**Fig. 4.** Evolution of the means (95 % CI) of the neurological outcomes. SARA, Scale for the Assessment and Rating of Ataxia; EAT-10, Eating Assessment Tool – 10; PDS, Pineda Disability Scale; WAIS, Wechsler Adult Intelligence Scale; V4, visit 4; V6, visit 6.

independent of disease duration. However, the clear divergence between the FR and UR subgroups, mainly differentiated by disease duration (with a cut-off point around 12 years), recommends caution at this point, since patients with shorter diseases were those most benefited. Taking together previous and current results into account, it seems reasonable to recommend starting efavirenz early, preferably within the first decade after the onset of neurological involvement. Moreover, with the exception of dysphagia, which improved particularly in the UR subgroup (*i.e.*, patients with longer diseases, in whom dysphagia is more probable), ataxia and disability barely changed, and were consistently better in the FR subgroup than in the UR subgroup. Thus, these 'hard' neurological outcomes seemed to be more resistant to efavirenz. Effects on dysphagia of course are worth highlighting, since this condition can lead to malnutrition and aspiration issues, characteristic of NPC and with important repercussions on quality of life [37], but it remains to be determined whether it was primarily a cognitive or motor effect, and whether ataxia and disability would have improved if efavirenz had started earlier or been given for a longer period. This could also be extended to brain and cerebellar atrophy, whose course seemed particularly untoward. Of note, beneficial effects of miglustat therapy in clinical studies were also greater the sooner this treatment was started [43].

The issue of when disease-modifying treatments (*e.g.*, enhancement of cholesterol turnover by efavirenz or reduction of sphingolipid synthesis by miglustat) may provide optimum benefits is not trivial from a pharmacodynamic perspective. The ascending pattern of beta amyloid CSF levels, which was more pronounced in the FR subgroup, may be proof of this. Increased CSF beta amyloid is a unique feature of NPC that is not shared with other neurodegenerative diseases that cause amyloid deposits [44,45]. But despite the inverse relationship that has been described with NPC severity and which may explain why increases were particularly evident in the FR subgroup [44], our findings no do not match the reductions or the absence of changes reported previously with miglustat [44,45]. Although preclinical data indicates that efavirenz may potentiate synaptic efficiency [33], an inflection point might exist when this effect cannot compensate for the loss of synapses, which could explain the differences in therapeutic effects observed between the two subgroups. In this vein, the level of brain atrophy might serve to anticipate treatment responses, and its predictive validity should be evaluated in further studies. Preliminary clinical studies with other agents have not provided details on this or other potential biomarkers of therapeutic response [46–48].

No efavirenz-related or serious adverse events were reported. Thus, this study does not raise any safety concern related to its continued use at low doses for the treatment of NPC, even when combined with miglustat. Since these two drugs have complementary mechanisms of action, this result suggests that efavirenz may be a suitable agent for combinatorial therapy with miglustat, a strategy recently postulated as key for therapeutic success [49].

The main limitation of this study relates to the fact that it was not controlled. Since patients with progressive neurodegenerative disorders such as NPC might show apparent improvement or stabilization with symptomatic treatments, we could not discount such effects by comparing treated patients with a control group receiving standard care alone. Our hypothesis related to synaptic functions, and not to neurodegeneration that may ultimately ensue in NPC. Studying effects on neurodegeneration, or other important aspects such as when the maximum benefit may be obtained or whether efavirenz can effectively modify the course of the disease, would have required longer follow-up times. The study may even have been too short to evaluate long-term cognitive effects. Lastly, since blood 24-hydroxycholesterol levels showed considerable variability, we were unable to personalize efavirenz doses accordingly, as initially planned [35], which could have resulted in greater effects on neurological endpoints.

In conclusion, this study shows, in line with previous research, that despite the NPC prognosis being bad in general, it is possible to slow the rate of progression after the onset of CNS involvement. In particular, efavirenz may be a safe, easy-to-use, new targeted therapeutic option to address NPC patients' unmet medical needs in the future. Benefits appear to be greater the earlier the treatment is started. The present findings will have to be confirmed in future extension or phase III clinical trials with longer follow-ups.

## Author contributions

Conceptualization, Jordi Gascón-Bayarri, María Dolores Ledesma, Helena Bejr-Kasem, Jaume Campdelacreu, Anna Ferrer and Sebastián Videla; methodology, Jordi Gascón-Bayarri and Sebastián Videla; software, Jesús Villoria; validation, Jordi Gascón-Bayarri and Sebastián Videla; formal analysis, Jesús Villoria; investigation, Jordi Gascón-Bayarri, Inmaculada Rico, Cristina Sánchez-Castañeda, Laura Rodríguez-Bel, Mónica Cos, Eugenia de Lama, Adolfo López de Munain, Idoia Rouco, Celia Pérez-Sousa, María Cerdán, Nuria Muelas, María Dolores Sevillano and Pablo Mir; resources, Jordi Gascón-Bayarri and Sebastián Videla; data curation, Jordi Gascón-Bayarri, Thiago Carnaval and Jesús Villoria; writing—original draft preparation, Thiago Carnaval and Jesús Villoria; writing—review and editing, Jordi Gascón Bayarri and Sebastián Videla; visualization, Thiago Carnaval and Jesús Villoria; supervision, Jordi Gascón Bayarri and Sebastián Videla; project administration, Jordi Gascón-Bayarri; funding acquisition, Jordi Gascón-Bayarri and Sebastián Videla. All authors have read and agreed to the published version of the manuscript.

## Data access and availability statements

Jordi Gascón-Bayarri, will oversee the dataset. Granting access to this information will be evaluated on a case-by-case basis, upon reasonable request by the interested party.

## Additional contributions

- The relatives association, Niemann-PicK Foundation España.
- Dr. Fina Casas, Lipidomic Service of the Institut for Advenced Chemistry of Catalonia (IQAC-CSIC).

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## Declaration of Competing Interest

None declared.

## Appendix A. Supplementary data

Supplementary data to this article can be found online at https://doi.org/10.1016/j.neurot.2025.e00706.

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