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Long-term efficacy and safety of arimoclomol in Niemann-Pick disease type C: Final results of the phase 2/3 NPC-002 48-month open-label extension trial

Eugen Mengel [a,*], Rosalia M. Da Riol [b], Mireia Del Toro [c], Federica Deodato [d], Matthias Gautschi [e], Stephanie Grunewald [f], Sabine Weller Grønborg [g], Paul Harmatz [h], Julia B. Hennermann [i], Bénédicte Héron [j], Esther M. Maier [k], Saikat Santra [l], Reena Sharma [m], Anna Tylki-Szymanska [n], Malene Cording [o], Louise Himmelstrup [o], Sven Guenther [p], Christine í Dali [o]

[a] SphinCS, Institute of Clinical Science for LSD, Hochheim, Germany
[b] Regional Coordination Center for Rare Diseases, Academic Hospital 'Santa Maria della Misericordia', Udine, Italy
[c] Pediatric Neurology Department, Vall d'Hebron University Hospital, Barcelona, Spain
[d] Division of Metabolic Diseases and Hepatology, Ospedale Pediatrico Bambino Gesù, IRCCS, Rome, Italy
[e] Department of Paediatrics, Division of Endocrinology, Diabetology and Metabolism, and Institute of Clinical Chemistry, Inselspital, University Hospital Bern, Bern, Switzerland
[f] Department of Metabolic Medicine, Great Ormond Street Hospital for Children NHS Foundation Trust, NIHR Biomedical Research Centre, London, UK
[g] Center for Inherited Metabolic Diseases, Department of Pediatrics and Adolescent Medicine and Department of Clinical Genetics, Copenhagen University Hospital Rigshospitalet, Copenhagen, Denmark
[h] Gastroenterology and Nutrition, University of California, San Francisco Benioff Children's Hospital Oakland, Oakland, CA, USA
[i] University Medical Center Mainz, Center for Pediatric and Adolescent Medicine, Villa Metabolica, Mainz, Germany
[j] Sorbonne University, Department of Pediatric Neurology –Development Pathology, Reference Center for Lysosomal Diseases, University Hospital Armand Trousseau, AP-HP.SU, FHU I2D2, Paris, France
[k] Department of Inborn Errors of Metabolism, University of Munich Children's Hospital, Munich, Germany
[l] Department of Inherited Metabolic Disorders, Birmingham Children's Hospital, Birmingham, UK
[m] Salford Royal NHS Foundation Trust, Salford, UK
[n] Department of Paediatrics, Nutrition and Metabolic Diseases, The Children's Memorial Institute, Warsaw, Poland
[o] Zevra Therapeutics, Copenhagen, Denmark
[p] Zevra Therapeutics, Celebration, FL, USA

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ABSTRACT

Background: This paper presents efficacy and safety outcomes from the 48-month open-label extension (OLE) of the phase 2/3 NPC-002 trial (NCT02612129) which evaluated arimoclomol treatment in patients with Niemann-Pick disease type C (NPC). Arimoclomol was recently approved by the US Food and Drug Administration for treatment of NPC in combination with miglustat.

Methods: Patients with NPC who completed the double-blind (DB) phase of the randomized controlled NPC-002 trial were eligible to continue in the OLE, during which all patients received arimoclomol in addition to routine clinical care. Primary efficacy outcomes were the 5-domain NPC Clinical Severity Scale (5DNPCCSS), and the rescored 4-domain NPCCSS (R4DNPCCSS), which was introduced *post-hoc*. Additional outcomes included NPC-specific measures (full scale NPCCSS, and NPC clinical database [NPC-cdb] score), and safety evaluations.

Results: Of the 50 patients who started the DB phase, 41 entered the OLE phase, with 29 completing 48 months. During the OLE, mean (SD) 5DNPCCS and R4DNPCCSS scores increased by 3.2 (4.8) and 2.7 (4.2) over 48

Abbreviations: 5D-NPCCSS, 5-domain Niemann-Pick disease type C Clinical Severity Scale; AE, adverse event; CLEAR, Coordinated Lysosomal Expression And Regulation; DB, double-blind; EAS, Extension Analysis Set; NPC, Niemann-Pick disease type C; NPC-cdb, Niemann-Pick disease type C clinical database; NPCCSS, Niemann-Pick disease type C Clinical Severity Scale; OLE, open-label extension; R4DNPCCSS, rescored 4-domain Niemann-Pick disease type C Clinical Severity Scale; SAE, serious adverse event; SD, standard deviation; SE, standard error.

* Corresponding author at: SphinCS, Institute of Clinical Science for LSD, 65239 Hochheim, Germany.
E-mail address: Eugen.Mengel@sphincs.de (E. Mengel).

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months, respectively. Among patients switching from placebo to arimoclomol after the DB phase, mean annual change in 5DNPCCSS decreased from 2.0 (on placebo) to 0.1 in the first year of receiving arimoclomol and mean annual change in R4DNPCCSS decreased from 1.9 to 0.2, indicating slowing of disease progression. Annual scores for both endpoints remained numerically smaller throughout the OLE than during the DB phase. The score pattern in the subset of patients who received miglustat as part of their standard care regime in addition to arimoclomol ($N = 33$) was similar to that seen in the total population. 17-domain NPCCSS (excluding hearing domains) and NPC-cdb results further supported sustained efficacy of arimoclomol. Arimoclomol was well-tolerated over 48 months, with no new safety concerns identified.

Conclusion: The OLE of the NPC-002 trial provides evidence for a sustained reduction in disease progression for at least 5 years in a heterogeneous population of NPC patients receiving arimoclomol in addition to routine clinical care, with no new safety concerns. These results align with the statistically significant and clinically meaningful reduction in disease progression observed over 12-months in the DB phase, further highlighting the potential of arimoclomol as an effective and well tolerated disease modifying treatment for NPC.

1. Introduction

Niemann-Pick disease type C (NPC) is an ultra-rare autosomal recessive neurovisceral lysosomal disorder caused by bi-allelic pathogenic variants in the *NPC1* (95 %) and *NPC2* (5 %) genes, encoding for proteins important for *endo*-lysosomal and lysosomal transport and metabolism of lipids, including cholesterol [1–3]. Loss of function in NPC1 or NPC2 proteins impedes cellular lipid trafficking, which in turn causes accumulation of cholesterol and other lipids in tissues, mainly the liver, spleen, and central nervous system. Upregulation of CLEAR (Coordinated Lysosomal Expression And Regulation) network genes, including *NPC1* and *NPC2*, in affected cells could help improve lysosomal function to reduce the toxic accumulation of lipid species [4]. Patients with NPC typically present with progressive symptoms including cerebellar ataxia, dysarthria, dysphagia, loss of motor function, cognitive impairment and vertical supranuclear gaze palsy, but the primary manifestations and prognosis are heterogenous, ranging from a rapidly progressive neonatal to a chronic neurodegenerative adult-onset disease course. Disease progression is generally not linear and differs considerably between individual patients [2].

Arimoclomol (MIPLYFFA™, Zevra Therapeutics) is an orally administered small molecule that crosses the blood brain barrier [5,6]. It activates the transcription factors TFEB and TFE3, initiating a downstream cascade that upregulates genes within the CLEAR network, including *NPC1*. This upregulation contributes to reduced lysosomal cholesterol accumulation [5]. In September 2024, arimoclomol became the first FDA-approved treatment for patients with NPC aged ≥2 years and older. Arimoclomol was approved for use in combination with miglustat, a glucosylceramide synthase inhibitor that was previously approved for the treatment of NPC in Europe and a number of other countries outside of the US. Clinical trials have shown that miglustat provides a modest reduction in the progression of NPC disease over the long term, with a positive impact on survival [7,8].

The efficacy and safety of arimoclomol in patients with NPC were established in the phase 2/3 CT-ORZY-NPC-002 trial (further referred to as the NPC-002 trial; ClinicalTrials.gov identifier: NCT02612129). In the 12-month double-blind (DB) phase of this trial, arimoclomol slowed disease progression through 12 months of treatment, as measured using the 5-domain NPC Clinical Severity Scale (5DNPCCSS) [9,10]. A *post-hoc* primary analysis of the NPC-002 trial data, using a rescored 4-domain NPCCSS (R4DNPCSS), confirmed these findings [11]. The 5DNPCCSS and the R4DNPCCSS are currently the only validated instruments for evaluating a treatment's clinical benefit in NPC [10,11]. When arimoclomol was used in combination with miglustat, the estimated placebo-adjusted mean change in the R4DNPCCSS score from baseline through month 12 was −2.2, indicating a statistically significant and clinically meaningful reduction in disease progression [11].

The current report describes the long-term results of the open-label extension (OLE) of the NPC-002 trial, which evaluated the safety and efficacy of arimoclomol in patients with NPC for up to 48 months following the end of the 12-month DB phase.

2. Methods

2.1. Study design and objectives

The international multicenter NPC-002 trial included a 12-month, randomized, DB, placebo-controlled phase and a subsequent single-arm, 48-month, OLE phase. Most patients ($N = 26$) entering the NPC-002 DB phase were rolled over from the prospective, observational NPC-001 study (NCT02435030), during which they received routine clinical care, including miglustat [12]. All patients who completed the NPC-002 DB phase were invited to continue in the OLE. In this final analysis, data from the OLE phase collected for up to month 48 (60 months from DB baseline) are included (Fig. 1).

The purpose of the OLE phase was to assess the long-term effects of arimoclomol administered in addition to the patients' prescribed routine clinical care, which could include miglustat.

The study complied with the International Council for Harmonisation of Technical Requirements for Pharmaceuticals for Human Use Guideline for Good Clinical Practice (June 1996), the ethical principles outlined in the Declaration of Helsinki, and all applicable local regulatory and legal standards. Approval for the study protocol was granted by the appropriate Institutional Review Board or Independent Ethics Committee. All participants, or their legal guardians provided written informed consent prior to participation.

2.2. Participants

Full eligibility criteria for the DB part of the study have been published previously [9]. Briefly, eligible patients were male or female, aged 2–18 years with genetically confirmed pathogenic variants in both alleles of *NPC1* or *NPC2*, or a pathogenic variant in one allele of *NPC1* or *NPC2* plus either positive filipin staining or elevated cholestane-triol level (>2 × upper limit of normal), with at least one neurological symptom, able to walk independently or with assistance and, if treated with miglustat, on a stable dose for at least 6 months. Exclusion criteria included severe liver or renal insufficiency, being neurologically asymptomatic, and having severe uncontrolled epileptic seizures. After the DB phase, patients were enrolled in the OLE phase if the investigator judged that the patient would have clinical benefits from continued trial participation.

2.3. Study treatment and procedures

Patients received arimoclomol orally or via gastric feeding tube in addition to their routine clinical care. Patient body weight was measured at each visit and used to calculate arimoclomol dose as described previously [9]. Therapy was discontinued in case of withdrawal of informed consent, safety concerns, investigator decision, participation in another interventional study, liver transplant, pregnancy, death, loss to follow-up, or if they met predefined stopping criteria. In addition to scheduled visits, telephone calls were performed

to assess for any safety and dosing issues.

2.4. Primary endpoint

The prespecified primary efficacy endpoint of the DB phase of NPC-002 was change in disease severity on the 5DNPCCSS, comprising the five domains of the disease-specific, clinician-reported 17-domain NPCCSS (Ambulation, Swallow, Cognition, Speech, and Fine Motor Skills) that were previously determined to be most clinically relevant to patients, caregivers, and clinicians [10]. Due to the overall slow progression rate, often marked by bouts of rapid increases in severity and sometimes extended periods of no apparent change, patients are typically assessed minimally over a 12-month period to determine the annual rate of progression [12–14].

To more accurately assess changes in disease state in a heterogeneous group of patients and to align with regulatory guidance, the 5DNPCCSS was later supplemented with a *post-hoc* primary endpoint, the rescored 4-domain NPCCSS (R4DNPCCSS) that includes the domains Ambulation, Speech, and Fine motor skills as well as a rescored Swallow domain [11]. The cognition domain was omitted to address regulatory concerns that a single item would be unable to fully evaluate a broad concept of cognition in a 12-month clinical trial in children with a wide age range. Changes in both the 5DNPCCSS score and the R4DNPCCSS score during the OLE are discussed for the total population and for the prespecified subgroups of patients receiving miglustat or no miglustat as part of routine clinical care.

2.5. Primary endpoint results in an independent crossover cohort

Because most patients in the NPC-002 trial were rolled over from the observational NPC-001 study (routine care/observation only ["no treatment"]) [12], the annual rate of change in disease progression as measured with the 5DNPCCSS and the R4DNPCCSS could be compared between treatment and no treatment for patients randomized to arimoclomol during the NPC-002 DB after completing NPC-001. Data from patients completing one year in the arimoclomol group during the NPC-002 DB phase after one year of routine care in NPC-001 can be used as a relevant comparison for the findings in patients who completed one year of the NPC-002 OLE after one year of placebo during the DB phase.

2.6. Other efficacy outcomes

Other NPC-specific endpoints, including the 17-domain NPCCSS (excluding Auditory brainstem response and Hearing domains) and the NPC clinical database (NPC-cdb) score, were assessed as previously described [9,15].

2.7. Safety analysis

Descriptive safety data collected across the 48-month OLE phase included adverse events (AEs), serious adverse events (SAEs), treatment-related adverse events, trial discontinuations, and deaths. All events were classified using the Medical Dictionary for Regulatory Activities version 19.0.

2.8. Statistical methods

Efficacy during the OLE phase was calculated as change from baseline in 5DNPCCSS score and the R4DNPCCSS score at 12, 24, 36, and 48 months of treatment in the Extension Analysis Set (EAS). The EAS comprised all patients who completed the 12-month DB phase of the trial, were eligible for and agreed to participate in the OLE, and subsequently received at least one dose of open-label arimoclomol. The safety analysis set was identical to the EAS.

Standard descriptive statistics were used for continuous variables (mean, standard error [SE], standard deviation [SD], median, minimum, and maximum). Statistical analyses were performed using SAS version 9.3 or higher.

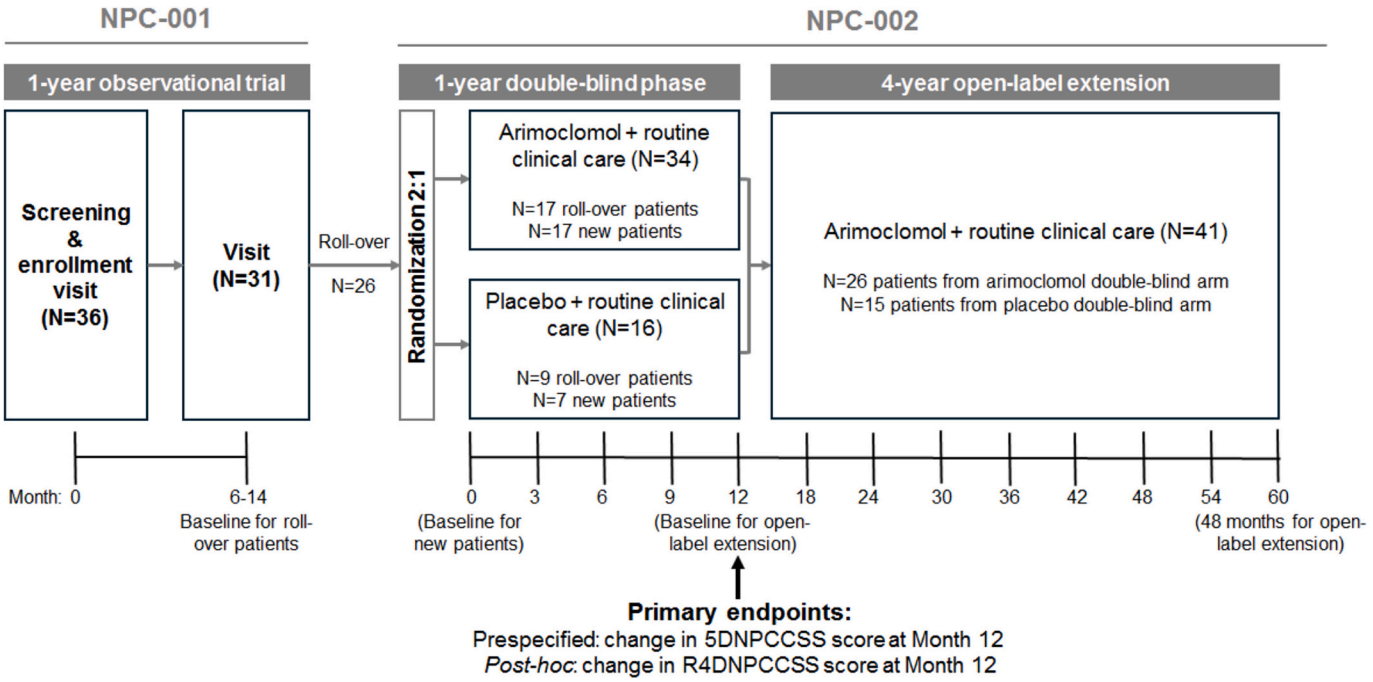

Fig. 1. Study design of NPC-001 [12] and NPC-002.
5DNPCCSS: 5-domain Niemann-Pick disease type C Clinical Severity Scale; N: number of patients; R4DNPCCSS: rescored 4-domain Niemann-Pick disease type C Clinical Severity Scale.

3. Results

3.1. Study population

The 48-month OLE phase began on June 16, 2017 (first person, first visit OLE phase) and was completed on June 22, 2022. Fifteen sites across nine countries (Denmark, Germany, Italy, France, Poland, Spain, Switzerland, United Kingdom, United States) took part in the OLE.

Of the 50 patients who started the DB placebo-controlled phase (arimoclomol $N = 34$; placebo $N = 16$), 42 completed the DB phase and 41 continued in the OLE phase (Fig. 2). Overall, 29/41 patients (70.7 %) completed the month 48 visit of the OLE phase. Reasons for early discontinuation included withdrawal by parent/guardian, death, physician decision, safety issues, and withdrawal of consent. More details on patients who were withdrawn early are summarized in Supplementary material 2 Table S1. There was no pattern with regard to age, gender, or duration of treatment, 5DNPCCSS score at withdrawal, or progression in 5DNPCCSS score prior to withdrawal.

Table 1 shows baseline demographics and disease characteristics for patients who entered the OLE. The mean (SD) age at the start of the OLE phase was 12.2 (4.8) years. A total of 33 patients (80.5 %) were receiving miglustat as part of their routine clinical care, equally distributed over the initially randomized treatment groups. Both groups were balanced for NPCCSS scores and mean age at first neurological symptom. Time since NPC diagnosis and mean age at baseline were higher in the arimoclomol-arimoclomol group. All patients had pathogenic variants in both *NPC1* alleles. A genotype analysis of pathogenic *NPC1* variants in patients enrolled in the DB phase of the NPC-002 study has been reported previously [9].

3.2. Primary outcome analyses

In patients who completed 48 months in the OLE ($N = 29$), mean (SD) and median changes in 5DNPCCSS score from OLE baseline to 48 months were 3.2 (4.8) and 2.0, respectively, indicating slight disease progression (Supplementary material 2 Table S2). Mean (SD) and median changes in the R4DNPCCSS score during the OLE were 2.7 (4.2) and 1.0, respectively (Supplementary material 2 Table S3). Fig. 3 shows longitudinal changes in both scores up to 48 months in the OLE phase.

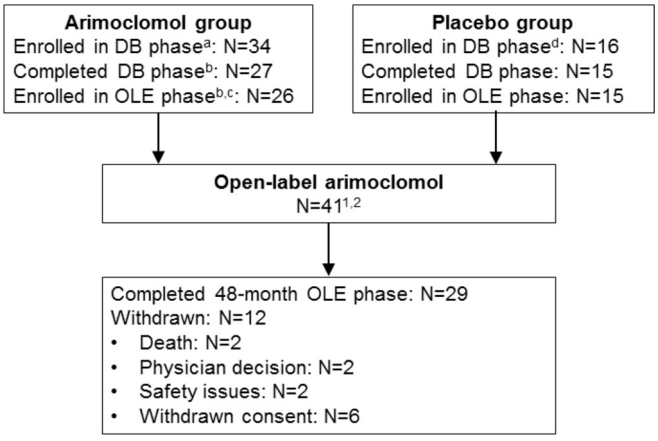

Fig. 2. Study disposition.
DB: double-blind; EAS: extension analysis set; N: number of patients; OLE: open-label extension.
[a]7 patients were withdrawn during the DB phase: 3 due to safety reasons, 2 early escape, 1 withdrew consent, 1 died.
[b]1 patient who completed the DB phase withdrew consent before being dosed in the OLE phase.
[c]1 patient who used the early escape clause in the DB phase continued into the OLE phase. The patient was not part of the EAS.
[d]1 patient was withdrawn during the DB phase due to meeting stopping criteria.

Table 1
Demographics and disease characteristics of participants at OLE baseline (EAS).

	Arimoclomol – arimoclomol (N = 26)	Placebo – arimoclomol (N = 15)	Total (N = 41)
Age (years), mean (SD)	12.6 (5.1)	11.5 (4.3)	12.2 (4.8)
Age group, n (%)			
< 4 years	2 (7.7 %)	0 (0.0 %)	2 (4.9 %)
4 - < 8 years	3 (11.5 %)	2 (13.3 %)	5 (12.2 %)
8 - < 12 years	6 (23.1 %)	6 (40.0 %)	12 (29.3 %)
≥ 12 years	14 (53.8 %)	7 (46.7 %)	21 (51.2 %)
Gender, n (%)			
Male	13 (50.0 %)	7 (46.7 %)	20 (48.8 %)
Female	13 (50.0 %)	8 (53.3 %)	21 (51.2 %)
Race, n (%)			
White	24 (92.3 %)	12 (80.0 %)	36 (87.8 %)
Asian	1 (3.8 %)	1 (6.7 %)	2 (4.9 %)
Native Hawaiian or other Pacific Islander	0 (0.0 %)	1 (6.7 %)	1 (2.4 %)
Other	1 (3.8 %)	1 (6.7 %)	2 (4.9 %)
Weight (kg), mean (SD)	39.7 (14.5)	41.0 (17.6)	40.8 (15.1)
Time since first NPC symptom (years), mean (SD)	8.0 (4.4)	8.5 (3.7)	8.2 (4.1)
Time since NPC diagnosis (years), mean (SD)[a]	6.4 (4.5)	5.3 (4.2)	6.0 (4.3)
Age at onset of first neurological symptom (years), mean (SD)	4.7 (3.3)	5.4 (4.0)	5.0 (3.5)
Currently treated with miglustat, n (%)	21 (80.8 %)	12 (80.0 %)	33 (80.5 %)
History of seizures or epilepsy, n (%)	11 (42.3 %)	2 (13.3 %)	13 (31.7 %)
NPCCSS full scale score, mean (SD)[b]	22.3 (12.8)	19.9 (13.3)	21.4 (12.8)
5DNPCCSS	12.7 (7.9)	11.5 (7.7)	12.3 (7.8)
R4DNPCCSS	9.5 (6.7)	8.7 (6.5)	9.2 (6.5)
NPCCSS individual domain scores, mean (SD)			
Ambulation score	2.8 (1.7)	2.5 (1.8)	2.7 (1.7)
Speech score	2.0 (1.6)	1.9 (1.5)	2.0 (1.6)
Swallow score	2.1 (2.1)	2.0 (2.0)	2.0 (2.0)
Swallow score, rescored	1.9 (2.0)	1.8 (1.9)	1.9 (1.9)
Fine Motor Skills score	2.8 (1.9)	2.5 (1.7)	2.7 (1.8)
Cognition score	3.0 (1.4)	2.6 (1.5)	2.9 (1.4)

R4DNPCCSS: 4-domain NPCCSS; 5DNPCCSS: 5-domain NPC Clinical Severity Scale; EAS: extension analysis set; N: number of patients in the EAS; n: number of patients with data; NPC: Niemann-Pick disease type C; OLE: open-label extension; SD: standard deviation.
Unless stated otherwise, data were available for all patients.
[a] N = 24, 14, and 38 for arimoclomol, placebo, and total, respectively.
[b] NPCCSS total score: all 17 domains minus Auditory brainstem response and Hearing (N = 25, 15, and 40 for arimoclomol, placebo, and total, respectively).

Patients who switched from placebo to open label arimoclomol after the DB phase showed slowing of disease progression, similar to what was seen in the arimoclomol group during the DB phase. The mean annual change in 5DNPCCSS decreased from 2.0 to 0.1 in the first year after starting treatment with arimoclomol; mean annual change in R4DNPCCSS decreased from 1.9 to 0.2 (Fig. 4). Scores of both endpoints continued to be numerically smaller for the rest of the trial as measured by the mean annual change.

In patients from the arimoclomol-arimoclomol group who completed the OLE phase, the mean annual increase in R4DNPCCSS from OLE baseline throughout the study was approximately 0.9 (3.7 total/4 years) (Supplementary material 2 Table S4).

Changes in the individual domains of the R4DNPCCSS during the OLE phase generally mirrored the trends for the R4DNPCCSS total score (Supplementary material 2 Table S5). The rate of progression in patients randomized to placebo in the DB phase decreased significantly after switching to arimoclomol with very minimal increases in severity across all four domains (mean annual change ≤0.11 in each domain). The

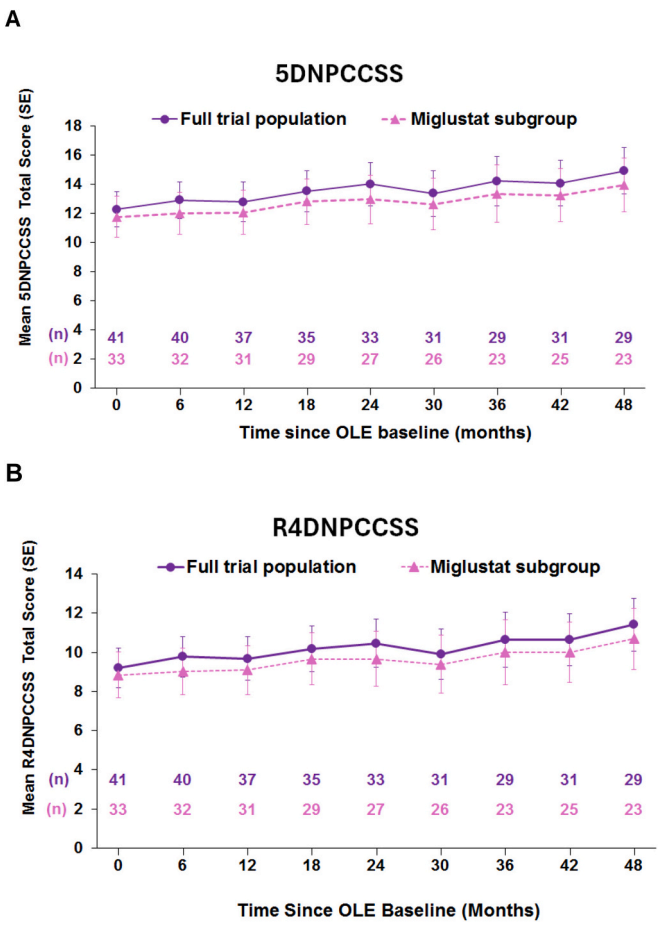

Fig. 3. Mean total score in the (A) 5DNPCCSS and (B) R4DNPCCSS up to 48 months in the OLE (EAS).
5DNPCCCS: 5-domain Niemann-Pick disease type C Clinical Severity Scale; EAS: extension analysis set; n: number of patients with data; OLE: open-label extension; R4DNPCCSS: rescored 4-domain Niemann-Pick disease type C Clinical Severity Scale.

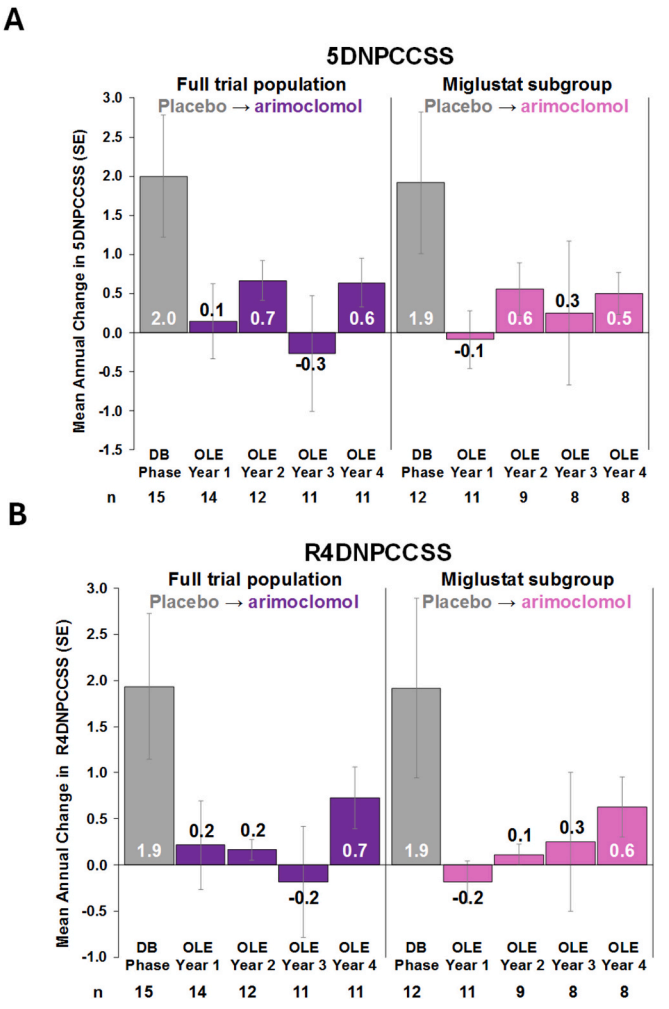

Fig. 4. Mean annual change in the (A) 5DNPCCSS and (B) R4DNPCCSS for patients who switched from placebo in the DB phase to arimoclomol in the OLE (EAS).
5DNPCCCS: 5-domain Niemann-Pick disease type C Clinical Severity Scale; DB: double-blind; EAS: extension analysis set; n: number of patients with data; OLE: open-label extension; R4DNPCCSS: rescored 4-domain Niemann-Pick disease type C Clinical Severity Scale.

annual progression in each domain also remained low in the arimoclomol-arimoclomol group after switching from blinded to open-label treatment (mean annual change ≤0.35 vs. ≤0.28 across domains in the DB and OLE phase, respectively).

3.3. Subgroup analysis by concomitant miglustat use

5DNPCCSS and R4DNPCCSS scores in the 33 patients of the OLE who received miglustat at study enrollment followed patterns similar to those in the total population (Fig. 3 and Fig. 4 and Supplementary material 2 Table S2 and Table S3). Mean (SD) and median 5DNPCCSS score changes over 48 months were 2.7 (3.8) and 2.0, respectively; mean (SD) and median R4DNPCCSS score changes were 2.3 (3.7) and 1.0, respectively. In patients of the miglustat subgroup who switched from placebo to open-label arimoclomol after the DB phase, the mean annual change in 5DNPCCSS decreased from 1.9 in the 12 months of placebo treatment to −0.1 in the 12 months following initiation of arimoclomol in the OLE. Similarly, the mean annual change in R4DNPCCSS decreased from 1.9 to −0.2 following initiation of arimoclomol in these patients. Annual scores of both endpoints continued to be numerically smaller for the rest of the trial. The mean annual disease progression in the OLE phase was 0.7 (2.7 total/4 years) for 5DNPCCSS and 0.6 (2.3 total/4 years) for R4DNPCCSS.

Only eight patients did not receive concomitant miglustat at enrollment; six of them completed the OLE. 5DNPCCSS and R4DNPCCSS score changes in these patients were overall higher than in the miglustat subgroup (Supplementary material 2 Table S2 and Table S3). Mean (SD) and median 5DNPCCSS score changes over 48 months were 5.2 (7.9) and 3.5, respectively; mean (SD) and median R4DNPCCSS score changes were 4.5 (6.0) and 3.5, respectively. Supplementary material 2 Table S6 shows individual progression rates. As previously reported, the non-miglustat subgroup represents a very heterogeneous group with marked imbalances in baseline characteristics, limiting the reliability and generalizability of these results [9].

3.4. Comparison of the primary endpoint in an independent crossover cohort

In patients who transitioned to arimoclomol during the NPC-002 DB phase after completing the NPC-001 natural history study (which involved routine care/observation only), the mean (SD) annual change in the 5DNPCCSS score decreased from 1.7 (3.8) under routine care to 1.1 (2.7) with arimoclomol (Fig. 5A). Similarly, the mean (SD) annual change in the R4DNPCCSS score dropped from 1.6 (3.0) during routine care in NPC-001 to 0.8 (2.5) with arimoclomol in NPC-002 (Fig. 5B).

5DNPCCSS: 5-domain Niemann-Pick disease type C Clinical Severity

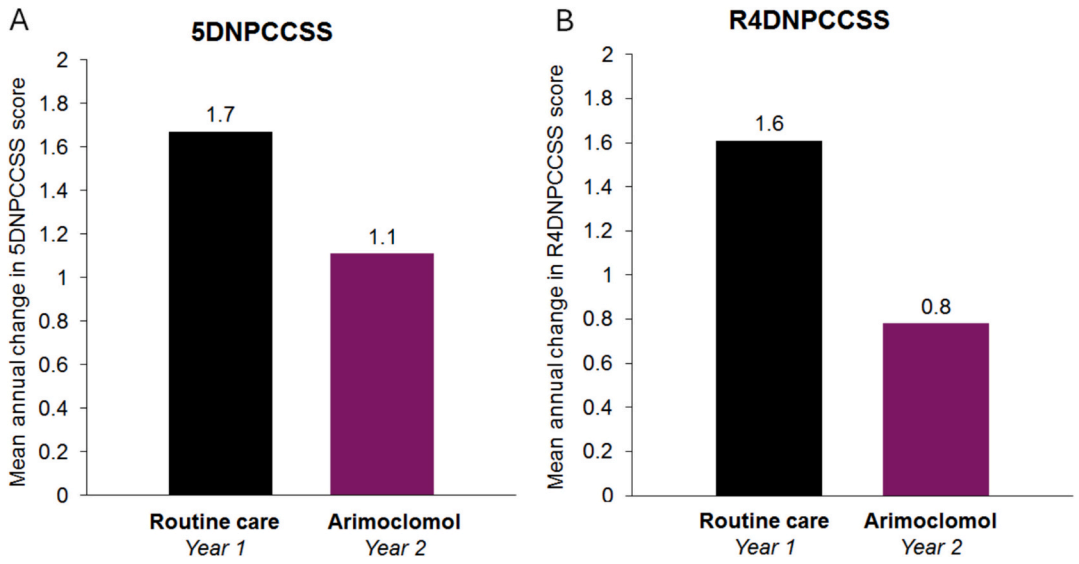

Fig. 5. Mean annual changes in (A) 5DNPCCSS score and (B) R4DNPCCSS score in patients who received routine care during the NPC-001 study [12] and switched to routine care plus arimoclomol in the DB phase of the NPC-002 trial [9] ($n = 18$) Higher values indicate faster disease progression.

Scale; DB: double-blind; n: number of patients with data; R4DNPCCSS: rescored 4-domain Niemann-Pick disease type C Clinical Severity Scale.

3.5. Other NPC-specific endpoints

Results during the OLE phase for the 17-domain NPCCSS (excluding Auditory brainstem response and Hearing domains) and NPC-cdb score are presented in the Supplementary material 2 Table S7 and Table S8 for the total group. Briefly, mean (SD) change in the 17-domain NPCCSS in patients with data at OLE baseline and 48 months ($N = 25$) was 4.4 (8.3), corresponding to a mean annual progression rate of 1.1. Mean (SD) change in NPC-cdb score from OLE baseline to 48 months ($N = 28$) was 8.6 (15.4), corresponding to a mean annual progression rate of 2.2.

3.6. Safety

During the OLE, 92.7 % of patients reported at least 1 AE. Most reported events were mild or moderate in severity, with 36.6 % of patients reporting SAEs. Out of the total number of reported AEs (460), 20 (4.3 %) in 12 patients (29.3 %), including one SAE, were assessed as related to treatment. The treatment-related SAE was a moderate event of proteinuria in a patient who developed a urinary tract infection approximately 2 weeks later.

Approximately one third (30.7 %) of all AEs, reported in 70.7 % of patients, were considered related to the underlying NPC disease (Table 2). Four AEs (severe lower respiratory tract infection, hypertonia and tremor, anxiety, and pneumonia aspiration) led to treatment discontinuation in four patients. The AE of hypertonia and tremor was assessed as possibly related to arimoclomol. The other events were considered not related to treatment. The events of severe lower respiratory tract infection and pneumonia aspiration had a fatal outcome. SAEs were mostly single patient events, with pneumonia being most frequently reported. SAEs that occurred in at least two patients are summarized in the Supplementary material 2 Table S9.

Treatment-related AEs were more frequent during the first and second year of arimoclomol treatment (18.4–20.0 % of patients) than during the third, fourth, and fifth year (5.9–7.1 % of patients). No obvious pattern related to the duration of arimoclomol treatment was observed for the occurrence of AEs, SAEs, AEs related to NPC, or AEs leading to treatment discontinuation or death.

Table 3 summarizes the AEs that were reported in >10 % of patients during the OLE phase. Among the treatment-related AEs, increases in aspartate aminotransferase and blood creatinine were each reported in two patients; increases in blood triglycerides were reported twice in one patient. All other treatment-related AEs were single occurrences.

Table 2
Summary of AEs during the 48-month OLE phase (EAS).

	Open-label arimoclomol ($N = 41$), n (%)
Any AEs	38 (92.7)
SAEs	15 (36.6)
Treatment-related AEs	12 (29.3)
Treatment-related SAEs	1 (2.4)
AEs related to NPC	29 (70.7)
AEs leading to study drug discontinuation	4 (9.8)
AEs leading to death	2 (4.9)

AE: adverse event; EAS: extension analysis set; N: number of patients in the EAS; n: number of patients experiencing the event at least once; NPC: Niemann-Pick disease type C; OLE: open-label extension; SAE: serious adverse event.

Table 3
AEs reported in >10 % of patients during OLE phase by PT (EAS).

Preferred Term	Open-label arimoclomol ($N = 41$)	
	n (%)	Total number of reported events
Diarrhea	10 (24.4)	28
Upper respiratory tract infection	10 (24.4)	18
Nasopharyngitis	8 (19.5)	18
Epilepsy	8 (19.5)	10
Corona virus infection	8 (19.5)	8
Seizure	7 (17.1)	13
Cough	7 (17.1)	9
Bronchitis	7 (17.1)	8
Weight decrease	6 (14.6)	10
Epistaxis	6 (14.6)	8
Constipation	6 (14.6)	7
Rhinitis	5 (12.2)	14
Influenza	5 (12.2)	7
Vomiting	5 (12.2)	7
Eczema	5 (12.2)	5

AE: adverse event; EAS: extension analysis set; N: number of patients in the EAS; n: number of patients experiencing the event at least once; OLE: open-label extension.

4. Discussion

Lysosomal disorders are notoriously heterogeneous in their initial clinical presentation and overall progression [16]. This combined with the rarity of these disorders makes it difficult to find a clinical endpoint that captures disease state and measures progression over the full spectrum of disease presentation and age range of the patients affected. This is not different for NPC. Presently, the 5DNPCCSS and the R4DNPCCSS are the only validated instruments to measure disease state and progression of NPC, with a well-defined minimal clinically important difference (MCID) [10,11]. The NPC-002 trial, including the OLE, demonstrated a persistent impact of arimoclomol on disease progression over 60 months in patients with NPC on the 5DNPCCSS and the R4DNPCCSS. With a safety and efficacy profile extending through five years in more than 270 patients worldwide, arimoclomol in combination with miglustat may have the potential to become a foundational treatment for NPC and a further advancement in the management of this disease.

Arimoclomol slowed down disease progression through 12 months of treatment in the randomized DB, placebo-controlled NPC-002 trial [9]. In combination with miglustat as part of routine care, arimoclomol treatment slowed down disease progression through 12 months. Treatment with arimoclomol plus miglustat was associated with a mean change in the 5DNPCCSS score of −0.1, compared to 2.0 in the placebo group, corresponding to a treatment effect of arimoclomol over placebo of −2.1 ($p = 0.006$) [9]. Similarly, arimoclomol in combination with miglustat resulted in a placebo-adjusted mean change from baseline to 12 months of −2.2 points in the R4DNPCSS score, a *post-hoc* primary endpoint introduced after the DB phase to provide a more linear measure of disease severity sensitive to change within a 12-month period [11].

The results of the 48-month OLE phase presented here extend the evidence of effectiveness shown in the DB phase by demonstrating a sustained reduction in disease progression with arimoclomol for up to 5 years when compared to the natural history of NPC disease progression in these patients. As expected, due to the progressive nature of NPC, 5DNPCCSS and R4DNPCCSS scores generally continued to increase during the OLE phase, with mean increases of 3.2 and 2.7, respectively, over 48 months. These increases correspond to annual progression rates of 0.8 and 0.7, respectively. Notably, the mean annual 5DNPCCSS progression rate of 0.8 in the OLE is identical to the previously reported progression rate for the arimoclomol group in the DB phase, but substantially lower than the progression rate of 2.2 in the placebo group [9]. It is also lower than the 1.5-point annual progression rate reported for patients who only received routine clinical care in the NPC-001 natural history study [12]. Mean age and disease severity at baseline were comparable for participants of the NPC-001 study and those receiving placebo in the NPC-002 DB phase. However, individual progression rates were highly variable between patients in both studies, reflecting the clinical heterogeneity of the disease [9,12].

Patients who received miglustat as part of their routine care in addition to arimoclomol exhibited similar progression patterns but generally lower progression rates compared to the overall study population, confirming findings from the DB phase [9]. Notably, anchor-based analyses for the 5DNPCCSS previously demonstrated that a 1-point worsening on the 5DNPCCSS can be considered clinically meaningful [10], suggesting a continued clinically meaningful impact of arimoclomol on disease progression during the OLE.

The decrease in mean annual progression rate observed in patients transitioning from placebo to arimoclomol after the DB phase, from 2.0 to 0.1 for 5DNPCCSS and from 1.9 to 0.2 for R4DNPCCSS, is similar to the treatment difference between placebo and arimoclomol observed in the DB phase [9,11]. In patients receiving arimoclomol in the DB phase and continuing during the OLE, the mean annual progression rate slightly increased during the first two years of the OLE. This increase was driven primarily by a few patients with more severe phenotypes being randomized by chance to the arimoclomol-arimoclomol group [9].

It should be noted that epilepsy and seizures, which commonly occur in patients with NPC, have been linked to a more rapid disease progression [15]. Therefore, when comparing disease progression in the OLE study to placebo data from the DB phase, it is important to consider the differing proportions of patients with a seizure history: 31.7 % in arimoclomol-treated patients in the OLE vs. 12.5 % in the placebo group [9]. Although this imbalance could have biased results in favor of the placebo group, arimoclomol-treated patients still exhibited slower disease progression, reinforcing its therapeutic benefit. Moreover, safety data from both the DB [9] and OLE phases showed no increased risk of seizures associated with arimoclomol.

The results for the 5DNPCCSS and R4DNPCCSS were supported by the positive impact of arimoclomol on secondary NPC-specific outcomes, which are widely used to evaluate disease progression in this population [9,12,14,17]. The mean annual change in NPC-cdb score of 2.15 in patients receiving arimoclomol in the OLE phase was markedly lower than the mean increase of 4.88 observed over 12 months in the placebo group of the NPC-002 trial and the increase of 5.0 over 6–14 months in the NPC-001 study [9,12]. Additionally, patients who received arimoclomol treatment in the OLE phase had a mean annual increase on the 17-domain NPCCSS (excluding hearing domains) of 1.1. This increase was considerably lower than the mean increase of 2.7 observed in the placebo group after one year in the NPC-002 DB phase, the increase of 2.7 over 6–14 months in the observational NPC-001 study, and the annual change of 2.9 documented in a comparable cohort of NPC patients [9,12,14]. Another similar natural history cohort, however, did not show progression after 1 year in the 17-domain NPCCSS score (https://clinicaltrials.gov/study/NCT02534844), underscoring that this outcome measure may be less suitable as an endpoint in clinical trials. Moreover, since the 5DNPCCSS was derived from the 17-domain NPCCSS, the 17-domain NPCCSS cannot be considered an independent outcome measure of the study.

Arimoclomol demonstrated good tolerability for up to 60 months, including the 48 months of the OLE phase, with no new safety concerns identified. Most patients in the OLE (92.7 %) reported at least one AE, the majority of which were assessed as mild or moderate and non-serious. Study drug-related events were infrequent, accounting for only 4.3 % of all events, including a single SAE. Two subjects died during the OLE phase due to causes unrelated to treatment (severe lower respiratory tract infection and pneumonia aspiration). These findings underscore the long-term tolerability and safety of arimoclomol in patients with NPC.

A key limitation of the OLE study is its open-label, uncontrolled design. To address the lack of a control group, disease progression in treated patients was compared with untreated and placebo data from the NPC-001 and NPC-002 trials. Additionally, due to the ultra-rare nature of NPC, with birth incidence estimates varying from 0.35 to 2.2 per 100,000 births across different countries, the sample size was relatively limited [18]. Due to the heterogenous nature of NPC, the NPC-002 trial included patients with varying rates of disease progression, and disease severity was not uniform across study groups. Collectively, these factors may have influenced the robustness of the results.

Continued research in real-world clinical settings are needed to confirm these clinical trial findings and provide evidence of the impact of arimoclomol on disease progression beyond 5 years.

5. Conclusions

NPC is a life-long neurovisceral lysosomal disorder with an estimated birth incidence of 1/120000 live births. The broad clinical spectrum ranges from a neonatal rapidly fatal disorder to an adult-onset chronic neurodegenerative disease. There is a need for treatments with clinical evidence establishing long-term clinical benefit with validated outcomes, including clinically meaningful slowing of disease progression, and long-term tolerability. The NPC-002 trial, including the OLE,

demonstrated a persistent impact of arimoclomol on disease progression over 60 months in patients with NPC on the 5DNPCCSS and the R4DNPCCSS, the only validated instruments for evaluating progression in NPC. No new safety issues were identified. The long-term open-label results presented herein, in extension to the statistically significant and clinically meaningful reduction in disease progression observed over 12 months in the DB phase, further establish arimoclomol as an effective and well-tolerated disease modifying treatment and a further advancement in NPC patient management.

Author contributions

Eugen Mengel and Christine í Dali designed the trial. All authors were involved in stages of data collection, analysis, and interpretation of the trial. Sven Guenther conducted statistical analyses. All authors were contributors in writing the manuscript, and all read and approved the final manuscript.

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Ethics approval and consent to participate

The trial (ClinicalTrials.gov identifier: NCT02612129) protocol and associated documentation were approved by the relevant independent ethics committees and/or institutional review boards, and written informed consent was obtained at enrollment from either the patient or their legal guardian.

CRediT authorship contribution statement

Eugen Mengel: Writing – review & editing, Methodology, Investigation, Data curation, Conceptualization. **Rosalia M. Da Riol:** Writing – review & editing, Investigation, Data curation. **Mireia Del Toro:** Writing – review & editing, Investigation, Data curation. **Federica Deodato:** Writing – review & editing, Investigation, Data curation. **Matthias Gautschi:** Writing – review & editing, Investigation, Data curation. **Stephanie Grunewald:** Writing – review & editing, Investigation, Data curation. **Sabine Weller Grønborg:** Writing – review & editing, Investigation, Data curation. **Paul Harmatz:** Writing – review & editing, Investigation, Data curation. **Julia B. Hennermann:** Writing – review & editing, Investigation, Data curation. **Bénédicte Héron:** Writing – review & editing, Investigation, Data curation. **Esther M. Maier:** Writing – review & editing, Investigation, Data curation. **Saikat Santra:** Writing – review & editing, Investigation, Data curation. **Reena Sharma:** Writing – review & editing, Investigation, Data curation. **Anna Tylki-Szymanska:** Writing – review & editing, Investigation, Data curation. **Malene Cording:** Writing – review & editing, Investigation, Data curation. **Louise Himmelstrup:** Writing – review & editing, Investigation, Data curation. **Sven Guenther:** Writing – review & editing, Investigation, Formal analysis, Data curation. **Christine í Dali:** Writing – review & editing, Methodology, Investigation, Data curation, Conceptualization.

Declaration of competing interest

Eugen Mengel has received investigator fees and/or consultant honoraria from Cyclo Therapeutics, Amicus, Idorsia, Intrabio, Denali, JCR, Prevail, Freeline Therapeutics, Alexion, Zevra, Sanofi Genzyme, and Takeda.

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Christine í Dali is an employee and shareholder of Zevra Therapeutics Inc.

Malene Cording Christensen and Louise Himmelstrup are employees of Zevra Therapeutics Inc. Sven Guenther was an employee of Zevra Therapeutics at the time of the study.

Data availability

The trial protocol and Statistical Analysis Plans will become publicly available. Study information will be posted on https://clinicaltrials.gov/ct2/show/NCT02612129. The data that support the findings of this trial are available from Zevra but restrictions apply to the availability of these data, which were used under license for the current trial, and so are not publicly available. Data are however available from the authors upon reasonable request and with permission of Zevra.

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Appendix A. Supplementary data

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