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CLINICAL RESEARCH ARTICLE

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An expanded access protocol of RT001 in amyotrophic lateral sclerosis—Initial experience with a lipid peroxidation inhibitor

Megan Yerton AB[1] | Allison Winter BS[1] | Anthony Kostov BA[1] | Cassandra Lieberman BA[1] | Dario Gelevski BS[1] | Harli Weber BS[1] | Michael Doyle BA[1] | Geli Kane BA[1] | Neil Parikh BA[1] | Katherine M. Burke DPT[1] | Margot Rohrer RN[1] | Taylor Stirrat RN[1] | Margaret Bruno RN[1] | Alison Hochman RN[1] | Sarah Luppino MSN, NP-BC[1] | Jennifer Scalia NP[1] | Debra Skoniecki MSN, NP-BC[1] | Derek D'Agostino BA[1] | Ervin Sinani BS[1] | Hong Yu MS[1] | Alexander V. Sherman MSc[1] | Suma Babu MBBS, MPH[1] | James D. Berry MD, MPH[1] | Mark G. Midei MD[2] | Peter G. Milner MD[2] | Merit E. Cudkowicz MD, MSc[1] | Sabrina Paganoni MD, PhD[1,3]

[1]Sean M. Healey and AMG Center for ALS & the Neurological Clinical Research Institute, Massachusetts General Hospital, Harvard Medical School, Boston, Massachusetts

[2]Retrotope, Los Altos, California

[3]Spaulding Rehabilitation Hospital, Harvard Medical School, Boston, Massachusetts

Correspondence
Sabrina Paganoni, Sean M. Healey and AMG Center for ALS, Massachusetts General Hospital, 165 Cambridge Street, Suite 600, Boston, MA 02114.
Email: spaganoni@mgh.harvard.edu.

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Sean M. Healey & AMG Center for ALS

Abstract

Introduction/Aims: Lipid peroxidation is thought to play a biologically important role in motor neuron death in amyotrophic lateral sclerosis (ALS). 11,11 Di-deuterated linoleic ethyl ester (RT001) prevents lipid peroxidation in cellular and mitochondrial membranes. Herein we report on the use of RT001 under expanded access (EA).

Methods: We provided RT001 to patients with ALS via EA at a single site. The starting dose was 2.88 g/day, which was increased to to 8.64 g/day as tolerated. Participants were not eligible for alternative clinical trials. Participants were followed for adverse events and pharmacokinetic (PK) parameters were measured approximately 3 months after RT001 initiation.

Results: Sixteen participants received RT001 (5.6 ± 1.6 g/day; dose range, 1.92 to 8.64 g/day) for a mean period of 10.8 ± 7.1 months. After 3 months of treatment, PK studies showed that RT001 was absorbed, metabolized, and incorporated into red blood cell membranes at concentrations expected to be therapeutic based on in vitro models. The most common adverse events were gastrointestinal, including diarrhea, which occurred in 25% of the participants, and were considered possibly related to RT001. One participant (6%) discontinued due to an adverse event. Ten serious adverse events occurred: these events were recognized complications of ALS and none were attributed to treatment with RT001.

Abbreviations: AA, arachidonic acid; ALS, amyotrophic lateral sclerosis; ALSFRS-R, ALS Functional Rating Scale---Revised; D2-AA, di-deuterated arachidonic acid; D2-LA, di-deuterated linoleic acid; EA, expanded access; EAP, expanded access protocol; FDA, US Food and Drug Administration; LA, linoleic acid; LPO, lipid peroxidation; PK, pharmacokinetic; PUFA,, polyunsaturated fatty acid; RBC, red blood cell; RT001, 11,11 di-deuterated linoleic ethyl ester; SVC, slow vital capacity

Discussion: RT001 was administered safely to a small group of people living with ALS in the context of an EA protocol. Currently, there is an ongoing randomized, double-blind, controlled study of RT001 in ALS.

KEYWORDS
amyotrophic lateral sclerosis, expanded access program, motor neuron disease, RT001

1 | INTRODUCTION

Whether as a primary cause of disease or a secondary consequence, oxidative stress is implicated in amyotrophic lateral sclerosis (ALS).[1] Oxidative stress and lipid peroxidation (LPO) have been documented in both ALS animal models and in clinical studies.[2,3] LPO is particularly pronounced in ALS, with several proteins important for motor neuron and axonal function and development being irreversibly modified by LPO products.[4] LPO leads to changes in membrane lipid composition and the generation of harmful reactive aldehydes that have a downstream effect on energy, structure, and signaling in motor neuron diseases,[5] and neuroinflammatory alterations in ALS further implicate LPO.[6]

RT001 is a deuterated homolog of linoleic acid (11,11 di-deuterated linoleic ethyl ester) that makes membrane polyunsaturated fatty acids (PUFAs) resistant to LPO. A strong protective effect against LPO is seen when deuterated PUFAs replace non-deuterated PUFAs in lipid bilayers.[7] Inhibition of LPO begins when concentrations of di-deuterated linoleic acid (D2-LA) reach 10% and these effects seem to plateau at 20%. Treatment with RT001 has shown early signs of efficacy in patients with Friedreich ataxia, a disorder of intracellular free-iron imbalance that initiates LPO, resulting in increased oxidative stress and mitochondrial dysfunction.[8] Because of the close association of oxidative damage with progression in ALS, RT001 has been proposed as a possible treatment for this disease and is now being tested in an ongoing randomized, double-blind, controlled study in ALS (NCT04762589 at ClinicalTrials.gov).

We provided RT001 to a small group of individuals with ALS who were not eligible for the trial via expanded access protocols (EAPs). EAPs or "compassionate-use" programs are available as regulatory mechanisms to grant access to investigational products outside clinical trials. These programs are intended for patients with serious or life-threatening conditions for which there are no satisfactory alternative treatment options. Given the rapidly progressive and fatal nature of ALS, there has been growing interest in developing EAPs for people living with ALS who are not eligible for clinical trials but wish to participate in clinical research. EAPs also provide a unique opportunity to collect preliminary safety and biomarker data in a broad patient population, thereby supplementing the clinical development program. Herein, we report the initial experience of this single-center EAP of RT001 in people with ALS.

2 | METHODS

Participants were enrolled at Massachusetts General Hospital through either a "single-patient" EAP or an "intermediate-size" EAP. Consistent with Food and Drug Administration (FDA) EAP guidelines, participants were not eligible for satisfactory alternative therapies or clinical trials. The protocols were designed to include a broad patient population; the only factors limiting inclusion were a life expectancy of less than 6 months and clinically significant laboratory abnormalities. The investigational site was responsible for protocol design, conduct, and regulatory filings. RT001 was provided by the manufacturer (Retrotope) to the site. Approvals were obtained according to the institutional review board and FDA, and all participants provided informed consent before participation.

Participants received oral RT001 in 960-mg gelcaps three times daily (total 2.88 g/day) with meals for 2 weeks. This was increased to two gelcaps three times daily (5.76 g/day) or three gelcaps three times daily (8.64 g/day), taken with meals as tolerated. If a participant demonstrated a D2-arachidonic acid red blood cell (RBC) membrane level of less than 2%, based on PK sample trough analysis while enrolled in the protocol, then the principal investigator was permitted to increase the RT001 total dose to 8.64 g/day. Dosing could also be reduced to a minimum of two gelcaps daily based on participant tolerance.

Adverse events (AEs) were reported during regular visits or during telephone follow-up by study staff. Site investigators determined whether AEs were related to the RT001. Pharmacokinetic (PK) sampling was performed at month 3 in participants who completed the study visit in person. PK sampling was not obtained if the month 3 visit was conducted by telemedicine. The analytes included plasma and RBC membrane levels of D2-LA and its centrally active metabolite D2-arachidonic acid (D2-AA).[9] The results for plasma and RBC membrane levels of D2-LA and D2-AA were reported as a percentage of the total LA and AA. Routine clinical safety laboratory analyses were collected at baseline, month 1, month 6, and every subsequent 6 months, including complete blood count with differential, electrolytes, alanine aminotransferase, and aspartate aminotransferase. Laboratory evaluations were collected either onsite or remotely, at local clinical laboratories. Results were reviewed by study staff upon receipt for safety monitoring.

The ALS Functional Rating Scale---Revised (ALSFRS-R) score and slow vital capacity (SVC) were obtained at baseline and approximately every 6 months after enrollment. The ALSFRS-R measures 12 items in four domains of function, each scored on a scale from 0 to 4, with higher scores indicating better function. Because the primary purpose of this EAP was to provide access to RT001 to a broad population not eligible for clinical trials, no comparative arm was included, and no statistical comparisons were made.

TABLE 1 Demographic and clinical characteristics of participants at baseline

Characteristic	RT001 EAP (N = 16)
Male sex, n (%)	11 (68.8%)
White race, n (%)[a]	15 (93.8%)
Age, years, mean ± SD	56.8 ± 10.3
Bulbar onset, n (%)	5 (31.3%)
Riluzole or edaravone use, n (%)	13 (81.3%)
Riluzole, n (%)	13 (81.3%)
Edaravone, n (%)	6 (37.5%)
Both, n (%)	4 (25.0%)
Slow vital capacity, % of predicted (n = 12), mean ± SD	72.7 ± 22.9
ALSFRS-R total score, mean ± SD	30.4 ± 12.8
Months since ALS symptom onset, mean ± SD	38.7 ± 26.0
Months since ALS diagnosis, mean ± SD	23.5 ± 18.5
Presence of tracheostomy, n (%)	1 (6.3%)

Abbreviations: ALS, amyotrophic lateral sclerosis; ALSFRS-R, ALS Functional Rating Scale---Revised; EAP, expanded access protocol; SD, standard deviation.
[a]Race reported by the trial participant.

3 | RESULTS

3.1 | Baseline characteristics

Sixteen participants with ALS received RT001 via two EAPs. The first protocol enrolled a single participant. This was followed by an intermediate-size EAP that included 15 participants. The baseline demographic and disease characteristics are summarized in Table 1. Because EAPs are designed to provide access to a broad population, most participants had a long disease duration, lack of upper motor neuron signs, or relatively advanced disease. Most participants were receiving either riluzole, edaravone, or both before trial entry.

3.2 | Screening, enrollment, and follow-up

Participants received RT001 for period of 10.8 ± 7.1 (mean ± standard deviation) months after enrollment. Participants received one gelcap three times daily with meals for 2 weeks. Of these participants, one reduced the dose to two gelcaps daily due to intolerance. One participant did not up-titrate the dose after discussion with the site investigator due to the presence of unrelated symptoms of chronic urinary tract infection and remained at the starting dose for the duration of the study. The remaining 14 participants increased to two gelcaps three times daily taken with meals. One of these participants reduced the dose to one gelcap three times daily after experiencing dizziness when the study drug was up-titrated. One participant had a dose escalation to three gelcaps three times daily.

Most AEs were attributed to ALS, such as falls, fatigue, and shortness of breath. Other common AEs were gastrointestinal, including four participants (25%) reporting diarrhea. These episodes were considered possibly related to RT001 and were expected based on the drug's safety profile characteristics. There were no abnormalities on clinical safety laboratory evaluations related to study drug. Ten serious AEs (SAEs) occurred in 8 of the participants. The most common SAE was respiratory failure. All these SAEs were attributed to ALS disease progression.

A diagrammatic representation of participant progress and the reasons for RT001 discontinuation are presented in Figure 1. One participant discontinued due to gastrointestinal discomfort. The remaining reasons for discontinuation included death, disease progression, enrollment in a different EAP, and perceived lack of efficacy. One participant has remained on RT001 (longest follow-up as of June 2022: 39 months). Individual ALSFRS-R and SVC plots are presented in Figures S1 and S2.

3.3 | Pharmacokinetics

A total of nine participants underwent PK sampling 2.7 ± 0.6 months after starting RT001. D2-LA as a percentage of total LA was 14.1 ± 7.9% in plasma samples and 13.0 ± 5.9% in RBC membranes. D2-AA as a percentage of total AA was 3.7 ± 2.4% in plasma samples and 3.0 ± 2.1% in RBC membranes.

4 | DISCUSSION

In this study, RT001 was administered safely to people living with ALS. RT001 was absorbed, elongated into D2-AA, and incorporated into RBC membranes in therapeutic concentrations. This EAP was conducted before an appropriate RT001 loading dose and period were firmly established. As a result, the doses of RT001 used in this study did not include loading doses, and maintenance doses were lower than the recommended doses in ongoing clinical trials in other neurodegenerative diseases such as Friedreich ataxia and progressive supranuclear palsy (NCT04102501 and NCT04937530 at ClinicalTrials.gov), and the phase 2 ALS trial currently underway. Consequently, the plasma and membrane levels achieved with RT001 in this early-stage safety experience are lower than those expected in ongoing trials. This expanded access experience helped to inform loading and more appropriate dosing in contemporary clinical trials. Current studies in adult patients recommend a 1-month loading period for RT001 of 8.64 g/day, followed by a maintenance dose of 5.76 g/day (usually divided into twice-daily portions). This regimen has been associated with D2-LA and D2-AA accounting for at least 20% of the total LA and AA, respectively, and this threshold has been shown to have a significant protective effect against LPO in cellular membranes.[7] Accumulating PK evidence of RT001 uptake, elongation into D2-AA, entry into the cerebrospinal fluid, and incorporation into cell membranes at these target therapeutic levels have been demonstrated at the higher doses currently recommended.[9]

Several factors limit interpretation of the present clinical results. The EAP was small, open-label, and, by design, was intended to

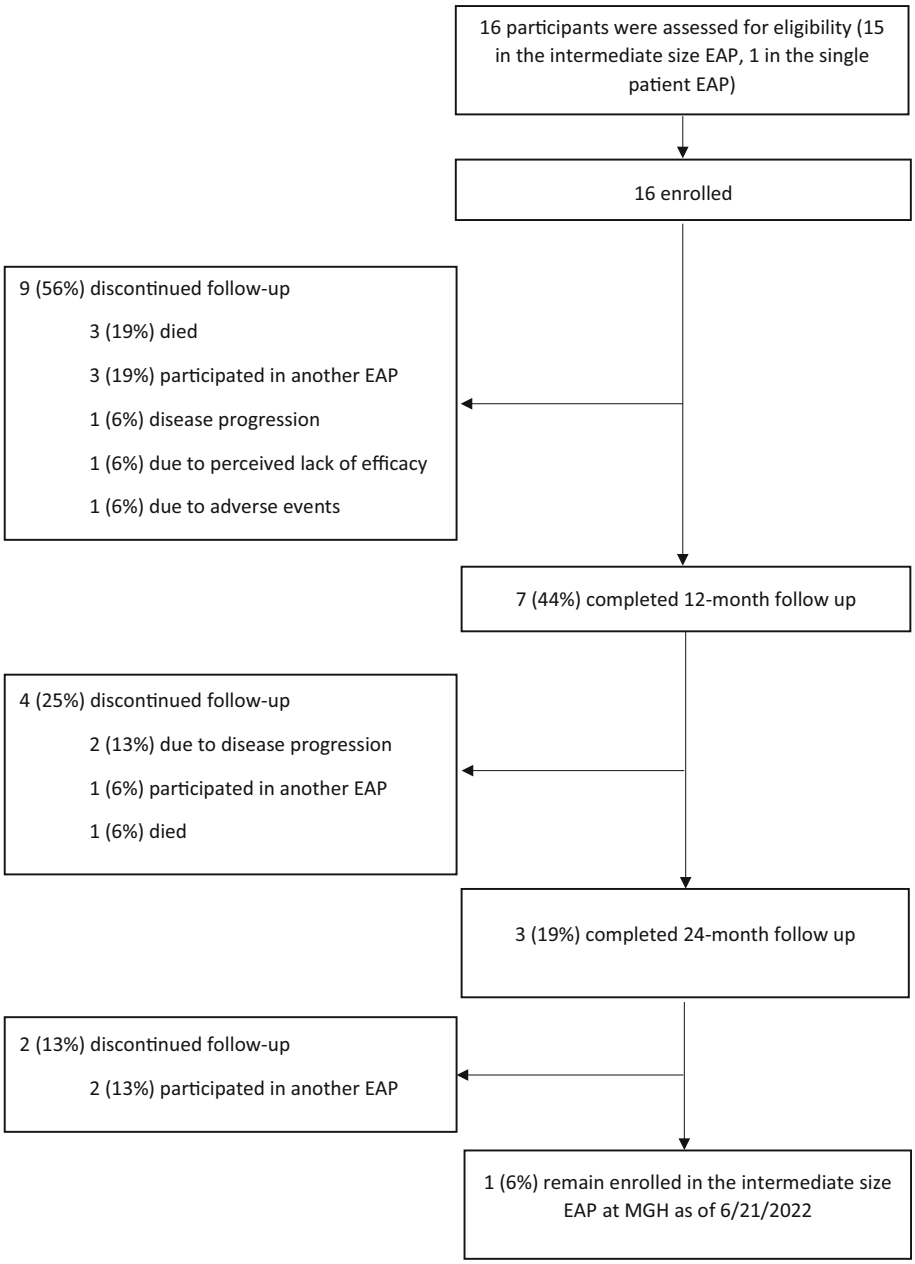

FIGURE 1 Flowchart of participant progress throughout the expanded access protocol (EAP).

provide access to a broad population. Several of the participants were in very advanced stages of disease at enrollment; several of them died or discontinued therapy due to disease progression. Of the 16 enrolled participants, 3 had ALSFRS-R scores of less than 20 at baseline, and 5 discontinued RT001 within the first 6 months due to death or advanced stage of disease. Although life expectancy longer than 6 months was one of the inclusion criteria, this is often hard to predict based on clinical characteristics.

Despite the widespread interest in EAPs among patients, EAPs are relatively new to ALS and most sites have limited experience offering this option. In our experience, substantial site resources are needed to support these programs and complete all necessary study coordination, safety monitoring, and regulatory activities. We estimate that the average site cost per month was $613.47 per participant. Costs included salaries for site staff (nurse, coordinator) to facilitate enrollment and safety monitoring, as well as costs associated with data collection and regulatory reporting. Investigators did not charge for their effort. The study drug was provided at no cost by the drug manufacturer, and program costs were covered by philanthropic donations. Our EAP team gained significant experience with study set-up and management, regulatory submissions, and reporting. Time from submission to approval was 44 days for FDA approval, and 60 days for institutional review board (IRB) approval. The first participant was enrolled 18 days after IRB approval. As sites gain more experience with the operational aspects of running EAPs and share their experiences, more sites may be able to leverage the collective knowledge and plan accordingly.

Our study has demonstrated that EAPs can be successfully implemented alongside clinical trials in ALS. In addition, EAPs can provide early safety and biomarker data. Experience gained the study has helped to guide design and dosing of an ongoing randomized, double-blind, placebo-controlled phase 2 ALS trial where the safety and efficacy of RT001 are being formally tested (NCT04762589 at ClinicalTrials.gov). This now fully enrolled study is scheduled to release data very soon.

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CONFLICT OF INTEREST

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DATA AVAILABILITY STATEMENT

Data available on request

ETHICAL APPROVAL STATEMENT

The authors confirm that we have read the Journal's position on issues involved in ethical publication and affirm that this report is consistent with those guidelines.

ORCID

Katherine M. Burke https://orcid.org/0000-0002-5820-5880
James D. Berry https://orcid.org/0000-0003-0898-6081
Merit E. Cudkowicz https://orcid.org/0000-0002-7075-1681
Sabrina Paganoni https://orcid.org/0000-0003-0505-1168

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SUPPORTING INFORMATION

Additional supporting information can be found online in the Supporting Information section at the end of this article.

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