Safety and efficacy of epigallocatechin gallate in multiple system atrophy (PROMESA): a randomised, double-blind, placebo-controlled trial

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Summary

Background Multiple system atrophy is a rare neurodegenerative disease characterised by aggregation of α-synuclein in oligodendrocytes and neurons. The polyphenol epigallocatechin gallate inhibits α-synuclein aggregation and reduces associated toxicity. We aimed to establish if epigallocatechin gallate could safely slow disease progression in patients with multiple system atrophy.

Methods We did a randomised, double-blind, parallel group, placebo-controlled clinical trial at 12 specialist centres in Germany. Eligible participants were older than 30 years; met consensus criteria for possible or probable multiple system atrophy and could ambulate independently (ie, were at Hoehn and Yahr stages 1–3); and were on stable anti-Parkinson's, anti-dysautonomia, anti-dementia, and anti-depressant regimens (if necessary) for at least 1 month. Participants were randomly assigned (1:1) to epigallocatechin gallate or placebo (mannitol) via a web-generated permuted blockwise randomisation list (block size=2) that was stratified by disease subtype (parkinsonism-predominant disease *vs* cerebellar-ataxia-predominant disease). All participants and study personnel were masked to treatment assignment. Participants were given one hard gelatin capsule (containing either 400 mg epigallocatechin gallate or mannitol) orally once daily for 4 weeks, then one capsule twice daily for 4 weeks, and then one capsule three times daily for 40 weeks. After 48 weeks, all patients underwent a 4-week wash-out period. The primary endpoint was change in motor examination score of the Unified Multiple System Atrophy Rating Scale (UMSARS) from baseline to 52 weeks. Efficacy analyses were done in all people who received at least one dose of study medication. Safety was analysed in all people who received at least one dose of the study medication to which they had been randomly assigned. This trial is registered with ClinicalTrials.gov (NCT02008721) and EudraCT (2012-000928-18), and is completed.

Findings Between April 23, 2014, and Sept 3, 2015, 127 participants were screened and 92 were randomly assigned—47 to epigallocatechin gallate and 45 to placebo. Of these, 67 completed treatment and 64 completed the study (altough one of these patients had a major protocol violation). There was no evidence of a difference in the mean change from baseline to week 52 in motor examination scores on UMSARS between the epigallocatechin gallate (5·66 [SE 1·01]) and placebo (6·60 [0·99]) groups (mean difference –0·94 [SE 1·41; 95% CI –3·71 to 1·83]; p=0·51). Four patients in the epigallocatechin gallate group and two in the placebo group died. Two patients in the epigallocatechin gallate group had to stop treatment because of hepatotoxicity.

Interpretation 48 weeks of epigallocatechin gallate treatment did not modify disease progression in patients with multiple system atrophy. Epigallocatechin gallate was overall well tolerated but was associated with hepatotoxic effects in some patients, and thus doses of more than 1200 mg should not be used.

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Introduction

Multiple system atrophy is a rare neurodenegerative disease characterised by aggregation of the protein α-synuclein in neurons and oligodendrocytes (glial cytoplasmic inclusions), neuronal loss, and astrogliosis. Pathological changes predominantly affect the autonomic, nigrostriatal, and pontocerebellar systems. Patients with multiple system atrophy present with dysautonomia combined with either predominant parkinsonism or cerebellar ataxia.[1,2] Mean survival after diagnosis is 3–10 years; cerebellar ataxia is prognostic of a slower disease course.[3,4] No effective therapies to slow disease progression are available.[5]

Inhibition of α-synuclein aggregation is a rational therapeutic intervention to target a key pathophysiological

Research in context

Evidence before this study

We searched PubMed with the terms "multiple system atrophy" OR "Shy-Drager syndrome" OR "olivo-ponto-cerebellar atrophy" OR "striato-nigral degeneration" AND "clinical trial" OR "treatment" for articles published in English up to March 19, 2019. We also searched ClinicalTrials.gov to identify trials that are underway but have yet to be published. We identified 13 randomised, placebo-controlled trials of putative disease-modifying agents—including riluzole, minocycline, rifampicine, and rasagiline—in patients with multiple system atrophy published between 1971 and 2015. Only four studies followed up participants for 1 year or longer, and no beneficial clinical effects were reported for any treatment. To our knowledge, no other interventional study of disease modification in patients with multiple system atrohy has been initiated or is ongoing.

Added value of this study

To our knowledge, this study is a first-in-class trial of oligomer modulation in synucleinopathies. At 12 months, epigallocatechin gallate did not slow progress of multiple system atrophy compared with placebo (as shown by changes to motor examination scores on the Unified Multiple System Atrophy Rating Scale). However, results of an exploratory MRI sub-study suggested that epigallocatechin gallate might halt cerebral volume reduction in affected brain areas. Hepatotoxic effects were more common in the epigallocatechin gallate group than in the placebo group, showing the need for stringent monitoring of liver enzymes and that doses of epigallocatechin gallate higher than 1200 mg should be avoided.

Implications of all the available evidence

Orally administered epigallocatechin gallate did not have clinical benefits in patients with multiple system atrophy. However, exploratory evidence support the assymption that α-synuclein oligomer formation might be a valid target for therapy in future trials.

process in multiple system atrophy.[6,7] The polyphenol epigallocatechin gallate modulates the formation of α-synuclein oligomers and reduces neurotoxicity in cell-free assays,[8–11] cultured neurons,[12] and animal models of synucleinopathies.[13,14] Other potentially beneficial effects of epigallocatechin gallate in multiple system atrophy include iron-chelation[15–17] and radical scavenging.[18,19] The compound is approved as a dietary supplement in many regions of the world including Europe, the USA, Canada, and Japan, but could be hepatotoxic at doses higher than 600 mg per day.[20] Grapefruit juice and catechol-o-methyltransferase (COMT) inhibitors can interfere with its metabolism and increase toxic effects.[20] Repeated oral intake of epigallocatechin gallate produces stable serum concentrations of the compound.[21] Studies in both mice and humans showed improved cognitive capacities after oral administration of epigallocatechin gallate, suggesting that the compound can permeate the blood–brain barrier and exert cerebral effects.[17,22] Although penetration of the blood–brain barrier has not yet been studied in humans, data from animal and cellular models suggest that 2·8% of epigallocatechin gallate might cross the human blood–brain barrier after 30 min,[22] and crossing of the barrier has also been shown in animals.[23] In this study, we aimed to investigate the safety and efficacy of epigallocatechin gallate as a first-in-class oligomeric modulator in patients with the prototypic synucleinopathy multiple system atrophy.

Methods

Study design and participants

We did a randomised, double-blind, placebo-controlled trial (PROMESA) at 12 specialist centres for diagnosis and treatment of parkinsonism in Germany. Eligible patients were older than 30 years; met the diagnostic criteria for possible or probable parkinsonism-predominant or cerebellar-ataxia-predominant multiple system atrophy;[2] could ambulate independently (ie, Hoehn and Yahr stages 1–3); and had to be on stable anti-Parkinson's, anti-dysautonomia, anti-dementia, and anti-depressant regimens (if necessary) for at least 1 month without a foreseeable need to change the regimens during the next year. Female patients of childbearing potential were required to use adequate contraceptive methods. All potential participants had to agree to abstain from regular consumption of epigallocatechin gallate, green tea, and more than two cups of black tea per day. Exclusion criteria included evidence of neurodegenerative diseases other than multiple system atrophy; Hoehn and Yahr stage 4–5; liver disease with aminotransferases and bilirubin concentrations twice the upper limit of normal or higher; regular intake of hepatotoxic drugs; known hypersensitivity to epigallocatechin gallate or to drugs with similar chemical structures; consumption of more than 500 mL grapefruit juice per day; contemporaneous participation in other interventional trials; treatment with bortezomib or the COMT inhibitors entacapone, tolcapone, and opicapone; clinically significant anaemia (ie, haemoglobin concentrations <100 g/L) at screening; history of plasmocytoma; and current or planned pregnancy. Furthermore, people with a history of persistent misuse of drugs or alcohol or a physical or psychiatric condition that, per the investigators' judgment, might have put them at risk, interfered with their participation in this trial, or confounded the trial results, were excluded. The appendix includes a full list of the inclusion and exclusion criteria.

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See **Online** for appendix

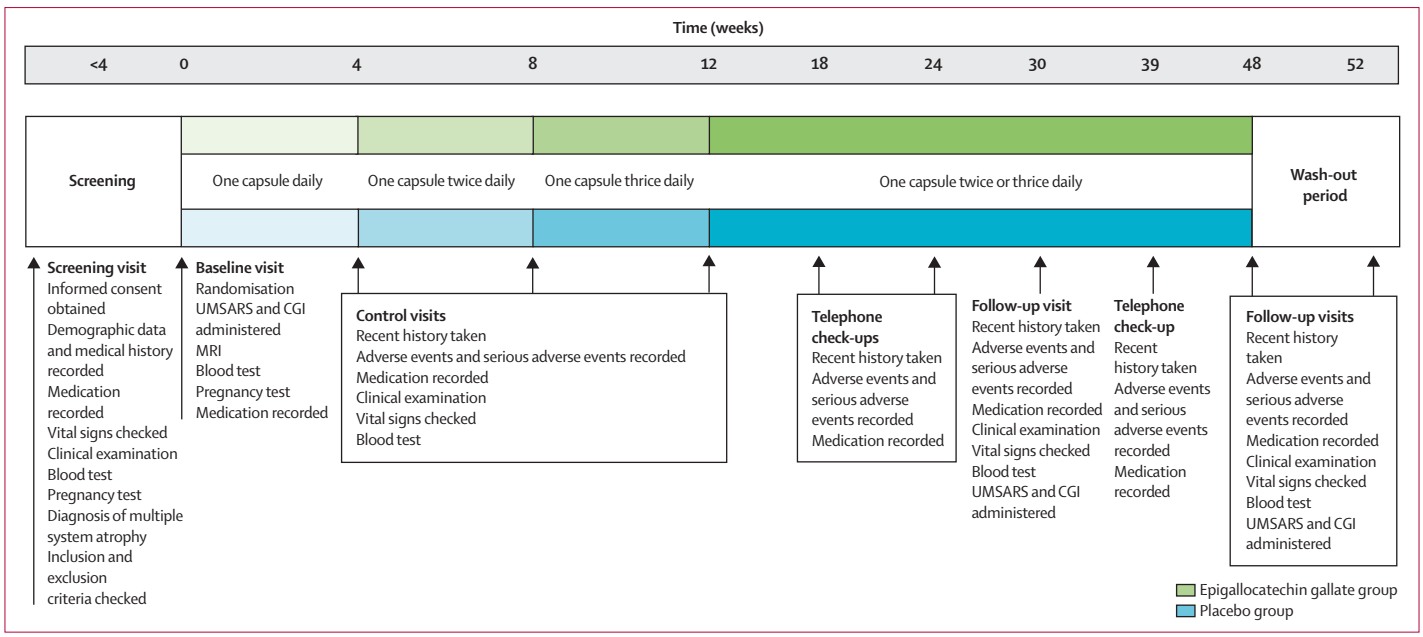

Figure 1: **Schedule of trial activities**
White-coloured squares show the periods of the trial in which participants did not take study medication. UMSARS=Unified Multiple System Atrophy Rating Scale. CGI=Clinical Global Impression.

Ethical approval for the study was obtained from the relevant committees at all participating institutions. All participants provided written informed consent and were asked to donate their brain tissue to the Neurobiobank Munich after death (for which separate approved informed consent was sought). Detailed descriptions of the study protocol have been published (NCT02008721; EudraCT 2012-000928-18).[24]

Randomisation and masking

Eligible participants were enrolled by investigators and randomly assigned (1:1) to receive either epigallocatechin gallate or matching placebo (mannitol). Randomisation was done by the central trial pharmacy at Charité—Universitätsmedizin Berlin (Berlin, Germany) and overseen by CE. Neither CE nor the pharmacy staff were involved in data analysis. Standard web-based software was used. Randomisation was stratified by centre and type of multiple system atrophy (parkinsonism-predominant *vs* cerebellar-ataxia-predominant) and based on random blocks of size two. All centres were equipped in advance with baseline kits with medication kit numbers for blockwise inclusion of patients with parkinsonism-predominant and cerebellar-ataxia-predominant multiple system atrophy. The study centres were instructed to use the medication kits in a consecutive manner. To communicate the randomisation, the centre number, medication kit number (which served as the randomisation number), and disease subtype were faxed to the trial pharmacy. All participants and study personnel were masked to treatment assignment. Epigallocatechin gallate and placebo looked physically identical.

For the **software used** see www.randomization.com

Procedures

Epigallocatechin gallate was purchased as Sunphenon, which is Taiyo International's (Yamadacho, Japan) highest-quality product and contains more than 94% epigallocatechin gallate and less than 0·1% caffeine. Before we encapsulated the epigallocatechin gallate (400 mg per hard gelatin capsule), the central trial pharmacy confirmed stability. We chose the highest trial dose that had been safely administered previously (ETON; NCT01357681) as the target dose. Patients took one capsule of epigallocatechin gallate (ie, 400 mg) or one matched placebo in the morning for 4 weeks, then one capsule twice a day (ie, 800 mg daily) for 4 weeks, and then one capsule three times a day (ie, 1200 mg daily) for 4 weeks. Patients then either remained on this dose for a further 36 weeks, or, in cases of hepatotoxicity—which was defined as an increase in aminotransferase concentrations (alanine aminotransferase and aspartate aminotransferase) to higher than three times the upper limit of normal—took a reduced dose of 400 mg twice a day (or two matching placebo capsules) until concentrations fell below this threshold. Subsequently, the dose could be increased back to 1200 mg per day at the investigators' discretion. Increases in aminotransferase concentrations to greater than five times the upper limit of normal led to termination of treatment (assessments continued, however).

Participants attended eight study visits over 52 weeks (figure 1). Within 28 days of the screening visit, they attended a randomisation or baseline visit, during which the initial study treatment was dispensed. Participants received new study medication after 4, 8, 12, and 30 weeks. At the 48-week visit, study treatments were stopped.

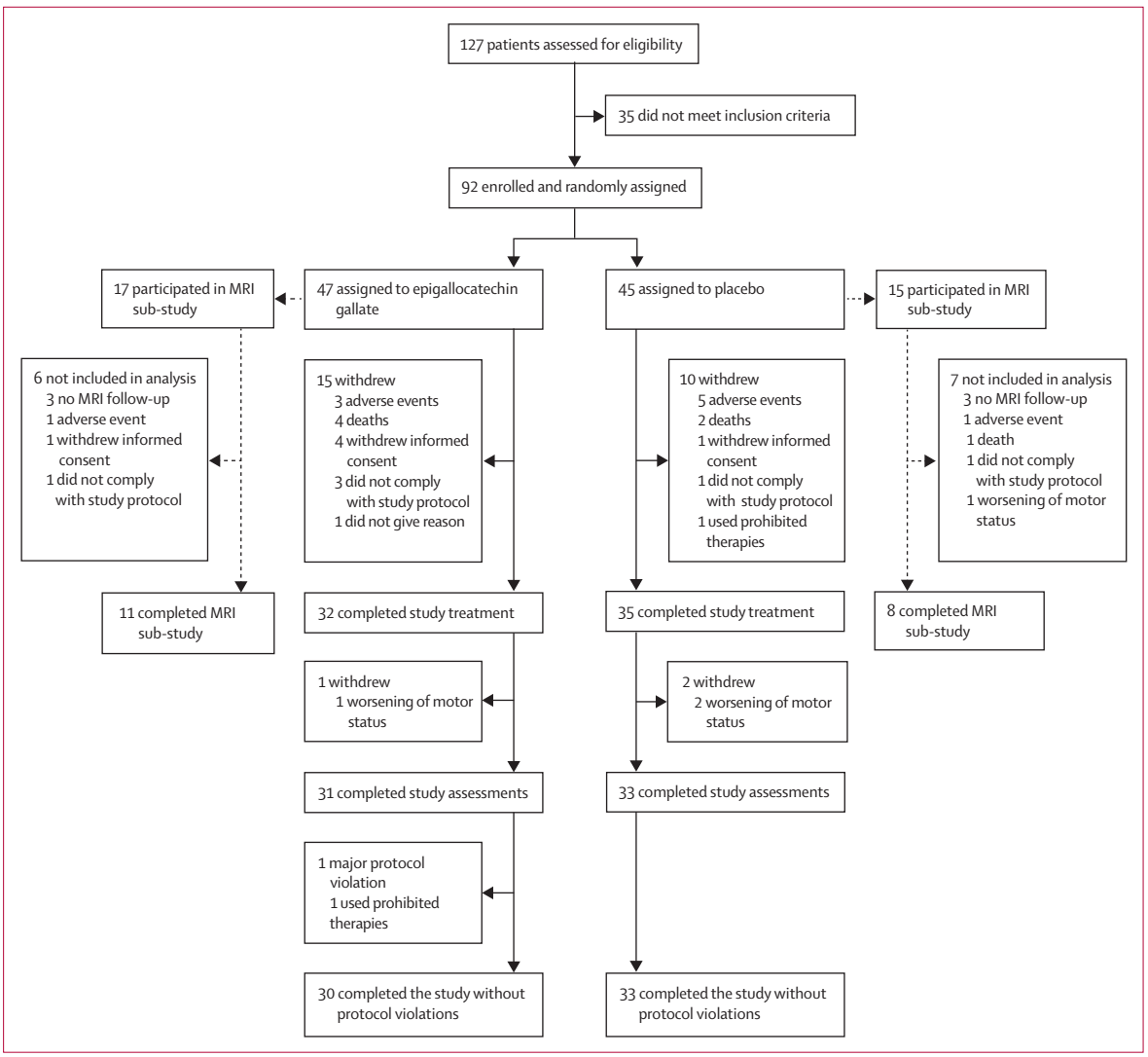

***Figure 2*: Trial profile**

Patients then attended a final assessment at week 52, after a 4-week washout period. Compliance was assessed by counting returned capsules. A paper case report form with duplicate carbon copies was used to capture data. Monitoring at all centres included a site-initiation visit, a visit after inclusion of the first participant, and a close-out visit by the Münchner Studienzentrum (Technical University Munich, Munich, Germany). Each site received on-site training during the site-initiation visit. In this training session, the Unified Multiple System Atrophy Rating Scale (UMSARS) was reviewed and the importance of maintaining the same raters for each assessment was emphasised. However, the monitoring protocol did not specify that the same rater had to be used. Additional monitoring visits were scheduled when sites recruited more than five participants or reported problems during regularly scheduled telephone conferences. All sites had 3–5 monitoring visits. Secondary to this monitoring, case report forms were sent by the centres to the Institute for Medical Information Processing, Biometry and Epidemiology (Ludwig-Maximilians-Universität, Munich, Germany), where database entries were managed. Safety was monitored at all visits.[24] Adverse events were grouped according to Medical Dictionary for Regulatory Activities (MedDRA) organ class. Serious adverse events were defined as adverse events that led to hospitalisation, discontinuation of study medication because of liver toxicity, or death.

Patients at three sites (Düsseldorf, Munich, and Ulm) were also invited to participate in an MRI sub-study. Those who agreed to participate underwent imaging at baseline and week 52. Images were obtained from participants in the MRI sub-study on 3T scanners (Siemens, Erlangen, Germany). The three imaging sites were experienced in multicentric neuroimaging of multiple system atrophy. Scanning parameters were audited by the radiology

	Epigallocatechin gallate group (n=47)	Placebo group (n=45)
Age, years	60 (56–71)	64 (60–70)
Sex		
Female	18 (38%)	19 (42%)
Male	29 (62%)	26 (58%)
Time since diagnosis, years	0·9 (0·4–2·1)	1·0 (0·3–2·5)
Time since first symptoms, years	3·7 (2·9–4·7)	3·9 (2·5–4·6)
Weight, kg	80 (72–95)	78 (66–85)
Multiple system atrophy phenotype		
Parkinsonian	25 (53%)	24 (53%)
Cerebellar	22 (47%)	21 (47%)
Diagnostic certainty		
Probable multiple system atrophy	46 (98%)	43 (96%)
Possible multiple system atrophy	1 (2%)	2 (4%)
Concomitant drugs		
Levodopa (%)	17 (36%)	21 (47%)
Amantadine (%)	5 (11%)	4 (9%)
UMSARS		
Motor examination score	23 (18–25)	22 (16–27)
Overall score	43 (38–49)	40 (35–56)
Clinical Global Impression of Severity score	2 (2–3)	2 (2–4)

Data are median (IQR) or n (%). UMSARS=Unified Multiple System Atrophy Rating Scale.

Table 1: **Baseline clinical and demographic characteristics**

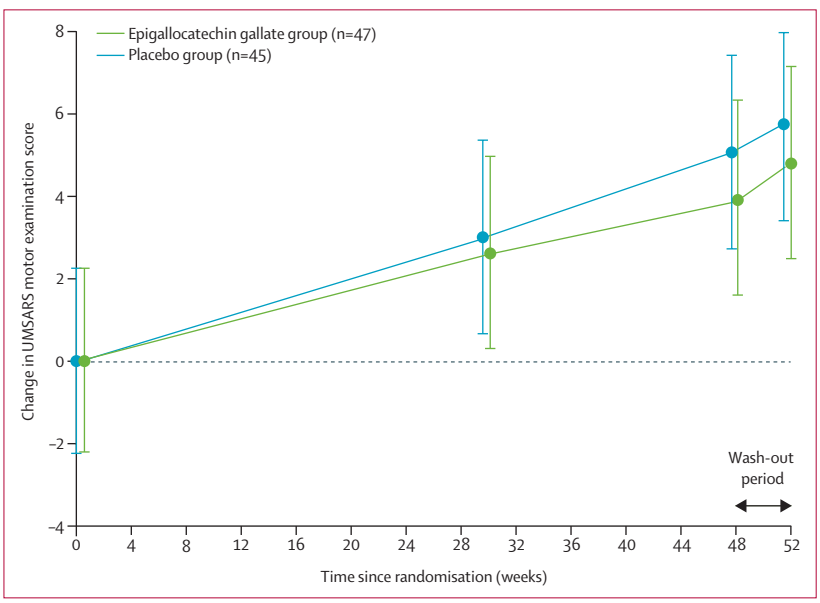

Figure 3: **Change from baseline in motor examination scores on UMSARS in the full analysis set**
Error bars show 95% CIs. The fitted values are derived from a linear mixed-effect model with multiple system atrophy phenotype (ie, parkinsonism predominant or cerebellar ataxia predominant), treatment, visit (considered here as a factor), and the interaction between visit and treatment as fixed effects, and patients as random effects. UMSARS=Unified Multiple System Atrophy Rating Scale.

department at Ludwig-Maximilians-Universität (Munich, Germany). BE-W oversaw this process. Volumetric image analysis was done by a specialist (HJ-H) who was blinded to group assignment. Predefined brain structures affected in multiple system atrophy (ie, the striatum, caudate nucleus, putamen, cerebellum, pons, and precentral gyrus grey matter) were measured by automated, observer-independent, atlas-based volumetry on the basis of SPM12 software algorithms, as used previously in patients with progressive supranuclear palsy.[30]

Outcomes

Clinical outcome measures were assessed at baseline and weeks 30, 48, and 52. The primary outcome was the change from baseline to week 52 in motor examination scores on UMSARS,[25] which assesses 14 operationalised signs of multiple system atrophy.[25] Scores for all 14 items range from 0 to 4, thus total scores range from 0 to 56. The final readout to assess disease modification was obtained at each centre by trained movement disorder specialists after the wash-out period at week 52 to control for possible symptomatic effects.

Secondary efficacy outcomes were change from baseline to week 52 and change from week 48 to week 52 (ie, during the wash-out period) in the UMSARS total score;[25] scores on the Clinical Global Impression of Severity and Clinical Global Impression of Change;[26] and, in participants in the MRI sub-study, parameters for global and regional atrophy, as assessed by high-resolution, isotropic T1-weighted, three-dimensional magnetisation-prepared rapid gradient-echo MRI sequences,[27,28] and iron deposition, assessed by MRI.[29]

Secondary safety and tolerability outcomes were discontinuation because of adverse events; incidence of specific adverse events (ie, treatment-emergent adverse events); changes in safety laboratory values (basic clinical chemistry); vital signs (blood pressure, heart rate, temperature); physical and neurological examinations; and overall survival and survival during the study period. There was a special focus on liver-related parameters, including aminotransferases and γ-glutamyltransferase. During the dose-escalation phase, liver parameters were assessed every 4 weeks, and thereafter at least every 9 weeks. Blinded safety assessments and reviews were done by a data safety monitoring committee, at least every 6 months during the trial.

Statistical analysis

Our power calculation was based on the subset of patients from the European Multiple System Atrophy Study Group's natural history data[31] who met the inclusion criteria for our trial.[24] This trial was designed to yield a two-sided α of 0·05 at 80% power for a treatment effect of 50% on the annual progression of the movement examination score on the UMSARS[25]—4 points in the epigallocatechin gallate group *vs* 8 points (SD 6) in the placebo group. This difference is above the level for a

minimal clinically important difference within 48 weeks of 3·8 points, below which effects cannot be reliably detected.[32] Hence, we designed this trial to establish if treatment with epigallocatechin gallate can lead to meaningful effects on disease progression in patients with multiple system atrophy. The target sample size was 90 patients—ie, 36 patients per group given an expected 20% drop-out rate. The competent authorities gave permission to continue randomisation of people who had already been screened when target recruitment was met.

For the primary and secondary outcomes, we did a modified intention-to-treat analysis, which included all participants who received at least one dose of study medication (ie, the full analysis set). Safety was analysed in the safety set, comprising all patients in the full analysis set who received the study medication to which they were randomly assigned. For sensitivity analyses, we defined two per-protocol analysis sets: the per-protocol study completer set, which comprised patients who completed all study visits without major protocol violations, and the imaging per-protocol study completer set, which comprised the members of the per-protocol study completer set who also completed the imaging sub-study. Missing individual UMSARS items were assumed to be missing at random. The maximum number of missing items was six. Thus, a simple proportionality rule was used to complete the scores.

We used a linear mixed-effects model to test the primary hypothesis—ie, to compare differences in the change in motor examination scores on UMSARS between baseline and week 52 between the study groups. The assumptions on which the model was based are summarised in the appendix. The progression of motor examination scores was supposed to be linear from baseline to week 48 (ie, the end of treatment). Departure from this linear trend between week 48 and week 52 (ie, the wash-out period) could be explained by the elimination of the symptomatic effect (in the intervention group only) or the possible elimination or diminution of the placebo effect (in both groups). To measure these effects, two parameters were included in the model: one for the placebo group, which took a potential placebo effect into account, and another for the epigallocatechin gallate group to account for a potential placebo effect and a potential symptomatic effect (appendix). The model also contained random intercept and slope effects to account for patient-to-patient variation within each treatment group. As a patient high intercept could be linked with a high or low slope, we added a parameter measuring the correlation between these two random effects. The difference in change from baseline to week 52 in motor examination scores on UMSARS between the groups was interpreted as disease modification (appendix). The difference in departure from the linear trend during the wash-out period was interpreted as a symptomatic effect. We used the same model to compare UMSARS total scores between groups. We did a post-hoc power calculation based on the mean change in motor examination scores on UMSARS and SDs in the placebo group of the per-protocol study completer set to test the assumptions of our initial power calculation.

	Epigallocatechin gallate group (n=47)	Placebo group (n=45)	Difference	p value
Motor examination score				
Change from baseline to treatment termination (disease modification)*	5·66 (1·01)	6·60 (0·99)	–0·94 (1·41; –3·71 to 1·83)	0·51
Change during wash-out phase (symptomatic effect)†	0·68 (0·60)	0·49 (0·58)	0·19 (0·84; –1·47 to 1·85)	0·82
Total score				
Change from baseline to treatment termination*	10·33 (1·73)	10·35 (1·71)	–0·02 (2·44; –4·79 to 4·76)	0·99
Change during wash-out phase†	0·70 (0·91)	–0·29 (0·88)	0·99 (1·26; –1·5 to 3·49)	0·43

Data are mean (SE) or mean (SE; 95% CI). UMSARS=Unified Multiple System Atrophy Rating Scale. *The change from baseline to treatment termination can be interpreted as the 1-year slope, because the final visit took place 52 weeks (364 days) after baseline. †Scores could deviate from the straight linear under-treatment slope at week 52 because of treatment termination at week 48.

Table 2: **Changes in UMSARS scores in the full analysis set**

	Inverse cumulative odds ratio* (95% CI)
Clinical Global Impression of Severity	
Change from baseline to termination	1·64 (0·44–6·20)
Change during wash-out phase	1·35 (0·15–12·33)
Clinical Global Impression of Change	
Change from baseline to termination	1·02 (0·46–2·26)
Change during wash-out phase	0·41 (0·05–3·44)

Assessed by cumulative logit link models with time, treatment, time x treatment interaction, and type of multiple system atrophy as fixed effects, and patient identity as a random effect. The random effect and the interaction effect were dropped when appropriate. Because of low numbers in some categories, the severity of illness levels 1, 2, and 3 were merged, as were levels 6 and 7. The global improvement levels 0–3, and levels 6 and 7 were also merged because numbers were low. If data for week 52 were missing, they were imputed with the last observation carried forward method. Only patients with data available for the 48-week and 52-week visits were included in comparisons of these two visits (delimiting the wash-out phase). The reference treatment for analyses was placebo, and the reference type of multiple system atrophy was cerebellar disease. *Inverse cumulative odds ratio is the odds ratio of the probability P(Y≥j), in which j is a level of the variable Y under consideration.

Table 3: **Effect of treatment (epigallocatechin gallate *vs* placebo) on Clinical Global Impression of Severity and Clinical Global Impression of Change in the full analysis set**

For the Clinical Global Impression of Severity and Clinical Global Impression of Change, we fitted a cumulative logit link model with time, treatment, time × treatment interaction, and multiple system atrophy type as fixed effects, and patient identity as a random effect.

Data were entered independently in two identical databases, then adjusted and corrected in SAS (version 9.2). Queries were created for completeness and plausibility for each dataset. Before database lock, the data for 10% of the patients were selected randomly and manually

	Epigallocatechin gallate group (n=47)	Placebo group (n=45)
By system		
Dysarthria	0	4 (4 [9%])
Dysphagia	5 (4 [9%])	0
Falls (due to postural instability, ataxia, or orthostatic hypotension)	26 (17 [36%])	31 (17 [38%])
Orthostatic hypotension	6 (3 [6%])	5 (5 [11%])
Worsening of parkinsonism, ataxia, or autonomic dysfunction	24 (10 [21%])	17 (9 [20%])
Swallowing problems	5 (3 [6%])	0
Pneumonia due to aspiration	3 (3 [6%])	0
Urinary tract infections due to vegetative dysfunction	14 (9 [19%])	20 (14 [31%])
Gastrointestinal adverse events	37 (22 [47%])	22 (14 [31%])
Hepatotoxicity (ie, increased aminotransferase concentrations)	8 (8 [17%])	0
Other adverse events	92 (30 [64%])	108 (32 [71%])
By outcome		
Recovered	96 (36 [77%])	111 (33 [73%])
Recovered with sequelae	20 (11 [23%])	13 (5 [11%])
Not recovered	66 (24 [51%])	63 (26 [58%])
Missing or unknown	26 (13 [28%])	18 (9 [20%])
By grade		
Mild	95 (32 [68%])	97 (33 [73%])
Moderate	95 (32 [68%])	88 (32 [71%])
Severe	20 (12 [26%])	19 (12 [27%])
Missing or unknown	2 (2 [4%])	3 (3 [7%])
By attribution to study treatment		
Definite	1 (1 [2%])	0
Probable	9 (3 [6%])	5 (5 [11%])
Possible	23 (14 [30%])	22 (14 [31%])
Unlikely	52 (22 [47%])	39 (16 [36%])
Not related	120 (31 [66%])	132 (33 [73%])
Unknown	7 (4 [9%])	9 (9 [20%])
By seriousness		
Serious adverse events	29 (18 [38%])	14 (8 [18%])
Adverse events but no serious adverse events	117 (25 [53%])	145 (33 [73%])
No adverse events	3 (6%)	1 (2%)
Discontinued because of adverse events	3 (6%)	5 (11%)
Discontinued because of hepatotoxicity	2 (4%)	0
Deaths	4 (9%)	2 (4%)

Data are number of events (number of patients [%]) or number of patients (%). The safety set is identical to the full analysis set.

Table 4: **Adverse events by system, outcome, grade, and attribution in the safety set**

checked for completeness and quality, and data were reviewed in a face-to-face meeting of the blinded data review committee (comprising JL, AG, WHO, WP, ACT, GKW, IR, and GUH). All analyses were done in R (version 3.5.1), unless otherwise specified.

Role of the funding source

The funders of the study had no role in study design, data collection, data analysis, data interpretation, or writing of the report. All authors had full access to all the data in the study and had final responsibility for the decision to submit for publication.

Results

Between April 23, 2014, and Sept 3, 2015, 127 people were assessed for eligibility, and 92 were enrolled and randomly assigned—47 to the epigallocatechin gallate group and 45 to the placebo group (figure 2). Overall, 67 participants completed treatment, and 64 completed the study (63 without major protocol violations). Study visits occurred between April 23, 2014, and Sept 11, 2016. 89 (97%) of the 92 participants fulfilled the criteria for probable multiple system atrophy (table 1). Post-mortem histopathological analysis confirmed the diagnosis of multiple system atrophy in all five participants whose brains have been donated for study so far. 17 (34%) of 47 participants in the epigallocatechin gallate group and 12 (27%) of 45 in the placebo group did not complete the study without major protocol violations (figure 2). Clinical and demographic characteristics of the two groups were similar at baseline (table 1). At baseline, median age overall was 62 years (IQR 57–70), 37 (40%) participants were female, and the median motor examination score on UMSARS was 22 (IQR 17–25). Patients in both groups took 84% of their scheduled doses (data not shown).

No patients were misrandomised, and all patients received the treatment that they were assigned to. Therefore, the safety set and full analysis set were identical. In the full analysis set, the change from baseline to week 52 in motor examination scores (difference –0·94 points [95% CI –3·71 to 1·83]; p=0·51) and total score (–0·02 [–4·79 to 4·76]; p=0·99) on UMSARS did not differ significantly between the epigallocatechin gallate and placebo groups (figure 3; table 2). Motor examination score data were missing in seven cases (three in the epigallocatechin gallate group and four in the placebo group). In four of these cases (two in each group), only one sub-item was missing). Data for UMSARS total scores were missing in 16 cases (six in the epigallocatechin gallate group and ten in the placebo group), 12 of which (four and eight in each group, respectively) were missing only one sub-item. Changes between baseline and week 52 in scores on the Clinical Global Impression of Severity and Clinical Global Impression of Change also did not differ significantly between groups (table 3). We identified no significant between-group differences in changes to motor examination or total scores on UMSARS (figure 3; table 2), or to Clinical Global Impression of Severity or Clinical Global Impression of Change scores (table 3), during the wash-out period. A table of detailed parameters drawn from the linear mixed-effect model in which motor examination and total scores on UMSARS were response variables is in the appendix, along with supplemental analyses for the primary outcome in each analysis set broken down by important clinical covariates and by centre. A mean change in the motor examination score of the UMSARS of 6·53 (SD 5·06) was noted in the placebo

group of the per-protocol study completer set. The required sample size estimated on the basis of these data in a post-hoc calculation was 38 patients per group (appendix).

Adverse events occurred in similar numbers in the two groups (table 4). Four patients died in the epigallocatechin gallate group and two in the placebo group. An autopsy was done in only one of these patients (death was attributed to autonomic failure). 29 serious adverse events (in 18 patients) were noted in the epigallocatechin gallate group, and 14 (in eight patients) in the placebo group. Most adverse events were mild to moderate (table 4). Five patients in the epigallocatechin gallate group reported dysphagia, and three reported pneumonia due to aspiration, whereas such adverse events were not reported in the placebo group (table 4). Seven patients in the epigallocatechin gallate group and seven in the placebo group discontinued the study because of adverse events or death (table 4). Two of these patients in the epigallocatechin gallate group discontinued because of severe liver toxicity (table 4). Post-baseline changes in aminotransferase concentrations were judged to be clinically significant by the investigators in 20 patients in the epigallocatechin gallate group and five patients in the placebo group. Eight of these changes to aminotransferase concentrations were classified as adverse events (all in the epigallocatechin gallate group; table 4). In six individuals (five in the epigallocatechin gallate group) the dose of study drug had to be reduced from three capsules per day to two capsules per day. Two people resumed the higher dose, two finished the trial on the reduced dose (including the one patient in the placebo group), and two individuals discontinued the trial subsequent to dose reduction. Safety laboratory values other than those pertaining to the liver did not differ between treatment groups (data not shown).

In sensitivity analyses including only people who completed the trial without major protocol violations (ie, the per-protocol study completer set), the change in motor examination scores on UMSARS (–1·76 points [95% CI –4·69 to 1·17]; p=0·24; figure 4A) and in secondary outcome scores from baseline to treatment termination or during the wash-out phase (appendix) did not differ significantly between groups.

Of the 36 patients enrolled at the three imaging sites, four (11%) had contraindications for MRI. Thus, 32 patients were incuded in the MRI sub-study (figure 2), 17 in the epigallocatechin gallate group and 15 in the placebo group, 11 (65%) and eight (53%) of whom completed the study per protocol, respectively. The baseline clinical and demographic characteristics of people in the imaging cohort who completed the study were similar to those of the full analysis set (appendix), and disease progression in placebo patients of the imaging sub-study who completed the study was similar to that in the placebo group overall (appendix). Quantitative MRI volumetry showed lower annual volume loss in the epigallocatechin gallate group than in the placebo group in the striatum and precentral gyrus grey matter (appendix). A sensitivity analysis in the patients who completed the imaging sub-study showed some evidence of a treatment effect for the primary clinical outcome, the change in motor examination scores on UMSARS between baseline and week 52 (mean difference –5·18 points [95% CI –9·32 to –1·04]; p=0·014; figure 4B; appendix). The iron-sensitive MRI sequences could not be assessed because of technical problems at two of the three imaging sites.

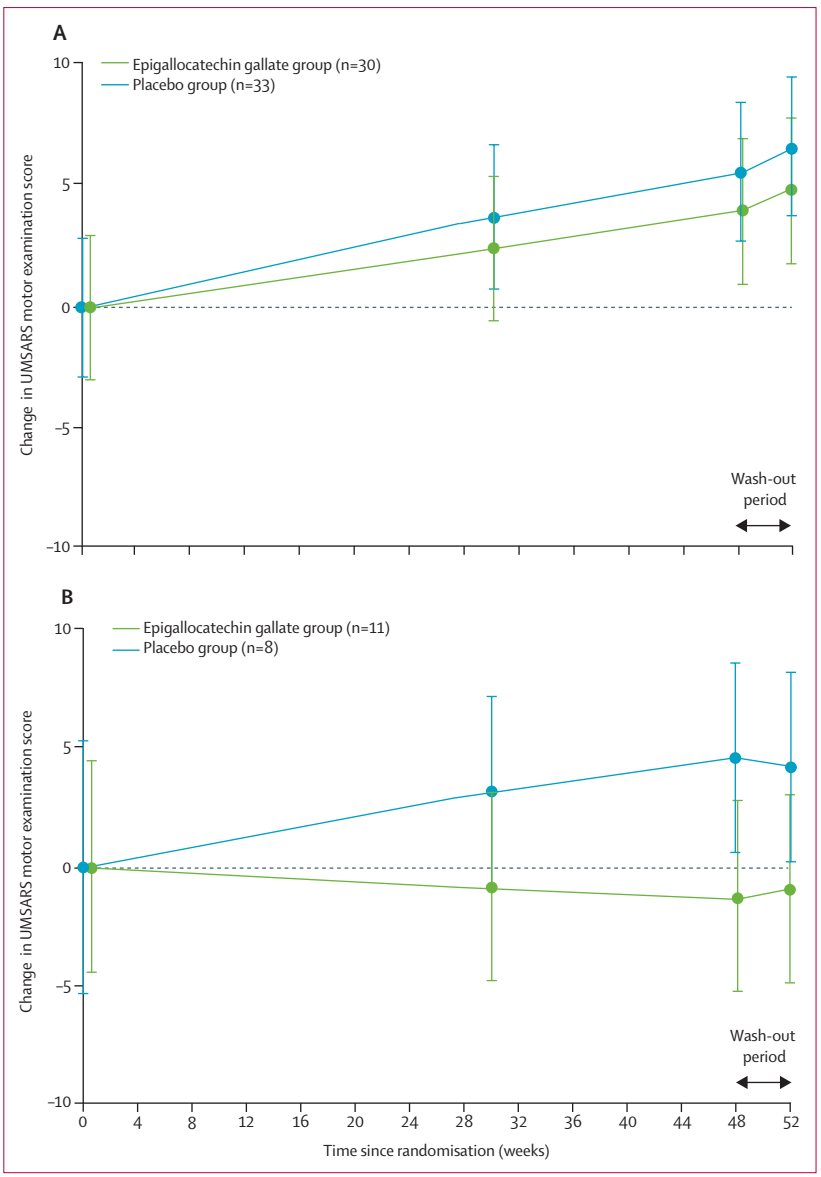

Figure 4: **Change from baseline in motor examination scores on UMSARS in study completers (A) and MRI sub-study completers (B)**

Error bars show 95% CIs. The fitted values are derived from a linear mixed-effect model with multiple system atrophy phenotype (ie, parkinsonism predominant or cerebellar ataxia predominant), treatment, visit (considered here as a factor), and the interaction between visit and treatment as fixed effects, and patients as random effects. UMSARS=Unified Multiple System Atrophy Rating Scale.

Discussion

In this randomised, double-blind, placebo-controlled trial, there was no evidence that epigallocatechin gallate modified disease progression in patients with multiple system atrophy as measured by the change in motor examination scores on UMSARS at 12 months. Epigallocatechin gallate was safe but was associated with more frequent increases in aminotransferase concentrations than was placebo, and serious liver toxicity occurred in two patients (a known side-effect of the compound[20]). In an exploratory MRI sub-study, there was weak evidence to show that patients in the epigallocatechin gallate group had less striatal atrophy and lower motor examination scores on the UMSARS at 52 weeks than those in the placebo group.

Basic science data provide a solid rationale for the use of small molecules to prevent α-synuclein aggregation and modify disease in multiple system atrophy.[6,7,33,34] Epigallocatechin gallate is an orally bioavailable polyphenol[21] that almost completely blocks pathological α-synuclein aggregation in in-vitro cellular and cell-free experiments and is approved for use in human beings.[8–10,12,14,35] In vivo, monkeys with parkinsonism that were given epigallocatechin gallate showed a reduction in disease progression of approximately 50% compared with those given placebo as measured by a validated parkinsonian clinical rating scale in monkeys.[8–10,12,14,35] Thus, the rationale for epigallocatechin gallate as a putative disease-modifying agent in multiple system atrophy is well established preclinically.[8–10,12,14,35]

The motor examination score of UMSARS was also used in the three most recent trials (of minocycline,[36] rifampicin,[37] and rasagiline,[38] respectively) investigating disease modification in patients with multiple system atrophy. In the trials of rifampicin[37] and rasagiline,[38] a combination of disease onset, expected survival, and UMSARS scores were used as inclusion criteria. Our trial had less complex inclusion criteria: we admitted only freely ambulatory patients to minimise the risk of dropouts, and aimed for a population with mild-to-moderate disease (ie, Hoehn and Yahr stages 1–3) within the full range of motor examination scores of UMSARS. Data from the use of riluzole in patients with amyotrophic lateral sclerosis[39] and from animal models of synucleinopathies suggest that disease modification can be achieved at advanced clinical stages in neurodegenerative diseases.[40] The exclusion criteria of our trial reflected the safety profile of epigallocatechin gallate.[20] We chose a 1-year observation period, which was sufficient in previous trials to investigate disease progression (as shown by motor examination scores on UMSARS) while ensuring patient retention. 1-year progression data for UMSARS motor examination scores from the subset of the European Multiple System Atrophy Study Group's natural history cohort who met our trial's inclusion criteria[31] provided the basis for our power calculation (ie, a sample size of 36 patients per group).[24] The assumptions of the power calculation were supported by data from a post-hoc power calculation in the placebo group of our trial, showing that a group size of 38 patients would be sufficient (appendix). The dose of epigallocatechin gallate (1200 mg per day) that we used was substantially higher than doses leading to cognitive improvements in individuals with Down's syndrome (9 mg/kg),[17] and is the highest dose trialled in human beings so far (NCT01357681).

Recruitment for our trial was completed within the planned timeframe of 18 months.[24] We recruited more participants than initially planned—a decision that was prospectively approved by the central ethics committee. Blockwise randomisation of patients with parkinsonism-predominant and celebellar-ataxia-predominant disease led to well matched treatment groups at baseline. Demographic and clinical baseline characteristics of the recruited patients are consistent with those of patients in previous large cohort studies, including the fact that patients with celebellar-ataxia-predominant multiple system atrophy tend to have lower motor examination scores on UMSARS at baseline but similar disease progression to those with parkinsonism-predominant disease.[31,41] Compared with the two most recent trials[37,38] of disease modification in patients with multiple system atrophy, we recruited more patients who fulfilled the criteria for probable multiple system atrophy, and compared with the trial[37] of rifampicin we achieved more balanced inclusion of patients with parkinsonism-predominant or celebellar-ataxia-predominant disease in the treatment groups. At 1 year, 86 (93%) of the 92 enrolled patients were still alive—a proportion similar to those in the previous rifampicin[37] and rasagiline[38] trials. However, the frequency of dropouts in our trials was slightly higher than that in previous trials,[37,38] probably because only requiring patients to be able to walk freely led to the inclusion in our trial of patients with more advanced disease. Baseline UMSARS motor examination scores in our trial (roughly 21 points) were higher than those in the trials of rasagiline[38] (roughly 17 points) or rifampicin[37] (roughly 12 points).

Even though we over-recruited relative to our sample size calculation, the unexpectedly high frequency of dropouts generates potential concern about the trial's power. However, although the number of trial completers was lower than expected, so was the reported SD for the change in motor examination scores in the placebo group (5·06 rather than 6) in the dataset of trial completers. Furthermore, the 95% CI for the between-group difference for the primary outcome (– 3·71 to 1·83) did not contain the treatment effect of –4 that we expected to detect. These findings suggest that the study was adequately powered to detect a disease-modifying treatment effect of 50% on annual progression of UMSARS motor examination scores and that epigallocatechin gallate does not have this large effect.

Epigallocatechin gallate was associated with hepatic adverse events and cessation of treatment in two patients

with aminotransferase concentrations more than five-times higher than the upper limit of normal. Changes in aminotransferase concentrations in eight patients in the epigallocatechin gallate group (17% overall) were associated with adverse events. We therefore conclude that 1200 mg epigallocatechin gallate daily is toxic for an substantial proportion of patients with multiple system atrophy, especially in view of the fact that patients with a priori chronic liver disease were excluded from our trial. Hence, studies of higher doses cannot be safely recommended in human beings, and hepatotoxic effects should be screened for in all studies of epigallocatechin gallate.

The main finding of this trial was that, at 12 months, epigallocatechin gallate was not associated with clinically relevant disease modification in patients with multiple system atrophy compared with placebo. We also found no evidence that epigallocatechin gallate had an effect on the secondary clinical outcome measures (ie, UMSARS total score, Clinical Global Impression of Severity, or Clinical Global Impression of Change). This study also included an exploratory MRI sub-study. In the cohort of patients in the imaging sub-study who completed the main study, brain regions affected by multiple system atrophy showed less volume loss in the epigallocatechin gallate group than in the placebo group. In the placebo group, the annual striatal atrophy rate (7·3%) was close to the annual striatal volume loss of roughly 6% reported previously in a single-centre natural history study,[42] whereas striatal volume loss was substantially lower in the epigallocatechin gallate group (3·4%; appendix). This finding might suggest that epigallocatechin gallate has neuroprotective effects, but other explanations cannot be ruled out—eg, epigallocatechin gallate might reduce brain volume loss by modulating inflammatory processes or increasing cerebral water content rather than by inhibiting neurodegeneration. Surprisingly, an exploratory sensitivity analysis in patients in the imaging sub-study who completed the main study seemed to suggest significant between-group differences favouring epigallocatechin gallate in the primary clinical outcome of change in motor examination scores on UMSARS between baseline and week 52. This finding raises questions about the difference between this group of patients and the full analysis set and the per-protocol study completer set. Selection, matching, or retention of patients did not differ between cohorts. Two of the centres at which the MRI sub-study was done were among the centres recruiting the highest numbers of patients for the trial overall (appendix). Previous analyses suggested that trial centres with large numbers of patients might provide data of higher quality than those with fewer patients.[43] On the basis of the atrophy data and suggestion of clinical efficacy from the imaging sub-study, atrophy rates might be a promising biomarker in future studies, and inhibition of α-synuclein aggregation warrants further investigation in multiple system atrophy and other synucleinopathies.

The PROMESA trial had several limitations. Even though the study included the highest number of participants so far completing a randomised controlled trial of disease modification in both subtypes of multiple system atrophy, the goal of reducing disease progression by 50% might have been too ambitious. The trial was not powered to detect smaller changes. Furthermore, the number of drop-outs was higher than expected. Only four of the 12 centres recruited ten or more patients. Study centres that recruited small numbers of patients might have introduced increased variability to the dataset. Overall, larger numbers of patients, longer observation periods, and larger trial sites, could have enabled disease-modifying efficacy to be detected.

Contributors

JL, AG, WHO, GKW, UM, and GUH designed the study, which was set up by JL, SM, MSc, SE-S, CE, FP, KB, BE-W, and GUH. JL, SM, MSc, CT, MSü, KE, BM, AL, ML, JC, AM, JK, FG, DP, SE-S, CE, FP, KB, BE-W, and GUH had roles in trial conduct performance. UM supervised the statistical analysis. HJ-H did the blinded imaging analyses. IR did the statistical analyses. GUH was the principal clinical investigator. JL was the sponsor delegated person of this trial, in which the Klinikum der Universität München of Ludwig-Maximilians-Universität München was the sponsor. JL, AG, WHO, WP, CT, GKW, IR, and GUH were on the blinded data review committee and the writing committee. JL, IR, and GUH wrote the first draft of the paper, which was revised by all authors.

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Data sharing statement

The study protocol, statistical analysis plan, informed consent form, and study data, including deidentified participant data and a data dictionary defining each field in the set, will be made available to others upon formal request and receipt of a signed material transfer agreement. Requests should be directed to the corresponding author. Data will only be shared via individual secured network connections.

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