Safety and efficacy of intra-erythrocyte dexamethasone sodium phosphate in children with ataxia telangiectasia (ATTeST): a multicentre, randomised, double-blind, placebo-controlled phase 3 trial

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Summary

Background Ataxia telangiectasia is a multisystem disorder with progressive neurodegeneration. Corticosteroids can improve neurological functioning in patients with the disorder but adrenal suppression and symptom recurrence on treatment discontinuation has limited their use, prompting the development of novel steroid delivery systems. The aim of the ATTeST study was to evaluate the efficacy and safety of intra-erythrocyte delivery of dexamethasone sodium phosphate compared with placebo in children with ataxia telangiectasia.

Methods This multicentre, randomised, double-blind, placebo-controlled, phase 3 trial was done at 22 centres in 12 countries (Australia, Belgium, Germany, India, Israel, Italy, Norway, Poland, Spain, Tunisia, the UK, and the USA). Eligible participants were children aged 6 years or older weighing more than 15 kg who met clinical criteria for ataxia telangiectasia but who had preserved autonomous gait. Participants were randomly assigned (1:1:1) to low-dose (approximately 5–10 mg), or high-dose (approximately 14–22 mg) intra-erythrocyte dexamethasone sodium phosphate, or placebo, using an independent interactive web response system, with minimisation for sex and age (6–9 years *vs* ≥10 years). Intravenous intra-erythrocyte dexamethasone sodium phosphate was administered once a month for 6 months. Participants, employees of the sponsor, investigators, all raters of efficacy endpoints, and central reviewers were masked to treatment assignment and dose allocations. The primary efficacy endpoint was change in the modified International Cooperative Ataxia Rating Scale (mICARS) from baseline to month 6, assessed in the modified intention-to-treat (mITT) population, which included all randomly assigned participants who received at least one dose of study drug and had at least one post-baseline efficacy assessment. This trial is registered with Clinicaltrials.gov (NCT02770807) and is complete.

Findings Between March 2, 2017, and May 13, 2021, 239 children were assessed for eligibility, of whom 176 were randomly assigned. One patient assigned to high-dose intra-erythrocyte dexamethasone sodium phosphate did not initiate treatment. 175 patients received at least one dose of treatment (59 patients received the low dose and 57 received the high dose of intra-erythrocyte dexamethasone sodium phosphate, and 59 received placebo). The mITT population comprised 164 participants (56 children in the low-dose group, 54 children in the high-dose group, and 54 in the placebo group). Compared with the placebo group, no differences were identified with regard to change in mICARS score from baseline to 6 months in the low-dose group (least squares mean difference –1·37 [95% CI –2·932 to 0·190]) or the high-dose group (–1·40 [–2·957 to 0·152]; p=0·0765). Adverse events were reported in 43 (73%) of 59 participants in the low-dose group, 47 (82%) of 57 participants in the high-dose group, and 43 (73%) of 59 participants in the placebo group. Serious adverse events were observed in six (10%) of 59 participants in the low-dose group, seven (12%) of 57 participants in the high-dose group, and seven (12%) of 59 participants in the placebo group. There were no reports of hyperglycaemia, hypertension, hirsutism, or Cushingoid appearance in any of the treatment groups, nor any treatment-related deaths.

Interpretation Although there were no safety concerns, the primary efficacy endpoint was not met, possibly related to delays in treatment reducing the number of participants who received treatment as outlined in the protocol, and potentially different treatment effects according to age. Studies of intra-erythrocyte delivery of dexamethasone sodium phosphate will continue in participants aged 6–9 years, on the basis of findings from subgroup analyses from this trial.

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Research in context

Evidence before this study

We searched PubMed on Jan 1, 2024 for any articles published since Jan 1, 2000, without language restrictions, using the search terms "ataxia telangiectasia" and "treatment". The search was updated on March 12, 2024, for articles published between Jan 1, 2024 and March 12, 2024. 3628 publications were identified in the first search and 116 in the second. We filtered the results by searching for only clinical trials, meta-analyses, randomised controlled trials, reviews, and systematic reviews, which yielded 514 publications. We focused on publications that evaluated the effects of therapy on neurological symptoms of ataxia telangiectasia or neuroinflammation. Studies describing cancer treatment, infectious complications, supportive care, and single patient observations were excluded. Five publications described the use of oral betamethasone, one described use of intra-erythrocyte dexamethasone sodium phosphate, one showed that the use of growth hormone had no effect on lymphocyte numbers or ataxia, and one showed that amantadine sulfate was effective in treating the motor symptoms. Nicotinamide riboside was used in two studies and resulted in improvement of ataxia and increases in serum IgG concentrations, and improvement in coordination and eye movements. One study reported that treatment with acetyl-DL-leucine improved ataxia and ocular stability. Published trials of different agents for the treatment of neurological symptoms of ataxia telangiectasia or neuroinflammation are limited to phase 2 trials.

Added value of this study

To our knowledge, ATTeST is the largest randomised, placebo-controlled phase 3 trial evaluating the efficacy of intra-erythrocyte dexamethasone sodium phosphate for the improvement of neurological symptoms in patients with ataxia telangiectasia. The primary efficacy endpoint was not met after the 6-month treatment in the entire study population. Hypothesis generating subgroup analyses identified a potential benefit of treatment in patients aged 6–9 years, but not in patients who were ≥10 years or older. Rather than excluding older patients from future studies, our results indicate the need for development of better biomarkers of clinical response in patients aged 10 years and older. Until those biomarkers are available, stratification of patients with ataxia telangiectasia by age might be important when evaluating the efficacy of neuroprotective agents. Our supportive analyses also indicate the importance of adhering to a predefined schedule of treatment to achieve a measurable response to therapy.

Implications of all the available evidence

Available evidence suggests that corticosteroids might ameliorate neurological symptoms of ataxia telangiectasia; however, our trial did not provide definitive confirmation of such an effect. Corticosteroids have complex mechanism of action, including changes in gene expression and reduction in neuroinflammation, and although they are considered supportive therapy, their effect on gene expression might contribute to modification of the disease course, such as in Diamond Blackfan anaemia. Remaining questions include: (1) whether intra-erythrocyte dexamethasone sodium phosphate has an effect in patients younger than 10 years, which is the aim of an ongoing randomised trial (NCT06193200); (2) whether a potential treatment effect could be maintained over time; and (3) when might be the optimal timing to initiate treatment. Current therapies are usually started once neurological symptoms develop, which might not be early enough if a goal of treatment is durable modification of gene expression. Additional studies of potential biomarkers of disease severity that could be used as a basis for earlier interventions are needed, as are treatments that can be given safely in young children without affecting their growth and development. In addition to investigating the efficacy of intra-erythrocyte dexamethasone sodium phosphate in a larger cohort of children aged 6–9 years, we will continue to study the mechanism of action of intra-erythrocyte dexamethasone sodium phosphate, with the emphasis on differences in gene expression between responders and those who did not respond.

Introduction

Ataxia telangiectasia is a multisystem disorder characterised by progressive neurodegeneration. 82·0–97·5% of people with ataxia telangiectasia have classic disease, in which wheelchair dependence occurs at a median of age 10 years, whereas in patients with variant disease, wheelchair dependence occurs at a median age of 26–27 years.[1] Delaying neurological progression is paramount to improve patients' quality of life. Studies in mice or in cell lines have suggested several pathways leading to neuronal injury in ataxia telangiectasia, including increased oxidative stress from sustained microglial activation, increased inflammation, mitochondrial exhaustion, and altered neuronal membrane polarisation and neurotransmitter levels.[2–5] No curative therapies are approved for ataxia telangiectasia; however, many agents, including nicotinamide riboside, α-lipoic acid, triheptanoin, acetyl-DL-leucine, amantadine sulfate, and myo-inositol, have been studied with the aim of ameliorating oxidative damage, inflammation, mitochondrial dysfunction, and neurological symptoms. Findings from these small clinical trials require confirmation in randomised trials.[6]

In 2006, clinicians in Italy observed substantial improvement in the neurological symptoms of a 3 year-old child with ataxia telangiectasia who was given betamethasone for asthma, prompting a single participant trial, which confirmed the observation.[7] Subsequent studies described a benefit of low-dose oral betamethasone on neurological symptoms in children with ataxia telangiectasia. However, treatment discontinuation was

accompanied by recurrence of symptoms, suggesting that long-term administration of steroids might be required to preserve the benefit.[8–10] In a study of betamethasone used for 2 years in six participants with ataxia telangiectasia, transient neurological improvement was documented in five of six participants, but after 2 years of treatment, improvement persisted in only one participant. Adrenal suppression was documented in all participants.[11] These trials indicated that prolonged use of oral steroids was not a viable option for treatment of children with ataxia telangiectasia.

The encapsulation of dexamethasone sodium phosphate into autologous erythrocytes (EryDex; EryDel, Medolla, Italy) was developed as a novel option for continuous delivery of steroids to patients who require prolonged use. After an initial short-lived peak, dexamethasone is released slowly from erythrocytes over a 4-week period, avoiding side-effects observed with daily steroid use.[12] Intra-erythrocyte dexamethasone sodium phosphate was studied in an open-label, phase 2 trial in 22 children with ataxia telangiectasia: children had significant improvement in International Cooperative Ataxia Rating Scale (ICARS) scores compared with baseline, with a mean reduction of 4 points after 6 months of treatment.[13] Treatment continued in four participants up to 24 months, confirming continuous neurological response and a favourable safety profile.[14] Previous studies provided preliminary dosing data and encouraging safety and efficacy results, which prompted this phase 3 study (ATTeST) to evaluate efficacy of intra-erythrocyte dexamethasone sodium phosphate compared with placebo, on neurological symptoms in children with ataxia telangiectasia.

Methods

Study design and participants

ATTesT was a multicentre, randomised, double-blind, placebo-controlled, phase 3 trial conducted in 22 academic, public, and private medical centres in 12 countries (Australia, Belgium, Germany, India, Israel, Italy, Norway, Poland, Spain, Tunisia, the UK, and the USA). After the initial 6-month trial period, participants were eligible to continue an additional 6-months of double-blind, placebo-controlled treatment, designed to collect longer term safety and efficacy data. All participants who completed ATTeST treatment were eligible to enrol in an open-label extension study (IEDAT-03-2018) and receive high-dose intra-erythrocyte dexamethasone sodium phosphate. Here, we present data from the initial 6-month treatment period.

Patients aged 6 years and older who weighed more than 15 kg were recruited by site investigators at participating study centres. Eligible participants had a diagnosis of ataxia telangiectasia defined by neurological signs, including incoordination of head and eyes in lateral gaze deflection and gait ataxia, but autonomous gait had to be preserved (ICARS walking score 0–4). Genetic testing for ataxia telangiectasia was obatined; however, diagnosis based on clinical criteria was sufficient for enrolment and treatment, which could have been initiated before receiving the results of genetic testing. Exclusion criteria included lymphopenia (CD4 count <400 cells per mm^3 for participants aged 6 years, or <150 cells per mm^3 for participants aged >6 years); history of severe immunodeficiency; severe or unstable pulmonary, hepatic, or renal disease; uncontrolled diabetes; haemoglobinopathies; or current neoplastic disease. The study protocol was amended on April 16, 2019, to modify eligibility criteria related to CD4 count (previously <200 cells per mm^3 in participants aged >6 years) to facilitate patient enrolment after observing that CD4 cell counts often varied between 150–200 cells per mm^3 without associated infections. A complete list of eligibility criteria are provided in the study protocol (appendix p 12).

See Online for appendix

This trial was conducted in accordance with the Good Clinical Practice guidelines of the International Conference on Harmonization and the ethical principles of the Declaration of Helsinki. Written informed consent, describing potential harms and benefits to participants, was obtained from all participants or parents or legal guardians before screening. The protocol, approved by regulatory authorities and ethics committees of all participating study sites is included in the appendix (pp 12–180). This trial is registered with ClinicalTrials.gov, NCT02770807.

Randomisation and masking

Participants were randomly assigned (1:1:1) to low-dose intra-erythrocyte dexamethasone sodium phosphate, high-dose intra-erythrocyte dexamethasone sodium phosphate, or placebo using an independent interactive web response system. A minimisation procedure ensured that the proportions of participants who were male versus female, and 6–9 years versus 10 years or older, were comparable across treatment groups. Participants, employees of the sponsor, clinical staff, investigators, all raters, and central reviewers were masked to treatment assignment and dose allocations. The administered infusions were not distinguishable by colour or volume. Three sets of masked raters were used for assessment of: (1) safety, (2) efficacy by ICARS, and (3) efficacy by Clinical Global Impression-Change scale (CGI-C). Raters did not have access to assessments other than from their domain, to minimise bias in efficacy assessment based on profile of adverse events, and to achieve two independent efficacy assessments.

Procedures

The EryDex system encapsulates dexamethasone sodium phosphate (ex vivo) in patients' red blood cells obtained by drawing 50 mL of whole blood during each monthly treatment visit (appendix p 2). The blood is washed after the encapsulation process and before infusion, to remove

processing by-products and lysed cells (appendix pp 2, 12). Participants assigned to the low-dose group received autologous erythrocytes with approximately 5–10 mg (expected dose) of encapsulated dexamethasone sodium phosphate. The product was prepared ex vivo in a multi-step process and 2·0 mL of the 25 mg/mL dexamethasone sodium phosphate solution, plus 11 mL sterile water for injection in the same syringe (total volume 13 mL), were added to red blood cells. This dose delivered a mean of 8·23 mg (SD 3·30) dexamethasone sodium phosphate. Participants randomly assigned to the high-dose group received autologous erythrocytes with approximately 14–22 mg of dexamethasone sodium phosphate, prepared using 5·0 mL of the 25 mg/mL dexamethasone sodium phosphate solution, plus 11 mL sterile water for injection in the same syringe (total volume 16 mL), which delivered a mean of 17·4 mg (5·38) dexamethasone sodium phosphate. The placebo group received autologous erythrocytes treated with a placebo solution (5 mL of 0·372% NaCl solution), plus 11 mL sterile water for injection in the same syringe (total volume 16 mL). Processing and intravenous infusion took 2–3h to complete.

Before the first intra-erythrocyte dexamethasone sodium phosphate dose, baseline ICARS and Clinical global impression (CGI) evaluations were videotaped. These assessments were repeated at 3 and 6 months during the initial treatment period. Intra-erythrocyte dexamethasone sodium phosphate was administered monthly for 6 months with 21–31 days between infusions. All endpoint efficacy assessments, including those for participants who discontinued treatment prematurely, were scheduled at the end of the initial treatment period (6-month visit). Blood was collected according to the protocol for safety surveillance and exploratory analyses, which are ongoing. The COVID-19 pandemic altered the conduct of the study: enrolment was stopped when 175 participants were randomly assigned and started therapy (176 enrolled), as opposed to the 180 participants planned, and treatment was delayed or omitted for some participants.

Outcomes

The primary efficacy endpoint was change in modified ICARS (mICARS) score from baseline to month 6. The mICARS score was calculated during analysis from the full ICARS score documented by investigators. The ICARS includes the assessment of posture and gait, kinetic functions, speech, and oculomotor function[15] and has been validated in children with ataxia telangiectasia aged 7–14 years.[16] The mICARS consists of 11 items across three domains (posture and gait, kinetic function, and speech) but does not include the oculomotor domain (gaze evoked nystagmus) and some items from the kinetic domain of ICARS (knee tibia test [right and left], action tremor in heel to knee test [right and left], finger to nose test [dysmetria; right and left], finger to nose test [intention tremor; right and left], and finger to finger test [right and left]). mICARS scores range from 0 to 54 (higher scores indicate worse neurological function), compared with 0–100 in ICARS. The rationale for modification was based on the request from the US Food and Drug Administration to focus on domains that better predict motor functioning and are more relevant when evaluating disease progression in patients with ataxia telangiectasia. Efficacy results were analysed using both mICARS (primary analyses) and ICARS (sensitivity analyses), to satisfy requirements of US (mICARS) and European (ICARS) regulatory agencies. The two scales are presented in the appendix (p 3).

All ICARS raters were neurologists or neuro-physiotherapists who underwent training and met study-specific qualification criteria before and during the study. Assessments performed by site raters were videotaped and reviewed remotely by a central rater to minimise inter-rater variability. The central raters' scores were used in the primary analysis, with the exception of speech and in instances where two different central raters could not score a certain item from the videotaped exam, in which case the site rater's score for that item was used.

The key secondary efficacy outcome was the CGI-C, which measured change in the impression of disease severity from baseline to month 6 among the three treatment groups. This assessment was adapted for children with ataxia telangiectasia as another method of evaluating change in disease severity and thus treatment response.[16] To determine severity of illness by CGI, clinicians conducted an interview and examination assessing the participant's appearance (grooming, evidence of fall), neurological functioning (ataxia, cognition, apraxia, dysarthria, extrapyramidal motor symptoms, eye movements), activities of daily living, and mood. CGI was described on a scale of 0 to 4 (0, no signs of disease; 1, mild disease; 2, moderate disease; 3, severe disease; 4, very severe disease). Once severity was determined at baseline, the CGI-C scale was used to assess change in severity from baseline to month 6, using a 7-point scale, ranging from 1 (very much improved) to 7 (very much worse), with a score of 4 indicating no change.

Additional secondary outcomes were change in CGI-Severity score and Vineland Adaptive Behavior Scale (VABS) score at 6 months; the methods for these outcomes are included in the appendix (pp 6–7). Quality of life (EQ-5D-5L, tertiary endpoint) and the Ataxia-Telangiectasia Neurological Examination Scale Toolkit (AT-NEST, exploratory endpoint) will be reported separately.

Safety and tolerability of the two doses of intra-erythrocyte dexamethasone sodium phosphate compared with placebo in patients with ataxia telangiectasia was based on the occurrence of treatment-emergent adverse events, serious adverse events, discontinuation of study treatment due to adverse events, and changes in vital signs, laboratory parameters, electrocardiograms, and physical or neurological examinations.

Statistical analysis

Sample size calculations were based on analysis of the primary efficacy endpoint from the phase 2 study[13] and showed that 54 participants per treatment group would provide sufficient power for this study. The estimate was based on a two repeated measure study design to assess change in mICARS from baseline between the low dose group or high dose group and placebo, with a two-sided 0·05 significance level, when the treatment effect ranged between 3·0 and 3·7 (SD 5·0–7·0) for the mICARS score, and 3·7–4·2 (SD 5·0–7·4) for the ICARS score (PASS version 12.0.10).

The primary efficacy variable, change from baseline to month 6 in mICARS, was analysed using a mixed model repeated measures (MMRM), which included month 3 and month 6 data to improve precision of estimates. The MMRM included the baseline mICARS value as a covariate, five fixed effects (treatment, age [6–9 years or ≥10 years], sex, region, and visit), and one interaction term (treatment-by-visit). We calculated the treatment effect at month 6, reported as least squares mean differences, together with the associated two-sided 95% CI and p value. Model effect estimation was based on restricted maximum likelihood. The primary MMRM assumed missing at random as a means of handling missing data. Sensitivity analyses of these primary analyses consisted of ANCOVA at month 6 with missing data imputed using five different methods. The results from each of the sensitivity analyses were compared with the primary MMRM analysis. The results of imputations of missing data are included in the appendix (p 9). Analyses for regulatory submission used a hierarchical approach to testing of efficacy endpoints to handle multiple comparisons. Once high-dose intra-erythrocyte dexamethasone sodium phosphate was found to be not effective (p>0·05), further statistical testing for the low dose did not proceed in analyses for regulatory submission (appendix p 4). To provide a comprehensive report, we present the results of all prespecified analyses of primary and secondary endpoints, and report nominal p values.

The primary efficacy endpoint was assessed in the mITT population, which included all randomly assigned participants who received at least one dose of study treatment and had at least one post-baseline efficacy assessment of the primary outcome (compared with placebo control). The primary efficacy endpoint was also assessed in the per-protocol population, which included all participants who did not have any major protocol violations and completed the treatment period of the study within 228 days, allowing one missed dose. Participants who prematurely discontinued the study treatment owing to adverse events, without protocol violations, and returned for their final evaluation, were included in the per-protocol population. All determinations regarding major protocol violations and exclusions from the per-protocol population were discussed and agreed on by representatives of the sponsor and of the clinical research organisation during a blinded data review meeting before breaking the treatment blind and commencing final analysis on the locked database. We did prespecified subgroup analyses by age (6–9 years and ≥10 years), sex, region (1, India; 2, all regions except India and the USA; 3, USA), and genetic confirmation of ataxia telangiectasia diagnosis (confirmed or not confirmed or missing).

In summary, we report the results of the following analyses related to the primary efficacy endpoint: (1) change in mICARS from baseline to 6-month follow-up in the mITT population (primary analysis); (2) change in ICARS from baseline to 6-month follow-up in the mITT population (sensitivity analysis); (3) change in mICARS from baseline to 6-month follow-up in the per-protocol population (supporting analysis); (4) changes in mICARS and ICARS from baseline to 6-month follow-up in the mITT population by age, sex, region, and confirmation of genetic testing (subgroup analysis). The statistical analysis plan was amended on Dec 20, 2022, regarding the definition of subgroups for genetic testing (adjudicated genetic disease characteristics were replaced with confirmation of genetic disease), and the analysis by severity subgroups (which was subsequently not done). These modifications were made because there was no concordance among experts in determining ataxia telangiectasia severity subgroups or in adjudication by genetic disease characteristics.

The key secondary efficacy measure, CGI-change from baseline to month 6, was analysed in the mITT population, using logistic regression with age (6–9 years and ≥10 years), sex, treatment, and region as fixed effects. This analysis compared the proportion of participants with improvements (scores 1–3; responders) with those with stable or worsening disease (scores 4–7; non-responders) between the two treated groups and the placebo group. Results are presented as proportions of participants and logistic analysis odds ratio (OR) with 95% CI and associated p values; a p value of less than 0·05 was used to establish statistical significance. Our analysis of CGI-C differs from that prespecified in the the protocol and statistical analysis plan because the normality assumption in the initially proposed ANCOVA analysis was not met, and thus responder logistic regression analysis was used.

Change in CGI-S score and VABS were assesssed in the mITT population.

Safety was assessed in the safety population, which included all participants who received at least one dose of study treatment. No statistical comparisons were done between the groups. Adverse events were monitored throughout the study and were coded using MedDRA (version 24·0). An independent data and safety monitoring board reviewed the safety data throughout the trial to address any potential harm to participants. Coding included system, organ class, and preferred term.

All verbatim descriptions and coded terms were listed for all adverse events. Adverse events of special interest, including those which were potentially steroid related and those indicative of adrenal insufficiency were summarised. Clinically significant changes in vital signs, laboratory tests, electrocardiograms, and physical examination are presented descriptively.

Role of the funding source

The funders had a role in the study design, data collection, data analyses, data interpretation, and writing of the report.

Results

Between March 2, 2017, and May 13, 2021, 239 participants were screened for eligibility, of whom 176 were randomly assigned (59 participants in the low-dose intra-erythrocyte dexamethasone sodium phosphate group, 58 participants in the high-dose intra-erythrocyte dexamethasone sodium phosphate group, and 59 participants in the placebo group). One participant in the high-dose group did not receive study treatment. 175 participants received at least one dose of study treatment (59 participants in the low-dose group, 57 participants in the high-dose group, and 59 participants in the placebo group), of whom

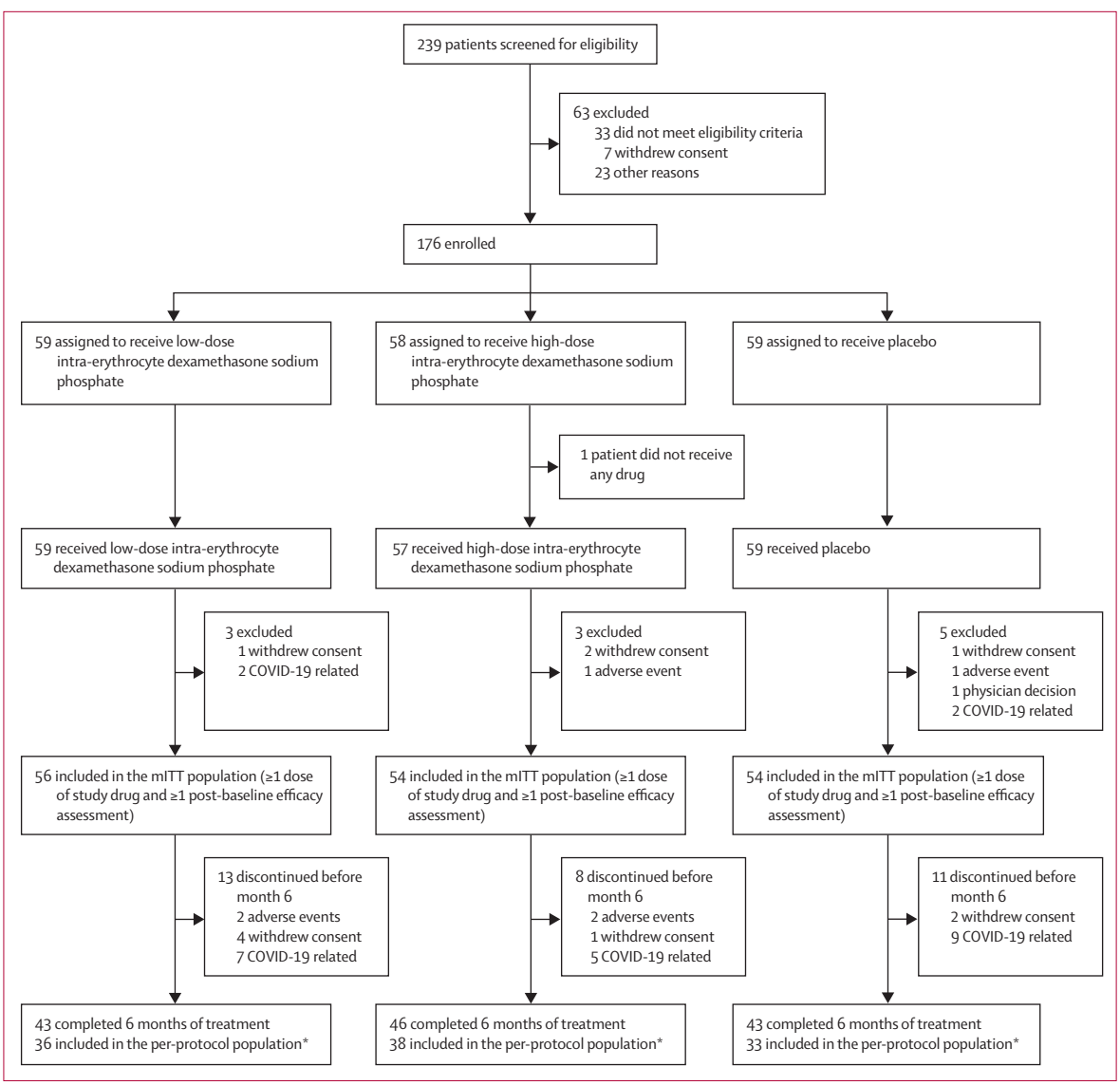

Figure 1: **Trial profile**

mITT=modified intention-to-treat. *57 patients from the mITT were excluded from the per-protocol population because they received fewer than five doses of drug (n=15; seven participants in low-dose group, five participants in the high-dose group, and three participants in the placebo group) or did not complete the initial treatment period within 228 days (n=42; 13 participants in low-dose group, 11 participants in the high-dose group, and 18 participants in the placebo group); reasons contributing to exclusions included a single, or a combination of these events: adverse events; delays in treatment due to COVID-19 disruption, travel, or any other reason; withdrawal of consent; or any other major protocol violation.

164 participants (56 participants in the low-dose group, 54 participants in the high-dose group, and 54 participants in the placebo group) had at least one post-baseline efficacy assessment, and thus were included in the mITT population (figure 1). 132 participants from the safety population completed the 6-month treatment period for the primary efficacy analysis (43 [73%] of 59 participants in the low-dose group, 46 [81%] of 57 participants in the high-dose group, and 43 [73%] of 59 participants in the placebo group). 107 (65%) of 164 participants in the mITT population completed treatment as per-protocol. Demographics and baseline neurological and clinical characteristics of all participants who received at least one dose of study treatment are presented in table 1.

Change in mICARS from baseline to 6 months did not differ between the treatment groups and the placebo group: least squares mean difference –1·37 (95% CI –2·932 to 0·190) in the low-dose group and –1·40 (–2·957 to 0·152; p=0·0765) in the high-dose group, compared with placebo. Sensitivity analysis for the primary efficacy endpoint of change in ICARS from baseline to month 6, as assessed by central review, confirmed non-significance for the primary efficacy endpoint results. In the supporting analysis for the primary efficacy endpoint, which included participants who received their therapy per-protocol, the change in mICARS from baseline to 6 months differed from placebo in both the low-dose group (least squares mean difference –2·80 [–4·668 to –0·932]) and high-dose group (–2·21 [–4·054 to –0·367]) compared with the placebo group (table 2).

The results of subgroup analyses, which were planned to examine potential differences in the response to low-dose and high-dose groups compared with placebo by age (6–9 years and ≥10 years), sex, genetic confirmation of ataxia telangiectasia diagnosis, and region, are shown in figure 2. Change in mICARS score from baseline differed from placebo among 6-9-year-olds who received high-dose intra-erythrocyte dexamethasone sodium phosphate (least squares mean difference –2·79 [95% CI –5·090 to–0·480]; nominal p=0·0185) and in participants from the USA (–4·79 [–8·889 to–0·698]; nominal p=0·0235). We found no effect in the other subgroups analysed. Change in ICARS score differed from that in the corresponding placebo subgroup only in participants aged 6-9 years who received high-dose intra-erythrocyte dexamethasone sodium phosphate (least squares mean difference –4·55 [95% CI –8·478 to –0·628]; nominal p=0·0236; appendix p 8).

Improvement in disease severity (CGI-C scores) between baseline and month 6 was observed in 19 (34%) of 56 participants in the low-dose group, 27 (50%) of 54 participants in the high-dose group, and 19 (35%) of 54 participants in the placebo group. The logistic regression ORs compared with placebo were 0·946 (95% CI 0·426 to 2·099; p=0·8919) for the low-dose group and 1·848 (0·842 to 4·053; p=0·1255) for the high-dose group. Stable disease (CGI-C score 4) was observed in 23 (41%) of 56 participants in the low-dose group, 17 (31%) of 54 (31%) participants in the high-dose group, and 22 (41%) of 54 participants in the placebo group (appendix p 5). Change in CGI-S score and VABS are described in the appendix (pp 6–7).

Adverse events were documented in 43 (73%) of 59 participants in the low-dose group, 47 (82%) of 57 participants in the high-dose group, and 43 (73%) of 59 participants in the placebo group (appendix p 10). Serious adverse events occurred in six (10%) of 59 participants in the low-dose group, seven (12%) of 57 participants in the high-dose group, and seven (12%) of 59 participants in the placebo group (table 3). The most common serious adverse event was a positive culture-based sterility test obtained at the end of processing (three [5%] of 59 participants in the low-dose group, five [9%] of 57 participants in the high-dose group, and four [7%] of 59 participants in the placebo group), which required reporting as a serious adverse event even though affected participants remained asymptomatic. The only treatment-related serious adverse event was severe anaemia in one (2%) patient in the high-dose

	Low-dose intra-erythrocyte dexamethasone sodium phosphate (n=59)	High-dose intra-erythrocyte dexamethasone sodium phosphate (n=57)	Placebo (n=59)
Age at enrolment, years			
Mean (SD)	9·5 (3·16)	10·2 (4·86)	10·3 (4·02)
6–9 years	34 (58%)	32 (56%)	32 (54%)
≥10 years	25 (42%)	25 (44%)	27 (46%)
Sex			
Male	30 (51%)	30 (53%)	30 (52%)
Female	29 (49%)	27 (47%)	29 (49%)
Ethnicity			
Hispanic or Latino	3 (5%)	2 (4%)	1 (2%)
Not Hispanic or Latino	56 (95%)	55 (96%)	58 (8%)
Race			
White	34 (58%)	36 (63%)	29 (49%)
Black	0	1 (2%)	2 (3%)
Asian	25 (42%)	20 (35%)	27 (46%)
Multiple	0	0	1 (2%)
Baseline modified ICARS total score			
Mean (SD)	27·9 (7·33)	27·5 (7·13)	28·2 (6·50)
α-fetoprotein			
Participants with data, n	58	55	58
Mean (SD), IU/mL	277·09 (179·689)	230·07 (198·72)	324·18 (187·34)
Mean CD4 cell count (SD), µL	489·5 (273·90)	498·1 (277·81)	422·9 (223·02)
Mean weight (SD), kg	27·49 (11·02)	26·92 (12·84)	27·79 (11·23)
Genetically confirmed ataxia telangiectasia	54 (92%)	54 (95%)	54 (92%)

Data are n (%), unless otherwise specified. Sex, race, and ethnicity were self-reported by participants or their parents. ICARS=International Cooperative Ataxia Rating Scale.

Table 1: **Baseline characteristics of the safety population**

group, which resolved, and treatment continued. Two (4%) of 57 participants in the high-dose group discontinued study participation owing to adverse events. Potentially steroid-related adverse events were reported in 30 (51%) of 59 participants in the low-dose group, 36 (63%) of 57 participants in the high-dose group, and 23 (39%) of 59 participants in the placebo group during the first 6-month treatment period (table 3). There were no adverse event reports of hyperglycaemia, hypertension, hirsutism, or Cushingoid appearance in any treatment group. Hypotension was reported in one participant in the high-dose group and one participant in the placebo group. No other clinically relevant adverse effects of treatment were noted in vital signs data, electrocardiograms, physical examinations, or neurological examinations.

Regarding laboratory findings, the anaemia described as a serious adverse event was identified in one participant in the high-dose group. Low cortisol levels and clinically significant hyperglycaemia were not reported during the initial treatment period. Participants in all three groups started treatment with normal values of haemoglobin A1c and values within normal ranges were sustained throughout treatment. The Columbia-Suicide Severity Scale showed no instances of suicidal ideation or behaviour at the 6-month evaluation. Irritability was the most common psychiatric complaint, reported for three (5%) of 59 participants in the low-dose group, one (2%) of 57 participants in the high-dose group, and one (2%) of 59 participants in the placebo group. There were no cases of steroid-induced psychosis. At baseline, the mean

	Low-dose intra-erythrocyte dexamethasone sodium phosphate	High-dose intra-erythrocyte dexamethasone sodium phosphate	Placebo
Primary efficacy analysis (mITT)			
Participants, n	56	54	54
Mean baseline mICARS score (SD)	28·0 (7·38)	27·5 (7·29)	28·4 (6·53)
Least squares mean difference* (95% CI; p value)	−1·37 (−2·93 to 0·19; p=0·0847†)	−1·40 (−2·96 to 0·15; p=0·0765)	..
Sensitivity analysis (mITT)			
Participants, n	56	54	54
Mean baseline ICARS score (SD)	49·7 (13·00)	50·0 (12·73)	51·1 (11·55)
Least squares mean difference* (95% CI; p value)	−0·71 (−3·31 to 1·90; p=0·5937†)	−1·84 (−4·44 to 0·76; p=0·1629†)	..
Supporting analysis (per-protocol population)			
Participants, n	36	38	33
Mean baseline mICARS score (SD)	27·3 (8·59)	27·6 (6·98)	28·2 (7·05)
Least squares mean difference* (95% CI; p value)	−2·80 (−4·67 to −0·93; p=0·0037†)	−2·21 (−4·05 to −0·37; p=0·0193†)	..

mITT=modified intention-to-treat population. mICARS=modified International Cooperative Ataxia Rating Scale. ICARS= International Cooperative Ataxia Rating Scale. *Compared with placebo at 6 months. †All p values are nominal; to adjust for multiple testing, the hierarchical approach required confirmation of significance in the high-dose group in the mITT population for the treatment to be considered effective.

Table 2: **Primary efficacy analysis, sensitivity analysis, and supporting analysis**

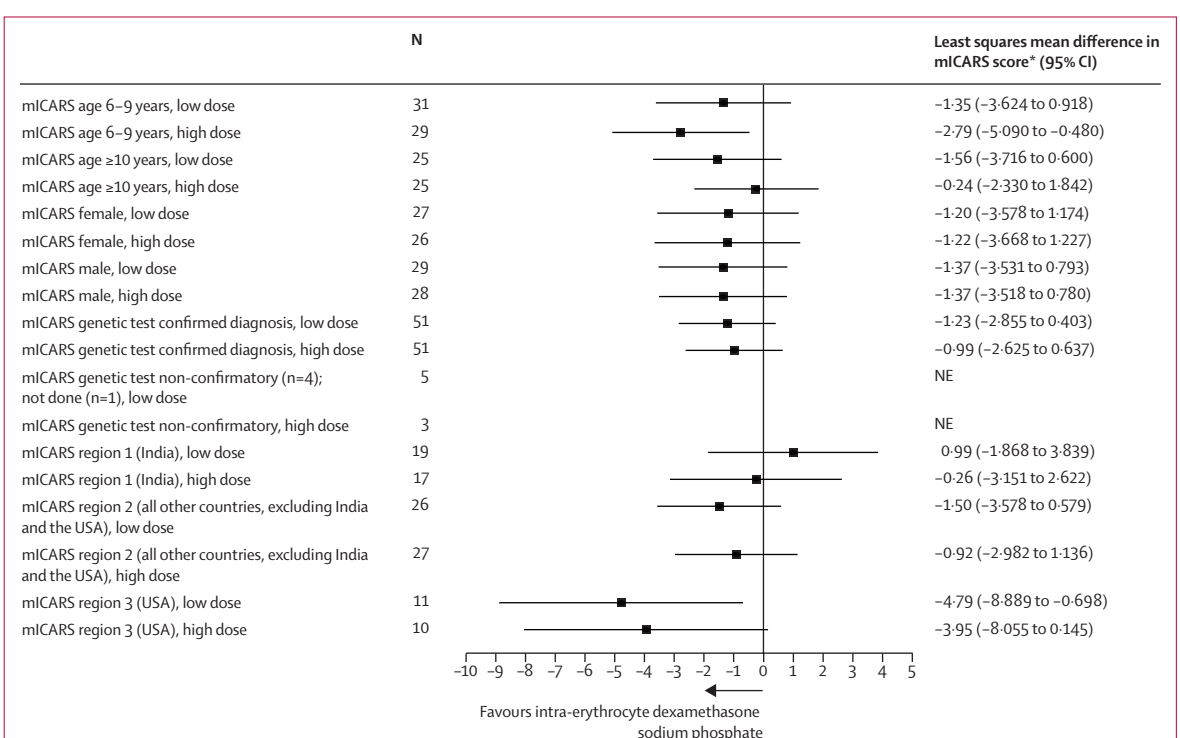

Figure 2: **Subgroup analyses of treatment response measured as change in mICARS score from baseline to month 6**
mICARS=modified International Cooperative Ataxia Rating Scale. N=number of participants at baseline. NE=not estimable. *Compared with placebo.

bone mineral density z-score was –1·08 (SD 1·39) in the low-dose group (50 patients had an available bone mineral density scan), –0·98 (1·43) in the high-dose group (43 patients with available scans), and –1·18 (1·66) in placebo group (52 patients with available scans). At baseline, seven (14%) of 50 participants in the low-dose group, seven (16%) of 43 participants in the high-dose group, and 11 (21%) of 52 participants in the placebo group had bone mineral density z-scores of less than 2·5, qualifying for a diagnosis of osteoporosis. At 6 months, the mean z-scores were –0·71 (SD 1·65) in the low-dose group (n=34), –1·28 (1·50) in the high-dose group (n=36), and –1·35 (1·59) in the placebo group (n=33). At 6 months four (12%) of 34 participants in the low-dose group, eight (22%) of 36 participants in the high-dose group, and eight (24%) of 33 participants in the placebo group qualified for diagnosis of osteoporosis. A full listing of treatment-emergent adverse events and an overall summary of adverse events are included in the appendix (pp 10–11).

Discussion

The primary analysis showed no statistically significant effect of intra-erythrocyte dexamethasone on neurological symptoms, as evaluated by mICARS or change in CGI-C scores. Inability to confirm the effect of treatment might be related to delays and omissions in treatments, as indicated by positive efficacy results in the per-protocol population, which excluded participants with delayed and missed treatments, and potential differences in treatment effect in children aged 6–9 years compared with children aged 10 years or older. Although a treatment effect was observed in the younger age group, when older patients were included, the effect was not significant.

Contributors to delayed treatments included difficulties with travel to treatment centres and disruptions caused by the COVID-19 pandemic. Pandemic control guidelines, including travel restrictions, which varied among countries and institutions, resulted in missed and delayed treatments. In some instances, treatment was delayed because investigators delayed visits to hospital to protect immunocompromised participants in the peak of the pandemic. Because of delays in treatment and missed doses, 35% of the mITT population did not receive treatment as planned.

In natural history studies, children with the classical type of ataxia telangiectasia aged younger than 6 years have few clinical signs of neurological deterioration; however, between age 6 and 10 years, there is rapid clinical decline, after which disease progression stabilises.[17] Rapid disease progression in children aged 6–9 years would allow for detection of divergence between treated patients and placebo controls over a shorter treatment period than in older patients, for whom slower disease progression would require a longer treatment period to confirm treatment effect. Additionally, treatment of neurodegenerative disorders is often more effective earlier in the disease course before significant neuronal damage occurs. Our subgroup analyses showed a positive effect of treatment in younger children using both mICARS and ICARS. This finding of differential response by age in subgroup analyses is important: it emphasises the need to start treatment in children with ataxia telangiectasia early; and, until a

	Low-dose intra-erythrocyte dexamethasone sodium phosphate (n=59)	High-dose intra-erythrocyte dexamethasone sodium phosphate (n=57)	Placebo (n=59)
Potentially steroid-related adverse events			
Any potentially steroid-related adverse events	30 (51%)	36 (63%)	23 (39%)
Blood and lymphatic system disorders	2 (3%)	1 (2%)	0
Leukopenia	2 (3%)	0	0
Gastrointestinal disorders	0	2 (4%)	1 (2%)
Anal pruritus	0	2 (4%)	1 (2%)
General disorders and administration site conditions	0	1 (2%)	0
Infusion site pruritus	0	1 (2%)	0
Infections and infestations*	22 (37%)	17 (30%)	13 (22%)
Bronchitis	3 (5%)	0	2 (3%)
Bacterial bronchitis	1 (2%)	1 (2%)	0
Conjunctivitis	2 (3%)	1 (2%)	0
Herpes zoster	1 (2%)	0	0
Influenza	2 (3%)	3 (5%)	0
Lower respiratory tract infection	2 (3%)	1 (2%)	0
Nasopharyngitis	6 (10%)	7 (12%)	4 (7%)
Otitis media	0	2 (4%)	0
Respiratory tract infection	1 (2%)	0	1 (2%)
Sinusitis	1 (2%)	0	0
Upper respiratory tract infection	3 (5%)	4 (7%)	4 (7%)
Investigations	4 (7%)	7 (12%)	3 (5%)
Blood triglycerides increased	0	2 (4%)	1 (2%)
Bone density decreased	1 (2%)	1 (2%)	0
Neutrophil count decreased	0	1 (2%)	0
Weight increased	1 (2%)	3 (5%)	2 (3%)
Metabolism and nutrition disorders	3 (5%)	2 (5%)	2 (3%)
Hypertriglyceridemia	0	2 (4)	0
Increased appetite	2 (3%)	0	2 (3%)
Musculoskeletal and connective tissue disorders	0	0	1 (2%)
Osteopenia	0	0	0
Osteoporosis	0	0	1 (2%)
Benign, malignant, and unspecified neoplasms (including cysts and polyps)	0	1 (2%)	1 (2%)
Skin papilloma	0	1 (2%)	1 (2%)
Respiratory, thoracic, and mediastinal disorders	8 (14%)	10 (18)	8 (14)
Cough	7 (12%)	9 (16%)	8 (14%)
Productive cough	1 (2%)	1 (2%)	0
Skin and subcutaneous tissue disorders	1 (2%)	9 (16%)	1 (2%)
Pruritus	1 (2%)	9 (16%)	0

(Table 3 continues on next page)

	Low-dose intra-erythrocyte dexamethasone sodium phosphate (n=59)	High-dose intra-erythrocyte dexamethasone sodium phosphate (n=57)	Placebo (n=59)
(Continued from previous page)			
Serious adverse events			
Any serious adverse event	6 (10%)	7 (12%)	7 (12%)
Blood and lymphatic system disorders	0	1 (2%)	0
Anaemia†	0	1 (2%)	0
Congenital, familial, and genetic disorders	0	0	1 (2%)
Hepato-lenticular degeneration	0	0	1 (2%)
General disorders and administration site conditions	0	0	1 (2%)
Pyrexia	0	0	1 (2%)
Infections and infestations	2* (3%)	1 (2%)	0
Herpes zoster	1 (2%)	0	0
Lower respiratory tract infection	1 (2%)	0	0
Pneumonia	1 (2%)	0	0
Sepsis	0	1 (2%)	0
Laboratory investigations	3 (5%)	5 (9%)	4 (7%)
Bacterial test positive	3 (5%)	5 (9%)	4 (7%)
Musculoskeletal and connective tissue disorders	0	0	1 (2%)
Juvenile idiopathic arthritis	0	0	1 (2%)
Nervous system disorders	1 (2%)	0	0
Dystonia	1 (2%)	0	0

Data are n (%). Adverse event coding included system, organ class, and preferred term. *Patients with more than one infection were counted only once. †Treatment related.

Table 3: **Potentially steroid-related adverse events (≥2 patients by preferred term) and serious adverse events in the safety population (n=175)**

better biomarker of response to therapy is identified, randomised therapeutic trials in patients with ataxia telangiectasia should be stratified by age and adequately powered within each age group.

We used mICARS as a new measure for assessment of neurological symptoms in patients with ataxia telangiectasia; mICARS uses a subset of the scores from the full ICARS score. Although no previous validation studies have been published for this measure, our sensitivity analyses showed no significant difference in responses to treatment whether they were measured by ICARS or mICARS. The clinical trial (NCT06193200), which is evaluating efficacy of intra-erythrocyte dexamethasone in a larger cohort of 6–9 year-olds, continues to gather full ICARS data and will validate abbreviated scales for efficacy assessment in children with ataxia telangiectasia.

In this trial, we collected blood specimens, which will be used to address questions related to the mechanism of action of steroids in this disease. Initial studies of betamethasone in patients with ataxia telangiectasia indicated that patients with the best neurological response to therapy also had the highest intracellular glutathione levels.[18,19] Molecular studies of nine patients treated with intra-erythrocyte dexamethasone sodium phosphate in the phase 2 study showed the effect of treatment on gene expression signature, with the upregulation of more than 500 genes and partial restoration of many metabolic pathways typically affected by loss of *ATM* activity.[20] Dexamethasone also induced alternative *ATM* gene splicing, resulting in production of a truncated but functional ATM protein.[21,22] Our analyses attempting to elucidate those findings on specimens collected during the ATTeST trial are ongoing.

The descriptive safety data, which showed no difference in the frequency of treatment-emergent adverse events or serious adverse events between treated groups and the placebo group, indicate a favourable safety profile of intra-erythrocyte dexamethasone sodium phosphate. Furthermore, side-effects typically observed with steroid use, such as Cushingoid features, were not reported. Low bone mineral density was present at baseline and slightly worsened in the high-dose and placebo groups after 6 months, indicating that this finding might be a part of the natural disease course of ataxia telangiectasia.

A major strength of the ATTeST trial is that it was a collaborative effort between leading academic clinical and basic science ataxia telangiectasia investigators, the sponsor, and regulatory agencies. This collaboration, in addition to evaluating a new drug in a large cohort of children, led to refinement of research assessment tools, such as mICARs and CGI-C, for children with ataxia telangiectasia. Many limitations of our study are inherent to studies of patients with ataxia telangiectasia, such as the absence of a biomarker for evaluation of treatment efficacy, incomplete understanding of the mechanism of neuronal damage and when it becomes irreversible, incomplete understanding of the natural history of progression of neurological symptoms at the start of our trial, difficulties in quantifying progression of disease and response to treatment, complexity of assessment tools, and day-to-day variability in symptoms. Other limitations were imposed by COVID-19-related research disruption, and difficulties with reaching treatment centres, compromising treatment delivery.

Our study in 6–9-year-olds with ataxia telangiectasia is ongoing (NCT06193200). The observed improved safety profile of intra-erythrocyte dexamethasone compared with oral corticosteroids requires confirmation through additional analyses of patients treated with intra-erythrocyte dexamethasone sodium phosphate for longer periods of time. Finally, considering the variety of indications for which corticosteroids are used, despite their numerous adverse effects, developing a treatment with maintained or enhanced efficacy and reduced side-effects, compared with oral corticosteroids, would have implications for patients with many other disorders.

Contributors

MM, PP, SIP, TC, LB, HL, WW, SZ, and GJ conceptualised the study. AS-P, MR, SIP, SW, MKK, HL, VU, AV, VL, RG, EF, GJ, MK, and BH curated data. WW and DT verified the data. DT and HL did the formal data analysis. AN, PP, RY, DT, LB, and SZ acquired funding. AN, AS-P, MR, PP, SIP, SG, SP, TC, MKK, HL, VU, AV, VL, AH, RG, BP, SZ, MK, and RB conducted the study. AS-P, PP, RY, SIP, TC, MR, SG, HL, WW, SZ, GJ, and RB were involved with methodology. AS-P, KV, PP, RY, SG, DT, MKK, HL, VU, WW, BP, and GJ were involved in project administration. AS-P, IM, MR, PP, RY, AH, SZ, and MK acquired resources for study implementation at study sites. AS-P, KV, PP, RY, MKK, LB, SG, HL, VU, WW, AV, VL, SZ, GJ, and MK supervised the study. AS-P, MR, SG, BP, SZ, and BH validated the data. SG, SZ, and BH visualised the data. DT, HL, SZ, and MK drafted the original manuscript. AS-P, IM, KV, PP, RY, SIP, SP, TC, MKK, HL, WW, VL, BP, EF, SZ, GJ, MK, RB, and BH wrote, reviewed, and edited the manuscript. All authors had full access to data, provided approval for the final submitted version to be published, and agreed to be accountable for all aspects of the work and take responsibility for the decision to submit for publication.

Declaration of interests

AN reports participation in a consortium that obtained the Horizon 2020 grant for this project. AS-P received study materials and the study drug from EryDel for this trial; reports grants for research in ataxia telangiectasia (AT children's project, AEFAT, Action for AT, Klinbeforsk, and Dam Foundation); and is the president of the Norwegian Society for Medical Genetics. EF received funding to her institution from EryDel for this project. GJ is employed as a chief medical officer by EryDel and Quince Therapeutics; was medical monitor for this trial; and received stock options from the sponsors. IM reports consulting fees, honoraria, or travel expenses from Boehringer-Ingelheim, Takeda, and CSL-Behring, for work unrelated to this project; and has held unpaid leadership positions in the past (president of the European Society for Immunodeficiencies Society, Monoclonal Antibodies for Children with Primary Immunodeficiencies, and International Patient Organisation for Primary Immunodeficiencies). KV reports honoraria from MedLink Neurology and holds leadership positions (secretary general of the Indian Epilepsy Society and Asian Epilepsy Academy). LB has a leadership role in Newron Pharmaceuticals; has received stock options from Quince Therapeutics; was the chief executive officer of EryDel; and holds a board position with Quince Therapeutics. MKK reports funding to her institution from EryDel for this trial; funding from Quince Therapeutics for the expanded access programme; and travel expenses from EryDel for attendance at the investigator meeting. MM received a grant and travel support from EryDel; holds a leadership position with Diatheva; and has stock options in EryDel and Quince Therapeutics. PP received grants from EryDel for this trial, paid to his institution; reports research grants from the Indian Council of Medical Research, Department of Science and Technology Science and Engineering Research Board, the Science and Engineering Research Board, Department of Biotechnology, Welcome-Department of Biotechnology, Promoting Academic research Conversion to Enterprise, Scientific Knowledge for Ageing and Neurological Ailments, and the Michael J Fox Foundation all paid to his institution; honoraria as a speaker from the International Parkinson and Movement Disorder Society, Movement Disorders Societies of Korea, Taiwan, and Bangladesh, and the National Institute of Mental Health and Neurosciences; holds leadership positions including chair of the education committee of the International Parkison's and Movement Disorders Society; and is the unpaid editor-in-chief of *Annals of Movement Disorders*. RY reports research grants from the Indian Council of Medical Research, Parkinson's and Movement Disorders Research Fund of the National Institute of Mental Health and Neurosciences, and the SKAN foundation; book royalties from Jaypee; speaker honoraria from International Parkison's and Movement Disorders Society; and holds a leadership role in the Parkinson's Society of Karnataka. RG reports participation on data safety monitoring or advisory boards for Biogen, Hikma, Merck, Roche, and Sanofi. TC received consulting fees from Syneos Health Communications and Scholar Rock; honoraria for CME educational programme development from Med Force and the Muscular Dystrophy Association; and participation on safety monitoring or advisory boards for Taysha Giant Axonal Neuropathy. WW reports grants from EryDel to their institution for this trial; is a member of a data safety monitoring board for a clinical trial of A-TC7 in ataxia telangiectasia; and is a trustee of the charity Syncope Trust & Reflex Anoxic Seizures. HL declares reports grants and equipment from EryDel to their institution for this trial; consulting fees from EryDel for analysis of adverse events and presentation to the US Food and Drug Administration; and travel expenses from EryDel for attending investigator meetings for this trial. VU received grants from EryDel to his institution for this trial. 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BH reports personal fees from Quince Therapeutics for her work in Clinical Development; received travel expenses from Quince Therapeutics for the investigator's meeting; is a consultant for Foundation for the Accreditation of Cellular Therapy; holds an unpaid position as the founder and chair of Florida Pediatric BMT and Cell Therapy Consortium (FPBCC) for 2018–23; and has received multiple grants for the work of the FPBCC. DT is the chief medical officer and chief executive officer of Quince Therapeutics. AV, BP, MR, RB, SIP, SG, SW, SP, VL, and AH declare no competing interests.

Data sharing

Any request for study data, including de-identified participant data, data dictionaries, and study documents (protocol, statistical analysis plan, and informed consent), will be reviewed by the sponsor's publication committee and granted based on scientific merit of the proposal, available funding, and signed data use agreement. Data will be available for 2 years from publication and can be requested via e-mail to dthye@quincetx.com.

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