Minimum effective low dose of antithymocyte globulin in people aged 5–25 years with recent-onset stage 3 type 1 diabetes (MELD-ATG): a phase 2, multicentre, double-blind, randomised, placebo-controlled, adaptive dose-ranging trial

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Summary

Background Type 1 diabetes remains an important health-care problem, with no disease-modifying therapies available in people with recent-onset, clinical type 1 diabetes. Adaptive trial designs, allowing faster evaluation of treatment modalities, remain underexplored in this stage of the disease. We aimed to identify the minimum effective dose of antithymocyte globulin (ATG) in people aged 5–25 years with recent-onset, clinical type 1 diabetes.

Methods MELD-ATG was a phase 2, double-blind, randomised, placebo-controlled, multi-arm, adaptive dose-ranging, parallel-cohort trial done in 14 accredited trial centres in eight countries (the UK, Denmark, Germany, Finland, Italy, Belgium, Austria, and Slovenia). Participants aged 5–25 years, diagnosed with clinical, stage 3 type 1 diabetes 3–9 weeks before treatment, with random C-peptide concentrations 0·2 nmol/L or more and at least one diabetes-related autoantibody (GADA, IA-2A, or ZnT8) were randomly assigned by a web-based randomisation system into seven consecutive cohorts receiving placebo, 2·5 mg/kg ATG, 1·5 mg/kg ATG, 0·5 mg/kg ATG, or 0·1 mg/kg ATG. Participants in cohort 1 were randomly assigned 1:1:1:1:1:1, participants in cohorts 2 and 3 were randomly assigned 1:1:1:1, and participants in cohorts 4–7 were randomly assigned 1:1:1. All cohorts included one placebo group and one 2·5 mg/kg ATG group. The other groups were assigned to ATG doses that were determined based on accruing data and the decision of the dose determining committee. The trial cohorts were stratified by age group (5–9 years, 10–17 years, and 18–25 years) with block sizes varying by cohort. Concealment lists, outlining the treatment allocation, were only available for the pharmacists; participants and study teams were masked to treatment allocation. ATG was administered by an intravenous infusion over 2 consecutive days. The primary outcome was the area under the curve (AUC) of the stimulated C-peptide concentration during a 2-h mixed-meal tolerance test at 12 months measured as ln(AUC C-peptide+1). Conditional on finding a statistically significant difference at p<0·05 for 2·5 mg/kg ATG versus placebo, the minimum effective dose of ATG was determined. All randomly assigned participants were included in the primary analysis. All participants who received the study drug were included in the safety analysis. The trial was registered at ClinicalTrials.gov (NCT04509791) and is completed.

Findings Between Nov 24, 2020, and Dec 13, 2023, 152 people were recruited and screened, 117 of whom were randomly assigned (placebo n=31, 0·1 mg/kg ATG n=6, 0·5 mg/kg ATG n=35, 1·5 mg/kg ATG n=12, and 2·5 mg/kg n=33). 54 (46%) of 117 participants were male and 63 (54%) were female. Participants were mainly European. The 0·1 mg/kg dose and the 1·5 mg/kg dose were progressively dropped from the study. At 12 months, the mean ln(AUC C-peptide+1) was 0·411 nmol/L per min (SD 0·032) in the placebo group and 0·535 nmol/L per min (0·032) in the 2·5 mg/kg ATG group. The mean difference in the ln(AUC C-peptide+1) between 2·5 mg/kg ATG and placebo was 0·124 nmol/L per min (95% CI 0·043–0·205; p=0·0028). At 12 months, the mean ln(AUC C-peptide+1) in the 0·5 mg/kg ATG group, the remaining middle dose, was 0·513 nmol/L per min (SD 0·032), with a mean baseline-adjusted difference from placebo of 0·102 nmol/L per min (95% CI 0·021–0·183; p=0·014). Cytokine release syndrome occurred in 11 (33%) of 33 participants in the 2·5 mg/kg ATG group, eight (24%) of 34 in the 0·5mg/kg ATG group, and no participants in the placebo group. Serum sickness occurred in 27 (82%) participants in the 2·5 mg/kg ATG group, 11 (32%) in the 0·5 mg/kg ATG group, and no participants in the placebo group. There were no deaths related to adverse events.

Interpretation In young people with recent-onset, clinical type 1 diabetes, 2·5 mg/kg and 0·5 mg/kg ATG reduced loss of β-cell function, showing the potential of an affordable, repurposed agent, ATG, in a low and safe dose, as a disease-modifying agent in this population.

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Introduction

Type 1 diabetes is a chronic disease affecting approximately 9·5 million people worldwide.[1,2] Type 1 diabetes affects both adults and children, but in children and adolescents, incidence rates have been increasing by more than 2% per annum in the past 20 years.[2] Growing insight into type 1 diabetes pathogenesis as an autoimmune disease in which destruction of pancreatic insulin-producing β cells leads to insulin dependence has allowed identification of promising disease-modifying interventions.[1,3] Several interventions have been tested in people with recent-onset clinical type 1 diabetes (stage 3), and showed some therapeutic success, with preservation of stimulated C-peptide in the first year after diagnosis.[4] However, the field is progressing slowly, with sequential testing of new drugs versus placebo.[5] Doses and administration schedules of these therapies are primarily based on data from animal models, the transplantation field, or other autoimmune conditions. As such, each trial takes years to complete, and, if the results are promising, the process needs to start again to answer additional questions, particularly related to optimal doses and target populations. The progression of type 1 diabetes is most aggressive in children, as reflected by more rapid loss of C-peptide than in adults,[6,7] with subanalyses of some intervention studies showing a higher potential for immunotherapy agents to preserve endogenous β-cell function in the youngest participants.[8,9] However, most clinical trials have limited the lower age of the study population to 8 years due to safety concerns.[10–12]

Traditional dose-ranging trial designs fix the number of people randomly assigned to several doses at trial initiation. An adaptive trial design has multiple biomarker-based interim analysis points, at which dose

Research in context

Evidence before this study

The efficacy and safety of antithymocyte globulin (ATG) in preventing C-peptide loss as a marker of functional β-cell mass in people with recently diagnosed type 1 diabetes has been previously reported in three clinical studies. We searched PubMed for articles published in English between Jan 1, 2000, and Jan 1, 2025, using the terms ("anti-thymocyte globulin" AND "type 1 diabetes" AND "C-peptide") as well as ("ATG" AND "type 1 diabetes" AND "C-peptide"). The first study (the START trial) reported an absence of efficacy of 6·5 mg/kg ATG. In contrast, two subsequent studies showed the efficacy and safety of a lower dose, 2·5 mg/kg, of ATG, in adolescents and adults with new onset, clinical type 1 diabetes. A preliminary study by Haller and colleagues suggested less C-peptide loss in individuals treated with ATG and granulocyte-colony stimulating factor than with placebo. These observations were partially confirmed in a subsequent Trialnet study, in which C-peptide loss was lower in adolescents and adults treated with ATG, but not in those treated with ATG and G-CSF. More recently, Haller and colleagues reported 2-year clinical trial outcome data confirming a sustained effect of 2·5 mg/kg ATG on C-peptide and glycated haemoglobin A_{1c} (HbA_{1c}). Mechanistic studies on the effects of ATG on lymphocyte subsets are emerging, but clarity is needed on dosing and whether the depletion of lymphocytes and the changes in CD4 to CD8 ratio observed with ATG are related to the metabolic treatment effect.

Added value of this study

We investigated the efficacy and safety of different doses of ATG in young people (aged 5–25 years) with recently diagnosed, clinical type 1 diabetes using an innovative, adaptive trial design, allowing dropping (or restarting) doses on the basis of prespecified criteria. We not only achieved our primary endpoint, showing prevention of functional β-cell mass loss, measured as the difference in stimulated C-peptide at 12 months, for 2·5 mg/kg ATG versus placebo, but also identified a minimum effective dose of 0·5 mg/kg. Those treated with 0·5 mg/kg also had a lower HbA_{1c} compared with placebo and had fewer side-effects compared with those treated with 2·5 mg/kg, in particular cytokine release syndrome and serum sickness. The novel, adaptive trial design of this study with progressive age drop-down and its execution in the context of a clinical trial platform with accredited clinical trial sites (INNODIA), allowed us to test multiple doses of ATG over a large age range, illustrating that this novel way of testing disease-modifying therapies could allow an increased pace of finding treatments to arrest type 1 diabetes progression.

Implications of all the available evidence

Our findings strengthen the potential of ATG as a safe agent for therapy in children and adolescents with recent-onset, stage 3 type 1 diabetes. Our study also emphasises the feasibility of adaptive trial designs for disease-modifying therapies in type 1 diabetes. The observations that a therapy such as ATG is most effective in the youngest participants suggest there should be an alteration in the regulatory pathways for testing and approving disease-modifying therapies in type 1 diabetes.

selections for subsequent recruitment of participants can be altered.[13,14] There is growing evidence on the potential of adaptive trial designs in type 1 diabetes,[15–17] as they limit experimentation at dose levels that show either a lack of response or unwanted side-effects, and can more rapidly and efficiently identify the lowest safe and efficacious dose.

Polyclonal antithymocyte globulin (ATG), a well known drug in transplantation immunology,[18] has shown disease-modifying effects in people with type 1 diabetes, with 2·5 mg/kg able to delay β-cell destruction in people with recent-onset, clinical, stage 3 type 1 diabetes, in contrast to the higher dose of 6·5 mg/kg, which showed an accelerated loss of C-peptide.[12,19–21] These doses, suggested by the transplantation experience, other autoimmune disease therapies, and mouse experiments, were tested in adults and adolescents, and showed different immune-modulatory properties, with the lower dose resulting in immune modulation, rather than immune suppression, compared with the higher dose.[12,22] However, no further dose-finding studies exploring even lower doses, or investigations in young children, have been done.

Our aim was to assess the efficacy and safety of a range of low ATG doses in preserving β-cell function 1 year after treatment in people with recent-onset, clinical type 1 diabetes, proceeding rapidly to include children as young as 5 years, using an adaptive trial design.

Methods

Study design

The Minimum Effective Low Dose: Anti-human Thymocyte Globulin (MELD-ATG) trial was a phase 2, multicentre, double-blind, randomised, placebo-controlled, multi-arm, adaptive dose-ranging, parallel-cohort trial done in 14 accredited trial centres in hospitals in eight countries in the INNODIA network (the UK, Denmark, Germany, Finland, Italy, Belgium, Austria, and Slovenia; the full list of centres is in appendix p 3).

The trial was conducted in accordance with the principles of the Declaration of Helsinki and Good Clinical Practice guidelines,[23] and its execution was guided by a trial management group. The INNODIA Patient Advisory Committee provided guidance in conception, realisation of educational materials for recruitment, and retention in the trial. Study results have been published on the European Clinical Trials Database. A trial steering committee monitored the progress of the study, and an independent data monitoring committee reviewed efficacy and safety data. Two polyclonal, rabbit-derived ATG batches were provided by Sanofi (Research and Development, Montpellier, France) through INNODIA. Ethical approval was obtained from all participating clinical centres after approval by the central ethics committee (University Hospitals Antwerp, Antwerp, Belgium; reference 2020/32/414). The authors vouch for the accuracy and completeness of the data and analysis, and for the fidelity of the trial to the protocol.[23] The trial was registered on Oct 8, 2020, with ClinicalTrials.gov (NCT04509791).

Participants

Participants were aged 5–25 years at consent; had a diagnosis of clinical, stage 3 type 1 diabetes 3–9 weeks before treatment day 1; had random C-peptide concentrations 0·2 nmol/L or more; and had at least one diabetes-related autoantibody (GADA, IA-2A, or ZnT8). Insulin antibodies were also measured, but because participants were receiving insulin injections at the time of screening, they were not taken as a criterion for inclusion. Key exclusion criteria were major systemic illnesses, active or chronic infections, malignancies, and treatment with other immunomodulatory agents (the full list of exclusion criteria is in appendix p 8). Sex and ethnicity were self-reported by study participants or their parents or legal guardian as female or male, and as European, African, Asian, or mixed ethnicity, respectively. Written informed consent was obtained from all participants older than 16 years in the UK or older than 18 years in all other countries, whereas younger participants gave assent and written informed consent was obtained from their parents or legal guardian.

Randomisation and masking

The adaptive trial design included one placebo group and four groups with active ATG doses (appendix pp 26–27). The trial had six planned interim analyses, resulting in seven cohorts. Cohort 1 included participants 1–30, randomly assigned 1:1:1:1:1; cohorts 2 and 3 included participants 31–54, randomly assigned 1:1:1:1; and cohorts 4–7 included participants 55–117, randomly assigned 1:1:1.[23] All cohorts included one placebo group and one 2·5 mg/kg ATG group. The other groups were assigned to ATG doses that were selected from 0·1 mg/kg, 0·5 mg/kg, and 1·5 mg/kg based on accruing data and the decision of the dose determining committee. The web-based randomisation system Sealed Envelope was used to generate treatment allocations and execute randomisation, based on block randomisation (with block size of five in cohort 1, four in cohorts 2 and 3, and three in cohorts 4–7) within age strata (5–9 years, 10–17 years, and 18–25 years). Concealment lists, outlining the treatment allocation, were only available for the pharmacists and, in case of unmasking, to specific study personnel. ATG doses and placebo were prepared by local unmasked pharmacists or nurses, and infusion bags were delivered to the study teams with a masked label, ensuring masking of participants and study teams (study nurses and principal investigators) who were responsible for collecting source data from participants. During the interim analyses, the dose determining committee, as well as trial and senior statisticians, were unmasked to treatment allocation in order to make decisions on doses

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See **Online** for appendix

For **NCT04509791** see https://clinicaltrials.gov/study/NCT04509791?term=MELD-ATG&rank=1

For **Sealed Envelope** see https://www.sealedenvelope.com/simple-randomiser/v1/

For the **study information on the European Clinical Trials Database** see https://www.clinicaltrialsregister.eu/ctr-search/trial/2019-003265-17/results

to be discontinued or continued. The independent data monitoring committee were masked to treatment allocation on request, and data by treatment allocation was coded A, B, C, D, and E. At prespecified timepoints, after each cohort was fully recruited and received the intervention, an unmasked dose determining committee selected doses to take forward in subsequent cohorts and approved age expansion to lower ages using prespecified criteria (including metabolic and immune biomarkers, namely stimulated C-peptide concentrations and CD4 to CD8 ratios).

Procedures

Details of the administration of ATG and placebo are outlined in the protocol.[23] Briefly, ATG was administered by an intravenous infusion over 2 consecutive days. On day 1, the infusion lasted at least 12 h, with a maximal dose of 0·5 mg/kg ATG. On day 2, the infusion lasted at least 8 h, with the remainder of the dose administered.

The trial duration per participant was approximately 13 months, including a 2–3-week screening period, 2 days of treatment, and 12 months of follow-up (including follow-up visits at 1 week, 2 weeks, 4 weeks, 3 months, 6 months, and 12 months after treatment). For assessments at each visit, see appendix pp 5–6. An age expansion to include participants aged 5–11 years was implemented after ten participants aged 12–17 years had been treated and observed for at least 4 weeks after receiving ATG, and data were reviewed by the independent data monitoring committee and dose determining committee (appendix pp 26–27).

At each interim analysis, the middle doses were selected by the dose determining committee using all available clinical, mechanistic, and safety data from the previous cohorts, assisted by a Bayesian model prediction, using all available mixed meal tolerance test (MMTT) C-peptide measurements and CD4 to CD8 T-cell ratios.[23] All available data were used in a statistical analysis to establish which of the doses (0·1 mg/kg, 0·5 mg/kg, 1·5 mg/kg, and 2·5 mg/kg) were predicted to give a significant result, from a two-sample *t*-test, for a 6-month dose effect at the end of the study. The reason for choosing a 6-month comparison for the interim analyses was to reduce the uncertainty in making predictions at the 12-month timepoint. Each interim analysis required the estimation of a Bayesian repeated measures model including fixed effects for categorical time and a linear (ie, continuous dose effect) dose level, along with an interaction term between time and dose, and a random effect for participant. Only vague prior distributions were used in this model and no external data or evidence had an influence on the analysis. This model was used to calculate the predictive probability that the mean ln(area under the curve [AUC] of C-peptide + 1) was different from placebo for each dose level, assuming that the remaining participants were allocated to the middle dose. The lowest dose that gave a predicted probability greater than 0·9 was selected for the next cohort. This dose could also be 2·5 mg/kg. Middle doses could be dropped or restarted at each dose decision moment. In addition, the interim analyses included information based on the accruing CD4 to CD8 T-cell count ratio outcome at 1, 2, 4, and 12 weeks using a repeated measures model with fixed effects of dose and nominal days along with an interaction term between time and dose since randomisation. The mean differences between each dose level and placebo were estimated with a 95% CI. 95% CIs that indicated no evidence of change in CD4 to CD8 T-cell count ratio from baseline (ie, included 0) were used as an indication that the dose might be inactive and dropped from further cohorts. These results were used in conjunction with the C-peptide modelling using a Bayesian model of transformed logarithm (ln) of AUC C-peptide. The data could only be soft locked a few days before the meeting of the dose determining committee and interim analysis to enable the collection of as many data as possible to inform the dose decision. The dose determining committee looked at the predictions, the ratio of CD4 to CD8 T cells, and clinical safety reports to make the decision of which doses to include in the subsequent cohorts.

Outcomes

The primary outcome was the AUC of the stimulated C-peptide concentration (nmol/L per min), calculated using the trapezoidal rule, during a 2-h MMTT at 12 months after treatment, and analysed centrally (appendix pp 6–7).

Secondary outcomes were MMTT AUC C-peptide at baseline, 3 months, 6 months, and 12 months after treatment; glycated haemoglobin A_{1c} (HbA_{1c}) at baseline, 3 months, 6 months, and 12 months after treatment; total daily insulin dose (calculated in the clinic as the average dose per kg over the 3 days preceding study visits) at baseline, 1 week, 2 weeks, 4 weeks, 3 months, 6 months, and 12 months after treatment; continuous glucose monitoring (CGM) metrics (time in range, time in tight range, time above range, and time below range) using a blinded Dexcom G6 for 14 days, at 3 months, 6 months, and 12 months after treatment; ratio of absolute counts of CD4 and CD8 T cells at baseline, 1 week, 2 weeks, 4 weeks, 3 months, 6 months, and 12 months after treatment; type 1 diabetes-associated autoantibodies (GAD65, IAA, IA-2A, and ZnT8A) at screening and 12 months after treatment; monthly fasting and stimulated dried blood spot C-peptide measurements after treatment, before and 60 min after consumption of a standard liquid meal at home (more detail on analytical methods is in the appendix pp 5–6); and descriptive analysis of the safety profile of different doses of ATG in different age groups. Additionally, insulin dose-adjusted HbA_{1c} was calculated as HbA_{1c} (%) + (4×insulin units/kg per day) as a prespecified outcome.

Exploratory outcomes were effects of treatment on other biomarkers related to immunological changes and β-cell death or survival; multi-dimensional analyses of changes in type 1 diabetes phenotypes by immunological, proteomic, metabolomic, and lipidomic studies and the relation of these to clinical outcomes and progression; fasting C-peptide, fasting glucose, and adjusted ratio of C-peptide and glucose at baseline, 3 months, 6 months, and 12 months after treatment; and β-cell responsiveness (measured as change in C-peptide 0–60 min per change in glucose) calculated separately from MMTT and dried blood spot data at 3 months, 6 months, and 12 months after treatment for MMTT and monthly for dried blood spot. All exploratory outcomes will be reported separately.[23]

Adverse events were summarised according to system organ class and preferred term using the Medical Dictionary for Regulatory Activities version 27.0. The severity of adverse events and their relationship to treatment were assessed by the investigators according to the National Cancer Institute Common Terminology for Adverse Events version 5.0.[24] In the case of serious adverse events, masking was maintained, if possible, but investigators could execute an unmasking procedure if deemed necessary. Reporting of adverse events was required during the entire trial participation. Cytokine release syndrome and serum sickness, which are known adverse events of ATG, were defined according to specific criteria (appendix p 9).

Statistical analysis

Sample size calculation was based on the primary hypothesis of comparing 2·5 mg/kg ATG with placebo for the primary endpoint, being the ln of the AUC of C-peptide during an MMTT. A between-person SD estimate of 0·264 nmol/L per min on the transformed ln(AUC C-peptide + 1) scale was obtained using INNODIA observational data from people aged 5–25 years with newly diagnosed clinical type 1 diabetes.[23] Assuming this SD and comparing 2·5 mg/kg ATG with placebo on the transformed ln(AUC C-peptide + 1) scale, 32 participants in each group would provide more than 90% power at a 5% significance level to detect a change of 0·22 nmol/L per min using a two-sided, two-sample *t*-test.

The primary and secondary analyses were carried out according to the intention-to-treat principle as described in the statistical analysis plan (appendix pp 53–165). All participants who were randomly assigned and part of the intention-to-treat population were included in the primary and secondary analyses, apart from the safety analysis, which included only participants who received treatment.

Continuous variables are summarised as sample size and mean (SD) or median (maximum, minimum, and IQR) where data were skewed. Frequency and percentages were reported for categorical measures. The 2-h MMTT mean C-peptide concentration from the AUC was transformed using the function ln(AUC C-peptide + 1).[25]

For all key endpoints, a repeated measures mixed effects model was used. We had high data availability for our primary outcome, with no evidence that missing observations were likely to be systematically different from those available. Thus, we relied on the repeated measures mixed effects model to incorporate missing observations under a missing at random assumption. The model was adjusted for baseline levels of the same endpoint. For the primary analysis, the family-wise error rate was controlled at 5% by using a gatekeeping procedure for the hypothesis test for 2·5 mg/kg ATG versus placebo. Specifically, conditional on finding a statistically significant difference ($p<0·05$), lower doses were then tested to establish the minimum effective dose. We formally explored differential treatment effects by age group (5–9 years, 10–17 years, and 18–25 years) by including a treatment by time by age group interaction for the primary analysis. The secondary outcomes and subgroup analysis by age group were not included in the multiplicity control, so individual findings should be interpreted as exploratory (additional statistical methods are in the appendix pp 6–7).

We conducted sensitivity analyses exploring differential treatment effects over time by sex and batch individually by refitting the primary analysis model that incorporates an interaction term between sex, treatment, and time and a second model that incorporates an interaction term between batch, sex, treatment, and time.

In a post-hoc analysis, we calculated the quantitative response C-peptide at 1 year, developed by Bundy and Krischer.[26] This estimates the expected C-peptide at 1 year (ln [x+1] scale), given baseline C-peptide (ln [x+1] scale) and age at randomisation, and compares it with that observed in the study to provide a standardised response metric, with values greater than 0 representing better than expected response and values less than 0 representing worse than expected response.

All treatment effect estimates are reported with associated 95% CIs. Stata version 18.5 was used for all analyses.[27]

For the **Medical Dictionary for Regulatory Activities** see https://www.meddra.org/

Role of the funding source

The funder of the study had no role in study design, data collection, data analysis, data interpretation, or writing of the report.

Results

Between Nov 24, 2020, and Dec 13, 2023, 152 people were recruited and screened, 117 of whom were randomly assigned (placebo n=31, 0·1 mg/kg ATG n=6, 0·5 mg/kg ATG n=35, 1·5 mg/kg ATG n=12, and 2·5 mg/kg n=33; figure 1; appendix pp 26–28). Reasons for ineligibility at screening were not meeting inclusion criteria (seven participants with C-peptide <0·2 nmol/L and seven with absence of autoantibodies), meeting safety exclusion criteria (seven participants), declining to

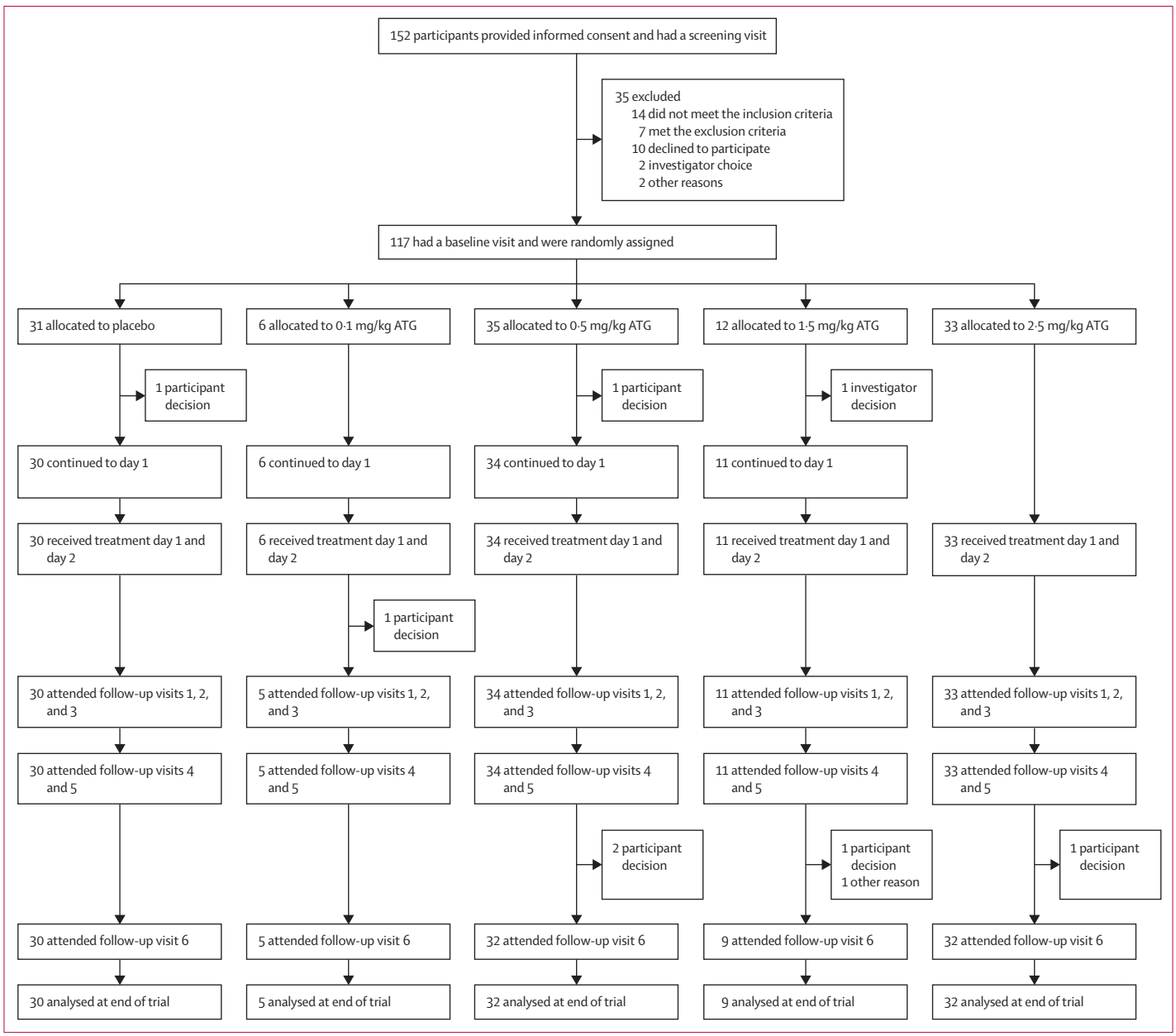

Figure 1: **Trial profile**
ATG=antithymocyte globulin

participate (ten), known allergy to rabbits (one), unable to cannulate (one), or other personal reasons (two; figure 1).

54 (46%) of 117 participants were male and 63 (54%) were female (table 1). 21 (18%) participants were aged 5–9 years, 76 (65%) were aged 10–17 years, and 20 (17%) were aged 18–25 years (table 1; appendix p 28). Cohort 1 included participants on placebo and all four ATG doses. The four groups for cohorts 2 and 3 were placebo, 0·5 mg/kg ATG, 1·5 mg/kg ATG, and 2·5 mg/kg ATG, following exclusion of 0·1 mg/kg ATG at the first interim analysis by the dose determining committee based on prespecified criteria, including clinical, metabolic (C-peptide), and immune (CD4 to CD8 ratio) data. The age expansion occurred after recruitment of cohort 2, which resulted in no participants aged 5–9 years receiving 0·1 mg/kg ATG. At the third interim analysis, 1·5 mg/kg ATG was dropped by the dose determining committee and the remaining cohorts 4–7 included placebo, 2·5 mg/kg ATG, and 0·5 mg/kg ATG (appendix pp 26–27). The last follow-up visit of the last recruited participant was on Dec 16, 2024.

Most participants were European, and baseline characteristics were well balanced between the three dose groups included in all cohorts (placebo, 0·5 mg/kg ATG, and 2·5 mg/kg ATG), except for sex, with more male participants in the placebo group than female participants (table 1). Three participants, one in the placebo group, one in the 0·5 mg/kg ATG group, and one in the 1·5 mg/kg ATG group, withdrew after randomisation and before treatment day 1 (figure 1). Of the 114 participants who received treatment, one in the 0·1 mg/kg ATG group, two in the 0·5 mg/kg ATG group, two in the 1·5 mg/kg ATG group, and one in the 2·5 mg/kg ATG group discontinued the study during follow-up (figure 1).

For the primary outcome, 434 (93%) of 468 datapoints were available, with 99 (85%) of 117 participants having complete data across all timepoints. The mean ln(AUC C-peptide+1) at 12 months was 0·411 nmol/L per min (SD 0·032) in the placebo group and 0·535 nmol/L per min (0·032) in the 2·5 mg/kg ATG group. The baseline-adjusted mean difference in ln(AUC C-peptide+1) between 2·5mg/kg ATG and placebo was 0·124 nmol/L per min (95% CI 0·043–0·205; p=0·0028). The mean ln(AUC C-peptide+1) in the 0·5 mg/kg ATG group, the remaining middle dose, at 12 months was 0·513 nmol/L per min (SD 0·032). The mean baseline-adjusted difference in ln(AUC C-peptide+1) between 0·5 mg/kg ATG and placebo was 0·102 nmol/L per min (95% CI 0·021–0·183; p=0·014). Results for all doses are shown in the appendix (p 40).

The change from baseline in mean ln(AUC C-peptide+1) at 3, 6, and 12 months is shown in figure 2A and the appendix (pp 29–31). We found no evidence of a statistically significant treatment effect by age group (p=0·42 for the age group by treatment by time interaction).

At 12 months, the adjusted mean difference in HbA_{1c} was –0·36% (95% CI –0·80 to 0·08; p=0·11) between the 2·5 mg/kg ATG group and the placebo group, and was –0·50% (–0·93 to –0·07; p=0·024) between the 0·5 mg/kg ATG group and the placebo group (figure 2B). For daily insulin doses, the adjusted difference was –0·036 units/kg per day (95% CI –0·128 to 0·056; p=0·45) between the 2·5 mg/kg ATG group and the placebo group and was –0·013 units/kg per day (–0·104 to 0·079; p=0·79) between the 0·5 mg/kg

	Placebo group (n=31)	0·1 mg/kg ATG group (n=6)	0·5 mg/kg ATG group (n=35)	1·5 mg/kg ATG group (n=12)	2·5 mg/kg ATG group (n=33)
Age at randomisation, years					
5–9	6 (19%)	0	7 (20%)	1 (8%)	7 (21%)
10–17	21 (68%)	4 (67%)	22 (63%)	8 (67%)	21 (64%)
18–25	4 (13%)	2 (33%)	6 (17%)	3 (25%)	5 (15%)
Sex					
Male	21 (68%)	3 (50%)	13 (37%)	4 (33%)	13 (39%)
Female	10 (32%)	3 (50%)	22 (63%)	8 (67%)	20 (61%)
Ethnicity					
European	28 (90%)	6 (100%)	31 (89%)	10 (83%)	31 (94%)
African	1 (3%)	0	1 (3%)	1 (8%)	1 (3%)
Asian	0	0	2 (6%)	1 (8%)	1 (3%)
Mixed	2 (6%)	0	1 (3%)	0	0
BMI, kg/m²	20·18 (3·68)	23·30 (3·76)	19·39 (3·25)	19·83 (3·77)	19·62 (3·46)
HbA_{1c}, %	7·64 (1·10)	7·20 (0·66)	7·89 (1·32)	7·97 (1·35)	7·88 (1·17)
Insulin dose-adjusted A_{1c}	9·34 (1·78)	8·32 (1·05)	9·56 (2·02)	9·45 (2·19)	9·51 (1·67)
C-peptide AUC from 2-h MMTT, nmol/L per min*	0·79 (0·62–0·97)	1·06 (0·80–1·63)	0·83 (0·67–1·15)	0·86 (0·70–1·30)	0·81 (0·68–0·95)
Time from type 1 diabetes diagnosis to randomisation, days	54 (47–57)	51 (43–58)	50 (40–56)	48 (34–57)	51 (40–56)
Insulin delivery regimen					
Pump	3 (10%)	0	3 (9%)	1 (8%)	4 (12%)
Multiple dose	28 (90%)	6 (100%)	32 (91%)	11 (92%)	29 (88%)
Number of positive autoantibodies at baseline					
1	3 (10%)	1 (17%)	8 (23%)	2 (17%)	6 (18%)
2	11 (35%)	2 (33%)	10 (29%)	1 (8%)	11 (33%)
3	17 (55%)	3 (50%)	17 (49%)	9 (75%)	16 (48%)

Data are n (%), mean (SD), or median (IQR). ATG=antithymocyte globulin. AUC=area under the curve. HbA_{1c}=glycated haemoglobin A_{1c}. MMTT=mixed-meal tolerance test.
*The mixed-meal-stimulated mean C-peptide concentration was calculated using the trapezoidal rule as the area under the concentration–time curve divided by 120 min.

Table 1: **Baseline characteristics of the trial population by ATG dose**

group and the placebo group (figure 2C). At all timepoints, data completeness for insulin requirements was more than 90%. The mean adjusted difference in insulin dose-adjusted HbA_{1c} was –0·576 (95% CI –1·284 to 0·133; p=0·11) between the 2·5 mg/kg ATG group and the placebo group and –0·587 (–1·295 to 0·120; p=0·10) between the 0·5 mg/kg ATG group and the placebo group (figure 2D). Metabolic parameters in children, adolescents, and adults are shown in the appendix (pp 32–37).

At 12 months, CGM metrics showed a mean time in range of 58% (SD 19) in the placebo group, 65% (25) in the 0·5 mg/kg ATG group, and 64% (20) in the 2·5 mg/kg ATG group (figure 3 and appendix pp 10–11). This difference was not statistically significant. Insulin delivery systems were not differently used between treatment groups, with eight (27%) of 31 participants in the placebo group, nine (29%) of 35 in the 0·5 mg/kg ATG group, and ten (32%) of 33 in the 2·5 mg/kg ATG group using insulin pumps at 12 months compared with three (10%) in the placebo group, three (9%) in the 0·5 mg/kg ATG group, and four (12%) in the 2·5 mg/kg ATG group at baseline. No automated insulin delivery systems were used during the study.

The CD4 to CD8 T-cell ratio decreased from baseline to 1 week after treatment start in both the 0·5 mg/kg ATG and 2·5 mg/kg ATG groups, with the decrease in the 2·5 mg/kg ATG group more than 3-times greater than in the 0·5 mg/kg group (figure 4; appendix pp 38–39). In contrast, the placebo group showed a small increase in CD4 to CD8 ratio from baseline to 1 week after treatment start. The mean adjusted difference in CD4 to CD8 ratio across the 12-month period was –0·585 (95% CI –0·740 to –0·430; p<0·0001) in the 2·5 mg/kg ATG group versus placebo and –0·033 (–0·186 to 0·120; p=0·68) in the 0·5 mg/kg ATG group versus placebo (figure 4). However, whereas the CD4 to CD8 ratio remained reduced relative to baseline at all timepoints in the 2·5 mg/kg ATG group, the ratio was not significantly different from baseline at 6 months or different to placebo at 12 months

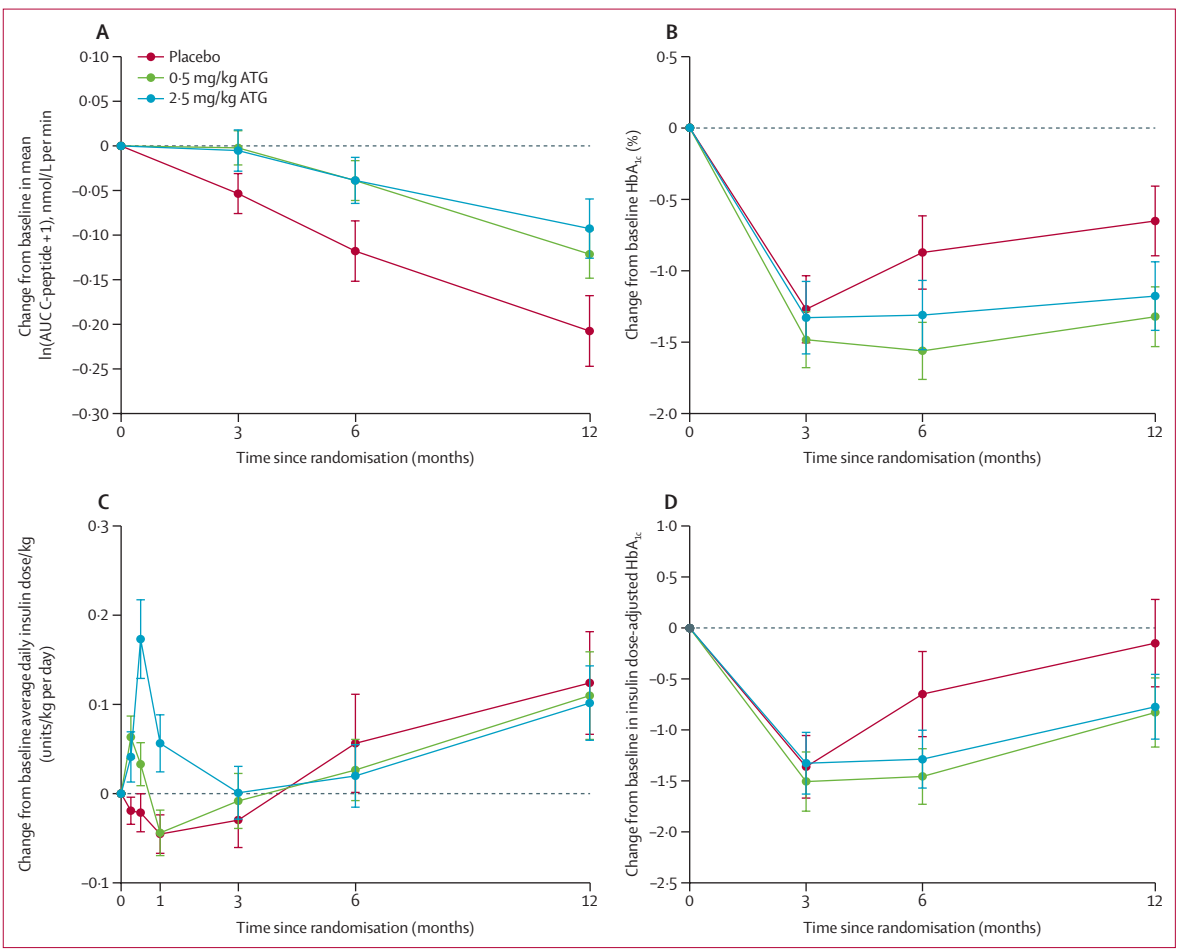

Figure 2: **Change from baseline over 12 months in efficacy outcomes**
(A) Change from baseline in ln(AUC C-peptide + 1). (B) Change from baseline in HbA_{1c}. (C) Change from baseline in daily insulin dose. (D) Change from baseline in insulin dose-adjusted A_{1c}. Data are shown for placebo (n=31), 0·5 mg/kg ATG (n=35), and 2·5 mg/kg ATG (n=33) groups. Data for 0·1 mg/kg ATG and 1·5 mg/kg ATG are shown in the appendix (pp 29–30, 32–37). Data are mean (SE). ATG=antithymocyte globulin. AUC=area under the curve. HbA_{1c}=glycated haemoglobin A_{1c}.

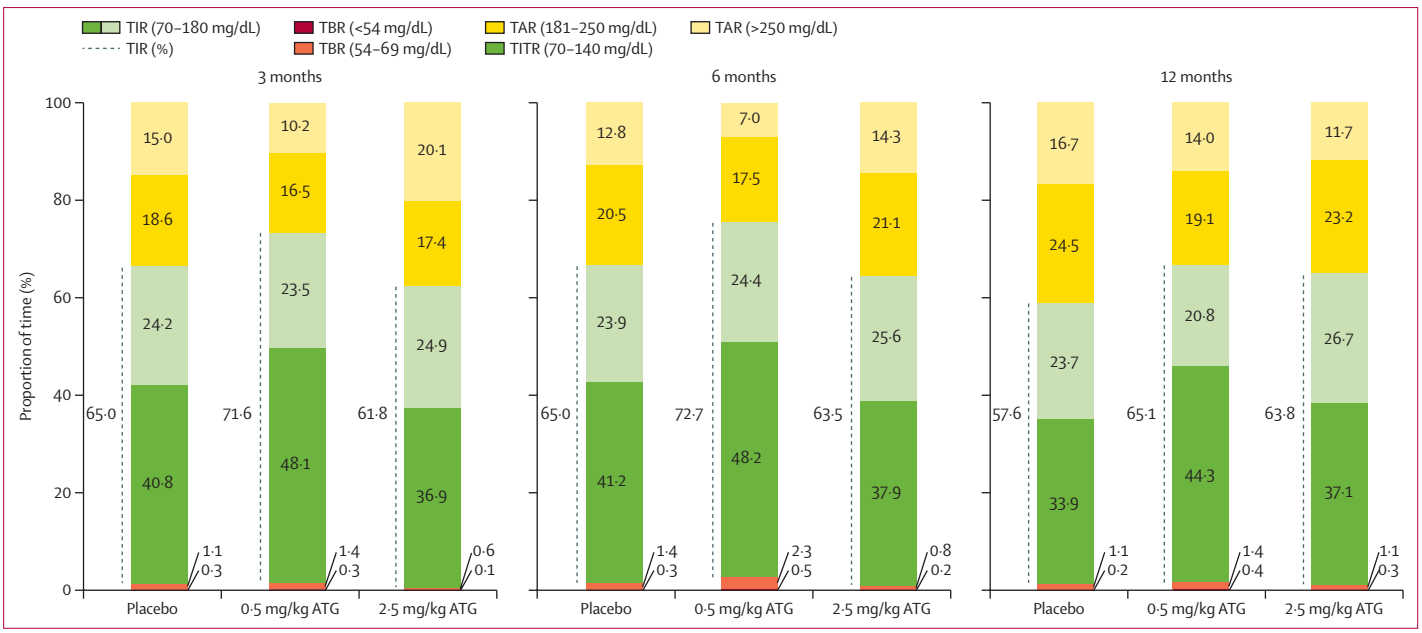

Figure 3: **Continuous glucose monitoring metrics**
ATG=antithymocyte globulin. TAR=time above range. TBR=time below range. TIR=time in range. TITR=time in tight range. Data are shown for placebo (n=31), 0·5 mg/kg ATG (n=35), and 2·5 mg/kg ATG (n=33) groups. Data for 0·1 mg/kg ATG and 1·5 mg/kg ATG are shown in the appendix (pp 10–11).

in the 0·5 mg/kg ATG group (figure 4; appendix pp 12–13, 38–39).

The overall proportion of people with positive autoantibodies did not substantially change for GAD, IA2, or ZnT8, whereas, as expected due to participants being on insulin therapy, the proportion with IAA increased (from 83 [71%] of 106 to 105 [99%] of 106; appendix pp 14–15). No statistically significant changes were noted between placebo and treatment groups for the proportion of participants with positive autoantibodies.

Change in fasting dried blood spot-collected C-peptide concentration versus baseline was small and similar in all groups (figure 5A; appendix pp 16–19). Dried blood spot-collected C-peptide concentrations measured 60 min after a standard liquid meal decreased in all groups, and, partly due to high variability of dried blood spot C-peptide concentrations and, in the latter 6 months of the trial, low data availability, were not significantly different between groups (figure 5B; appendix pp 16–19).

The safety population included all participants who received the allocated treatment (n=114), all of whom had at least one adverse event (table 2; appendix pp 20–24). Most adverse events were grade 1 or 2, with only 11 (10%) participants having grade 3 events (three [9%] in the 0·5 mg/kg ATG group, four [36%] in the 1·5 mg/kg ATG group, and four [18%] in the 2·5 mg/kg ATG group). There were two grade 4 events (severe hypoglycaemia), one in the placebo group and one in the 0·5 mg/kg ATG group. Lymphopenia occurred in 39 (34%) participants, with increasing rates with higher ATG doses, but infection rates were not different between the groups.

There were no cytokine release syndrome events in the placebo group, whereas 11 (33%) of 33 participants in the 2·5 mg/kg ATG group and eight (24%) of 34 in the 0·5 mg/kg ATG group had cytokine release syndrome. Serum sickness occurred in 27 (82%) participants in the 2·5 mg/kg ATG group compared with 11 (32%) in the 0·5 mg/kg ATG group and none in the placebo group.

There were two emergency unmaskings (one serious adverse reaction of hospital admission due to suspected serum sickness and one severe adverse event of subcutaneous infection at infusion site), for which the investigator deemed it necessary to know the treatment allocation, but the rest of the team remained masked.

In the sensitivity analyses, we found no evidence of any differential treatment effects by sex (p=0·18 for sex by treatment by time interaction) or batch (p=0·94 for batch by treatment by time interaction).

In the post-hoc analysis, the quantitative response was calculated and the between-group difference of quantitative response C-peptide at 1 year compared with placebo was 0·12 (95% CI 0·03–0·21; p=0·009) in the 2·5 mg/kg ATG group and 0·10 (0·01–0·19; p=0·029) in the 0·5 mg/kg ATG group (appendix p 25).

Discussion

The MELD-ATG trial showed that an adaptive trial design for testing an intervention aiming to arrest the loss of functional β-cell mass in young people with recent-onset, clinical, stage 3 type 1 diabetes successfully identified a minimum effective dose of 0·5 mg/kg ATG. In addition, it supports previous efficacy and safety findings of

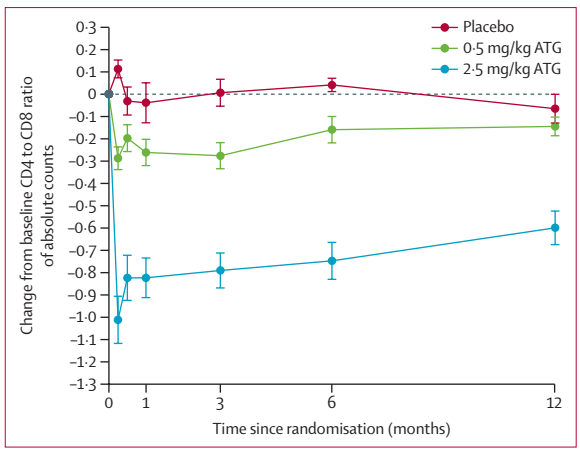

Figure 4: **Change from baseline in the ratio of absolute counts of CD4 to CD8 T cells**
Data are shown for placebo (n=31), 0·5 mg/kg ATG (n=35), and 2·5 mg/kg ATG (n=33) groups at week 0 (baseline), week 1, week 2, month 1, month 3, month 6, and month 12. Data are mean (SE). ATG=antithymocyte globulin.

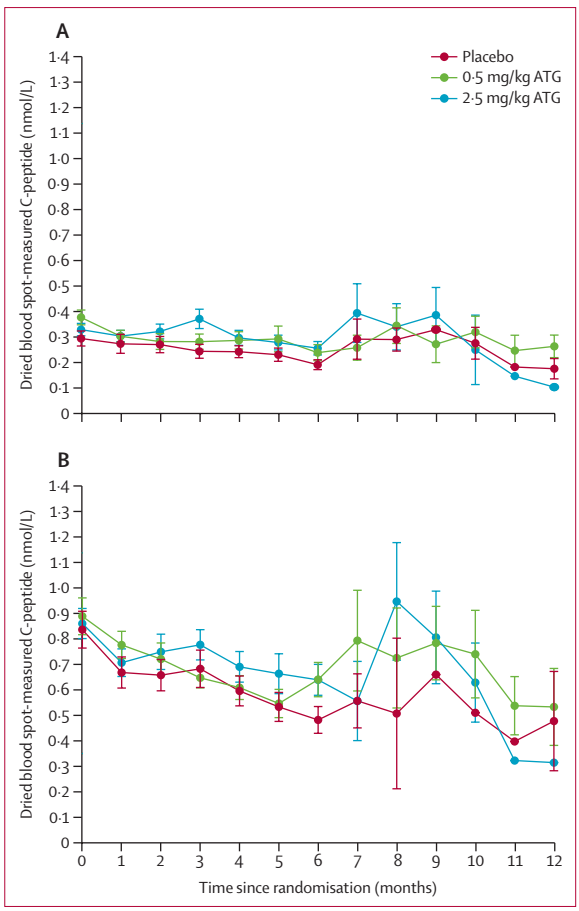

Figure 5: **Dried blood spot-collected C-peptide concentrations**
(A) Home dried blood spot-collected C-peptide concentrations in the fasted state. (B) Home dried blood spot-collected C-peptide concentrations 60 min after a standard liquid meal test. Data are shown for placebo (n=31), 0·5 mg/kg ATG (n=35), and 2·5 mg/kg ATG (n=33) groups. Data are mean (SE). Note that after 6 months, data capture fell below 75% completeness.

2·5 mg/kg ATG, including in children as young as 5 years. The findings suggest that low-dose ATG is an efficacious intervention for arresting or at least delaying progression of type 1 diabetes, with mostly mild and moderate adverse events.

The adaptive trial design allowed for exploration of several questions at once and yielded suggestive answers for the field.[15–17] As such, we were able to explore different doses through dose selection based on prespecified criteria. The unblinded dose determining committee decided on doses retained in such a way that the placebo and 2·5 mg/kg groups would remain powered to provide the primary endpoint, but middle doses could be dropped or restarted during the recruitment period, although the committee only dropped doses and restarted none. This strategy allowed us to confirm previous observations[12,19] that 2·5 mg/kg ATG slows the decline in stimulated C-peptide concentrations. The adverse events profile for the 2·5 mg/kg dose was in line with previous observations in all age groups.[12,19] Importantly, the adaptive trial design provided the power to identify a minimum effective dose of ATG at 0·5 mg/kg. This dose not only achieved the primary endpoint, reducing C-peptide decline compared with placebo at 12 months, but also resulted in lower HbA_{1c} concentrations.

Although a similar frequency of total adverse events between ATG doses was observed, a major difference was observed for serum sickness, a reaction of the body against the infusion of xenogeneic (rabbit) antibodies.[28] Dose-dependent prevalence and duration of this event over different ATG doses were observed, but this needs to be interpreted with caution due to low numbers of participants in the 0·1 mg/kg and 1·5 mg/kg ATG groups. Another typical ATG-associated adverse event, cytokine release syndrome, caused by release of cytokines on infusion of an immune-cell targeting antibody,[29] had a slightly lower incidence in the 0·5 mg/kg ATG group than in the 2·5 mg/kg ATG group. Of note, in this lower dose group, cytokine release syndrome occurred mostly on the first day of infusion. This finding can be explained by the fact that both groups received 0·5 mg/kg ATG on day 1, whereas on day 2, the 0·5 mg/kg group received placebo and the 2·5 mg/kg group received the remaining 2 mg/kg ATG. The small difference in cytokine release syndrome occurrence compared with previous studies using 2·5 mg/kg ATG might be explained by the criteria used to define cytokine release syndrome, because in our study a minimum of fever together with two other constitutional symptoms was a predetermined criterion. Note that, particularly in the 2·5 mg/kg ATG group, a transient increase in insulin doses was observed in the first weeks of the trial, likely reflecting insulin resistance induced by inflammation and transient steroid use on occurrence of serum sickness.

Dose decisions were based on safety information and C-peptide predictions, as well as CD4 to CD8 ratio after

	Placebo group (n=30)		0·1 mg/kg ATG group (n=6)		0·5 mg/kg ATG group (n=34)		1·5 mg/kg ATG group (n=11)		2·5 mg/kg ATG group (n=33)	
	n (%)	Number of events or mean (SD)	n (%)	Number of events or mean (SD)	n (%)	Number of events or mean (SD)	n (%)	Number of events or mean (SD)	n (%)	Number of events or mean (SD)
Any adverse event	30 (100%)	272	6 (100%)	58	34 (100%)	334	11 (100%)	99	33 (100%)	422
Any serious adverse event	0	0	1 (17%)	1	0	0	2 (18%)	4	5 (15%)	26
Adverse events by severity										
Grade 1 (mild)	29 (97%)	191	6 (100%)	37	31 (91%)	237	10 (91%)	60	30 (91%)	235
Grade 2 (moderate)	23 77%)	80	5 (83%)	21	28 (82%)	92	9 (82%)	33	31 (94%)	180
Grade 3 (severe)	0	0	0	0	3 (9%)	4	4 (36%)	6	4 (12%)	7
Grade 4 (life-threatening)	1 (3%)	1	0	0	1 (3%)	1	0	0	0	0
Grade 5 (death related to adverse event)	0	0	0	0	0	0	0	0	0	0
Cytokine release syndrome	0	0	2 (33%)	2	8 (24%)	9	2 (18%)	3	11 (33%)	16
Occurred day 1	0	0	2 (33%)	2	7 (21%)	7	1 (9%)	1	4 (12%)	4
Occurred day 2	0	0	0	0	0	0	0	0	2 (6%)	2
Occurred days 1 and 2	0	0	0	0	1 (3%)	1	1 (9%)	1	5 (15%)	5
Serum sickness	0	0	0	0	11 (32%)	11	6 (55%)	6	27 (82%)	27
Time to onset, days*	..	NA	..	NA	..	9·5 (2·1)	..	12·0 (1·9)	..	10·6 (1·5)
Duration, days	..	NA	..	NA	..	2·9 (2·5)	..	6·3 (2·4)	..	5·5 (4·7)
Steroid treatment	0	..	0	..	4 (12%)	..	0	..	5 (15%)	..
Lymphopenia	6 (20%)	6	2 (33%)	2	12 (35%)	14	5 (45%)	6	14 (42%)	17
Anaemia	4 (13%)	4	0	0	1 (3%)	1	0	0	4 (12%)	4
Thrombocytopenia	0	0	0	0	0	0	1 (9%)	1	3 (9%)	3
Abnormal liver enzymes†	2 (7%)	2	2 (33%)	4	0	0	0	0	4 (12%)	6
Infections (including sepsis)	9 (30%)	12	2 (33%)	3	9 (26%)	14	3 (27%)	4	13 (39%)	16

Data are n (%), except where otherwise specified. ATG=antithymocyte globulin. NA=not applicable. *Time to onset from treatment day 1. †Aminotransferase increases or hyperbilirubinaemia.

Table 2: **Adverse events across all visits**

infusion. The latter was decided based on earlier reports on effects of ATG.[19] However, the MELD-ATG study now shows that, although there is a clear ATG dose-dependent effect on CD4 to CD8 ratio, the effect of 0·5 mg/kg ATG was not maintained at 12 months, whereas its effect on C-peptide and metabolic parameters was. This observation supports previous data suggesting that the efficacy of ATG is not strictly related to the level of lymphocyte depletion[22] and triggers the need for additional research on the mechanism of action of low-dose ATG in people with type 1 diabetes, including effects on other immunological changes and their pattern over time.[30] Following previous ATG-related findings,[22] potential mechanisms explaining the beneficial effect of the 0·5 mg/kg dose could be sparing of regulatory T cells, exhausted signature of CD4 T cells, or other immunological changes. Future exploratory immunological analyses in our study population are needed to clarify the mechanism of action of the identified lower efficacious dose of ATG, understand dose–response differences in relation to immunological changes, and establish how these might vary across different age groups. These investigations could offer insights into how dosing might be tailored to individuals based on their clinical or immunological characteristics. In addition, exploration of novel treatment options allowing redosing of ATG once other forms of ATG than the rabbit ATG are available might provide additional insights on the contribution of persistent versus transient CD4 to CD8 ratio changes.

Previous observations suggest that effectiveness of immune modulatory interventions in individuals with recent-onset, clinical, stage 3 type 1 diabetes might vary by age.[8,9] This might be related to the more aggressive autoimmune process in children, as reflected by the more rapid C-peptide loss, and carries major implications for drug development in this heterogeneous disease.[31,32] Our study design allowed us to rapidly lower the age for participants' inclusion and test the efficacy and safety of ATG in children as young as 5 years. The primary and secondary metabolic outcomes showed some variation across predefined age categories in the present study; however, the study was not powered to detect statistically significant differences by age. We included a post-hoc analysis, calculating the quantitative response, that takes into account baseline C-peptide concentrations, but also age. This analysis confirmed the model used in the present trial. The MELD-ATG results underscore the need to perform immune modulatory intervention studies directly in young individuals with type 1 diabetes,

in contrast to current drug development strategies that, driven by regulatory guidance, typically target adults first. Only after safety is shown and efficacy is observed in this age group can new agents can be tested in younger people. This process might fail to identify agents potentially effective in younger people but not in adults and might lead to the premature rejection of effective treatments. Identifying new effective therapies with an acceptable safety profile, such as low-dose ATG, able to preserve endogenous β-cell function in young people, will have substantial benefits. The incidence of type 1 diabetes in this young age group is increasing, and, as a result, this will become a growing population in need of disease-modifying interventions.[2] Such interventions might offer protection against both short-term and long-term complications of diabetes, while also improving overall quality of life and life expectancy.

The MELD-ATG trial has several strengths, including its unique design, inclusion of children as young as 5 years, and strict adherence to the protocol and statistical analysis plan, allowing solid conclusions based on relatively small group sizes. Nevertheless, some limitations need to be acknowledged. Regulatory age stepdown requirements resulted in dropping the first lowest ATG dose (0·1 mg/kg) before the enrolment of children aged 5–11 years, leading to the absence of data on the effect of this lowest dose in that age group. The design forced several interim analyses, making the design complex and losing potentially interesting doses, such as the very low (0·1 mg/kg) or intermediate (1·5 mg/kg) doses, with numbers of participants in these groups preventing useful conclusions. Another potential weakness is that the adaptive study design might not have identified other interesting doses due to the middle dose selection being based, among other factors, on CD4 to CD8 T-cell ratios soon after dosing. Other biomarkers might have provided even better guidance on dose selection. Although the study population covered a wide age range and both male and female participants, most participants were European,[7] which might limit the generalisability of our findings to people of other backgrounds. Finally, although all precautions were taken to make this trial double-blind, we cannot guarantee full masking of all participants and personnel because of the occurrence of expected treatment side-effects. This study is expected to generate substantial clinical interest, with clinicians in the field of type 1 diabetes awaiting these results for several years, as it shows the potential of an affordable, repurposed agent, ATG, in a low and safe dose, in children and adolescents with newly diagnosed, clinical type 1 diabetes. Especially in the youngest age group, the 0·5 mg/kg dose was efficacious with a good safety profile and would be the recommended dose for treatment. Of interest, being able to limit the administration of ATG to 0·5 mg/kg would also mean only needing one infusion on 1 day, instead of the 2 days of infusion with the previously studied 2·5 mg/kg. However, we acknowledge that ATG did not fully arrest β-cell destruction, as stimulated C-peptide concentrations continued to decline, in particular during the latter months of the trial, suggesting that combination treatments or re-administration of ATG, in case humanised ATG forgoing immunisation becomes available, might be needed to achieve a more durable β-cell-protective effect.

In conclusion, the MELD-ATG adaptive trial design allowed the identification of a minimum efficacious dose of ATG at 0·5 mg/kg in people with recent-onset, clinical type 1 diabetes. It also confirmed the efficacy and safety of the previously reported 2·5 mg/kg ATG dose, extending these observations to children as young as 5 years. This adaptive trial design could be considered for further exploration of novel therapies in type 1 diabetes, and even for other fields.

Contributors

CMa, JW, DG, APM, CW-B, AMS, AEJH, MLM, TT, LO, AMS, and MP conceptualised the study and designed the protocol. JW, CW-B, DG, and APM developed the statistical analysis plan, curated data, and performed statistical analyses. PC and CMö developed and managed the electronic case report form database. KC, TD, FR, DSS, TB, JJ, BR-M, TP, CDB, ME, RH, EB, RHW, SB, M-AP, MK, and MC collected data. TT, MK, and AEJH performed experimental analyses. AN, AMS, EN, and MP provided ATG. CMa, JW, DG, AEJH, MLM, LVR, TT, and LO analysed and interpreted data and wrote the manuscript. CMa, JW, DG, LVR, and MLM directly accessed and verified the underlying data reported in the manuscript. All authors contributed to the execution of the trial, interpretation of the results, reviewing, editing, and approval of the manuscript. All authors had access to all the data and had final responsibility for the decision to submit for publication.

Declaration of interests

CMa serves or has served on an advisory panel for Bayer, Biomea Fusion, Boehringer Ingelheim, Eli Lilly, Abbott, Insulet, Medtronic, Novartis, Novo Nordisk, Roche, SAB Bio, Sanofi, and Vertex. Financial compensation for these activities has been received by KU Leuven. KU Leuven has received research support for CMa from Dexcom, Abbott, Novo Nordisk, and Sanofi. CMa serves or has served on the speakers bureau for Novo Nordisk, Sanofi, Eli Lilly, Medtronic, Roche, Dexcom, Insulet, Vertex, and Abbott. Financial compensation for these activities has been received by KU Leuven. CMa is president of the European Association for the Study of Diabetes (EASD). All external support of EASD is on www.easd.org. AEJH has received research support from Dexcom. TT serves on an advisory panel for and has received research support from Sanofi. TD serves or has served on an advisory panel or speakers bureau for AstraZeneca, Bayer, Boehringer Ingelheim, Abbott, Dexcom, Eli Lilly, Insulet, Medtronic, Menarini, Roche, Sanofi, Vitalaire, and Ypsomed. FR has served on an advisory panel Boehringer Ingelheim; and serves or has served on the speakers bureau for Insulet, Kyowa Kirin, Novo Nordisk, and Sanofi. TB serves or has served on an advisory panel for Eli Lilly, Abbott, Medtronic, Novartis, Novo Nordisk, Roche, and Sanofi; has received research support from Dexcom, Abbott, Novartis, Novo Nordisk, Medtronic, and Sanofi; and serves or has served on the speakers bureau for Eli Lilly Roche, Dexcom, Abbott, AstraZeneca, Medtronic, Novo Nordisk, Novartis, and Sanofi. BR-M serves on an advisory panel for Sanofi; and serves or has served on the speakers bureau for Eli Lilly, Dexcom, Medtronic, and Sanofi Ypsomed. CDB serves or has served on an advisory panel for Abbott, Eli Lilly, and Novo Nordisk. University Hospital Antwerp has received research support for CDB from AstraZeneca, Boehringer Ingelheim, Indigo Diabetes NV, and Medtronic. CDB serves or has served on the speakers bureau for Abbott, AstraZeneca, Boehringer Ingelheim, Eli Lilly, Insulet, Medtronic, and Novo Nordisk. ME serves or has served

on an advisory panel for Medtronic, Abbott Diabetes Care, Novo Nordisk, Eli Lilly, ITB Medical, Sanofi, Vertex, Provention Bio, and Pila Pharma. University of Cambridge has received research support for ME from Medtronic, Abbott, Novo Nordisk, Eli Lilly, ITB Medical, and Sanofi. ME serves or has served on the speakers bureau for Eli Lilly, Abbott, and Sanofi. RH has served as speaker for Medtronic. EB serves on an advisory panel for Sanofi; and is or has been on the speakers bureau for Abbott, Medtronic, Sanofi, and Roche. RHW serves on an advisory panel for Sanofi; and has been a speaker for Insulet. SB has been a speaker for Sandoz; financial compensation for these activities has been received by Oxford University. M-AP serves or has served on an advisory panel for Sanofi and Novo Nordisk and has been a speaker for Novo Nordisk and Nordic Infucare. AN and AMS are former employees of Sanofi. MP and EN are employees of Sanofi. MLM has served on an advisory panel for Sanofi and SAB Bio. All other authors declare no competing interests.

Data sharing

1 year after publication, de-identified trial data will be available on request to the corresponding author (chantal.mathieu@uzleuven.be). Requests should outline the specified purpose for use of the data and will require a signed data access agreement.

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References

1 Quattrin T, Mastrandrea LD, Walker LSK. Type 1 diabetes. *Lancet* 2023; **401:** 2149–62.

2 Ogle GD, Wang F, Haynes A, et al. Global type 1 diabetes prevalence, incidence, and mortality estimates 2025: results from the International Diabetes Federation Atlas, 11th edition, and the T1D Index version 3.0. *Diabetes Res Clin Pract* 2025; **225**: 112277.

3 Herold KC, Delong T, Perdigoto AL, Biru N, Brusko TM, Walker LSK. The immunology of type 1 diabetes. *Nat Rev Immunol* 2024; **24:** 435–51.

4 O'Donovan AJ, Gorelik S, Nally LM. Shifting the paradigm of type 1 diabetes: a narrative review of disease modifying therapies. *Front Endocrinol (Lausanne)* 2024; **15:** 1477101.

5 Atkinson MA, Haller MJ, Schatz DA, Battaglia M, Mathieu C. Time for changes in type 1 diabetes intervention trial designs. *Lancet Diabetes Endocrinol* 2023; **11:** 789–91.

6 Samuelsson U, Lindblad B, Carlsson A, et al. Residual beta cell function at diagnosis of type 1 diabetes in children and adolescents varies with gender and season. *Diabetes Metab Res Rev* 2013; **29:** 85–89.

7 Marcovecchio ML, Hendriks AEJ, Delfin C, et al. The INNODIA Type 1 Diabetes Natural History Study: a European cohort of newly diagnosed children, adolescents and adults. *Diabetologia* 2024; **67:** 995–1008.

8 Keymeulen B, Walter M, Mathieu C, et al. Four-year metabolic outcome of a randomised controlled CD3-antibody trial in recent-onset type 1 diabetic patients depends on their age and baseline residual beta cell mass. *Diabetologia* 2010; **53:** 614–23.

9 Orban T, Bundy B, Becker DJ, et al. Co-stimulation modulation with abatacept in patients with recent-onset type 1 diabetes: a randomised, double-blind, placebo-controlled trial. *Lancet* 2011; **378:** 412–19.

10 Ramos EL, Dayan CM, Chatenoud L, et al. Teplizumab and β-cell function in newly diagnosed type 1 diabetes. *N Engl J Med* 2023; **389:** 2151–61.

11 Waibel M, Wentworth JM, So M, et al. Baricitinib and β-cell function in patients with new-onset type 1 diabetes. *N Engl J Med* 2023; **389:** 2140–50.

12 Haller MJ, Long SA, Blanchfield JL, et al. Low-dose anti-thymocyte globulin preserves C-peptide, reduces HbA_{1c}, and increases regulatory to conventional T-cell ratios in new-onset type 1 diabetes: two-year clinical trial data. *Diabetes* 2019; **68:** 1267–76.

13 Pallmann P, Bedding AW, Choodari-Oskooei B, et al. Adaptive designs in clinical trials: why use them, and how to run and report them. *BMC Med* 2018; **16:** 29.

14 Bhatt DL, Mehta C. Adaptive designs for clinical trials. *N Engl J Med* 2016; **375:** 65–74.

15 Anderson RL, DiMeglio LA, Mander AP, et al. Innovative designs and logistical considerations for expedited clinical development of combination disease-modifying treatments for type 1 diabetes. *Diabetes Care* 2022; **45:** 2189–2201.

16 Seelig E, Howlett J, Porter L, et al. The DILfrequency study is an adaptive trial to identify optimal IL-2 dosing in patients with type 1 diabetes. *JCI Insight* 2018; **3:** e99306.

17 Todd JA, Evangelou M, Cutler AJ, et al. Regulatory T cell responses in participants with type 1 diabetes after a single dose of interleukin-2: a non-randomised, open label, adaptive dose-finding trial. *PLoS Med* 2016; **13:** e1002139.

18 Osama Gaber A, Monaco AP, Russell JA, Lebranchu Y, Mohty M. Rabbit antithymocyte globulin (thymoglobulin): 25 years and new frontiers in solid organ transplantation and haematology. *Drugs* 2010; **70:** 691–732.

19 Haller MJ, Schatz DA, Skyler JS, et al. Low-dose anti-thymocyte globulin (ATG) preserves β-cell function and improves HbA_{1c} in new-onset type 1 diabetes. *Diabetes Care* 2018; **41:** 1917–25.

20 Haller MJ, Gitelman SE, Gottlieb PA, et al. Anti-thymocyte globulin/G-CSF treatment preserves β cell function in patients with established type 1 diabetes. *J Clin Invest* 2015; **125:** 448–55.

21 Gitelman SE, Gottlieb PA, Rigby MR, et al. Antithymocyte globulin treatment for patients with recent-onset type 1 diabetes: 12-month results of a randomised, placebo-controlled, phase 2 trial. *Lancet Diabetes Endocrinol* 2013; **1:** 306–16.

22 Jacobsen LM, Diggins K, Blanchfield L, et al. Responders to low-dose ATG induce CD4+ T cell exhaustion in type 1 diabetes. *JCI Insight* 2023; **8:** e161812.

23 Wilhelm-Benartzi CS, Miller SE, Bruggraber S, et al. Study protocol: minimum effective low dose: anti-human thymocyte globulin (MELD-ATG): phase II, dose ranging, efficacy study of antithymocyte globulin (ATG) within 6 weeks of diagnosis of type 1 diabetes. *BMJ Open* 2021; **11:** e053669.

24 National Cancer Institute. Common Terminology Criteria for Adverse Events (CTCAE) version 5.0. National Cancer Institute, 2017.

25 Lachin JMMP, McGee PL, Greenbaum CJ, et al. Sample size requirements for studies of treatment effects on beta-cell function in newly diagnosed type 1 diabetes. *PLoS One* 2011; **6:** e26471.

26 Bundy BN, Krischer JP. A quantitative measure of treatment response in recent-onset type 1 diabetes. *Endocrinol Diabetes Metab* 2020; **3:** e00143.

27 StataCorp. Stata Statistical Software: release 18.5. StataCorp, 2024.

28 Couvrat-Desvergnes G, Salama A, Le Berre L, et al. Rabbit antithymocyte globulin-induced serum sickness disease and human kidney graft survival. *J Clin Invest* 2015; **125:** 4655–65.

29 Shimabukuro-Vornhagen A, Gödel P, Subklewe M, et al. Cytokine release syndrome. *J Immunother Cancer* 2018; **6:** 56.
30 Mohty M. Mechanisms of action of antithymocyte globulin: T-cell depletion and beyond. *Leukemia* 2007; **21:** 1387–94.
31 Leete P, Mallone R, Richardson SJ, Sosenko JM, Redondo MJ, Evans-Molina C. The effect of age on the progression and severity of type 1 diabetes: potential effects on disease mechanisms. *Curr Diab Rep* 2018; **18:** 115.
32 Battaglia M, Ahmed S, Anderson MS, et al. Introducing the endotype concept to address the challenge of disease heterogeneity in type 1 diabetes. *Diabetes Care* 2020; **43:** 5–12.

ATG as disease-modifying therapy for new-onset type 1 diabetes

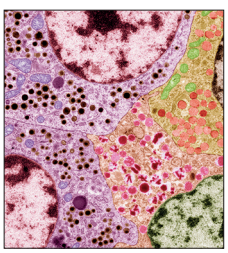
Type 1 diabetes remains a persistent health-care burden despite substantial advances in care. Its preclinical disease course proceeds through well characterised stages,[1,2] but, despite this knowledge, clinical disease management remains centred on insulin replacement, rather than underlying disease modification. Partly prompted by US regulatory approval in 2022 of an immunotherapy to delay clinical disease onset,[3] there has been renewed energy worldwide in testing disease-modifying immunotherapies in type 1 diabetes. One such agent is rabbit antithymocyte globulin (ATG), which depletes lymphocytes; pilot and fully powered clinical trial data[4-6] have suggested that ATG might be effective in people with type 1 diabetes. Of note, ATG is an affordable, repurposed medication that might be accessible in many health systems.

In *The Lancet,* Chantal Mathieu and colleagues[7] from the INNODIA network report 12-month data from the multicentre European MELD-ATG trial using an adaptive dose-ranging design to establish the minimum effective dose of ATG to preserve β-cell function in new-onset (stage 3) type 1 diabetes. This double-masked study in people aged 5–25 years started with five groups randomly allocated (1:1:1:1:1) to placebo plus four ATG doses (2·5 mg/kg, 1·5 mg/kg, 0·5 mg/kg, and 0·1 mg/kg). As the study progressed, the 1·5 mg/kg and 0·1 mg/kg ATG doses were dropped based on planned interim analyses of insulin secretion and pharmacokinetic (CD4 to CD8 T-cell ratio) markers. The placebo group (n=30) and the 2·5 mg/kg (n=33) and 0·5 mg/kg (n=34) ATG groups were maintained in the study and fully enrolled. Younger cohorts of children were also sequentially allowed to enrol in the study as safety data were established; of note, no children aged 5–11 years were enrolled in the 0·1 mg/kg group as this dose had been dropped before expansion of the trial to that age group. In general, the groups were well balanced for sex and ethnicity, although the placebo group had a higher proportion of male participants than other groups. The trial primarily enrolled Europeans.

The trial showed that both 2·5 mg/kg ATG and 0·5 mg/kg ATG significantly preserved insulin secretion compared with placebo (baseline adjusted mean difference in C-peptide area under the curve 0·124 nmol/L per min [95% CI 0·043–0·205]; p=0·0028 for 2·5 mg/kg ATG and 0·102 nmol/L per min [0·021–0·183]; p=0·014 for 0·5 mg/kg ATG).[8] Trial investigators concluded that the 0·5 mg/kg ATG dose had an acceptable safety profile and represented a minimal effective dose that could be used in future studies.

Similar to previous ATG trials in people with type 1 diabetes, 2·5 mg/kg ATG was associated with serum sickness in 27 (82%) of 33 participants, and cytokine release syndrome in 11 (33%); 0·5 mg/kg ATG was associated with a lower rate of these adverse events (11 [32%] of 34 participants with serum sickness and eight [24%] with cytokine release syndrome). The formulation of this drug in rabbits limits repeat dosing of ATG and might in future be circumvented by novel ATG formulations. Given that other autoimmune diseases require ongoing treatment to continually address symptoms, a new ability to re-dose with ATG or trials of sequential agents for ongoing therapy after ATG will likely be needed.

This is not the first trial of ATG in new-onset type 1 diabetes. In 2013, Gitelman and colleagues[5] assessed the effectiveness and safety of 6·5 mg/kg ATG given over 4 days for preserving β-cell function in people with new-onset diabetes, and in 2018, Type 1 Diabetes TrialNet[6] tested ATG at 2·5 mg/kg with and without granulocyte-colony stimulating factor in a similar population. Intriguingly, the higher dose study did not meet its primary endpoint, but the lower dose study did, with significant preservation of insulin secretion compared with placebo. Although differences in immune response to therapy might explain this discrepancy, we have suggested in a quantitative response analysis comparing results across many type 1 diabetes clinical trials[8] that the primary difference between the trials was embedded in trial design. Small placebo groups can have substantively different rates of loss of insulin secretion by chance. Both earlier ATG trials had a similar improvement in loss of insulin secretion in the treated groups, but the participants receiving placebo in the high dose trial happened to have better outcomes than



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expected, and the participants receiving placebo in the low dose trial happened to have worse outcomes than expected, driving different apparent treatment effects. In MELD-ATG,[7] exploratory quantitative response analysis confirmed the primary trial results for 2·5 mg/kg ATG and 0·5 mg/kg ATG. It is possible that small group effects could help explain why non-consecutive doses were dropped from MELD-ATG. Novel trial designs such as that used in the MELD-ATG trial might continue to be augmented or be supplanted by quantitative response analyses. Similar comparisons for any immunotherapy will likely be required as the field moves towards optimised dosing.

The robust trial design of MELD-ATG tested four doses with only 117 participants, representing a more efficient design compared with traditional head-to-head studies comparing a single fixed dose with placebo. Moreover, this study enrolled children younger than 12 years, extending the population that might be treated in future. The study also raises unanswered questions, particularly whether the effect might have been different if young children were enrolled at all dosing levels; however, there was no significant treatment effect by age cohort in the fully enrolled dosing groups of MELD-ATG.[7]

As with other autoimmune diseases, appropriate treatment of type 1 diabetes is likely to require a variety of therapies to address patient-specific immune responses, and might require combination therapy as applied in cancers. The results of the MELD-ATG trial suggest that further studies with ATG are warranted, and remind the field that small dose-finding trials can be feasible in people with new-onset type 1 diabetes. Although there are not yet durable cures for type 1 diabetes, this study firmly maintains ATG as part of the existing list of plausible options.

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1 Insel RA, Dunne JL, Atkinson MA, et al. Staging presymptomatic type 1 diabetes: a scientific statement of JDRF, the Endocrine Society, and the American Diabetes Association. *Diabetes Care* 2015; **38:** 1964–74.
2 Haller MJ, Bell KJ, Besser REJ, et al. ISPAD Clinical Practice Consensus Guidelines 2024: screening, staging, and strategies to preserve beta-cell function in children and adolescents with type 1 diabetes. *Horm Res Paediatr* 2024; **97:** 529–45.
3 Herold KC, Bundy BN, Long SA, et al. An anti-CD3 antibody, teplizumab, in relatives at risk for type 1 diabetes. *N Engl J Med* 2019; **381:** 603–13.
4 Haller MJ, Gitelman SE, Gottlieb PA, et al. Anti-thymocyte globulin/G-CSF treatment preserves β cell function in patients with established type 1 diabetes. *J Clin Invest* 2015; **125:** 448–55.
5 Gitelman SE, Gottlieb PA, Rigby MR, et al. Antithymocyte globulin treatment for patients with recent-onset type 1 diabetes: 12-month results of a randomised, placebo-controlled, phase 2 trial. *Lancet Diabetes Endocrinol* 2013; **1:** 306–16.
6 Haller MJ, Schatz DA, Skyler JS, et al. Low-dose anti-thymocyte globulin (ATG) preserves β-cell function and improves HbA_{1c} in new-onset type 1 diabetes. *Diabetes Care* 2018; **41:** 1917–25.
7 Mathieu C, Wych J, Hendriks AEJ, et al. Minimum effective low dose of antithymocyte globulin in people aged 5–25 years with recent-onset stage 3 type 1 diabetes (MELD-ATG): a phase 2, multicentre, double-blind, randomised, placebocontrolled, adaptive dose-ranging trial. *Lancet* 2025; published online Sept 18. https://doi.org/10.1016/S0140-6736(25)01674-5.
8 Ylescupidez A, Bahnson HT, O'Rourke C, Lord S, Speake C, Greenbaum CJ. A standardized metric to enhance clinical trial design and outcome interpretation in type 1 diabetes. *Nat Commun* 2023; **14:** 7214.