Efficacy of once-daily, high-dose, oral insulin immunotherapy in children genetically at risk for type 1 diabetes (POInT): a European, randomised, placebo-controlled, primary prevention trial

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Summary

Background Type 1 diabetes begins with autoimmunity against pancreatic islet antigens, including insulin. The aim of the Primary Oral Insulin Trial (POInT) was to evaluate the efficacy and safety of daily high-dose oral insulin to prevent the development of islet autoantibodies and diabetes.

Methods In this randomised, controlled, primary prevention trial, genetic screening in seven obstetric and paediatric clinics in Germany, Poland, Sweden, Belgium, and the UK identified newborns with a greater than 10% risk of developing islet autoimmunity. Eligible infants aged 4–7 months were randomly assigned in a 1:1 ratio to receive insulin manufactured from human zinc–insulin crystals administered orally at a once-daily dose of 7·5 mg for 2 months, increasing to 22·5 mg for 2 months and 67·5 mg until age 3 years, or placebo. Participants were randomly assigned via a web-based application and were stratified by site. The primary outcome was the development of two or more islet autoantibodies or diabetes assessed throughout follow-up until a maximum age of 6·5 years. A secondary outcome was the development of dysglycaemia or diabetes. Islet autoantibodies were measured in samples collected at baseline and during study visits conducted at outpatient clinics at 2, 4, and 8 months after randomisation, at age 18 months, and every 6 months thereafter. All participants and their family members, investigators of the study, and laboratory personnel remained masked to treatment allocation during the whole study. All randomly assigned participants who correctly fulfilled eligibility criteria and had not reached the primary outcome at the baseline visit (modified intention-to-treat) were included in the primary analysis. All participants who received at least one dose of study drug were included in the safety analysis. POInT is registered with ClinicalTrials.gov (NCT03364868) and is complete.

Findings Of 241 977 screened newborns, 2750 (1·14%) had an elevated genetic risk of developing islet autoimmunity and 1050 (38·2%) of the eligible infants (531 males [51%], 519 females [49%]), were assigned to oral insulin or placebo between Feb 7, 2018, and March 24, 2021. Two participants in the oral insulin group and none in the placebo group were excluded from the modified intention-to-treat analysis. The primary outcome developed in 52 (10%) participants in the insulin group and 46 (9%) in the placebo group (hazard ratio 1·12 [95% CI 0·76–1·67], p=0·57). An interaction between treatment and the *INS* rs1004446 genotype was observed, with an increase in the primary outcome in participants in the insulin group carrying non-susceptible *INS* genotypes compared with the placebo group (2·10 [1·08–4·09]) and protection against diabetes or dysglycaemia in participants in the insulin group carrying susceptible *INS* genotypes compared with the placebo group (0·38 [0·17–0·86]). Blood glucose values less than 50 mg/dL were observed in two (0·03%) of 7210 measurements in the insulin group and six (0·08%) of 7070 measurements in the placebo group. Of 10 252 reported adverse events, 5076 (49·5%) occurred in 507 (96·0%) of 528 participants in the oral insulin group and 5176 (50·5%) occurred in 500 (95·8%) of 522 participants in the placebo group. One death occurred in the oral insulin group and was unrelated to the study drug following independent review.

Interpretation There was no evidence that high-dose, daily oral insulin prevents the development of islet autoantibodies. Further studies are needed to assess the benefit of primary oral insulin therapy for preventing diabetes in *INS* genotype-selected infants.

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Research in context

Evidence before this study

For the background in preparing the protocol (submitted to regulators on July 6, 2017) we searched MEDLINE, PubMed, ClinicalTrials.gov, EudraCT, Embase, the Cochrane Central Register of Clinical Trials, and WHO Clinical Trials Registry Platform from Jan 1, 1990, to March 31, 2017, using the keywords "T1D", "type 1 diabetes", "oral insulin", "oral immunotherapy", "randomised clinical trials", AND "islet autoantibodies" without language restrictions. We also hand-searched reviews with these search terms published between Jan 1, 1990, and March 31, 2017. The search revealed one phase 2b, randomised, double-blind, placebo-controlled secondary prevention trial evaluating the efficacy of once-daily 7·5 mg oral insulin to delay the onset of type 1 diabetes in individuals who were islet autoantibody positive. No treatment effect was observed in the trial, although a post-hoc analysis showed a significant delay in type 1 diabetes in a subgroup with high-titre insulin autoantibodies who received oral insulin. A small, dose-finding, double-blind, randomised controlled study in islet autoantibody-negative children with high genetic risk for type 1 diabetes (Pre-POInT) identified an immune response to insulin in participants who received a once-daily dose of 67·5 mg oral insulin. Searches were updated to March 31, 2025, revealing one phase 2a, randomised, double-blind, placebo-controlled trial of oral insulin at the doses used in POInT (Pre-POInT early), which showed no safety concerns down to an age of 6 months and an association of an immune response to insulin with type 1 diabetes-susceptible *INS* genotypes, but was not designed to assess efficacy. A second phase 2b, randomised, double-blind, placebo-controlled trial done in individuals after the onset of islet autoantibodies (TN07) reported no overall effect of once-daily 7·5 mg oral insulin to delay the onset of type 1 diabetes, but a treatment effect in prespecified strata and in post-hoc analyses in participants with HLA DR4 alleles and IA-2 autoantibodies. No randomised controlled trial assessing the efficacy of treatment with a type 1 diabetes autoantigen administered before the appearance of islet autoantibodies was found. Additional searches were done using the keywords "autoimmune disease", "autoantigen", "oral immunotherapy", "randomised clinical trials", AND "autoantibodies", revealing no additional trials evaluating the efficacy of oral autoantigen immunotherapy for the prevention of autoimmunity before the development of autoantibodies or disease symptoms.

Added value of this study

POInT is the first randomised, double-blind, placebo-controlled trial to test the efficacy of autoantigen-based therapy (oral insulin) for preventing islet autoimmunity and the first to examine the effect of high-dose oral insulin on the development of type 1 diabetes. It is also the first trial to use newborn genetic screening to enrol infants from the general population who are at risk for type 1 diabetes. The study showed the feasibility of newborn screening and recruitment into primary prevention trials, randomly assigning 1050 infants in 3·1 years, and confirmation of the predicted risk of greater than 10% for early stage type 1 diabetes in eligible infants. The primary outcome was the development of early stage 1, 2, or 3 type 1 diabetes (two or more islet autoantibodies or diabetes). The study found that daily oral insulin treatment did not reduce the incidence of islet autoantibodies. A prespecified analysis showed that treatment was associated with a slower progression to clinical (stage 3) type 1 diabetes in participants who developed islet autoantibodies, suggesting that high-dose oral insulin therapy commenced before the onset of autoimmunity delays the onset of diabetes. A key susceptibility gene for type 1 diabetes is the *INS* gene, which encodes the treatment antigen—a major autoantigen target of childhood type 1 diabetes. The study found a pharmacogenetic interaction between the treatment and genotypes of this gene. The treatment protected against developing stage 2 or 3 type 1 diabetes in participants with a susceptible genotype. In contrast, treatment was associated with an increased incidence of islet autoantibodies in participants with a non-susceptible genotype. High-dose oral insulin immunotherapy was safe and well tolerated, suggesting that it is suitable for further trials assessing its therapeutic value in preventing type 1 diabetes.

Implications of all the available evidence

At present, teplizumab is the only drug approved in some countries, including the USA, for delaying the onset of clinical type 1 diabetes in individuals with stage 2 type 1 diabetes. No drug is approved or has shown efficacy in earlier stages or given as a primary prevention treatment. Despite no evidence of an effect on the development of islet autoantibodies, our prespecified analyses suggest that daily oral insulin given as a primary prevention therapy can safely modify disease progression. This provides a premise for suitably powered future trials that test this hypothesis. Furthermore, the novel pharmacogenetic interaction supports the concept of personalised antigen-specific therapy based on a priori genetic selection for susceptibility to insulin autoimmunity (HLA DR4 and susceptible *INS* genotypes) and is supported by the post-hoc observation of oral insulin treatment efficacy in HLA DR4-positive individuals in the TN07 trial. All available evidence, therefore, indicates that autoantigen-specific therapy should be considered as a worthwhile strategy to prevent or delay clinical type 1 diabetes and that the success of this strategy will likely depend on appropriate genetic selection for treatment and timing of the intervention. Genetic selection for trial participation is feasible and successful through newborn screening. Further trials are required to support our observations and to explore different treatment schedules.

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Introduction

Preventing disease through early intervention is a compelling alternative to chronic disease management. Primary prevention of food allergy can be achieved by oral immunotherapy during infancy.[1,2] However, this approach has not been tested for autoimmune diseases.

Type 1 diabetes is an autoimmune disease with an incidence that has increased globally over recent decades.[3] Over 9 million people are living with type 1 diabetes, including 2·7 million in Europe and 1·8 million children and adolescents worldwide.[4] Insulin is a key early autoantigen in childhood type 1 diabetes. Autoantibodies against insulin often appear in genetically susceptible children in the first years of life.[5] This loss of immune tolerance to insulin frequently leads to more generalised islet autoimmunity and clinical diabetes.[6] The autoimmunity against insulin is strongly associated with the HLA DRB1*04-DQB1*0302 haplotype and genotypes of the *INS* gene, which encodes insulin.[7,8]

See Online for appendix

Attempts have been made to prevent type 1 diabetes in individuals with established islet autoimmunity by administering the insulin autoantigen orally,[9,10] intranasally,[11,12] intravenously, or subcutaneously.[13] Treatment-associated changes in the immune response to insulin were observed in some of the studies, suggesting that the treatment might be immunomodulatory.[12,13] None of these trials achieved their primary outcome of diabetes prevention. However, beneficial treatment effects were observed in subgroup analyses of the oral insulin immunotherapy trials.[9,10,14]

We reasoned that the efficacy of autoantigen-specific therapy would improve if the autoantigen is administered before the development of autoantibodies. Key challenges included the optimal antigen dose and identification of at-risk infants. We previously showed that daily oral administration of high doses (67·5 mg) of insulin was well tolerated, without inducing hypoglycaemia. Treatment was associated with immune responses to insulin with features of immune regulation, primarily in children with a susceptible *INS* genotype.[15,16] We also established a polygenic risk score for islet autoantibodies and diabetes, and assembled a European network to screen newborns for type 1 diabetes genetic risk.[17,18]

The Primary Oral Insulin Trial (POInT) was conducted to establish whether daily oral administration of insulin from infancy is safe and reduces the incidence of autoantibodies and diabetes in children with elevated genetic risk for type 1 diabetes.[19] This is the first trial to assess the efficacy of active oral exposure to an autoantigen before the onset of autoimmunity.

Methods

Study design

This investigator-initiated, multicentre, double-blind, randomised, placebo-controlled trial was developed by the Global Platform for the Prevention of Autoimmune Diabetes (GPPAD), and conducted at clinical trial centres in seven GPPAD sites (three in Germany, and one each in Poland, Sweden, Belgium, and the UK) between Feb 7, 2018, and June 28, 2024. All sites had previous experience in prospective paediatric studies and were screening newborns for genetic risk for type 1 diabetes and eligibility for the trial. The trial was registered at ClinicalTrials.gov (NCT03364868) on Dec 6, 2017, and is complete. It was overseen by the Technical University Munich Faculty of Medicine (trial sponsor) and Helmholtz Munich, Germany. An independent data and safety monitoring board provided trial oversight at prespecified meetings. The full trial protocol (appendix pp 25–210)[19] was reviewed by individual European and UK health authorities (appendix p 2), and approved by the local ethical committees of the Technical University Munich, Medical Faculty (326/17 Af), the Medical University of Warsaw (199/2017), the UK Health Research Authority (18/SC/0019), Onderzoek UZ/KU Leuven (S60711), and the Regionala etikprövningsnämnden i Lund (2017/918). Families from the POInT and type 1 diabetes natural history studies advised and participated in the development of informational materials explaining the conduct of the trial and educational material supporting recruitment and protocol adherence. The trial was conducted according to International Council for Harmonization Good Clinical Practice guidelines and the ethical principles of the Declaration of Helsinki.

Participants

Infants aged 4–7 months who were on solid food and had a predicted genetic risk of greater than 10% for developing two or more islet autoantibodies by the age of 6 years were eligible. Infants were identified through the GPPAD genetic screening programmes.[18] Eligibility required the presence of HLA DRB1*04-DQB1*0302 and either a genetic risk score of greater than 14·4 derived from 46 single nucleotide polymorphisms (SNPs) including *INS* rs1004446 (appendix pp 2, 6–7) or a first-degree family history of type 1 diabetes without protective HLA class II alleles. A complete list of inclusion and exclusion criteria is provided (appendix p 2). Infant sex was stated by the parents of the participants and was confirmed by the genetic screening results. Race and ethnicity data were not collected. Custodial parents gave written informed consent for genetic screening and for the trial.

Randomisation and masking

Participants were randomly assigned, via a web-based application (InVentory management, Randomisation & Supplies system [IVRS]; GxP Brain, Berlin, Germany), to receive either oral insulin or placebo in a 1:1 ratio and were stratified by site. Centre-specific lists with block randomisation (block size four) were generated by an independent statistician. Investigators were unaware of randomisation block sizes. All participants and their families, investigators of the study, and laboratory personnel remained masked to the block size and the

treatment allocation during the whole study until unmasking, following freezing of the database. Oral insulin and placebo were indistinguishable by sight and were prepared in identical capsules. Treatment allocation was provided to the central pharmacy responsible for treatment manufacturing. Emergency unmasking was available through the IVRS system.

Procedures

Recombinant human zinc–insulin crystals were provided by Eli Lilly (Indianapolis, IN, USA) through their investigator-initiated trials programme. The recombinant human insulin crystals were formulated in capsules at doses of 7·5 mg (215·3 IU), 22·5 mg (645·8 IU), and 67·5 mg (1937·3 IU). Microcrystalline cellulose was added as a filling substance to a total content of 200 mg. The reference placebo capsules contained microcrystalline cellulose. Compounding, preparation, and labelling of the investigational medicinal product (IMP) were done by Allphamed Pharbil Arzneimittel (Göttingen, Germany) under Good Manufacturing Practices. The IMP (oral insulin or placebo) was administered orally as one capsule per day with a small meal, preferably in the morning (0700–1000 h). The participants received either placebo or 7·5 mg oral insulin for 2 months, escalating to 22·5 mg for 2 months, and 67·5 mg daily until age 3 years (figure 1). Participants were followed up for a maximum of 6·35 years from randomisation.

Participants had follow-up visits at 2, 4, and 8 months after treatment initiation, at the age of 18 months, and every 6 months thereafter until the last participant visit on June 28, 2024 (figure 1). Islet autoantibodies were collected in blood samples at each visit and measured centrally at the Institute of Diabetes Research, Helmholtz Munich, Germany, using radiobinding assays (appendix p 3). All samples positive for islet autoantibodies were sent to a second central laboratory located at the University of Bristol Medical School, Diabetes and Metabolism, Learning and Research, Southmead Hospital (Bristol, UK) for confirmation. If a participant developed confirmed islet autoantibodies on two consecutive occasions, the family was instructed to take home measurements of urine and blood glucose, and oral glucose tolerance tests (OGTTs) were done every 6 months at the study visits from the age of 3 years to establish the onset of diabetes or dysglycaemia. Blood glucose concentrations on OGTT samples were measured centrally at the Institute of Laboratory Medicine, Clinical Chemistry and Molecular Diagnostics (Leipzig, Germany) using a photometric hexokinase method. Serum 25-OH-vitamin-D3 was measured locally in a certified laboratory and vitamin D supplementation was recommended in participants with 25-OH-vitamin-D3 concentrations below 30 ng/mL (75 nmol/L).[20] Parents of the participants were asked to complete questionnaires at visits 3, 5, 8, and the end of the study to assess their degree of anxiety or distress. The major findings from these questionnaires have been published.[21] Protocol deviations were classified before unmasking as errors in applying inclusion or exclusion criteria, administration of expired IMP, missing blood samples for measurement of islet autoantibodies, and missed visits.

Outcomes

The primary outcome was the development of two or more islet autoantibodies, which were defined as autoantibodies to insulin (IAA), glutamic acid decarboxylase (GADA), insulinoma-associated antigen-2 (IA-2A), or zinc transporter-8 (ZnT8A), confirmed in both central laboratories and in two consecutive samples, and a second confirmed autoantibody in at least one sample. Participants who were diagnosed with diabetes before the development of two or more islet autoantibodies were also considered to have reached the primary outcome. We planned to assess the primary outcome throughout follow-up until a maximum age of 6·5 years, which was the elapsed time from random treatment assignment to the development of a second autoantibody or diabetes. Participants not reaching the primary outcome were censored at the date of their last sample.

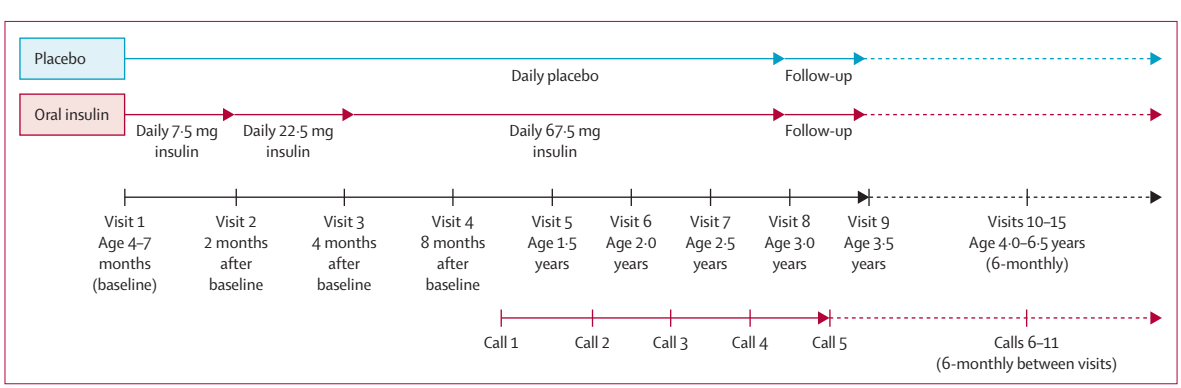

Figure 1: **Trial design**

Each study participant was treated with the study drug until visit 8 (age 3 years) and followed up for at least another 6 months until visit 9 (age 3·5 years, indicated by solid lines). Thereafter, each study participant continued to be followed up until the last study participant completed the minimum follow-up of 6 months, with a maximal follow-up until visit 15 (age 6·5 years, indicated by dashed lines).

Secondary outcomes included the development of clinical diabetes or dysglycaemia, which was the elapsed time from random treatment assignment to the date of the first occurrence of dysglycaemia or diabetes. Criteria for clinical diabetes were symptoms of diabetes and a random plasma glucose ≥200 mg/dL (≥11·1 mmol/L) or confirmed fasting blood glucose ≥126 mg/dL (≥7 mmol/L) or 2-h plasma glucose ≥200 mg/dL (≥11·1 mmol/L) in the OGTT. Dysglycaemia was defined as an impaired fasting plasma glucose ≥110 mg/dL (≥6·1 mmol/L), or an impaired 2-h glucose ≥140 mg/dL (≥7·8 mmol/L), or glucose concentration ≥200 mg/dL (≥11·1 mmol/L) at 30-min, 60-min, or 90-min timepoints during the OGTT at two consecutive occasions or at one occasion followed by clinical diabetes at the next contact. A trial committee evaluated and confirmed all cases of diabetes and dysglycaemia. Participants not reaching this secondary outcome were censored at the date of their last sample.

	Placebo (n=522)	Oral insulin (n=528)	Oral insulin (mITT population*, n=526)
Sex			
Female	260 (50%)	259 (49%)	257 (49%)
Male	262 (50%)	269 (51%)	269 (51%)
First-degree family history of type 1 diabetes	283 (54%)	272 (52%)	270 (51%)
Mother	118 (23%)	105 (20%)	105 (20%)
Father	121 (23%)	127 (24%)	127 (24%)
Sibling	33 (6%)	28 (5%)	27 (5%)
Multiple	11 (2%)	12 (2%)	11 (2%)
HLA genotype			
DR3/DR4-DQ8	280 (54%)	285 (54%)	284 (54%)
DR4-DQ8/DR4-DQ8	44 (8%)	51 (10%)	51 (10%)
DR4-DQ8/other	198 (38%)	192 (36%)	191 (36%)
Study site (country)			
Munich (Germany)	122 (23%)	120 (23%)	120 (23%)
Dresden (Germany)	74 (14%)	77 (15%)	77 (15%)
Hanover (Germany)	55 (11%)	56 (11%)	55 (10%)
Warsaw (Poland)	121 (23%)	121 (23%)	120 (23%)
Malmö (Sweden)	85 (16%)	88 (17%)	88 (17%)
Leuven (Belgium)	40 (8%)	40 (8%)	40 (8%)
Oxford (UK)	25 (5%)	26 (5%)	26 (5%)
INS SNP rs1004446			
CC (T1D risk genotype)	290 (56%)	296 (56%)	295 (56%)
Other	228 (44%)	228 (43%)	227 (43%)
Missing	4 (1%)	4 (1%)	4 (1%)
Age, months	6·1 (5·4–6·5)	6·0 (5·4–6·5)	6·0 (5·4–6·5)
Weight, kg	7·7 (7·2–8·4)	7·8 (7·1–8·5)	7·8 (7·1–8·5)
BMI, kg/m²	17·1 (15·9–18·2)	16·9 (16·0–18·1)	16·9 (16·0–18·1)
Vitamin D3, ng/mL	40·1 (33·0–47·8)	39·2 (32·7–47·0)	39·2 (32·6–46·9)

Data are n (%) or median (IQR). *INS* SNP=insulin gene single nucleotide polymorphism. mITT=modified intention-to-treat. T1D=type 1 diabetes. *For the placebo group, both the modified and initial intent-to-treat populations of the primary outcome were identical.

Table: **Baseline characteristics of participants enrolled in the trial**

Other secondary outcomes were the development of one or more islet autoantibodies, the development of IAA, and the development of GADA. The islet autoantibody outcomes required confirmation of positive results in both central laboratories in two consecutive samples. The secondary outcomes of one or more islet autoantibodies, IAA, and GADA were the elapsed times from random treatment assignment to the date of the first respective islet autoantibody-positive sample. Participants not reaching the outcome were censored at the date of their last tested blood sample that was islet autoantibody negative.

A prespecified exploratory outcome was the progression from the primary outcome to clinical diabetes in participants who reached the primary outcome. This exploratory outcome was defined as the elapsed time from the date of the primary outcome to the date of diagnosis of diabetes. Participants who reached the primary outcome but did not develop diabetes were censored at the date of their last visit or study protocol telephone contact.

The safety population included all participants who received at least one dose of the study medication. Safety was systematically assessed by site study doctors who recorded and graded adverse events according to the National Cancer Institute Common Terminology Criteria for Adverse Events. Adverse events were recorded until 60 days after the end of treatment. As part of the safety assessment, blood glucose was monitored before (–10 min) and at 30, 60, and 120 min after study drug intake at baseline, and at the visits at 2, 4, and 8 months. Pharmacovigilance was done by Dr Nibler & Partner (Munich, Germany). Onsite monitoring was overseen by the regulatory team of the GPPAD coordinating centre at Helmholtz Munich and the Technical University Munich.

Statistical analysis

The total number of participants was calculated for the primary outcome.[22] Assuming an exponential distribution, the hazard rate for the primary outcome was estimated at 0·0227 in the placebo group. With an accrual period of 3·5 years, an additional follow-up of 3·5 years, a 20% drop-out rate, and 1:1 randomisation, a sample size of 1046 participants was calculated to provide 80% power to detect a 50% reduction of the hazard rate in the oral insulin group at a two-sided α level of 0·05. At a mean follow-up from randomisation of 5·25 years, this corresponded to an absolute event probability reduction of 5·4%. The actual accrual included 1050 participants in a period of 3·17 years. Therefore, a masked sample size re-estimation was provided for protocol version 4.0 (Dec 9, 2021) incorporating the actual hazard rate of the placebo group of 0·0246. This re-estimation predicted 81·3% power to detect an absolute difference of 5·4% at a mean follow-up of 4·835 years. An interim analysis, initially planned in case of slower than expected enrolment, was not required and not undertaken (see protocol summary of changes, appendix p 24). The

statistical analysis plan was approved on March 24, 2024, and amended on Oct 15, 2024, before database lock on Oct 23, 2024, and is provided in the appendix (p 211).

Descriptive statistics were used to summarise the dataset, with medians and IQR for continuous variables and counts and percentages (n, %) for categorical variables. Baseline characteristics and measurements were recorded after randomisation and before the first administration of IMP. Analyses excluded missing data.

The primary analysis was conducted in a modified intention-to-treat population, which excluded participants who were randomly assigned to treatment but had reached the primary outcome of two or more islet autoantibodies at the baseline visit. This modification was introduced on Dec 8, 2021, after proposal by the data safety monitoring board (appendix p 24). The cumulative incidences of the primary outcome over time in each group were estimated using the Kaplan–Meier method. The difference between the treatment groups was tested using the hazard ratio (HR) estimated using the Cox model, and evaluated using the Wald test in the Cox model, including site as a covariate.

Analyses of secondary outcomes were conducted in the modified intention-to-treat population, excluding participants who were randomly assigned to treatment but had already met the secondary outcome at the baseline visit. All analysed secondary outcomes were prespecified. The cumulative incidences of the secondary outcomes over time in each group were estimated using the Kaplan–Meier method. The difference between the treatment groups was tested using the log-rank test and the HR was estimated using the Cox model. Analysis of the prespecified exploratory analysis progression from the primary outcome to diabetes was conducted in the modified intention-to-treat population. The cumulative incidences of progression to diabetes over time in each group were estimated using the Kaplan–Meier method. The difference between the treatment groups was tested using the log-rank test. The hazard rate of annualised progression from the primary outcome to clinical diabetes was estimated assuming an exponential survival model.

Prespecified subgroup analyses for the primary and secondary outcomes included stratification by *INS* rs1004446 genotype, sex, site, and first-degree relative with type 1 diabetes. Differences in the treatment effect between subgroups were tested using a covariate×treatment group interaction effect in a Cox model. Statistical analyses of the prespecified secondary and exploratory outcomes and of subgroups were exploratory and not adjusted for multiple testing.

The number and percentage of all adverse events were categorised according to the Medical Dictionary for Regulatory Affairs and by severity. Probabilities of a first observation of any serious and non-serious adverse events and of a first record of serious and non-serious adverse events for each system organ class between treatment groups were estimated by the Kaplan–Meier method and compared between treatment groups using the log-rank test. Adherence to treatment was assessed by counting the number of capsules dispensed and returned, and defined as administration greater than 85% of the expected number of IMP doses.

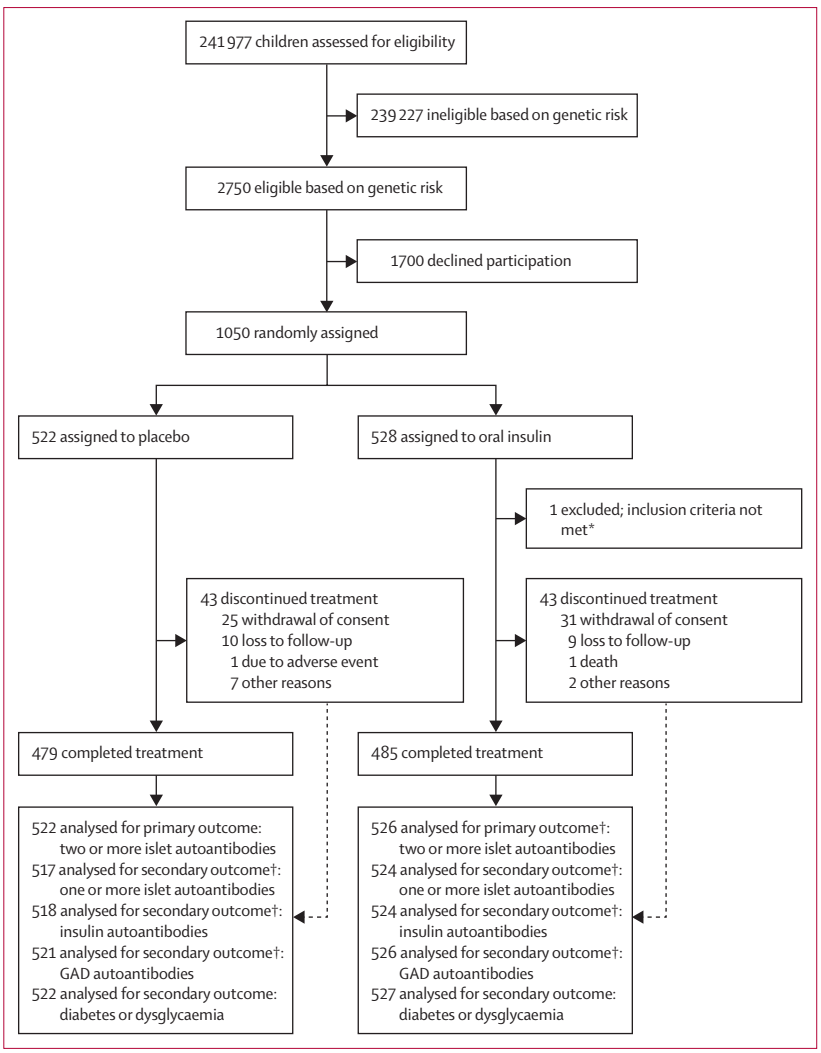

Figure 2: **Distribution of participants in the treatment groups of the trial**
*After randomisation, it was found that the genetic inclusion criteria were not met, as there was no first-degree family history of type 1 diabetes, but only a half-sibling with type 1 diabetes, and the genetic risk score was <14·4. †Outcomes already present at baseline were excluded from the respective analyses.

In all analyses, estimates were reported with 95% CI. The threshold for statistical inference was set at a two-sided $p<0·05$.

All statistical analyses were done using SAS version 9.4 M6 in a secure environment that was validated as compliant with the Code of Federal Regulation, Part 11. Codes used for the statistical analysis are available on request.

Role of the funding source

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

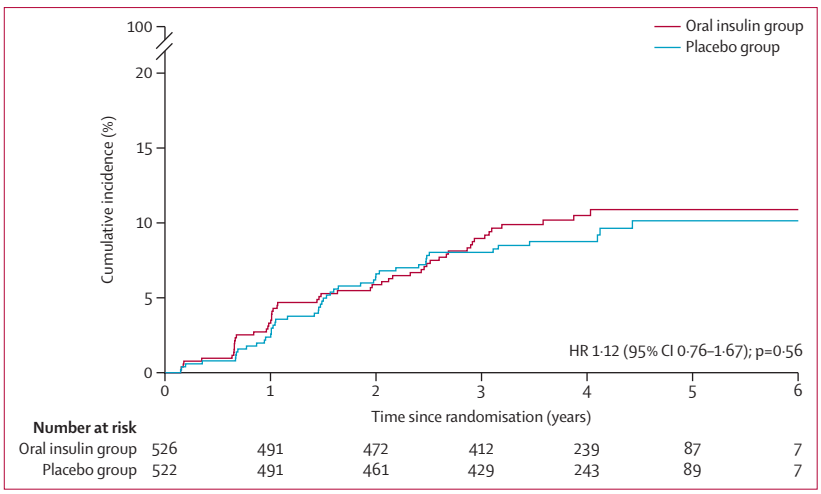

***Figure 3*: Kaplan–Meier curves for the effects of treatment with oral insulin on the development of the primary outcome (two or more islet autoantibodies)**
The red line shows the estimate of the proportions of participants who received oral insulin who developed the primary outcome after randomisation; the blue line shows participants who received placebo and developed the primary outcome. Five participants (two in the insulin group, three in the placebo group) developed diabetes with one preceding islet autoantibody without developing a second islet autoantibody and, therefore, reached the primary outcome at diabetes onset. There is no evidence of a difference in the cumulative risk of developing the primary outcome between the treatment groups. HR=hazard ratio.

writing of the report. Employees of Eli Lilly reviewed the manuscript before submission.

Results

From July 24, 2017, to Feb 2, 2021, 241 977 infants were tested for genetic susceptibility to type 1 diabetes (appendix p 8). Of these, 2750 (1·14%) met the eligibility criteria and 1050 (38·2%) were randomly assigned to receive oral insulin (n=528) or placebo (n=522) at a median age of 6·0 months (range 4·0–7·0) between Feb 7, 2018, and March 24, 2021 (appendix p 8). Overall, the two treatment groups were balanced with respect to baseline characteristics (table). One child in the oral insulin group was excluded due to incorrect reporting of a family history of type 1 diabetes. A second child in the oral insulin group had two or more islet autoantibodies at baseline, leaving 526 participants in the oral insulin group and 522 in the placebo group for analysis of the primary outcome (figure 2). A total of 86 (8%) participants did not complete the trial (43 [8%] of 526 in the oral insulin group *vs* 43 [8%] of 522 in the placebo group). Participants were treated for a median time of 2·49 years (IQR 2·45–2·55) and followed up for a maximum time from randomisation of 6·35 years (median follow-up from randomisation 4·0 years [IQR 3·4–4·6]) at a maximum age of 6·9 years. Adherence was achieved in 909 (87%) participants (458 [87%] in the oral insulin group *vs* 451 [86%] in the placebo group; appendix p 9). There were 23 major (12 in the oral insulin group *vs* 11 in the placebo group) and 468 minor (230 *vs* 238) protocol deviations during the trial (appendix p 22).

The primary outcome (two or more islet autoantibodies) developed in 52 (10%) participants in the oral insulin group versus 46 (9%) participants in the placebo group, including five (two in the oral insulin group) who developed diabetes with one preceding islet autoantibody. No evidence of a difference between the treatment groups was observed. The HR for oral insulin treatment versus placebo was 1·12 (95% CI 0·76–1·67, p=0·57). The 5-year probability of developing the primary outcome was 10·9% (95% CI 8·0–13·7) in the oral insulin group and 10·1% (7·2–13·1) in the placebo group (figure 3; appendix p 10). Among the 98 participants who developed the primary outcome, 40 (8%) participants in the oral insulin group and 40 (8%) participants in the placebo group developed the primary outcome while receiving study drug (until age 3 years) versus 12 (2%; insulin) and six (1%; placebo) who developed the primary outcome after treatment (appendix p 11). Autoantibodies persisted until the end of follow-up in all participants who reached the primary outcome. The combinations of islet autoantibodies as well as the islet autoantibody titres were similar between the insulin and placebo groups (appendix pp 12–13). A post-hoc analysis of IgG1, IgG3, and IgG4 subclasses of IAA suggested an increased frequency of IgG3 IAA in the insulin group compared with the placebo group (six [13%] of 45 participants *vs* none of 39 participants, p=0·010; appendix p 13).

The secondary outcome of one or more islet autoantibodies developed in 68 (13%) of 517 participants in the oral insulin group versus 55 (10%) of 524 in the placebo group (HR 1·23 [95% CI 0·86–1·76]). The 5-year probability of developing one or more islet autoantibodies was 14·6% (95% CI 11·0–18·1) in the oral insulin group and 13·5% (9·6–17·4) in the placebo group (p=0·25; appendix p 10). The probability of developing IAA and developing GADA did not differ between the insulin and placebo groups (appendix p 10).

The secondary outcome of diabetes or dysglycaemia developed in 18 (3%) of 522 participants in the oral insulin group versus 24 (5%) of 527 participants in the placebo group (HR 0·74 [95% CI 0·40–1·37]). The 5-year probability of developing diabetes or dysglycaemia was 4·2% (95% CI 2·1–6·2) in the oral insulin group and 6·3% (3·5–9·0) in the placebo group (p=0·34; figure 4A; appendix p 10). All participants with dysglycaemia also developed type 1 diabetes. Among participants who developed the primary outcome, the 3-year diabetes-free survival rate was 63·2% (95% CI 47·5–79·0) in insulin-treated participants and 35·5% (16·9–54·0) in placebo-treated participants (p=0·048; figure 4B; appendix p 10). The annualised progression from primary outcome to diabetes was 16·6% (95% CI 9·7–26·6) in the oral insulin group and 29·4% (18·9–43·8) in the placebo group.

Prespecified subanalyses found an interaction between treatment and the *INS* rs1004446 genotype for the

primary outcome (p=0·017) and the secondary outcome of diabetes or dysglycaemia (p=0·0081). The primary outcome was increased in the oral insulin group versus the placebo group among the 455 participants with the non-susceptible *INS* CT and TT genotypes (HR 2·10 [95% CI 1·08–4·09]; figure 5). The 5-year probability of developing two or more islet autoantibodies was 12·8% (95% CI 8·1–17·5) in the oral insulin group and 7·1% (3·2–11·0) in the placebo group (p=0·025; appendix p 14). In comparison, among the 586 participants with the type 1 diabetes-susceptible *INS* CC genotype, the 5-year probability of developing two or more islet autoantibodies was 9·6% (6·1–13.1) in the oral insulin group and 12·6% (8·4–16·8) in the placebo group (p=0·28; appendix p 14). The secondary outcome of diabetes or dysglycaemia was decreased in the oral insulin group compared with the placebo group among the 586 participants with the type 1 diabetes-susceptible *INS* CC genotype (HR 0·38 [95% CI 0·17–0·86]; figure 5). The 5-year probability of developing diabetes or dysglycaemia in this subgroup was 3·5% (95% CI 1·0–6·1) in the oral insulin group and 10·1% (5·1–15·0) in the placebo group (p=0·016; appendix p 14). DNA methylation data, available in 794 participants in POInT, showed rs1004446 genotype-associated differences across the *INS-IGF2* gene region (appendix p 23). No treatment differences were observed in subgroup analyses of sex, type 1 diabetes first-degree relative status, and country (appendix p 15).

The safety analyses included all 1050 participants. Blood glucose values measured before and after administration of the study drug at visits 1–4 did not differ between the oral insulin and placebo groups (appendix pp 16–17). Blood glucose values less than 50 mg/dL were observed in six (0·08%) of 7070 measurements from the placebo group and in two (0·03%) of 7210 measurements from the insulin group. Blood counts at baseline and at end of treatment did not differ between the two treatment groups (appendix p 18).

A total of 10 252 adverse events were reported, 5076 (49·5%) of which occurred in 507 (96·0%) of 528 participants in the oral insulin group and 5176 (50·5%) of which occurred in 500 (95·8%) of 522 participants in the placebo group (appendix pp 19–21). The most common adverse event was infection. An increased incidence of ear and labyrinth disorders was found in the oral insulin group (15 events in 15 [2·8%] participants) compared with the placebo group (six events in three [0·6%] participants, p=0·0051). In total, 250 adverse events were classified as serious (130 [52·0%] in 90 [17·0%] participants in the oral insulin group; 120 [48·0%] in 85 [16·3%] participants in the placebo group). Of all adverse events, 95 (0·9%) were severe (54 [1·1%] in the oral insulin group *vs* 41 [0·8%] in the placebo group), two were life-threatening (placebo group), and one was associated with death (oral insulin group). This case was defined as unrelated to the study drug following independent review.

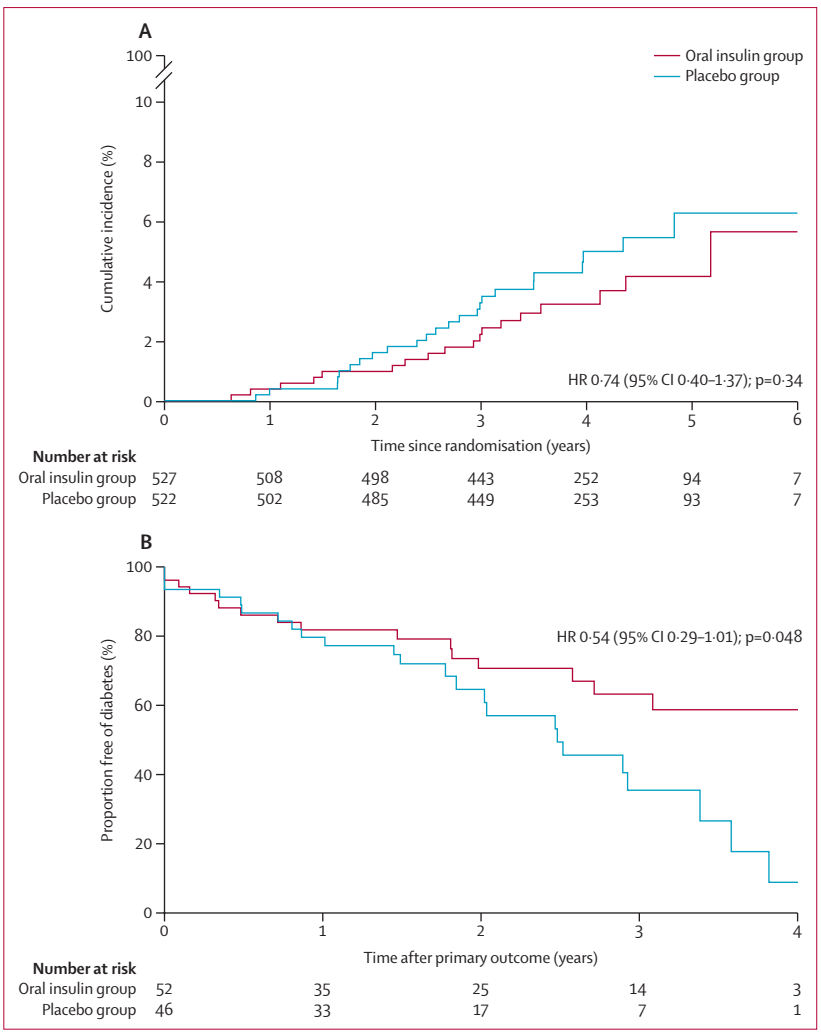

Figure 4: **Kaplan–Meier curves or the effects of treatment with oral insulin on the development of secondary and exploratory outcomes**

(A) Estimates of the proportions of participants who developed diabetes or dysglycaemia after randomisation among those who received oral insulin or placebo. No evidence of a difference in the cumulative risks was observed between the treatment groups. (B) Proportion of participants with the primary outcome who remained diabetes-free among those who received oral insulin or placebo. HR=hazard ratio.

Discussion

In infants with a high genetic risk for type 1 diabetes, daily administration of oral insulin, initiated between 4 and 7 months of age, failed to reduce the incidence of islet autoantibodies compared with a placebo. However, oral insulin delayed progression from autoantibody development to diabetes. A pharmacogenetic interaction between treatment and the *INS* type 1 diabetes susceptibility gene was observed.

This is the first trial to test the efficacy of active exposure to an autoantigen in children before the onset

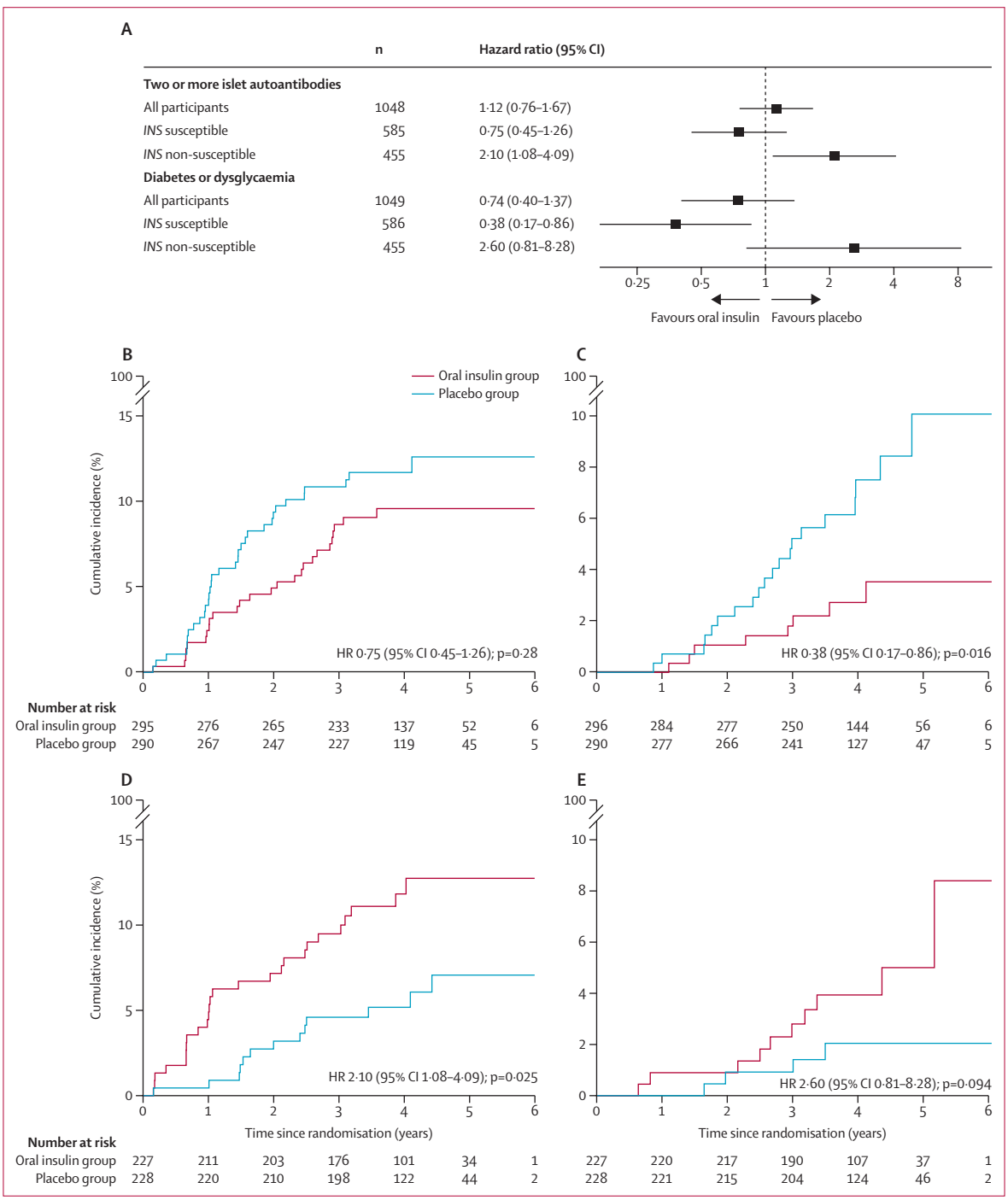

Figure 5: **Subgroup analyses of the effects of treatment with oral insulin, stratified by *INS* genotype (rs1004446)**
(A) Forest plots of the hazard ratios and their 95% CIs for the development of two or more islet autoantibodies (primary outcome) and for the development of diabetes or dysglycaemia (secondary outcome) in the oral insulin group compared with the placebo group, calculated in univariate Cox models. Hazard ratios are reported for all participants and separately for participants with the diabetes-susceptible (CC) or non-susceptible (CT and TT) *INS* rs1004446 genotypes. Kaplan–Meier estimates of the proportions of participants developing the primary outcome (B) and the secondary outcome of diabetes or dysglycaemia after randomisation among participants carrying the type 1 diabetes-susceptible *INS* genotype (C) who received oral insulin or placebo. Kaplan–Meier estimates of the proportions of participants developing the primary outcome (D) and the secondary outcome of diabetes or dysglycaemia since randomisation among participants carrying the type 1 diabetes non-susceptible *INS* genotypes (E) who received oral insulin or placebo. HR=hazard ratio.

of autoimmunity. It is also the first study to recruit infants without a family history of type 1 diabetes into a type 1 diabetes primary prevention trial. The recruitment was possible due to large-scale genetic screening across Europe using a genetic risk score that identifies newborns with greater than 10% risk for developing two or more islet autoantibodies.[18] Consistent with this predicted risk, the 5-year probability of developing the primary outcome was 10·1% in the placebo group. Screening and enrolment of 1050 infants were faster than planned. Consent was obtained for almost 40% of the 2750 eligible infants to enter a trial that required daily treatment for 2·5 years. Consent was highest in families with a family history of type 1 diabetes, but was also close to 30% in the absence of the disease in family members. Furthermore, the dropout rate was less than half of the predicted rate and adherence to the study treatment was high. This suggests high interest and motivation in early intervention to prevent type 1 diabetes among families with young children. Screening for risk in infants can lead to increased anxiety and depression in parents. In the POInT trial, we previously reported that only 5% of parents experienced panic-related anxiety after being informed about their child's increased risk, a rate similar to that of the general German population.[21] Symptoms of depression were present in 19·4% of parents at the visit in which results were communicated and declined over the course of participation in POInT.

The main finding of the trial was the inability of oral insulin to prevent the development of islet autoantibodies. This lack of efficacy could be due to incorrect assumptions regarding the importance of insulin as an autoantigen in the disease process, or suboptimal dose, timing, route, or formulation of insulin administration. Participants were treated with insulin daily, starting at 7·5 mg and increasing to 67·5 mg over 4 months and maintenance at 67·5 mg (472 mg per week) for 2 years. In comparison, efficacy in the prevention of peanut allergy was obtained with a weekly dose of 6000 mg of total peanut protein.[1] Furthermore, current dosing used for the desensitisation of peanut allergy starts at 0·5 mg, increasing to 300 mg peanut protein per day with maintenance for 18 months. Since the allergen content in peanut protein is 30% or more, we expect the daily 67·5 mg oral insulin dosing used in POInT to be similar to that used to desensitise peanut allergy in older children and likely, therefore, to have reached the immune system. However, we cannot exclude that the initiating or maintenance doses of oral insulin, or both, were too high in the setting of autoimmunity. A difference between autoimmunity in type 1 diabetes and IgE-mediated food allergy is that the unwanted immune response in food allergy is directed against antigen presented orally, whereas the response in type 1 diabetes is against antigen in the pancreatic islets. Therefore, it is possible that tolerance to insulin was achieved in the oral cavity or gut, but this could not prevent the immune responses that initiate in and around the pancreatic islets. It is also possible that the primary immune responses in type 1 diabetes might be against modified insulin or proinsulin.[23-25] Last, islet autoantibodies might not always be suitable as primary endpoints for assessing efficacy in primary prevention trials. Although they reliably signal the initiation of autoimmunity and strongly predict the development of type 1 diabetes, they offer little insight into the pace of disease progression. Moreover, they have shown little utility in evaluating the clinical effectiveness of disease-modifying therapies. Future trials should consider using clinical diabetes or progression to clinical diabetes as co-primary measures of therapeutic success.

Despite the lack of protection against islet autoantibodies, the trial provided evidence that the treatment elicited changes in the natural course of the disease. Type 1 diabetes starts with the development of autoimmunity and is followed by a distinct progression phase to clinical diabetes. The rate of progression from the occurrence of two or more islet autoantibodies to clinical diabetes was reduced by almost 50% in oral insulin-treated participants. Treatment was given until age 3 years to cover the period of greatest risk for islet autoimmunity in genetically at-risk children. It is possible that continued treatment might have resulted in greater or extended protection against progression. The mechanism of the slower progression is unclear and could include both immune changes or metabolic effects of the oral insulin if it reached the bloodstream. Other exposures during infancy can modify the rate of progression to disease without an apparent effect on the development of autoantibodies.[26] The possibility that oral insulin and such exposures modify the phenotype of the islet autoimmunity requires further investigation. In a post-hoc analysis we were able to find preliminary evidence that autoantibody characteristics such as IgG subclasses of IAA differed in participants who received oral insulin as compared with placebo, with an increase of IgG3 IAA responses in the oral insulin group. No analyses of T-cell responses to insulin have been done.

Additionally, we observed a notable interaction between oral insulin treatment and the type 1 diabetes susceptibility gene *INS* in prespecified subanalyses of the primary and secondary outcomes. Oral insulin was associated with substantial protection against the development of diabetes or dysglycaemia in participants with the type 1 diabetes-susceptible CC genotype, which was present in over half of the participants, and is found in around 40% of the population and 60% of people with type 1 diabetes.[8,27] In contrast, treatment was associated with an increased risk of two or more islet autoantibodies in participants with a non-susceptible CT or TT genotype. This pharmacogenetic interaction, therefore, identifies a subgroup that could benefit from primary oral insulin therapy and a subgroup that does not benefit and in whom exposure might increase autoimmunity. Treatment success and failure with adverse reactions to

oral immunotherapy is also observed in food allergy.[28] An interaction between active exposure to the autoantigen insulin and its genotypic variation on the development of islet autoimmunity suggests that exposure to insulin might be essential in the disease process and that antigen-specific therapy can modulate islet autoimmunity and type 1 diabetes risk. All trial participants were a priori selected to have HLA DR4-DQ8, which is strongly associated with the development of insulin autoimmunity. Therefore, the interaction was observed within a relatively homogeneous HLA class II susceptibility background. It is not known whether a similar interaction between treatment and the *INS* genotype occurs in high-risk HLA DR4-DQ8-negative children. The mechanism of the interaction is, however, unclear.

The *INS* gene is remarkable in the pathogenesis of type 1 diabetes, both encoding a major autoantigen and conferring the highest genetic susceptibility for the disease after HLA. Multiple SNPs within the *INS-IGF2* gene region, including rs1004446, are associated with susceptibility to type 1 diabetes.[27] The rs1004446 SNP was included in the polygenic risk score used for eligibility selection of infants and was, therefore, preselected for subgroup analyses. The rs1004446 SNP is in the *IGF2* portion of the *INS-IGF2* gene susceptibility region and is associated with the risk for islet autoantibodies in children with HLA DR4-DQ8 genotypes.[29] Substantial rs1004446 genotype-associated DNA methylation differences were observed across the *INS-IGF2* gene region, including the *INS* gene. In addition to epigenetic differences,[30] genotypic variation in the *INS* gene is associated with insulin secretion, early blood glucose concentrations, immune tolerance and immune responsiveness, β-cell stress, and microbiome diversity.[16,30-35] The mechanisms by which the *INS* gene influences susceptibility to or protection against islet autoimmunity and type 1 diabetes likely involve an insufficient pool of insulin-specific regulatory T cells in individuals carrying susceptible genotypes, and enhanced protection against β-cell stress in those with protective genotypes. Further investigations are needed to establish if these factors underlie the potentially opposing effects of oral insulin on efficacy in participants with susceptible and non-susceptible *INS* genotypes. A possible hypothesis is that insulin exposure increases both the number and stability of insulin-specific regulatory T cells in individuals with susceptible genotypes, whereas in those with protective genotypes it might instead destabilise or exhaust these cells.

Overall, the intervention was well tolerated. No adverse metabolic effects on glucose were observed after oral insulin intake, even at the highest dose, suggesting that the insulin was only minimally absorbed into the blood. Adverse events were also similar in the oral insulin and placebo groups, with the exception of a higher incidence of ear and labyrinth disorders observed in 2·8% of participants receiving oral insulin, compared with 0·6% in the placebo group. These events were classified as moderate (one event) or mild (20 events). The underlying cause remains unclear.

The trial had several limitations. It was not powered to assess disease progression or to conduct subgroup analyses, and there was no adjustment of significance thresholds for multiplicity of analyses. Furthermore, although randomisation appeared well balanced, it is possible that differences observed in subgroups might be confounded by randomisation-associated variation in background risks between treatment groups. Vitamin D3 supplementation was offered to participants with vitamin D3 insufficiency and, since vitamin D3 concentrations can be associated with islet autoantibody risk,[36] we cannot exclude that outcomes, including treatment effects, were modified by the supplementation. The absence of mechanistic studies to examine treatment effects on T-cell and B-cell immunity against insulin is a notable limitation, as is the lack of long-term follow-up to assess outcomes beyond the study period. Due to the eligibility criteria, which were mainly based on genetic susceptibility in cohorts of European descent, and due to the informed consent requirements and the complexity of explaining the study, individuals with minority ethnic or migrant backgrounds are likely to be under-represented in the trial. Furthermore, the study did not include high-risk infants without the HLA DR4-DQ8 haplotype and low-risk infants, which further limits the generalisability of the findings.

In this randomised controlled trial involving infants genetically at risk for type 1 diabetes, the high-dose oral insulin treatment schedule did not prevent islet autoantibodies but might have modified the natural course of type 1 diabetes. The findings warrant further exploration in *INS* genotype-targeted trials.

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Contributors

A-GZ and EB conceived the clinical trial. A-GZ was the sponsor delegate of the clinical trial and PA was the deputy sponsor delegate. A-GZ, EB, and HEL led protocol development and design of clinical trial governance. FH and CW led screening for genetic risk governance, IT, and data management. A-GZ and PA had full access to all of the data in the study and take responsibility for the integrity of the data. AW had full access to all of the data in the study and did the statistical analysis; MP had full access to all of the data in the study and verified the statistical analysis. A-GZ, PA, AW, and EB take responsibility for the accuracy of the data analysis. A-GZ, EB, PA, and AW drafted the manuscript. PA, RB, EB, KC, HEL, AH, AJ, OK, ML, MO, MDS, AS, JAT, MV, TvdB, CW, and A-GZ acquired data and contributed to the interpretation of data. PA and EB supervised central laboratory assessments. PA, EB, HEL, OK, and A-GZ verified the diagnoses of type 1 diabetes. A-GZ obtained funding for the GPPAD clinical coordination centre, the screening for genetic risk, and the clinical trial. All authors critically reviewed the manuscript. The corresponding author confirms that all authors have seen and approved the final text. All authors had full access to the complete data analysis and had final responsibility for the decision to submit for publication.

Declaration of interests

A-GZ, EB, and PA are inventors of the patent 'Method for determining the risk to develop type 1 diabetes' (WO 2019/002364). A-GZ served as a member of advisory boards for Sanofi-Aventis and Novo Nordisk, and received support to give lectures sponsored by Sanofi-Aventis. EB received support from Sanofi-Aventis for travel and accommodation to attend international conferences and to give sponsored lectures. PA served as a member of advisory boards for Sanofi-Aventis and received support to give lectures sponsored by Sanofi-Aventis and Eli Lilly. HEL received support to give lectures by Sanofi-Aventis and Novo Nordisk. While working at the University of Oxford, MDS received research grants paid to his institution for work as an investigator on clinical trials funded by GSK, Pfizer, Janssen, Novavax, MedImmune, MCM Vaccine, Alios BioPharma, and Ablynx. He has also received support from the GSK group of companies for travel and accommodation to attend international conferences, and, before 2017, received support paid to his institution as a member of an advisory board for Sanofi-Pasteur MSD. He received no direct personal payment for the current work. MDS has also received royalties from AstraZeneca related to his work on COVID-19 vaccine trials. After his work on this study, MDS is employed by Moderna Manufacturing and Distribution UK and holds equity in this company. AS received support from Synoptis Pharma for travel and accommodation to attend international conferences, was a member of advisory boards for Sanofi-Aventis, Proglikemia, and Medtronic Poland, and gave lectures sponsored by Sanofi-Aventis and Synoptis Pharma. MP received honoraria for lectures from Rubin Medical and Sanofi. AW, RB, KC, FH, AH, AJ, OK, ML, MO, JAT, MV, TvdB, and CW declare no competing interests.

Data sharing

Deidentified participant data will be made available for specified purposes on request to cc@gppad.org. Requests will be reviewed by the GPPAD Steering Committee. Data will be made available after approval of a proposal and after a signed data transfer agreement. Codes used for the statistical analysis are also available on request.

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