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Oral insulin therapy for primary prevention of type 1 diabetes in infants with high genetic risk: the GPPAD-POInT (global platform for the prevention of autoimmune diabetes primary oral insulin trial) study protocol

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ABSTRACT

Introduction The POInT study, an investigator initiated, randomised, placebo-controlled, double-blind, multicentre primary prevention trial is conducted to determine whether daily administration of oral insulin, from age 4.0 months to 7.0 months until age 36.0 months to children with elevated genetic risk for type 1 diabetes, reduces the incidence of beta-cell autoantibodies and diabetes.

Methods and analysis Infants aged 4.0 to 7.0 months from Germany, Poland, Belgium, UK and Sweden are eligible if they have a >10.0% expected risk for developing multiple beta-cell autoantibodies as determined by genetic risk score or family history and human leucocyte antigen genotype. Infants are randomised 1:1 to daily oral insulin (7.5 mg for 2 months, 22.5 mg for 2 months, 67.5 mg until age 36.0 months) or placebo, and followed for a maximum of 7 years. Treatment and follow-up is stopped if a child develops diabetes. The primary outcome is the development of persistent confirmed multiple beta-cell autoantibodies or diabetes. Other outcomes are: (1) Any persistent confirmed beta-cell autoantibody (glutamic acid decarboxylase (GADA), IA-2A, autoantibodies to insulin (IAA) and zinc transporter 8 or tetraspanin 7), or diabetes, (2) Persistent confirmed IAA, (3) Persistent confirmed GADA and (4) Abnormal glucose tolerance or diabetes.

Ethics and dissemination The study is approved by the ethical committees of all participating clinical sites. The results will be disseminated through peer-reviewed journals and conference presentations and will be openly shared after completion of the trial.

Trial registration number NCT03364868.

Strengths and limitations of this study

- Conducted in children with an increased genetic risk for disease regardless of family history status.
- Based on previous safety findings in children.
- Includes attention to nutritional care such as vitamin D status and monitors and cares for adverse psychological impact of screening and participation.
- No previous prevention efficacy demonstrated for oral insulin.
- Requires extensive population screening to identify eligible infants as well as over 1000 participants to achieve reasonable study power.

INTRODUCTION

Type 1 diabetes (T1D) results from an immune-mediated destruction of the pancreatic islet beta-cells resulting in insulin deficiency. This process is clinically silent and can be identified by circulating autoantibodies to beta-cell antigens (glutamic acid decarboxylase (GADA), IA-2 (IA-2A), autoantibodies to insulin (IAA) and zinc transporter 8 (ZnT8A)). Beta-cell autoantibody seroconversion has a clear peak incidence period between age 9 months and 3 years demonstrated in German,[1] Finnish[2] and international (TEDDY)[3] studies. In a recent combined analysis of over 13 000 prospectively followed children from the BABYDIAB, DAISY (Diabetes Autoimmunity Study in the Young) and DIPP (Type 1 Diabetes Prediction and Prevention) studies, 80.0% of the children who developed T1D before the age of 20.0 years already developed beta-cell autoantibodies before the age of 5.0 years.[4]

Almost all children who develop the stage of multiple beta-cell autoantibodies progress to clinical diabetes. The earlier the process of beta-cell autoimmunity is initiated, the more rapid is the progression to T1D.[4] On the basis of these findings, it is concluded that immune therapy given as a primary prevention strategy must be started early in life. Prevention of beta-cell autoimmunity and T1D would clearly represent a significant advancement.

GPPAD – global platform for the prevention of autoimmune diabetes

The Global Platform for the Prevention of Autoimmune Diabetes (GPPAD) was initiated in 2015. It is a consortium of several European research institutions providing an international infrastructure that enables type 1 diabetes primary prevention trials. GPPAD conducts testing for the identification of newborns and infants who have an increased risk for type 1 diabetes, and clinical trials that test primary prevention strategies.

Identification of subjects at increased risk for beta-cell autoimmunity and T1D

The prevalence of T1D in Europe is around 0.4%, while having a first-degree relative with T1D is associated with a 5.0% risk for T1D.[5] Infants without a family history of T1D have a 5.0% risk of T1D if they have the human leucocyte antigen (HLA) DR3/DR4-DQ8 or the DR4-DQ8/DR4-DQ8 genotype.[6 7] Typing at additional T1D susceptibility regions can improve risk stratification for T1D over HLA alone.[8] Genetic risk scores generated from HLA class I and II genotypes and additional single nucleotide polymorphisms (SNPs) of non-HLA genes associated with T1D predisposition can identify infants with risks that are 10.0% or more.[8–10] In the TEDDY study, children with no family history of T1D who have the HLA DR3/DR4-DQ8 or HLA DR4/DR4-DQ8 genotype and a genetic risk score of >14.4 have a risk of 15.9% (95% CI 13.3% to 18.6%) for developing beta-cell autoantibodies by age 5.0 years and 11.4% (95% CI 8.7% to 13.3%) for developing multiple beta-cell autoantibodies by age 6.0 years. In first-degree relatives of a patient with T1D, the presence of at least one HLA DR4-DQ8 haplotype and no protective HLA DR and DQB1 alleles is associated with a genetic risk of >10.0% for developing multiple beta-cell autoantibodies by age 6.0 years.[5 7] Thus, family history and genetic markers can be used to identify neonates or infants with an over 25-fold increased risk for T1D compared with the general population.

Rationale for use of oral insulin as immune tolerance induction therapy

It is widely held that if infant tolerance to beta-cell autoantigens could be enhanced, this could prevent or delay the onset of presymptomatic or asymptomatic T1D (defined as multiple beta-cell autoantibodies), and hence prevent or delay disease diagnosis. Immunological tolerance can be achieved by administration of antigen under appropriate conditions.[11 12] Evidence is now emerging in humans that these approaches may be effective in inflammatory diseases such as multiple sclerosis, allergy and T1D.[13–15] Our goal is to introduce immune tolerance to autoantigen before the start of beta-cell autoimmunity as primary prevention for T1D.[9 16] Early introduction of autoantigen when the natural mechanisms of immune tolerance are fully active as the child becomes tolerant to commensal microorganisms and dietary components may be more beneficial than attempts later in life.

There is strong evidence from man[17 18] that insulin is a key early target and potentially the primary autoantigen in childhood diabetes. There is also a genetic rationale for loss of tolerance against insulin as a primary cause of T1D. Allelic variation in the *INSULIN* gene is associated with T1D[19] and beta-cell autoimmunity[20] via an impaired mechanism of thymic T cell deletion.[21] Children who have an increased exposure to insulin in foetal and neonatal life as a result of having a mother with T1D,[22] have a reduced risk for developing beta cell autoantibodies.[23] Moreover, insulin autoimmunity is closely linked to the HLA DR4-DQ8 haplotype present in the majority of children who develop T1D.[24 25] Daily oral administration of 7.5 mg insulin has been used repeatedly in hundreds of subjects in attempts to prevent the progression to diabetes after the appearance of autoantibodies.[26 27] It is shown to be safe, but not sufficiently effective in preventing diabetes in this setting and dose. Administration of an almost 10-fold higher dose in genetically at risk children prior to the development of autoantibodies is also shown to be safe and to potentially engage the immune system in a manner that is consistent with immune-mediated, tolerogenic protection.[11] Importantly, the study shows no evidence of a 67.5 mg dose of oral insulin causing hypoglycaemia in young children, suggesting that it can

Table 1 Number of people already treated with the study medication

Study	Reference	Dose of oral insulin	Number of participants	Duration of treatment
DPT-1	26	7.5 mg	186 (incl. children)	4.3 years (median period)
Pre-POINT	11	7.5 mg, 22.5 mg, 67.5 mg	15 children	up to 18 months
TrialNet TN07	27	7.5 mg	276 (incl. children)	up to 8.0 years
Pre-POINT Early	Unpublished data	7.5 mg, 22.5 mg, 67.5 mg	22 children	12.0 months

incl, including.

be safely administered at a young age. These findings lay the foundation for the current Primary Oral Insulin Trial (POInT). Table 1 summarises the number of people already treated with oral insulin in different trials. No adverse reactions have been evidenced by case reports and by statistical comparisons of treatment and placebo groups for all dosages (7.5 mg, 22.5 mg and 67.5 mg) as previously published.[11 26 27]

METHODS

Study organisation

POInT is organised through the GPPAD, a network of collaborating clinical study centres from European countries with sites in Belgium (Leuven), Germany (Dresden, Hannover, Munich), Poland (Warsaw), Sweden (Malmö) and UK (Oxford). The clinical trial sponsor of POInT is the Technische Universität München, Faculty of Medicine. The trial coordination centre (GPPAD CC) is located at the Institute of Diabetes Research, Helmholtz Zentrum München. It provides communication and coordination among the POInT clinical study centres, and manages the collection, analysis and storage of clinical data; together with the Technische Universität München, Faculty of Medicine, it oversees regulatory activities, clinical research organisation activities, the manufacturer of the investigational medical product and the central laboratories.

Study population

Study participants are identified by testing for T1D risk in infancy at delivery (cord blood), and/or capillary blood taken at the regular newborn screening or an infant check-up visit before age 5.0 months. Infants are tested for genetic risk of T1D based on risk scores derived from SNPs that define the susceptible HLA DRB1*03, HLA DRB1*04 and HLA DQB1*0302 alleles, the protective HLA DRB1*1501 and DQB1*0503 alleles, SNPs for specific HLA class I alleles and SNPs in non-HLA T1D susceptibility genes. Infants with a predicted risk of >10.0% to develop multiple beta-cell autoimmunity by age 6.0 years and who fulfil the inclusion criteria are asked to participate in the GPPAD-POInT study. A total of 1040 infants will be enrolled and randomised in the POInT study (see figure 1).

Consenting

Testing for T1D risk is offered to families together with the regular newborn screening as a supplemental test with separate consent (Belgium, Germany, Poland, UK). Alternatively, it is offered at delivery using cord blood (Sweden), or at a paediatric visit before the age of 5 months (Germany, Sweden). If a child is eligible for POInT, families are contacted and offered the possibility to participate in POInT with further informed consent. A qualified physician or study nurse in accordance with country-specific guidelines and ethical review board requirements performs the informed consent. The objectives of the

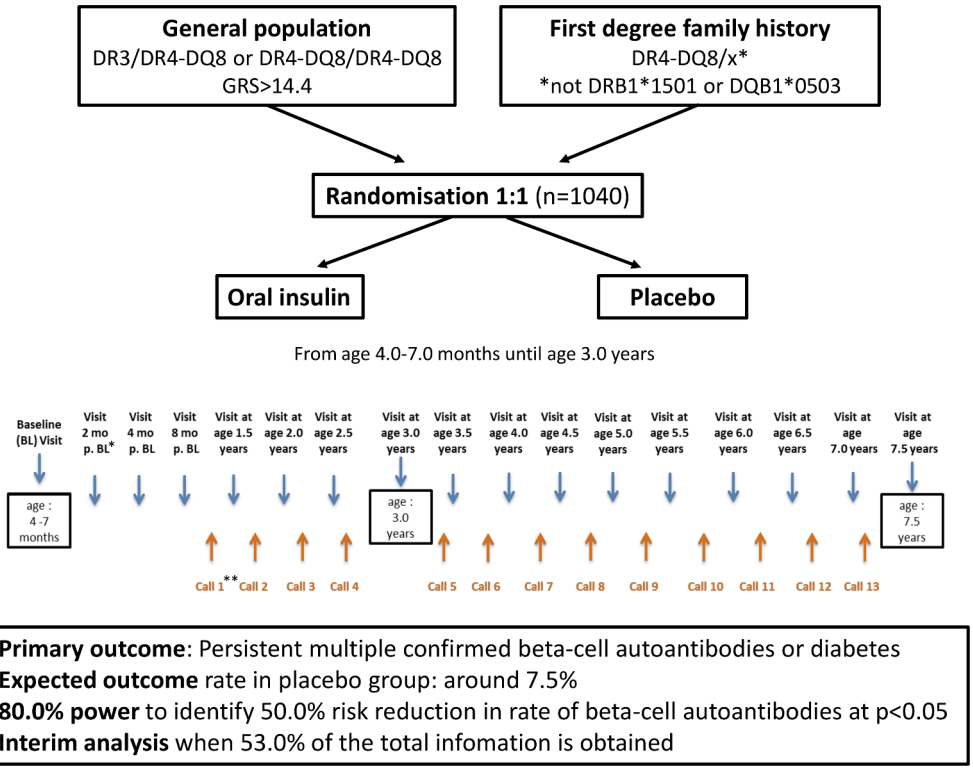

Figure 1 POInT study flow and time schedule for a participant with maximum follow-up of 54 months. * p. BL: post baseline visit, ** Call: interim telephone calls with families to asses adverse events and support trial adherence. mo, months; POInT, Primary Oral Insulin Trial.

trial, and that prevention with oral insulin may help to train the immune system to develop tolerance and no autoimmune disease such as T1D during early life along with the risks and burden of participation, are discussed with the families during the informed consent procedure. The trial is presented with a copy of the relevant trial material. The informed consent form must be signed and dated by one or both parent(s)/guardian(s) according to country-specific guidelines.

Patient and public involvement

Patients were not involved in the study design but in the prioritisation of the research question of T1D prevention. Patients support recruitment through dissemination, and participation in press conferences. Participating families will be informed about the outcome of the trial via webcast, letter and personal communication on the completion of the trial. The burden of intervention was previously assessed by participating families in a prior pilot prevention trial.[11]

Inclusion and exclusion criteria

Participants must meet all entry criteria for the protocol as outlined below.

- Age between 4.0 months and 7.0 months at randomisation and start of treatment.
- A predicted genetic risk of >10.0% to develop multiple beta-cell autoantibodies by age 6.0 years defined as:

a. For infants without a first-degree family history of T1D, eligible genetic risk is defined as a DR3/DR4-DQ8 or DR4-DQ8/DR4-DQ8 genotype, and a genetic risk score that is >14.4 (10). These represent approximately 1.0% of all newborns.

b. For infants with a first-degree family history of T1D, eligible genetic risk is defined as the presence of HLA DR4 and DQ8, and none of the following protective alleles: DRB1*1501, DQB1*0503. These represent around 30.0% of infants with a first-degree family history of T1D.

- Solid foods introduced into diet of infant.
- Written informed consent signed by the custodial parent(s).

Infants meeting any of the following criteria will NOT be eligible for inclusion into the study:

- Concomitant disease or treatment that may interfere with the assessments, as judged by the investigators.
- Any condition that could be associated with poor compliance.
- Any medical condition or coexisting medical condition, which, in the opinion of the investigator, may jeopardise the participant's safe participation in the study.
- Diagnosis of diabetes at the time of recruitment.
- Participation in another clinical trial.
- Non-Caucasians should not be excluded if they fulfil the inclusion criteria and were not excluded for other reasons.

Randomisation

Randomisation is performed by an **In**Ventory Management, **R**andomisation & **S**upplies system using a predefined randomisation list. During the randomisation process the lowest, not participant-assigned randomisation number will be assigned to the participant and determines the treatment arm of the participant.

Study outcomes

The primary outcome of the POInT study is the development of persistent confirmed multiple beta-cell autoantibodies or diabetes. Multiple beta-cell autoantibodies are defined as a positive result in two consecutive samples (persistent) for two or more of the following autoantibodies GADA, IA-2A, ZnT8A, or high affinity IAA (see figure 1). Antibodies are considered positive if they are detected above the threshold for positivity in two independent GPPAD Core laboratories, located at the Institute of Diabetes Research, Helmholtz Zentrum München, Germany, and at the University of Bristol, Medical School, Diabetes and Metabolism, Learning and Research, Southmead Hospital, UK (for confirmation of results). Diabetes is defined using American Diabetes Association criteria.[28] The age at the first positive sample or of diabetes is identified as the time point for developing the primary outcome.

Other outcomes are the development of one or more persistent confirmed beta-cell autoantibodies (GADA, IA-2A, ZnT8A, IAA, or autoantibodies to tetraspanin 7), the development of persistent confirmed IAA, the development of persistent confirmed GADA and the development of an abnormal glucose tolerance test. Persistent means positive autoantibodies at two subsequent visits and confirmed means positive autoantibodies in both GPPAD laboratories.

Study timeline

The study is expected to take 7.0 years to complete. This includes an enrolment period of 3.5 years and a further 3.5 years of follow-up. The first participant was enrolled in February 2018.

Treatment

Participants are randomised in a 1:1 ratio to receive either oral insulin or placebo. Recombinant human (rH) insulin crystals are provided by Lilly Pharmaceuticals, Indianapolis, Indiana, USA. The crystals are prepared at three doses: 7.5 mg rH-insulin crystals (215.3 IU insulin), 22.5 mg rH-insulin crystals (645.8 IU insulin), 67.5 mg rH-insulin crystals (1937.3 IU insulin). The insulin crystals are formulated together with filling substance (microcrystalline cellulose to a total weight of 200.0 mg) and contained in hard gelatin capsules. Placebo capsules of the same appearance contain only the filling substance. The medication is provided in a capsule box, 32 hard gelatin capsules, containing rH-insulin crystals or placebo.

Participants start treatment at age 4.0 months (earliest start) to 7.0 months (latest start) and are treated for a

period of 29 up to 32 months (until 36 months of age). Participants are followed thereafter until completion of the trial for a period of 6 to 54 months at last follow-up visit. The children in the insulin group receive daily oral insulin at a dose of 7.5 mg for 2 months, increasing to a dose of 22.5 mg for 2 months and finally at a dose of 67.5 mg. The placebo group receive daily oral placebo until age 36.0 months.

The study medication is given orally as a powder spread on a small quantity meal serving for example, with infant formula, tea spoon of water, commercial baby food or yoghourt. The investigational product (oral insulin or placebo) is self-administered by the child's parents as content of one capsule per day. Treatment is administered preferably in the morning (7 to 10 am). Parent(s) are instructed on how to administer and store the study drug at the baseline visit. Participants are observed for 2 hours after administration of the study drug at visits one, two, thee and four. They are advised to immediately report any adverse events experienced following treatment.

Study assessment

The study schedule is shown in figure 1. Follow-up study visits are planned after 2 months, 4 months, 8 months and then at the age of 1.5, 2.0, 2.5 and 3.0 years. A physical examination and blood drawing for the measurement of beta-cell autoantibodies and 25-hydroxyvitamin (25-OH-Vitamin) D3 concentrations are performed at all visits. In addition, blood glucose is monitored before and 30, 60 and 120 min after administration of the study drug (oral insulin or placebo) at the baseline, 2, 4 and 8 month visits; for all later visits only one single blood glucose measurement is carried out. If a participant develops beta-cell autoantibodies during the trial an oral glucose tolerance test (OGTT) will be performed at visit eight and all later visits. A detailed study flow chart is shown in online supplementary file 1. All study relevant subject data and laboratory results are documented in corresponding electronic case report forms.

Efficacy (beta-cell autoantibodies and dysglycaemia/T1D)

Blood samples for beta-cell autoantibodies (autoantibodies to insulin (IAA), GAD65 (GADA), IA-2 (IA-2A), ZnT8 (ZnT8RA, ZnT8WA) and tetraspanin 7 (TSP7A)) are obtained at all visits and tested centrally in the GPPAD laboratory (Institute of Diabetes Research, Helmholtz Zentrum München, Germany). IAA are measured by competitive immunoprecipitation of ^{125}I-insulin,[29] autoantibodies to IA-2 and ZnT8 by radiobinding assay (RBA),[30] autoantibodies to GAD65 by RBA or ELISA, and TSP7A by LIPS (Luciferase Immunoprecipitation System).[31] If the participant develops one or more beta-cell autoantibodies during the study, the beta-cell autoantibody positive status is confirmed in the same blood sample by a second central autoantibody laboratory (University of Bristol, Medical School, Diabetes and Metabolism, Learning and Research, Southmead Hospital, UK). If the sample is confirmed autoantibody positive by both central autoantibody laboratories, a confirmation sample is drawn within 4.0 to 12.0 weeks. If positive, the custodial parent(s) are informed that the child has developed persistent confirmed beta-cell autoantibodies early presymptomatic stage of T1D. The child remains in the study and continues to be treated or followed as planned until the child has developed T1D. The parents are asked to participate in an educational programme informing about the diagnosis of beta-cell autoantibody positivity and symptoms of hyperglycaemia and metabolic decompensation.

Additionally, participants with beta-cell autoantibodies will have fasting glucose and OGTT evaluations at the regular scheduled study visits from age 3.0 years or from when the child has a confirmed persistent beta-cell autoantibody status, whichever is last. Fasting blood glucose and blood glucose after OGTT are determined centrally in a certified GPPAD laboratory (Labor Becker & Kollegen MVZ GbR, München, Germany).

Vitamin D

Low concentrations of vitamin D are common in children with T1D,[32] and may contribute to immune dysfunction.[32 33] Therefore, 25-OH-Vitamin D3 concentrations are monitored at every visit. Measurements are performed in local certified laboratories. Children identified as having concentrations of vitamin D less than 75 nmol/L will be managed locally. The custodial parent(s) and/or family paediatrician are notified and are advised to evaluate and, if appropriate, adjust the daily vitamin D supplementation of the study participant up to 1000 IU/day.

Safety

Hypoglycaemia: Blood glucose levels are assessed by local certified laboratories and by glucose metres before and 30, 60 and 120 min after study drug administration during study visits at baseline, 2, 4 and 8 months post baseline. Additionally, families are instructed to monitor their participating child for symptoms of hypoglycaemia after study drug intake.

Allergy: No allergy to orally administered insulin has been reported. IgE anti-insulin levels have been measured in Pre-POINT[11] and no child has developed an IgE response to insulin. Nevertheless, families are asked to report any adverse reaction such as wheezing seen within 2 hours of taking study medication that may be considered as indicative of a hypersensitive response to study drug. Families will report these to the study physician.

Adverse events (AEs) and serious adverse events are assessed at all visits during the intervention phase and at 6 months after completing the intervention phase.

Physical examinations including measurement of height and weight are performed at all visits. Blood samples for differential blood counts are collected at start and at the end of the study.

Psychological impact

The psychological effect of trial participation is monitored by the standardised Patient Health Questionnaire at visit three, five, eight and at the last visit at the end of participation. When a parent is identified with high levels of anxiety and/or distress, a structured concept of psychological care is provided according to local guidelines.

Retention

Regular telephone calls are made to the families of the participants between the study visits. The general compliance and AEs are assessed and documented during calls made in the intervention phase.

Ancillary

As an ancillary component of the trial, biobank repository samples are obtained and stored on consent at a central biobank and in local biobanks at each study site for future research related to T1D. Biobank samples include serum, plasma, peripheral blood mononuclear cells (PBMC), PBMC-RNA and PBMC-DNA.

Analysis

All efficacy analyses will be conducted under the intention-to-treat principle whereby all outcome data in all randomised subjects who have received at least one dose of trial drug or placebo will be included in all analyses as appropriate. Subjects who drop-out will not be replaced. All data acquired prior to termination will be included in the primary analysis unless a participant withdraws consent.

Primary outcome and analysis

The primary outcome is the elapsed time from random treatment assignment to the development of persistent confirmed multiple beta-cell autoantibodies or diabetes among those enrolled in the primary analysis cohort. It is expected that beta-cell autoantibodies will be detected prior to diabetes onset; however, the presence of diabetes in the absence of beta-cell autoantibodies is also considered as a primary outcome endpoint, and in this case situation, the age at diagnosis is used to determine the elapsed time to the primary outcome.

The cumulative incidence of multiple beta-cell autoantibodies over time since randomisation within each treatment group will be estimated from a Kaplan-Meier estimate of the 'beta-cell autoantibody-free' survival function. The difference between groups in the cumulative incidence functions, and the associated hazard functions, will be tested at the 0.05 level, two-sided, using the Cox regression including first-degree relative status as covariate. The estimates of cumulative incidence and the test will adjust for periodic outcome assessment visits to assess beta-cell autoantibody status. The critical value for the test statistic, and CIs in this primary analysis will be determined by the prespecified group-sequential procedure.

Secondary outcomes and analyses

In addition to the primary outcome of multiple beta-cell autoantibodies, four secondary outcomes are included for analysis of efficacy. Secondary outcomes are the development of one or more persistent confirmed beta-cell autoantibodies (GADA, IA-2A, ZnT8A, IAA), the development of persistent confirmed IAA, the development of persistent confirmed GADA and the development of an abnormal OGTT. The treatment arms will be compared on the corresponding cumulative incidence of each secondary outcome using the log rank statistic. Subgroup analyses will be conducted comparing the effects of oral insulin versus placebo on the risk of multiple beta-cell autoantibodies with a test of the group by subgroup factor interaction in a Cox proportional hazard model. Subgroups of the population classified by sex, first degree relative status, beta-cell autoantibody status at baseline, maternally transferred beta cell autoantibody status at baseline, genetic risk score tertiles and INS genotype. Differences in the treatment effect between subgroups will be tested using a covariate by treatment group effect in a Cox proportional hazard model.

Study power and accrual target

The study has been designed to provide 80% power to detect a 50% risk reduction in the rate of multiple beta-cell autoantibodies using a two-sided test at the 0.05 level after 7.0 years of study duration.

For the sample size estimation, an event probability of 7.5% in the placebo group at 3.5 years follow-up (approximate age of participants, 4.0 years), has been assumed. Based on the exponential distribution, this leads to a hazard of 0.02227. It is expected that the hazard is halved by the treatment (HR 0.5). Planned accrual time is 3.5 years, follow-up time is 3.5 years. A dropout rate of 20.0% has been anticipated.

An interim analysis will be performed when over 50% of the total expected information (events) is obtained. This is anticipated to be at 4.5 years study duration. The interim analysis is based on the adaptive design of O'Brien and Fleming.[34] At the interim analysis, it will be possible to reject the null hypothesis, if the standardised normal-distributed Z-statistic (which can be directly calculated from the Wald test statistic of the Cox model) is either below the boundary −2.65176 or above the boundary 2.65176. Futility will also be considered. At the interim analysis, the study will be stopped due to futility, if the standardised normal-distributed Z-statistic lies between the boundaries −0.80692 and 0.80692.

All sample size calculations were performed using the SEQDESIGN programme in SAS 9.4.

Benefits and risks

Benefits

The potential benefit for a participating child is the prevention (or delay in onset) of beta-cell autoantibodies and diabetes. Because all participating children,

including children who receive placebo, have a relatively high risk (>10.0%) of developing beta-cell autoantibodies and diabetes, testing blood samples in the study will allow early recognition of an immune response against the beta-cells, close monitoring and regular blood glucose testing. Children identified as beta-cell autoantibody positive, will be invited to receive education and teaching to learn about the risk of hyperglycaemia and means to prevent diabetic ketoacidosis. Participation in other ongoing prevention trials that aim to prevent disease progression may be possible with separate consent (Including, but not limited to TrialNet studies https://www.diabetestrialnet.org/). If a participating child develops T1D during the trial, the disease can be diagnosed very early, that is before the child shows the typical symptoms of severe metabolic dysfunction, and an appropriate therapy could be started immediately, potentially reducing complications at the onset of diabetes[35 36] and later in life. Furthermore, information about available treatments and intervention studies that include children with recently diagnosed T1D in order to preserve the remaining beta-cells can be given to families.

Risks

The risks of venous blood sampling include the occurrence of discomfort and bruising. Discomfort for the child at blood draws will be minimised by the use of anaesthetic cream at the venepuncture site. The volume of blood drawn for the trial endpoints is <1.0% of the total blood volume, within the suggested limits from the European guidelines for a paediatric population.[37] With local ethical approval and specific informed consent, additional blood volumes may be requested for ancillary purposes and storage. The total blood volume for the trial protocol and ancillary purposes is less than 3.0%, calculated from the expected per kg body weight blood volumes in childhood, and is within the limits of National Institute for Health guidelines for a paediatric population and which has been demonstrated to be safe in children in previous studies.[38]

Although there is a theoretical, but very low, risk of oral insulin inducing hypoglycaemia, as described earlier this has not been observed in multiple previous studies[11 26 27] (table 1).

Allergy to oral insulin is theoretically possible. There have been no reported allergic reactions or alterations in routine chemistry laboratory values in individuals receiving oral insulin.

Oral insulin has not been shown to increase the risk of beta-cell autoimmunity or diabetes. The data safety monitoring board will monitor the development of beta-cell autoantibodies and diabetes in trial participants and can request unblinding of data if there is reasonable concern that the frequency of beta-cell autoantibodies or diabetes development in participants exceeds expectations. Parents of participating children will be informed about the likelihood of their child to develop beta-cell autoantibodies, dysglycaemia and T1D.

Current status of POInT

The first participant was enrolled into POInT in February 2018. Since then, a total of 214 participants (status March 2019) were enrolled. Recruitment is meeting its target (online supplementary file 2).

ETHICS AND DISSEMINATION

Dissemination

GPPAD is committed to open data sharing in compliance with all applicable European and GPPAD Consortium Member State, Data Protection and Privacy Protection laws, rules and regulations. The results and the respective data of the POInT study results will be shared no later than 12 months after completion of the trial. GPPAD provides access to anonymised biobank material gathered from study participants to external investigators. One goal is to make all generated research available in the manner most conducive to furthering scientific research. Study participants' privacy rights are always respected. The findings of the study will be disseminated through peer reviewed journals, national and international conferences and printed and online media. Primary care physicians and paediatricians are additionally informed via newsletters and quality circles.

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Contributors AGZ and EB conceived the trial. AGZ, EB, JH and HEL led protocol development, and design of clinical trial governance. AGZ, PA, EB and JH led regulatory authority submission. MG, AGZ and EB wrote the manuscript. All authors (AGZ, PA, RB, KC, TD, MG, JH, VH, OK, KL, HEL, ML, MS, AS, JAT, EB) contributed to protocol development. AGZ, MS, KC, HEL and AS coordinated site specific ethical board application and review. EB, JH and VH developed the statistical design for the trial and wrote the statistical section of the protocol. EB and PA developed the outcome definition of the trial and wrote the autoantibody and outcome section of the protocol. KL developed the psychological section of the study. All authors reviewed the protocol as well as this manuscript.

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