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# Anti-viral action against Type 1 diabetes autoimmunity

| Submission date | Recruitment status | [X] Prospectively registered |
|---|---|---|
| 02/05/2024 | Recruiting | [X] Protocol |
| **Registration date** | **Overall study status** | [ ] Statistical analysis plan |
| 26/07/2024 | Ongoing | [ ] Results |
| **Last Edited** | **Condition category** | [ ] Individual participant data |
| 26/11/2025 | Nutritional, Metabolic, Endocrine | [ ] Record updated in last year |

## Plain English summary of protocol

Background and study aims
The incidence of type 1 diabetes (T1D) increased sharply during the COVID-19 pandemic. Islet autoantibodies in the blood are the first signs of a child developing T1D. Research has shown that early childhood infection with the SARS-CoV-2 virus more than doubles the risk of developing islet autoantibodies. This virus can enter and infect the islet cells of the pancreas, so it is plausible this may increase susceptibility. The main aim of this study is to investigate whether vaccination against COVID-19 at the age of 6 months is superior to placebo in preventing the development of islet autoantibodies in children at increased genetic risk of T1D.

Who can participate?
Patients aged between 3 and 4 months with a high genetic risk of developing T1D (identified from the currently running INGRID-2 trial)

What does the study involve?
Participants will receive vaccination with BioNTech/Pfizer Comirnaty 3 mcg in three doses between 6 and 11 months of age. Half of the recruited patients will receive the SARS-CoV-2 vaccine and half will receive placebo vaccination (normal saline). Ongoing monitoring visits will occur post-vaccination for 2-1/2 to 6 years, depending on when the participants is recruited into the study. Blood and stool samples will be collected at each visit and participants will collect weekly saliva samples and monthly stool samples at home for infection surveillance. They will also complete a fortnightly questionnaires for the first 24 months around infections and twice during the study around physical and mental health.

What are the possible benefits and risks of participating?
A potential benefit is the prevention or delay of developing islet autoantibodies and type 1 diabetes. Such a benefit can not be guaranteed, however, regular blood testing will help to detect and closely monitor the early stages of type 1 diabetes which can reduce the risk of complications.
The vaccine that will be used in the study will be Comirnaty® Omicron XBB.1.5 or future variant developments replacing current Comirnaty vaccines, which is approved in the UK from 6 months of age. For primary vaccination it is given in three doses of 3 µg each; the first two doses are given 3 to 6 weeks apart, followed by a third dose given at least 8 weeks after the second dose.

For children within these age groups, the vaccine is given as injections in the muscles of the thigh. The most common side effects (listed in SmPC as >1/1,000) in children aged from 6 months to 4 or 5 years were comparable to those seen in older age groups. Irritability, sleepiness, loss of appetite, rash, mild temperatures, diarrhoea and less commonly vomiting, lymphadenopathy and night sweats. Redness, swelling and tenderness at the injection site were also common side effects in children aged 6 to 23 months. These effects were usually mild or moderate and improved within a few days of vaccination. Rarer side effects (<1/1,000) are detailed in the SmPC for the vaccine. The researchers will ensure participants' families are aware of these potential side effects and will be given advice on how to minimise these.
The blood samples taken as part of the trial involve risks such as slight pain or bruising at the injection site and occasional discomfort. This will be minimised as much as possible by using on-site staff who are skilled in paediatric phlebotomy and distraction techniques, as well as the use of anaesthetic cream/spray at the puncture site.
The study involves a large number of procedures, especially up to age 2 years. These include frequent study visits and blood draws, up to weekly collection of saliva samples, monthly collection of stool samples and responding to questions fortnightly. This is considerably more than what is standard care during this age and may be burdensome for children and participating families. The extent of the procedures as compared to standard care will be explained during the consent process. In a previous study, which enrolled children from age 4 months for a similar study duration and blood draw schedule, the study drop-out rate was low (<10%). Therefore, the study procedures are considered tolerable to the majority of participants and families. The psychological questionnaire will monitor and identify families requiring attention due to participation demands and solutions to reduce the demands such as less frequent sampling or questionnaires will be discussed with these families. The researchers will try to ensure that all appointments are run as promptly and smoothly as possible to minimise time commitment.
Children in the placebo group will be denied access to the benefits of a COVID-19 vaccine, including the possible prevention of serious early and late complications from a COVID-19 infection. The current number of children below the age of 5 years who are provided with this benefit through vaccination is extremely low (<0.1%). Further mitigation of the risk includes excluding children with diseases or treatments that lead to immune deficiency. This exclusion helps minimize the potential risk for this specific group of participants. In the UK, COVID-19 vaccination for children this age is only advised for those in a clinical risk group, so participation would not be depriving them of routinely receiving the vaccination.
Other viral infections such as Coxsackie B virus infection are associated with the development of islet autoantibodies. Therefore, the effectiveness of COVID-19 vaccination in preventing islet autoimmunity associated with COVID-19 infection will not prevent the occurrence of islet autoimmunity associated with other causes. The development of islet autoantibodies or type 1 diabetes may alter the behaviour of parents or guardians to the child and may affect further family planning or might cause psychological stress. Parental/guardian well-being is monitored via a psychological questionnaire. The development of islet autoantibodies may also affect the insurance options of the participant.

Where is the study run from?
Newcastle upon Tyne Hospitals NHS Foundation Trust (UK)

When is the study starting and how long is it expected to run for?
April 2024 to October 2029

Who is funding the study?
Leona M and Harry B Helmsley Charitable Trust (USA)

Who is the main contact?

# Contact information

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Scientific

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# Additional identifiers

**ClinicalTrials.gov (NCT)**
NCT06452654

**Clinical Trials Information System (CTIS)**
2023-507348-35

**Clinical Trials Information System (CTIS)**
2023-507348-35-00

**Integrated Research Application System (IRAS)**
1009668

**Protocol serial number**
EU Trial number:

# Study information

**Scientific Title**
Anti-viral action against Type 1 diabetes autoimmunity

**Acronym**
GPPAD-05-AVAnT1A

**Study objectives**
Primary objective:
1. To determine whether vaccination of children with elevated genetic risk for type 1 diabetes against COVID-19 from age 6 months reduces the cumulative incidence of islet autoantibodies or type 1 diabetes in childhood.

Secondary objectives:
1. To determine whether vaccination against COVID-19 similarly reduces the cumulative incidence of multiple islet autoantibodies in childhood.
2. To determine whether vaccination against COVID-19 similarly reduces the cumulative incidence of coeliac disease-associated transglutaminase autoantibodies in childhood.
3. There are also planned exploratory objectives (outside of this clinical trial), as detailed in the protocol, which will be decided on as the trial progresses by the steering committee, and the collection of samples for these is included in the patient informed consent form.

## Ethics approval required
Ethics approval required

## Ethics approval(s)
Approved 24/06/2024, East of England - Cambridge South Research Ethics Committee (Equinox House, City Link, Nottingham, NG2 4LA, United Kingdom; +44 (0)2071048084; cambridgesouth.rec@hra.nhs.uk), ref: 24/EE/0112

## Primary study design
Interventional

## Study design
Randomized double-blind placebo-controlled trial

## Study type(s)
Treatment

## Health condition(s) or problem(s) studied
Type 1 diabetes

## Interventions
IMP - Comirnaty® 3 µg Omicron XBB.1.5 or future new variant developments re-placing current Comirnaty vaccines for children
Suspension for injection, for intramuscular use
Manufacturer: BioNTech /Pfizer

Comparator - 0.9 % Sodium Chloride Solution (saline) for injection

Dosing: three doses
1st dose at age 6.0 to 7.0 months
2nd dose at least 3 weeks through to 6 weeks after 1st dose
3rd dose at least 8 weeks after 2nd dose (around age 8.5 to 11 months)

For the development of persistent confirmed islet autoantibodies, the observation time will be censored at the last time when no persistence of a confirmed islet antibody could be verified in the corresponding blood sample. Regarding type 1 diabetes, the observation time will be censored for children who are free from diabetes at the time of their last contact with the trial centre. For the primary endpoint considering either the development of a persistent confirmed islet autoantibody or type I diabetes – whatever occurs first – observation time will be censored at the last time when neither the persistence of a confirmed antibody nor type I diabetes was recorded, taking the minimum of both times into account. The cumulative incidences of islet autoantibodies over time since randomisation within each treatment group will be estimated by the Kaplan-Meier method. The overall difference between the groups in the cumulative incidence functions will be tested by the log-rank test at the two-sided significance level of 0.05. The hazard ratio of the two groups and its 95% confidence interval will be determined by the Cox model. As a sensitivity analysis, the hazard ratio of the two groups will be assessed using the Cox regression when including site as covariate. The estimates of cumulative incidence and the log-rank test will adjust for periodic outcome assessment visits to assess islet autoantibody status.

Criteria are based on the measurement of islet autoantibodies against insulin (IAA), GAD65 (GADA), IA-2 (IA-2A), and ZnT8 (ZnT8A) tested in the GPPAD central autoantibody laboratory.
1. Confirmed IAA is defined as sample positive for IAA in both a screening and confirmatory assay that has a different format to the screening assay.
2. Confirmed GADA is defined as sample positive for GADA in both a screening and confirmatory assay that has a different format to the screening assay.
3. Confirmed IA-2A is defined as sample positive for IA-2A in both a screening and confirmatory assay that has a different format to the screening assay.
4. Confirmed ZnT8A is defined as sample positive for ZnT8RA or ZnT8WA in both a screening and confirmatory assay that has a different format to the screening assay.
The status persistent confirmed islet autoantibody-positive is defined as confirmed IAA, confirmed GADA, confirmed IA-2A, or confirmed ZnT8A in two consecutive samples. Persistence of at least one confirmed islet autoantibody until the last follow-up sample is required for an outcome of persistent confirmed islet autoantibody.
Islet autoantibodies that are considered maternally derived are NOT positive for the primary outcome.

Criteria for type 1 diabetes onset are based on criteria defined by the American Diabetes Association which include glucose testing, or HbA1c or the presence of unequivocal hyperglycaemia with acute metabolic decompensation (diabetic ketoacidosis):
1. Fasting plasma glucose (FPG) ≥126 mg/dl (7 mmol/l). Fasting is defined as no caloric intake for at least 8 hours. OR
2. Two-hour plasma glucose (PG) ≥200 mg/dl (11.1 mmol/l) during an OGTT (The test should be performed using a glucose load containing the equivalent of 1.75g/kg body weight to a maximum of 75g anhydrous glucose dissolved in water). OR
3. HbA1c ≥6.5% (48mmol/mol) (The test should be performed in a certified laboratory). OR
4. In a patient with classic symptoms of hyperglycaemia or hyperglycaemic crisis, a random plasma glucose ≥ 200 mg/dl (11.1 mmol/l). OR
5. In a patient without classic symptoms of hyperglycaemia, a random plasma glucose ≥ 200 mg /dl (11.1 mmol/l).

The primary endpoint of the development of persistent confirmed islet autoantibodies will be evaluated through blood samples taken prior to receiving COVID-19 vaccination, at the time of the 3rd vaccination, then 3 monthly between the ages of 12 to 24 months, 6 monthly between the ages of 24 to 36 months, and then annually thereafter.
HbA1c is evaluated at 12, 18 and 24 months, then annually thereafter.
Fasting blood glucose is checked at every visit (with each of 3 vaccination visits between 6-11 months; 3 monthly from 12 months to 24 months; 6 monthly between the ages of 24 to 36 months, and then annually thereafter). 30 min postprandial glucose is checked at all bar visits 2 & 7.
OGTT done annually from 36 months if islet antibody positive.

## Intervention Type
Drug

## Phase
Phase IV

## Drug/device/biological/vaccine name(s)
Comirnaty Omicron XBB.1.5 3 µg/dose [one dose (0.2 ml) contains 3 micrograms of raxtozinameran, a COVID-19 mRNA vaccine]

### Primary outcome(s)
The elapsed time from random treatment assignment to the development of persistent confirmed islet autoantibodies (evaluated through blood samples taken prior to receiving COVID-19 vaccination, at the time of the 3rd vaccination, then 3 monthly between the ages of 12 to 24 months, 6 monthly between the ages of 24 to 36 months, and then annually thereafter) or the development of type 1 diabetes (based on criteria defined by the American Diabetes Association)

### Key secondary outcome(s)
1. The elapsed time from random treatment assignment to the development of multiple islet autoantibodies, evaluated through blood samples taken prior to receiving COVID-19 vaccination, at the time of the 3rd vaccination, then 3 monthly between the ages of 12 to 24 months, 6 monthly between the ages of 24 to 36 months, and then annually thereafter
2. The elapsed time from random treatment assignment to the development of type 1 diabetes based on criteria defined by the American Diabetes Association
3. The elapsed time from random treatment assignment to the development of persistent confirmed transglutaminase antibodies, evaluated through blood samples taken 6 monthly between 12 and 36 months of age, and then annually thereafter

### Completion date
31/10/2029

## Eligibility

### Key inclusion criteria
1. Age between 3.00 and 4.00 months at the time of enrolment
2. A high genetic risk (>10%) to develop islet autoantibodies by age 6 years:
2.1. For children without a first-degree family history of type 1 diabetes, high genetic risk is defined as a DR3/DR4-DQ8, DR4-DQ8/DR4-DQ8 or DR3/DR4-DQ7 rs6901541 C/T genotype and an elevated sex-specific genetic risk score that is at the 98.75th centile, in other words identifies around 1.25% of newborns without a first-degree family history with type 1 diabetes.
2.2. For children with a first-degree family history of type 1 diabetes, high genetic risk is defined as having HLA DR4 and DQ8, none of the following protective alleles: DRB1*1501, DQB1*0503, DRB1*1303, and a sex-specific genetic risk score >50th centile of the background population. These represent around 25% of children with a first-degree family history of type 1 diabetes.
3. Written informed consent signed by the custodial parent(s)

### Participant type(s)
Healthy volunteer

### Healthy volunteers allowed
No

### Age group
Child

### Lower age limit
3 Months

### Upper age limit

4 Months

### Sex
All

### Total final enrolment
0

### Key exclusion criteria
1. Previous hypersensitivity to the excipients of the vaccine. These include:
1.1. ((4-hydroxybutyl)azanediyl)bis(hexane-6,1-diyl)bis(2-hexyldecanoate) (ALC-0315)
1.2. 2-[(polyethylene glycol)-2000]-N,N-ditetradecylacetamide (ALC-0159)
1.3. 1,2-Distearoyl-sn-glycero-3-phosphocholine (DSPC)
1.4. Cholesterol
1.5. Trometamol
1.6. Trometamol hydrochloride
1.7. Sucrose
2. Any medical condition, concomitant disease or treatment that may interfere with the assessments or may jeopardize the participant's safe participation in the study. These include immune deficiencies, and conditions or treatments that lead to immune suppression.
3. Likely poor compliance due to expected change in residency.
4. Diagnosis of diabetes prior to recruitment or randomisation.
5. Current use of any other investigational drug.

### Date of first enrolment
23/10/2024

### Date of final enrolment
31/07/2027

## Locations

### Countries of recruitment
United Kingdom

England

Austria

Belgium

Germany

Sweden

### Study participating centre
### The Royal Victoria Infirmary
Queen Victoria Road
Newcastle upon Tyne

England
TS1 4LP

**Study participating centre**
**Cambridge Biomedical Campus**
Hills Road
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CB2 0QQ

**Study participating centre**
**Klinikum rechts der Isar of Technical University Munich and Institute for Diabetes Research**
Helmholtz Munich
Heidemannstr.1
Munich
Germany
80939

**Study participating centre**
**AUF DER BULT, Kinder- und Jugendkrankenhaus**
Hannover
Germany
-

**Study participating centre**
**Klinik und Poliklinik f. Kinder und Jugendmedizin**
Universitätsklinikum Carl Gustav Carus
Technische Universität Dresden
Dresden
Germany
-

**Study participating centre**
**Lund University**
Skane University Hospital SUS
Malmö
Sweden
-

**Study participating centre**
**University Hospitals Leuven**
Faculty of Medicine
Catholic University of Leuven
Leuven
Belgium
-

**Study participating centre**
**Medical University of Vienna**
Waehringer Guertel 18-20
Vienna
Austria
1090

# Sponsor information

**Organisation**
Klinikum rechts der Isar Technische Universitat

# Funder(s)

**Funder type**
Charity

**Funder Name**
Leona M. and Harry B. Helmsley Charitable Trust

**Alternative Name(s)**
Helmsley Charitable Trust, The Leona M. and Harry B. Helmsley Charitable Trust, Leona M. & Harry B. Helmsley Charitable Trust, The Helmsley Charitable Trust, The Leona M and Harry B Helmsley Charitable Trust, Helmsley

**Funding Body Type**
Private sector organisation

**Funding Body Subtype**
Trusts, charities, foundations (both public and private)

**Location**
United States of America

# Results and Publications

## Individual participant data (IPD) sharing plan

Access to raw data and right to publish freely by all investigators in the study or by the Independent Steering Committee on behalf of all investigators. The ICF asks for consent that data and samples obtained as part of the clinical trial may also be used for further medical research. It is planned therefore that data will be made available between research teams for future diabetes research and research into related diseases and development of the immune system. It is intended that all the clinical study sites involved in the current trial can use the pseudonymised data and samples obtained in the study for shared or own research purposes that build on the current study. Pseudonymised data will also be made available to other researchers for their medical research projects, but only for predetermined and requested research purposes and may not be passed on for other purposes; they will not be sold. However, the Klinikum rechts der Isar and the Helmholtz Zentrum Munich may charge the respective user an appropriate fee for the provision of quality-controlled data. The admissibility of each individual research project is checked in advance by an independent ethics committee and requires its approval. Information about the research projects, their purpose and the research institutions involved will be detailed on the website https://www.gppad.org.

## IPD sharing plan summary

Available on request

## Study outputs

| Output type | Details | Date created | Date added | Peer reviewed? | Patient-facing? |
|---|---|---|---|---|---|
| Protocol file | version 2.1 | 12/06/2024 | 28/08/2024 | No | No |
| Study website | Study website | 11/11/2025 | 11/11/2025 | No | Yes |