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Semaglutide as an add-on treatment to optimise glycaemic control in children and young people with type 1 diabetes (Smile T1D)

Submission date
19/03/2025

Recruitment status
Not yet recruiting

Registration date
17/09/2025

Overall study status
Ongoing

Last Edited
03/10/2025

Condition category
Nutritional, Metabolic, Endocrine

[X] Prospectively registered
[_] Protocol
[_] Statistical analysis plan
[_] Results
[_] Individual participant data
[X] Record updated in last year

Plain English summary of protocol

Background and study aims
There is a treatment used for adults with type 2 diabetes called semaglutide, which is given by an injection under the skin once a week. Semaglutide works by helping people feel full so they eat less and lose weight. This helps people bring down and better control their blood sugar levels. When given alongside their standard care, we want to find out if Semaglutide can help bring down blood sugar levels in children and young people with Type 1 diabetes so making their diabetes management easier.

Who can participate?
Children and young people aged between 10 and 24 years with Type 1 diabetes whose care is overseen by NHS hospitals

What does the study involve?
Participants will be divided into two groups; one will continue with their usual treatment, while the other group will have semaglutide in addition to their usual treatment. The researchers will compare the blood sugar readings from the continuous glucose monitors worn by people in the two groups to see if there is a difference. Members of both groups will be given a test to see if their pancreas is making any C-peptide. Those who are will have this test repeated 26 weeks later to compare how taking semaglutide has affected their pancreatic function.

What are the possible benefits and risks of participating?
Study visits are aligned with routine clinic visits where possible to reduce the burden on trial participants and their parent/carer if under 16 years; however, participants and parents /guardians will be required to attend hospital for extra study visits in addition to usual care clinic visits. Visit 1 and Visit 5 will also include the completion of a Mixed Meal Tolerance Test for eligible participants. All patients (or parent/guardian if aged under 16 years) will consent to do the MMTT if they are eligible. It is expected that no more than 10% of patients will be eligible. Mixed Meal Tolerance Tests will last for a duration of approximately 150 minutes at each of these visits, in addition to the trial procedures and assessments set out in the trial protocol. During their participation in the trial, participants and parents/guardians will be required to be

available for assessments by telephone or video calls in order to monitor for adverse events and for glucose and ketone monitoring.
Patients randomised to receive semaglutide will need to have an extra injection every week from visit 1 to visit 4 (week 0 to week 26). Type 1 diabetes patients are used to having regular injections so this should not cause undue distress to the participant.
Patients randomised to receive semaglutide will be required to attend hospital between visits for a pregnancy test (Week 8, week 16, week 20 and week 24), as part of safety monitoring for the trial. Hypoglycaemic episodes are a potential side effect of treatment with semaglutide. This is mitigated by regular monitoring for adverse events, and by regular assessment of insulin and semaglutide treatment and dose adjustment (or temporary pause or discontinuation) where necessary. A Semaglutide Dose Adjustment Guideline has been included in the protocol for PIs (and clinical delegates) to refer to when making treatment decisions.
Trained staff will take all blood samples. The amount of blood sampled will not cause any risk of harm to the participants. Consent will be obtained for blood samples to be taken for the purpose of the study.
Overnight fasting will be required in advance of undergoing a Mixed Meal Tolerance Test which has the potential to lower blood sugar. To mitigate this, Mixed Meal Tolerance Tests will take place in the morning following an overnight fast. In addition, to confirm that the Mixed Meal Tolerance Test can be undertaken at that visit, blood glucose taken by finger prick will be measured using a point-of-care blood glucose meter. The Mixed Meal Tolerance Test will be performed if the blood glucose level is between 4 mmol/l and 11.1 mmol/l. On completion of the Mixed Meal Tolerance Test, participants will be offered a light meal or snack before ending their visit. This will be in line with usual local practice following a Mixed Meal Tolerance Test. A single sample will be requested from the participant if it is not possible to complete a Mixed Meal Tolerance Test (e.g. blood glucose is not in the required range, or the participant has not fasted before the Mixed Meal Tolerance Test.

Where is the study run from?
University of Birmingham (UK)

When is the study starting and how long is it expected to run for?
March 2025 to August 2028

Who is funding the study?
Breakthrough T1D (USA)

Who is the main contact?
smile@trials.bham.ac.uk

Contact information

Type(s)
Scientific, Principal investigator

Contact name
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Additional identifiers

Clinical Trials Information System (CTIS)
Nil known

Integrated Research Application System (IRAS)
1008052

ClinicalTrials.gov (NCT)
Nil known

Protocol serial number
RG_24-060, CPMS 56423

Study information

Scientific Title
Semaglutide as an add-on treatment to optimise glycaemic control in children and young people with type 1 diabetes (Smile T1D)

Acronym
Smile T1D

Study objectives
To assess whether semaglutide added on to usual insulin treatment improves glycaemic control, measured using HbA1C, throughout 26 weeks of treatment, compared to usual care with insulin in children and young people with type 1 diabetes (CYPD).

The study is designed to assess the efficacy and safety of the semaglutide in this patient population. This will be undertaken by monitoring glucose (continuous glucose monitoring systems (CGMS) throughout the trial period. The trial will also monitor the side effects of semaglutide, including hypoglycaemic (low glucose) episodes throughout the trial, and if any change is seen in body mass index between the two groups, as well as monitoring if semaglutide influences any residual pancreatic function.

Ethics approval required
Ethics approval required

Ethics approval(s)
approved 17/07/2025, London – Brighton & Sussex REC (Health Research Authority, 2 Redman Place, Stratford, London, E20 1JQ, United Kingdom; +44 (0)207 104 8202, +44 (0)207 104 8055, +44 (0)207 104 8140; brightonandsussex.rec@hra.nhs.uk), ref: 25/LO/0261

Study design
Open-label randomized controlled trial

Primary study design
Interventional

Study type(s)
Safety, Efficacy

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

Interventions
Randomised (online tool) open-label trial.

Intervention arm:
Insulin as standard of care plus semaglutide by subcutaneous injection once weekly, starting dose 0.25 mg increasing to 1.0 mg.

Control arm:
Insulin as standard of care.

Follow-up: 26 weeks.

Intervention Type
Drug

Phase
Phase III

Drug/device/biological/vaccine name(s)
Ozempic (semaglutide)

Primary outcome(s)
HbA1c measured using capillary electrophoresis at 26 weeks post-randomisation

Key secondary outcome(s))
Clinical:
(Outcomes ranked by importance; first outcome ranked highest)
1. HbA1c measured using capillary electrophoresis at 5 and 12 weeks post-randomisation
2. Achieving target HbA1c of 48 mmol/mol or less, measured using capillary electrophoresis at 26 weeks post-randomisation
3. Glucose time in range (TIR) as a percentage, measured by continuous glucose monitoring sensor (CGMS) at 5, 12 and 26 weeks post-randomisation
4. BMI-Standard Deviation Score measured using the formula weight in kg divided by height in metres squared at 26 weeks post-randomisation
5. Total daily dose (TDD) of insulin (mean over last 3 calendar days) calculated from patient- or device-reported dose at 26 weeks post-randomisation

Safety:
1. The proportion of participants who experienced at least one of the following targeted AEs (anaphylaxis, nausea, vomiting, heartburn [reflux], diarrhoea, abdominal pain, heart palpitation /racing heart, skin itching, hives, dizziness, blurred vision, lack of concentration, fatigue, diabetic ketoacidosis, hypoglycaemia) which will be considered individually, and also as the total number

of these targeted AEs over the 26-week post-randomisation period, measured using AE collection form at 3, 4 7, 9, 12, 18 and 26 weeks post-randomisation
2. The proportion of participants who experienced at least one of the following targeted SAEs (anaphylaxis, nausea, vomiting, heartburn [reflux], diarrhoea, abdominal pain, heart palpitation /racing heart, skin itching, hives, dizziness, blurred vision, lack of concentration, fatigue, diabetic ketoacidosis, hypoglycaemia) which will be considered individually, and also as the total number of these targeted serious adverse events over the 26-week post-randomisation period. measured using an SAE collection form at 3, 4, 7, 9, 12, 18 and 26 weeks post-randomisation
3. Height-Standard Deviation Score in participants who are under 16 years old and have not completed puberty at 26 weeks post-randomisation

Exploratory outcomes:
Participants with a residual C-peptide secretion above 33 pmol/L at screening will undergo a more detailed assessment of pancreatic function (using the Mixed Meal Tolerance Test [MMTT]) to explore if semaglutide helps to maintain pancreatic beta cell function in CYPD. We will assess:
1. Change in the area under the curve (AUC) of C-peptide levels between the groups after 26 weeks of treatment, measured using MMTT AUC at baseline and 26 weeks
2. Change in peak stimulated C-peptide value between the groups at 26 weeks, measured using MMTT at baseline and 26 weeks
3. Change in fasting C-peptide value between the groups at 26 weeks, measured using MMTT at baseline and 26 weeks
4. Percentage change in the number of CYPD who have a C-peptide level above a meaningful threshold; C-peptide thresholds, e.g., greater than 10 pmol/l, greater than 30 pmol/l, greater than 100pmol/l or greater than 200 pmol/l, from baseline to 26 weeks, measured using MMTT at 26 weeks
5. Review differences in baseline characteristics between participants grouped by level of residual C-peptide:
5.1. HbA1c measured using capillary electrophoresis at baseline
5.2. TDD of insulin (mean over last 3 calendar days) measured using mean daily insulin usage (units/kg/day) at baseline
5.3. Percentage TIR measured using Continuous Glucose Monitoring Sensor (CGMS) at baseline
5.4. Rates of hypoglycaemia (TBR and number of Level 2 hypoglycaemia events) measured using Continuous Glucose Monitoring Sensor (CGMS) at baseline
5.5. Hypoglycaemia Fear score, measured using the Hypoglycaemia Fear Survey (HFS) questionnaire at baseline

Other exploratory outcomes will include differences in the other CGMS measurements between the semaglutide and usual care groups at 26 weeks:
1. Time above range (TAR), measured by CGMS
2. Time below range (TBR), measured by CGMS
3. Change in glucose variability (coefficient of variability), measured by CGMS

Completion date
31/08/2028

Eligibility

Key inclusion criteria
1. Children and young people aged between 10 and 24 years inclusive at screening
2. Clinical diagnosis of T1D mellitus according to World Health Organisation (WHO) or American Diabetes Association (ADA) criteria for at least 12 months prior to screening

3. On supplementary insulin of more than 0.5 unit/kg/day, using either multiple daily injections (MDI) or Continuous Subcutaneous Insulin Infusion (CSII)
4. Stable insulin requirements for the previous 3 months prior to screening (plus or minus 20% TTD between the screening visit and last NHS clinic visit)
5. Already on Continuous Glucose Monitoring Sensor (CGMS) for at least the previous 4 weeks prior to screening
6. HbA1c between 58mmol/mol and 86mmol/mol (IFCC) at screening, inclusive. This is aligned to 7.5% and 10.0% (DCCT)
7. Willingness to submit CGMS data for monitoring hypoglycaemic events
8. Able and willing to comply with all relevant protocol procedures
9. If female of childbearing potential, or male of reproductive potential, is willing to abstain from heterosexual intercourse or use a highly effective contraception method for the duration of the study
10. Able to provide informed consent (if under the age of 16 years old, informed consent will be given by parent/guardian)

Participant type(s)
Patient

Healthy volunteers allowed
No

Age group
Mixed

Lower age limit
10 years

Upper age limit
24 years

Sex
All

Key exclusion criteria
1. T2D or known monogenic diabetes
2. BMI less than 25th centile for age and gender (based on WHO 2007 BMI charts) if under 18 years old, and BMI less than 20 kg/m2 if 18 years or older
3. Use of any anti-diabetic agent other than insulin within 90 days prior to screening
4. Using Do-It-Yourself Closed Loop systems/Open Artificial Pancreas System
5. History of more than two severe (level 3) hypoglycaemia episodes in the last 12 months (severe hypoglycaemia is defined as a hypoglycaemic event with severe cognitive impairment (including coma and convulsions) and/or altered physical functioning that requires assistance by another person to administer carbohydrates, glucagon, or intravenous dextrose for recovery)
6. History of hypoglycaemia unawareness or a Gold score (assessment of impaired awareness of hypoglycaemia) of more than 4, as judged by the local investigator
7. History of chronic pancreatitis or idiopathic acute pancreatitis
8. Suspicion of pancreatitis as determined amylase above 150 U/L at screening
9. Any episode of diabetic ketoacidosis requiring hospital admission in the last 6 months
10. Renal function impairment defined as estimated glomerular filtration rate less than 45 ml /min/1.73m2 or creatinine above 200 µmol/L at screening:

10.1. In participants under 18 years old: eGFR will be calculated using the Schwartz equation
10.2. In participants over 18 years old: eGFR will be calculated using the CKD-EPI Equation for Estimating GFR on the Natural Scale (see Appendix 2) (of protocol)
11. Serum creatinine within age and sex specific reference ranges (see Appendix 2 of protocol)
12. Proliferative Retinopathy (R3, NHS diabetic retinopathy screening programme)
13. Calcitonin value more than 18.7 ng/L at screening
14. Personal or family history of medullary thyroid carcinoma or Multiple Endocrine Neoplasia type 2 (MEN2)
15. Diagnosis of severe gastroparesis
16. If female of childbearing potential, is pregnant at the time of screening (confirmed by a positive pregnancy test)
17. If female of childbearing potential, is actively trying to get pregnant
18. Is currently breastfeeding
19. Has a known allergy relating to semaglutide that precludes their participation in the study, in the opinion of the local investigator
20. Has a medical, social, or psychological issue that precludes their participation in the study, in the opinion of the local investigator
21. Participation in another Clinical Trial of an Investigational Medicinal Product (CTIMP)

Date of first enrolment
28/02/2026

Date of final enrolment
31/03/2027

Locations

Countries of recruitment
United Kingdom

England

Study participating centre
Addenbrookes
Addenbrookes Hospital
Hills Road
Cambridge
United Kingdom
CB2 0QQ

Study participating centre
Birmingham Children's Hospital
Steelhouse Lane
Birmingham
United Kingdom
B4 6NH

Study participating centre
Heartlands Hospital
Bordesley Green East
Bordesley Green
Birmingham
United Kingdom
B9 5ST

Study participating centre
Leicester Royal Infirmary
Infirmary Square
Leicester
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LE1 5WW

Study participating centre
Royal Hallamshire Hospital
Glossop Road
Sheffield
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S10 2JF

Study participating centre
Sheffield Children's Hospital
Western Bank
Sheffield
United Kingdom
S10 2TH

Study participating centre
Queen Elizabeth Hospital
Mindelsohn Way
Edgbaston
Birmingham
United Kingdom
B15 2GW

Sponsor information

Organisation
University of Birmingham

ROR
https://ror.org/03angcq70

Funder(s)

Funder type
Charity

Funder Name
Breakthrough T1D

Results and Publications

Individual participant data (IPD) sharing plan
The datasets generated during and/or analysed during the current study will be available upon request from the Birmingham Clinical Trials Unit (BCTU): requests for data generated during this study will be considered by BCTU. Data will typically be available 6 months after the primary publication unless it is not possible to share the data (for example: the trial results are to be used as part of a regulatory submission, the release of the data is subject to the approval of a third party who withholds their consent, or BCTU is not the controller of the data). Only scientifically sound proposals from appropriately qualified Research Groups will be considered for data sharing. The request will be reviewed by the BCTU Data Sharing Committee in discussion with the CI and, where appropriate (or in the absence of the CI) any of the following: the Trial Sponsor, the relevant TMG, and independent TSC. A formal Data Sharing Agreement (DSA) may be required between respective organisations once the release of the data is approved and before data can be released. Data will be fully de-identified (anonymised) unless the DSA covers the transfer of participant identifiable information. Any data transfer will use a secure and encrypted method.

IPD sharing plan summary
Available on request

Study outputs

Output type	Details	Date created	Date added	Peer reviewed?	Patient-facing?
Participant information sheet	Participant information sheet	11/11/2025	11/11/2025	No	Yes