ISRCTN49549481 https://doi.org/10.1186/ISRCTN49549481

Exploratory effect of long-term Verapamil therapy in adults with Type 1 diabetes mellitus (Ver-A-Long)

Submission date	Recruitment status	[ ] Prospectively registered
16/01/2025	No longer recruiting	[ ] Protocol
Registration date	**Overall study status**	[ ] Statistical analysis plan
24/02/2025	Ongoing	[ ] Results
Last Edited	**Condition category**	[ ] Individual participant data
23/05/2025	Nutritional, Metabolic, Endocrine	[X] Record updated in last year

Plain English summary of protocol
Background and study aims
Verapamil SR (sustained release), a medication used for high blood pressure, has been shown to help beta cells in the pancreas produce more insulin. This may help in managing Type 1 diabetes (T1D). Previous studies in animals and humans with newly diagnosed T1D suggest that Verapamil could improve beta-cell function, reduce the need for insulin, and potentially prevent or reverse the disease. The Ver-A-Long study aims to explore whether long-term treatment with Verapamil SR (360 mg daily) can help preserve beta-cell function in adults with T1D and evaluate its safety over 24 months.

Who can participate?
This study is for adults diagnosed with T1D who are currently participating in the Ver-A-T1D study and have received Verapamil SR or a placebo for 11-12 months. Participants must be aged 18 or older and have a fasting C-peptide level of at least 50 pmol/L.

What does the study involve?
Participants will take 360 mg of Verapamil SR daily for 24 months, with a gradual increase from 120 mg to 360 mg over the first 3 weeks. They will visit the clinic 6 to 7 times during the study, depending on their entry option, and will also have 4 telephone visits. The study will track the effects of Verapamil on beta-cell function, insulin requirements, blood glucose control, and the occurrence of severe low blood sugar or diabetic ketoacidosis (DKA). Safety will be monitored through vital signs,
ECG, and lab tests.

What are the possible benefits and risks of participating?
Participants may not directly benefit from participating in this study, but the information gathered during their participation could potentially help future patients with Type 1 Diabetes Mellitus. Participants may benefit from having tests, checks and general talks with their study doctor. However, as with any clinical trial, there may be risks, including side effects from the

medication or possible complications from low blood sugar or DKA episodes. There are no physical risks to participating other than the usual risks associated with any medication trial. Participants will have access to regular monitoring and safety checks.

Where is the study run from?
University Hospital of Wales, UK. The trial is being run from seven centres in the UK and six centres in Europe (excluding the UK).

When is the study starting and how long is it expected to run for?
January 2025 to May 2027. Recruitment started in November 2024 (Europe) and is expected to end by May 2027.

Who is funding the study?
The study is funded by Breakthrough T1D.

Who is the main contact?
Dr. Colin Dayan, DayanCM@cardiff.ac.uk

Contact information

Type(s)
Public, Scientific, Principal investigator

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Additional identifiers

Clinical Trials Information System (CTIS)
2024-515234-33

Integrated Research Application System (IRAS)
1010702

ClinicalTrials.gov (NCT)
Nil known

Protocol serial number
Nil known

Study information

Scientific Title
An open-label extension multi-centre trial in adult subjects diagnosed with Type 1 diabetes mellitus exploring the effect of long-term Verapamil SR therapy on the preservation of beta-cell function.

Acronym
Ver-A-Long

Study objectives
To determine the changes in Beta-cell function in type 1 diabetes patients measured by C-peptide response to a mixed-meal tolerance test (MMTT) at baseline and after 24 months for 360 mg Verapamil SR administration orally once daily. This will be assessed separately in those with a fasting C-peptide ≥ 50 pmol/L previously treated with a) placebo or b) Verapamil SR for 12 months in the Ver-A-T1D trial.

To determine the changes in Beta-cell function in T1D patients measured by C-peptide response to a mixed-meal tolerance test at baseline and after 6,12 and 18 months for 360mg Verapamil SR administered orally once daily
To determine the changes in HbA1c in T1D patients measured at baseline and after 6,12,18 and 24 months for 360mg Verapamil SR administered orally once daily
To determine the changes in insulin requirements as the daily total insulin dose (seven days average) in units per kg body weight in T1D patients measured at baseline and after 6,12,18,24 months for 360mg Verapamil SR administered orally once daily
To determine the number of severe hypoglycaemic and ketoacidosis episodes in adults diagnosed with T1D given 360mg oral Verapamil SR once daily
To determine safety of short-term (weekly) titration of Verapamil SR (titrated over the first 3 weeks from 120 to 360mg)
To determine safety over 24 months in adults diagnosed with T1D given 360mg oral Verapamil SR once daily

Ethics approval required
Ethics approval required

Ethics approval(s)
approved 18/02/2025, Westminster Research Ethics Committee (2 Redman Place, Stratford, London, E20 1JQ, United Kingdom; +44 (0)207 104 8066; westminster.rec@hra.nhs.uk), ref: 25/LO/0103

Study design
Open-label extension multi-centre trial

Primary study design
Interventional

Study type(s)
Safety, Efficacy

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

Interventions

The Ver-A-Long study involves a single treatment group receiving Verapamil SR, which is administered orally once daily. As this study involves only one treatment group, randomisation is not applicable. The treatment begins with a dose escalation from 120 mg to 240 mg and eventually to 360 mg, with a weekly increase over the first 3 weeks, monitored via telephone visits (P1-P3). Participants will start the study after informed consent, followed by Visit -1 (V-1), which occurs on the same day as Visit 6 of the Ver-A-T1D study. At V-1, fasting C-peptide will be measured locally to assess eligibility and baseline data (e.g., vital signs, ECG, medical history, safety labs) will be collected. The study medication will be dispensed at V-1 but intake will only begin after confirmation by the study team during
Phone Visit 0 (P0), which is scheduled within 3 days (Entry Option 2) or within 10 days (Entry Option 1) of V-1. Follow-up visits are scheduled as follows: Clinic Visits (V4-V8) will occur at 28 days ± 2 days (V4), 6 months ± 14 days (V5), 12 months ± 14 days (V6), 18 months ± 14 days (V7), and 24 months ± 14 days (V8). During these visits, participants will undergo assessments for adverse events, concomitant medications (including vaccinations), vital signs, ECG, diabetes care, physical examinations, and safety laboratory tests, including HbA1c. A mixed meal tolerance test (MMTT) with fasting C-peptide and blood glucose will be performed at visits V-1 and V5-V8. Verapamil SR will be dispensed at visits V-1 and V4-V7. The trial will conclude at V8 (24 months), at which point participants will continue to receive the appropriate standard of care, which will persist beyond the study's conclusion.

Intervention Type
Drug

Phase
Phase II

Drug/device/biological/vaccine name(s)
Verapamil [Verapamil hydrochloride]

Primary outcome(s)
Changes in C-peptide response to a mixed-meal tolerance test (MMTT) in adults diagnosed with T1D receiving 360 mg oral Verapamil SR daily is measured using the area under the curve at baseline (V-1) and at 24 months (V8) of therapy.

Key secondary outcome(s))
1. Changes in C-peptide response to a mixed-meal tolerance test (MMTT) in adults diagnosed with T1D receiving 360 mg oral Verapamil SR daily is measured using the area under the curve at 6 months (V5), 12 months (V6), and 18 months (V7) of therapy.
2. Changes in blood glucose control as assessed by HbA1c in adults diagnosed with T1D receiving 360 mg oral Verapamil daily is measured at baseline (V-1) and at 6 months (V5), 12 months (V6), 18 months (V7), and 24 months (V8) of therapy.
3. Changes in insulin requirements as the total daily insulin dose (seven-day average) in units per kg body weight (BW) in adults diagnosed with T1D receiving 360 mg oral Verapamil daily is measured at baseline (V-1) and at 6 months (V5), 12 months (V6), 18 months (V7), and 24 months (V8) of therapy.
4. The number of treatment-emergent severe hypoglycaemic episodes, defined as severe cognitive impairment requiring external assistance for recovery is measured as per the American Diabetes Association (ADA) criteria.
5. The number of treatment-emergent episodes of diabetic ketoacidosis (DKA) is measured throughout the study period.
6. Adverse events, vital signs variation, ECG, and laboratory safety parameters are measured at

baseline (V-1) and at 6 months (V5), 12 months (V6), 18 months (V7), and 24 months (V8) of therapy.

Completion date
30/05/2027

Eligibility

Key inclusion criteria
1. Be either eligible for Visit 6 of Ver-A-T1D trial on active treatment defined as Placebo or Verapamil SR (240 mg or 360 mg) (option 1) OR have completed V5 of the Ver-A-T1D study and plan to continue with Ver-A-T1D Visit 6 on active treatment defined as Placebo or Verapamil SR (240mg or 360mg) up to 28 days prior to Ver-A-T1D Visit 6 (option 2).
2. Have given written informed consent (Ver-A-Long).
3. Age ≥18 years at consent.
4. Must have fasting C-peptide levels ≥ 50 pmol/L measured at V-1 (according to option 1) or measured at V-2 (according to option 2).

Participant type(s)
Patient

Healthy volunteers allowed
No

Age group
Adult

Lower age limit
18 years

Sex
All

Total final enrolment
19

Key exclusion criteria
1. Be currently pregnant, lactating or anticipate getting pregnant during the 24 months study period.
2. Have any complicating medical issues or history that may interfere with the study conduct, as judged by the investigator.
3. Have persistent history of malignancies other than skin.
4. History of liver insufficiency or laboratory evidence of liver dysfunction with aspartate aminotransferase (AST) or alanine transaminase (ALT) greater than 3 times the upper limits of normal.
5. History of renal insufficiency or evidence of renal dysfunction with creatinine greater than 1.5 times the upper limit of normal.
6. Current use of calcium channel blockers (except IMP administrated in the Ver-A-T1D trial).
7. Known hypersensitivity to Verapamil SR or to any of its excipients.
8. Concomitant medication known for inducing or inhibiting CYP3A4 and/or glycoprotein-P

metabolism.
9. Intake of grapefruit juice, licorice, St. John’s Wort, cannabidiol, ginkgo biloba.
10. Substrate intake of CYP3A4 and/or glycoprotein-P metabolism, as judged by the investigator.

Date of first enrolment
04/11/2024

Date of final enrolment
12/05/2025

Locations

Countries of recruitment
United Kingdom

England

Scotland

Wales

Austria

Belgium

France

Germany

Italy

Study participating centre
St. Bartholomews Hospital
West Smithfield
London
United Kingdom
EC1A 7BE

Study participating centre
Queen Elizabeth Hospital
Edgbaston
Birmingham
United Kingdom
B15 2TH

Study participating centre
Oxford Centre for Diabetes, Endocrinology and Metabolism
University Of Oxford, Churchill Hospital, Old Road
Oxford
United Kingdom
OX3 7LE

Study participating centre
University Hospital of Wales
Heath Park
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CF14 4XW

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

Study participating centre
Queen Elizabeth University Hospital
1345 Govan Road
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United Kingdom
G51 4TF

Study participating centre
Cochin Hospital, Department Diabetology and Clinical Immunology Department
Groupe Hospitalier Cochin-Port Royal, Bâtiment Copernic
123, Boulevard de Port Royal
Paris
France
75014

Study participating centre
Medical University of Graz
Department of Endocrinology and Diabetology
Auenbruggerplatz 15
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Austria
8036

Study participating centre
UZ Leuven
Herestraat 49
Leuven
Belgium
3000

Study participating centre
Diabetes centre for children and adolescents
AUF DER BULT
Paediatric and Adolescent Hospital
Janusz-Korczak-Allee 12
Hanover
Germany
30173

Study participating centre
I.R.C.C.S San Raffaele Hospital
Via Olgettina 60
Milan
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20132

Study participating centre
University of Siena
UOC Diabetology and Metabolic Diseases, Policlinico Santa Maria alle Scotte, Viale Bracci 16
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53100

Sponsor information

Organisation
Medical University of Graz

ROR

https://ror.org/02n0bts35

Funder(s)

Funder type
Research organisation

Funder Name
Breakthrough T1D

Results and Publications

Individual participant data (IPD) sharing plan
The data-sharing plans for the current study are unknown and will be made available at a later date.

IPD sharing plan summary
Data sharing statement to be made available at a later date