CARDIFF UNIVERSITY
PRIFYSGOL CAERDYDD

ORCA – Online Research @ Cardiff

This is an Open Access document downloaded from ORCA, Cardiff University's institutional repository:https://orca.cardiff.ac.uk/id/eprint/173517/

This is the author's version of a work that was submitted to / accepted for publication.

Citation for final published version:

Wych, Julie, Brunner, Martina, Stenson, Rachel, Chumura, Piotr, Danne, Thomas, Mander, Adrian , Mathieu, Chantal, Dayan, Colin and Pieber, Thomas 2024. Investigating the effect of verapamil on preservation of beta-cell function in adults with newly diagnosed type 1 diabetes mellitus (Ver-A-T1D): protocol for a randomized, double-blind, placebo-controlled, parallel-group, multi-centre trial. BMJ Open 10.1136/bmjopen-2024-091597

Publishers page:

Please note:
Changes made as a result of publishing processes such as copy-editing, formatting and page numbers may not be reflected in this version. For the definitive version of this publication, please refer to the published source. You are advised to consult the publisher's version if you wish to cite this paper.

This version is being made available in accordance with publisher policies. See http://orca.cf.ac.uk/policies.html for usage policies. Copyright and moral rights for publications made available in ORCA are retained by the copyright holders.

BMJ Open

Investigating the effect of verapamil on preservation of beta-cell function in adults with newly diagnosed type 1 diabetes mellitus (Ver-A-T1D): protocol for a randomised, double-blind, placebo-controlled, parallel-group, multi-centre trial

Journal:	*BMJ Open*
Manuscript ID	bmjopen-2024-091597.R1
Article Type:	Protocol
Date Submitted by the Author:	n/a
Complete List of Authors:	Wych, Julie; Cardiff University, Centre for Trials Research Brunner, Martina; Medical University of Graz, Department of Internal Medicine, Division of Endocrinology and Diabetology Stenson, Rachel; Cardiff University, Diabetes Research Group Chmura , Piotr; Kobenhavns Universitet Sundhedsvidenskabelige Fakultet, Center for protein research Danne, Thomas; Auf der Bult Children's Hospital, Department of General Pediatrics Endocrinology/Diabetology & Clinical Research Mander, Adrian; Cardiff University, Centre for Trials Research Mathieu, Chantal; Katholieke Universiteit Leuven UZ Leuven Dayan, Colin; Cardiff University, Cardiff University School of Medicine Pieber, Thomas; Medical University of Graz, Department of Internal Medicine, Division of Endocrinology and Diabetology
Primary Subject Heading:	Diabetes and endocrinology
Secondary Subject Heading:	Diabetes and endocrinology
Keywords:	DIABETES & ENDOCRINOLOGY, Randomized Controlled Trial, Clinical Trial

SCHOLARONE™
Manuscripts

Investigating the effect of verapamil on preservation of beta-cell function in adults with newly diagnosed type 1 diabetes mellitus (Ver-A-T1D): protocol for a randomised, double-blind, placebo-controlled, parallel-group, multi-centre trial

AUTHOR LIST: Julie Wych[1*], Martina Brunner[2], Rachel Stenson[3], Piotr Jaroslaw Chmura[4], Thomas Danne[5], Adrian Mander[1], Chantal Mathieu[6], Colin Dayan[3], Thomas R. Pieber[2]

SHORT TITLE: Diabetes and Endocrinology Protocol

AFFILIATIONS:

1) Centre for Trials Research, College of Biomedical and Life Sciences, Cardiff University, Cardiff, UK

2) Medical University of Graz, Department of Internal Medicine, Division of Endocrinology and Diabetology, Austria

3) Cardiff University School of Medicine, Cardiff University, Cardiff, UK

4) Novo Nordisk Foundation Center for Protein Research, University of Copenhagen, Copenhagen, Denmark

5) Department of General Paediatrics, Endocrinology/Diabetology and Clinical Research, Auf der Bult Hospital for Children and Adolescents, Hannover Medical School, Germany

6) Katholieke Universiteit Leuven/ Universitaire Ziekenhuizen Leuven, Belgium

CORRESPONDING AUTHOR* Julie Wych (wychj@cardiff.ac.uk)

KEY WORDS: Type 1 diabetes, Phase 2, Adults, Beta-cell function, C-peptide, Verapamil 360 mg.

WORD COUNT: 12,699 (excluding title page, abstract, references, figures, tables, acknowledgements)

ABSTRACT:

Introduction: Type 1 diabetes mellitus (T1DM) is a disorder that arises following the selective autoimmune destruction of the insulin-producing beta-cells. Beta-cell protective or beta-cell regenerative approaches have gained wider attention, and pharmacological approaches to protect the patient's own insulin-producing beta cell mass have been proposed. Verapamil is a L-type calcium channel blocker that has been reported to effectively lowers beta cell TXNIP expression in rodent beta cells and islets as well as in human islets, and thus promotes functional beta cell mass. **Methods and analysis**: The trial is a multi-centre, randomised, double-blind, placebo-controlled trial in participants with T1DM, investigating the effect of Verapamil on preservation of beta-cell function (Ver-A-T1D). A total of 120 participants will be randomised 2:1 between 360mg Verapamil and placebo administered orally once daily. T1DM patients aged ≥18 and <45 years will be eligible for recruitment within 6 weeks of diagnosis (defined as day of starting insulin therapy). The primary objective will be to determine the changes in stimulated C-peptide response during the first two hours of a mixed meal tolerance test (MMTT) at baseline and after 12 months for 360mg Verapamil administered orally once daily versus placebo. Secondary objectives include the effects of 360mg Verapamil on 1) fasting C-peptide, 2) Dried Blood Spot (DBS) C-peptide, 3) HbA1c, 4) daily total insulin dose, 5) time in range by intermittent continuous glucose monitoring (CGM) measures, 6) other biomarkers related to immunological changes and beta-cell death and 6) safety (vital signs, ECG). ***Ethics and dissemination***: Ethics approval was sought from the research ethics committee (REC) of all participating countries. All participants provided written informed consent before joining the study. Ver-A-T1D received first regulatory and ethical approvals in Austria. The publication policy is set in the INNODIA grant agreement (www.innodia.eu).

TRIAL REGISTRATION

For peer review only - http://bmjopen.bmj.com/site/about/guidelines.xhtml

Sponsor: Medical University of Graz, Department of Internal Medicine, Division of Endocrinology and Diabetology, Austria

Sponsor Number: Ver-A-T1D

Central Coordination: Medical University of Graz, Department of Internal Medicine, Division of Endocrinology and Diabetology, Austria (ver-a-t1d@medunigraz.at)

EudraCT Number: 2020-000435-45

ClinicalTrials.gov Identifier: NCT04545151

Protocol Version: Version 8.0; dated November 08, 2021

Chief Investigator and Address: Professor Thomas R. Pieber, MD. Medical University of Graz, Department of Internal Medicine, Division of Endocrinology and Diabetology, Austria, Auenbruggerplatz 15, A8036 Graz, Austria

ARTICLE SUMMARY:

Strengths and limitations of this study:

- The investigational agent is a repurposed product with a well-established safety profile from over 50 years of use in different indications and if effective could be available at low cost.
- In contrast to previous treatments developed to alter the disease course in this autoimmune condition, the agent targets the beta cell rather than the immune system directly and hence has the potential to be used in the future in combination with immune modulatory interventions.
- The trial is based on a master protocol with standard efficacy and mechanistic outcomes which has been designed to form the basis of a future platform trial of combined interventions.
- A limitations of the study is that it does not include children, which comprise around 40% of the newly diagnosed type 1 diabetes population.
- The study will not establish the durability of the intervention since it only spans one year of treatment.

LIST OF ABBREVIATIONS:

ADA: American Diabetes Association

ADDQoL: Audit of Diabetes-Dependent Quality of Life

AE: Adverse event

AR: Adverse reaction

ALT: Alanine transaminase

AST: Aspartate aminotransferase

AUC: Area under the curve

BW: Body weight

CA: Competent authority

CI: Chief investigator

CGM: Continuous glucose monitoring

eCRF: Electronic case report form

CRP: C-reactive protein

For peer review only - http://bmjopen.bmj.com/site/about/guidelines.xhtml

CTIMP: Clinical trial of investigational medicinal product

COPD: Chronic obstructive pulmonary disease

DBS: Dry blood spot

DTSQc: Diabetes Treatment Satisfaction Questionnaire change

DTSQs: Diabetes Treatment Satisfaction Questionnaire status

ECG: Electrocardiogram

EMA: European Medicines Agency

eGFR: Estimated glomerular filtration rate

FACS: Fluorescence-activated cell sorting

FBC: Full blood count

FDA: Food and Drug Administration

GADA: Glutamic acid decarboxylase antibodies

GDPR: General data protection regulations

GCP: Good Clinical Practice

HbA1c: Glycated haemoglobin

HDL: High-density lipoprotein

HFS: Hypoglycaemia Fear Survey

HIV: Human immunodeficiency virus

HRA: Health research authority

IA-2A: IA-2 antibodies

IAA: Insulin auto-antibodies

IB: Investigators brochure

IC: Informed consent

ICF: Informed consent form / informed assent form

IDMC: Independent data monitoring committee

IEC: Independent ethics committee

IMP: Investigational medicinal product

INNODIA consortium: An innovative approach towards understanding and arresting Type 1 diabetes consortium (www.innodia.eu)

INNODIA longitudinal study: An innovative approach towards understanding and arresting Type 1 diabetes longitudinal study (ClinicalTrials.gov: NCT03936634), part of the INNODIA consortium

ISF: Investigator Site File

ITT: Intention to treat

LDL: Low-density lipoprotein

MHRA: Medicines and Healthcare products Regulatory Agency

MMTT: Mixed meal tolerance test

For peer review only

For peer review only - http://bmjopen.bmj.com/site/about/guidelines.xhtml

MUG: Medical University of Graz

NA: Not applicable

NIMP: Non investigational medicinal product

PAC: Patient Advisory Committee

PBMC: Peripheral blood mononuclear cell

PI: Principal investigator

PIS: Participant information sheet

PROMs: Patient Reported Outcome Measures

PSF: Pharmacy site file

R&D: Research and Development

RA: Regulatory agency

REC: Research ethics committee

RSI: Reference safety information

SAE: Serious adverse event

SAR: Serious adverse reaction

SAP: Statistical analysis plan

SARS-CoV-2: Severe Acute Respiratory Syndrome CoronaVirus-2

SD: Standard deviation

SDVAF: Source Data Verification Agreement Form

SmPC: Summary of product characteristics

SOP: Standard operating procedure

SR: Sustained release

SUSAR: Suspected unexpected serious adverse reaction

T1D: Type 1 diabetes

TMF: Trial master file

TMG: Trial management group

TSC: Trial steering committee

ZnT8A: Zinc transporter 8 antibody

TXNIP: Thioredoxin-interacting protein

INTRODUCTION:

Background:

INNODIA is an Innovative Medicines Initiative consortium (IMI-2), established through Horizon 2020 initiative of the European Union, involving academic, industry and charitable partners. Recruitment to this INNODIA study is defined by the recruitment of subjects with a diagnosis of T1D identified within the first six weeks from diagnosis. INNODIA provides a standardised routine centralised assessment of critical immunological biological factors which determine the rate of progression of T1D with reference to declines in beta cell function and the potential impact of IMPs which could alter these trajectories.

For peer review only - http://bmjopen.bmj.com/site/about/guidelines.xhtml

Rationale for the trial:

Type 1 diabetes mellitus (T1DM) is a disorder that arises following the selective autoimmune destruction of the insulin-producing beta-cells.[1, 2] A cure for T1DM would aim at ensuring that the necessary endogenous functional beta-cell mass required for adequate insulin production is preserved or increased. The Diabetes Control and Complications Trial has shown that even a small amount of preserved endogenous insulin production has beneficial effects in terms of outcome, overall glycaemic control and prevention of severe hypoglycaemia.[3-5] Beta-cell destruction is considered to be mainly immune-mediated, and many efforts to stop or modify this destruction have focused on immunomodulatory, antigen-specific or anti-inflammatory interventions.[6] Attempts to replace beta cells by pancreas or islet transplantation are associated with potentially severe side effects due to the necessary immunosuppression. Recently beta-cell protective or beta-cell regenerative approaches have gained wider attention, and pharmacological approaches to protect the patient's own insulin-producing beta cell mass have been proposed.[6]

Pharmacokinetics & pharmacodynamics of Verapamil:

Verapamil (ATC: C08DA01) is a L-type calcium channel blocker that has been used as an antihypertensive compound for more than 3 decades and approved by the US Food and Drug Administration (FDA) and the European Medicine Agency (EMA). Verapamil effectively lowers beta cell Thioredoxin-interacting protein (TXNIP) expression in rodent beta cells and islets as well as in human islets. This effect is based on the established mode of action of verapamil , blockade of L-type calcium channels and the resulting decrease in intracellular free calcium leading to inhibition of TXNIP transcription. In mouse models of diabetes, oral administration of verapamil promotes functional beta cell mass and prevents and even reverses overt diabetes. In addition, downregulation of TXNIP also improves beta cell function including insulin production and secretion.[7-13] In a randomised, double-blind, placebo-controlled phase 2 clinical trial the efficacy and safety of oral verapamil added for 12 months to a standard insulin regimen in adult subjects with recent-onset T1D was assessed. Verapamil treatment, compared with placebo was well tolerated and associated with an improved mixed-meal-stimulated C-peptide area under the curve, a measure of endogenous beta cell function, at 3 and 12 months, as well as with a lower increase in insulin requirements and fewer hypoglycaemic events.[14] Two year follow-up of this study has since been published suggesting a continued effect[15] and the beneficial effect on C-peptide preservation has been replicated in a study in children and adolescents.[16]

Several retrospective studies have reported that verapamil use is associated with a lower risk of developing type 2 diabetes.[17, 18] Recently it has been demonstrated that thioredoxin-interacting protein (TXNIP), a cellular redox regulator, is overexpressed during hyperglycaemia and induces beta-cell apoptosis.[10] As verapamil effectively lowers beta cell TXNIP expression in rodent beta cells and islets as well as in human islets, it therefore promotes functional beta cell mass and prevents and even reverses overt diabetes.[19]

Verapamil inhibits the entry of calcium into smooth muscle cells of the systemic and coronary arteries and in the cells of cardiac muscle and the intracardiac conduction system. Verapamil lowers peripheral vascular resistance with little or no reflex tachycardia. Its efficacy in reducing both raised systolic and diastolic blood pressure is thought to be primarily due to this mode of action. Due to the effect on the movement of calcium in the intracardiac conduction system, verapamil reduces automaticity, decreases conduction velocity and increases the refractory period. This may cause the following cardiovascular side effects: bradycardic arrhythmias such as sinus bradycardia, sinus arrest with asystole, 2nd and 3rd degree AV block, bradyarrhythmia in atrial fibrillation, palpitations, tachycardia, development or aggravation of heart failure, and hypotension.

After oral administration verapamil is absorbed well (more than 90%) but undergoes extensive first-pass hepatic metabolism so that bioavailability is only 10–23%. Verapamil is metabolized to several active and inactive metabolites. Most of the metabolites are excreted in bile. The most common side

For peer review only - http://bmjopen.bmj.com/site/about/guidelines.xhtml

effects of verapamil are dose dependent and include constipation, dizziness, nausea, low blood pressure, and headache. Other side effects seen include: edema, congestive heart failure, pulmonary edema, fatigue, elevated liver enzymes, shortness of breath, low heart rate, atrioventricular block, rash and flushing.

The target dose of 360 mg once daily and the minimum target dose of 240 mg was chosen according to the study of Ovalle et al.[14] In this already published randomized, double-blind, placebo-controlled phase 2 clinical trial, the participants were randomly assigned to receive a once-daily oral dose of sustained-release verapamil (titrated over the first 3 months from 120 mg to 360 mg) or placebo for a total of 12 months in addition to their insulin therapy. This dose was chosen according to its demonstrated tolerability and effectiveness in terms of calcium-channel blockade and considering that the maximal recommended daily dose for verapamil is 480 mg. The rationale for the selected target dose in the current trial is based on the efficacy demonstrated in this trial.[14]

The Ver-A-T1D trial is run using the INNODIA Master Protocol within the INNODIA clinical trial network (www.INNODIA.eu).[20] The aim of this trial is to confirm the effect of 360mg verapamil administered orally once daily (titrated over the first 3 months from 120 mg to 360 mg) on the preservation of stimulated C-peptide at 12 months compared to placebo.

METHODS AND ANALYSIS:

Objectives:

The primary objective of Ver-A-T1D is to determine the changes in stimulated C-peptide response during the first two hours of a mixed meal tolerance test (MMTT) at baseline and after 12 months for 360mg verapamil administered orally once daily versus placebo in adult people with new onset T1D. The secondary objectives are to determine the effect of 360mg verapamil administered orally once daily on 1) fasting C-peptide and DBS C-peptide measurements, 2) HbA1c, 3) daily total insulin dose, 4) CGM time in range over time, 5) to determine the effects of treatment on other biomarkers related to immunological changes and beta-cell death and survival in this population, and 6) to determine the effects of 360mg verapamil administered orally once daily on safety (vital signs, ECG). The tertiary objective will compare between treatment arms and across the course of treatment the PROMs scores completed by participants. Table 1 reports the specific trial objectives and related outcome measures.

SPIRIT reporting guidelines were used for this protocol.[21]

For peer review only

For peer review only - http://bmjopen.bmj.com/site/about/guidelines.xhtml

Table 1: Study objectives and outcomes.

Objectives	Outcome measures	Timepoints(s) of evaluation of outcome measure
Primary Objective		
1) To determine the changes in stimulated C-peptide response during the first two hours of a mixed meal tolerance test (MMTT) at baseline and after 12 months for 360mg Verapamil SR administered orally once daily versus placebo.	1) The area under the stimulated C-peptide response curve over the first two hours of a mixed meal tolerance test (MMTT) for the verapamil 360 mg and placebo arms	1) 12 months
Secondary Objectives		
2) To determine the effects of 360mg Verapamil SR administered orally once daily on fasting C-peptide and Dried Blood Spot (DBS) C-peptide measurements over time.	2) Fasting C-peptide after 12 months therapy compared to placebo and home DBS for C-peptide	2) Baseline, 1, 2, 3, 6, 9 and 12 months
3) To determine the effects of 360mg Verapamil SR administered orally once daily on HbA1c, daily total insulin dose and continuous glucose monitoring (CGM) time in range.	3) Change in HbA1c baseline to 12 months, change in HbA1c baseline to 12 month, change in insulin requirements, baseline to 12 months as the daily total dose (three days average) in units per kg body weight (BW), continuous glucose monitoring (CGM) time in range (70-140 mg/dL, 3.9-7.8 mmol/L) and (70-180 mg/dL, 3.9-10.0 mmol/L), time above range (>180 mg/dL, >10.0 mmol/L), time below range (<70 mg/dL, < 3.9 mmol/L)	3) Baseline and monthly from 1-12 months
4) To determine the effects of treatment on other biomarkers related to immunological changes and beta-cell death and survival in this population		
5) To determine the effects of 360mg Verapamil SR administered orally once daily on safety (vital signs, ECG)	5) Systolic blood pressure (mmHg), Diastolic blood pressure (mmHg), Pulse (bpm), ECG	5) Baseline, 1, 2, 3, 6, 9 and 12 months
Tertiary Objective		

For peer review only

For peer review only - http://bmjopen.bmj.com/site/about/guidelines.xhtml

6) To compare between treatment arms and across the course of treatment the PROMs scores completed by participants.	6) DTSQ, ADDQoL, HypoFear questionnaires	6) HFS & DTSQ at 1, 6 and 12 months ADDQoL at 6 and 12 months

For peer review only

For peer review only - http://bmjopen.bmj.com/site/about/guidelines.xhtml

Study Summary:

Ver-A-T1D is a multi-centre, randomised, double-blind, placebo-controlled trial testing the efficacy of 360mg verapamil administered orally once daily (titrated over the first 3 months from 120 mg to 360 mg) on protection of stimulated C-peptide decline in subjects with diagnosis of T1D within 6 weeks of diagnosis. The Ver-A-T1D trial design is shown in Figure 1.

A multi-centre and multinational design has been chosen to ensure that the results are applicable for participants with different demographic characteristics. All sites are part of the existing INNODIA clinical network and are confirmed suitable for undertaking this specific study from the accreditation undertaken as part of INNODIA. However, to recruit the required number of participants, suitable INNODIA sites may work with their local existing network to identify and recruit potential participants. Additional sites in the UK that form part of the UK Type 1 Diabetes Research Consortium and can perform studies to appropriate standards consistent with the INNODIA platform will also be considered.

Further details on participating sites can be obtained from the Ver-A-T1D Coordinating team contact (ver-a-t1d@medunigraz.at) and via the INNODIA web page (innodia.eu - Clinical Trials).

Trial participants, Study Design and Oversight:

The aim is to randomise 138 participants in this trial to two arms, namely verapamil and placebo in a 2:1 allocation ratio, that will compensate for an estimated drop-out rate of 15%. It is anticipated that approximately 230 participants will be required to be screened (approximately 60% consent rate), with 40 participants on the control arm and 80 on the experimental arm (a total of 120 subjects) are expected to complete the trial.

The rationale for the trial design is to investigate the effect of 360mg verapamil administered orally once daily (titrated over the first 3 months from 120 mg to 360 mg) on preservation of beta-cell function compared to placebo at week 52 in adult subjects with newly diagnosed T1DM with residual beta-cell function. The duration of the trial with 52 weeks of exposure of 360mg verapamil administered orally once daily (titrated over the first 3 months from 120 mg to 360 mg) has been chosen to align with the regulatory requirements from FDA and EMA. The FDA and EMA guidelines advise that studies of products aimed at preservation of beta-cell function in recent-onset T1DM with remaining endogenous insulin reserve, should evaluate metabolic outcomes, such as stimulated C-peptide levels. Therefore, the MMTT stimulated AUC0-2h C-peptide concentration has been chosen as the primary efficacy outcome.

The day-to-day management of the trial is the responsibility of the trial management group. The Chief Investigator will be responsible for the preparation and submission of annual safety reports and annual progress reports.

Trial Steering Committee (TSC):

The sponsor will constitute a Trial Steering Committee (TSC) to provide the overall supervision of the trial. The TSC will monitor the trial progress, the safety data, the critical efficacy endpoints and conduct and advise on scientific credibility. The TSC will ultimately carry the responsibility for deciding whether a trial needs to be stopped on grounds of safety or efficacy. The TSC may recommend unblinding of any data for further analysis.

The TSC will consider recommendations from the Independent Data Monitoring Committee (IDMC). The TSC will decide whether to modify the trial, or to seek additional data.

Independent Data Monitoring Committee (IDMC):

The IDMC charter will detail the purpose of this committee including: the description of the membership, terms of reference, roles, responsibilities, authority, decision-making and relationships of the IDMC for this trial. The charter will further include the timing of meetings, methods of

For peer review only - http://bmjopen.bmj.com/site/about/guidelines.xhtml

providing information to and from the IDMC, frequency and format of meetings, statistical issues, and relationships with other committees. Briefly, it is planned that one interim analysis will be undertaken during this trial and considering these interim analyses and safety endpoints, the IDMC will advise the TSC of its recommendations regarding trial modification, continuation or termination of the trial. The IDMC charter will expand on the above.

Trial Management Group (TMG):

The TMG comprise investigators and individuals closely involved in running of the trial. The TMG aims to meet more frequently than the TSC to ensure that all practical details of the trial are progressing well.

Patient and Public Involvement statement:

A clear priority of INNODIA is to keep the needs and concerns of patients with Type 1 Diabetes at the centre of the project. Ver-A-T1D involvement of patients is organized by a Patient Advisory Committee (PAC). The specific activities of the PAC are to advise the Management Board of INNODIA on areas including informed consent, clinical protocol review and relationships with regulatory authorities. In addition, the PAC members act as T1D ambassadors, helping to communicate results to the wider public across 15 European countries.

More information can be found at the INNODIA webpage (https://www.innodia.eu/pac/).

Inclusion and exclusion criteria:

Table 2 lists the study's inclusion and exclusion criteria. Potential participants may not enter the trial if any of the exclusion criteria listed in Table 2 apply.

Table 2: Eligibility criteria.

Inclusion Criteria
1. Have given written informed consent 2. Age ≥18 and <45 years at consent 3. Must have a diagnosis of T1D of within 6 weeks duration at screening (from date of the first insulin injection) 4. Must have at least one or more of the following diabetes-related autoantibodies present at screening: GADA, IA-2A and/or ZnT8A 5. Must have fasting C-peptide levels ≥100 pmol/L measured at screening 6. Be willing to comply with intensive diabetes management
Exclusion Criteria
1. Be immunodeficient or have clinically significant chronic lymphopenia: Leukopenia (< 3,000 leukocytes /µL), neutropenia (<1,500 neutrophils/µL), lymphopenia (<800 lymphocytes/µL), or thrombocytopenia (<100,000 platelets/µL) 2. Have active signs or symptoms of acute infection at the time of screening 3. Be currently pregnant or lactating, or anticipate getting pregnant during the 12 months study period 4. Require use of immunosuppressive agents including chronic use of systemic steroids 5. Have evidence of current or past human immunodeficiency virus (HIV), Hepatitis B or Hepatitis C infection 6. Have any complicating medical issues or abnormal clinical laboratory results that may interfere with study conduct, or cause increased risk to include pre-existing cardiac disease, chronic obstructive pulmonary disease (COPD), sickle cell disease, neurological, or blood count abnormalities, as judged by the investigator 7. Have persistent history of malignancies other than skin

For peer review only - http://bmjopen.bmj.com/site/about/guidelines.xhtml

8. 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
9. History of renal insufficiency or evidence of renal dysfunction with creatinine greater than 1.5 times the upper limit of normal
10. Current or ongoing use of non-insulin pharmaceuticals that affect glycaemic control within prior 7 days of screening
11. Use of any other investigational drug in the previous 30 days and/or intent on using any investigational drug for the duration of the trial
12. Current use of Verapamil or other calcium channel blockers
13. Known hypersensitivity to Verapamil or to any of its excipients
14. Concomitant medication known for inducing or inhibiting CYP3A4 and/or glycoprotein-P metabolism
15. Intake of grapefruit juice, liquorice, St. John's Wort, cannabidiol, ginkgo biloba
16. Substrate intake of CYP3A4 and/or glycoprotein-P metabolism, as judged by the investigator
17. Hypotension (of less than 100mmHg systolic), sick sinus syndrome (except patients with a functioning artificial pacemaker), uncompensated heart failure or severe left ventricular dysfunction; marked bradycardia (less than 50 beats/minute), atrial flutter or atrial fibrillation in the presence of an accessory bypass tract (e.g. Wolff-Parkinson-White syndrome), hypertrophic cardiomyopathy, acute myocardial infarction, attenuated neuromuscular transmission (e.g. by myasthenia gravis, Lambert-Eaton syndrome, advanced Duchenne muscular dystrophy)
18. ECG second or third degree atrioventricular block
19. Any condition that in the investigator's opinion may adversely affect study participation or may compromise the study results.
20. Current use of ß-blockers.

Trial procedures:

The study procedures are reported in detail in online supplemental information (see Ver-A_T1D Table 3 SUPPLEMENTARY MATERIAL) and the trial flow chart is shown in Figure 2. The trial duration will be approximately 24 months, consisting of screening, randomisation, 12 months treatment period and an additional 12 months INNODIA follow-up. Throughout the trial investigators work in accordance with (ICH GCP) and local regulations and ensure that trial procedures are performed as described in the protocol. Any discrepancies that result in protocol and/or GCP deviations, the investigator takes appropriate action to avoid recurrence of the detected discrepancies. If deviations do occur, the investigator must inform the monitor and the implications of the deviation must be reviewed and discussed. Deviations are documented and explained in a protocol deviation by stating the reason, date and the action(s) taken (if applicable).

The timing of the assessments and procedures are specified in the trial flow chart (Figure 2) and detailed in online supplemental information (see Ver-A_T1D Table 3 SUPPLEMENTARY MATERIAL). A subject screening log, a subject identification code list and a subject enrolment log are kept by the investigator and may be combined in one list. Additional logs kept include a pre-screening log and staff and delegations of task(s) at sites. The investigator signs off the log of staff and the delegation of task(s) at site at the time of delegation. Protocol waivers or exemptions are not allowed. Immediate safety concerns should be discussed with the sponsor immediately upon occurrence or awareness to determine if the participant should continue or discontinue study treatment.

Adherence to the study design requirements, including those specified in the Trial Flow Chart (Figure 2), is essential and required for study conduct. All screening evaluations must be completed and reviewed to confirm that potential participants meet all eligibility criteria. The investigator will maintain a screening log to record details of all participants screened and to confirm eligibility or record reasons for screening failure, as applicable. Procedures conducted as part of the participant's

For peer review only - http://bmjopen.bmj.com/site/about/guidelines.xhtml

routine clinical management (e.g., blood count) and obtained before signing of the ICF may be utilized for screening or baseline purposes provided the procedures met the protocol-specified criteria and were performed within the time frame defined in the Trial Flow Chart (Figure 2). Throughout the trial, a maximum of 3 ml per Kg of blood will be taken at each visit; no more than 204 ml per visit maximum. Repeated or unscheduled samples may be taken for safety reasons or for technical issues with the samples.

Participants who fail to satisfy eligibility criteria may be offered participation in the INNODIA longitudinal study (Figures 1 & 2).

Participant identification:

Potentially eligible individuals are approached by health care professionals and/or local research teams during routine clinical appointment. The study is also advertised by poster and flyers in diabetes clinics, on social media, for example Facebook and Twitter, via INNODIA or local sites own pages, on the INNODIA website, UK T1D Research Consortium website and other diabetes related websites and via newspaper if applicable. All potential individuals approached or that have contacted the research teams are provided with a verbal explanation of the study and written information sheets. Once they have been given sufficient time to consider their participation in the study consent will be obtained.

Informed consent:

The informed consent form (ICF) has been approved by the local ethics committee and complies with GCP, local regulatory requirements and legal requirements and can be found in the online supplemental information (see Ver-A-T1D Informed Consent Version 5.0 11-Mar-2022). The investigator or designee must ensure that each trial participant, or their legally acceptable representative, is fully informed about the nature and objectives of the trial and possible risks associated with their participation. The investigator or designee will obtain written informed consent from each participant or the participant's legally acceptable representative before any trial-specific activity is performed. The ICF used for this trial and any change made during the trial, must be prospectively approved by the Research Ethics Committee (REC). The investigator will retain the original of each participant signed ICF and a copy will be provided to the participant.

Informed consent (IC) is sought upon joining the study to confirm that participants are happy to be contacted to inform them of study results and future intervention and research diabetes studies organised by INNODIA. After completion of treatment at 12 months from diagnosis, participants will continue for a further 12 months in the observation part of the study. This will involve a single visit 24 months from randomisation. During IC, the investigator will explain the nature of the study to the participant and answer all questions regarding the study. Participants must be informed that their participation is voluntary and will be required to sign a statement of informed consent that meets the requirements of local regulations, ICH guidelines, and the Independent Ethics Committee (IEC) or study centre. The medical record must include a statement that written informed consent was obtained before the participant was enrolled in the study and the date the written consent was obtained. The authorized person obtaining the informed consent must also sign the ICF. A copy of the ICF(s) must be provided to the participant or the participant's legally authorized representative.

Where participants require a verbal translation of the trial documentation by a locally approved interpreter/translator, it is the responsibility of the individual investigator to use locally approved translators. If the trial requires documentation in a different language (other than English) the translation and back translation documents need to be reviewed and approved by the sponsor prior to use with all sections of the approved documents must appear in the translation. The translated version must be appropriately dated and version controlled. Any new information that becomes available, that might affect the participant's willingness to continue participating in the trial will be

For peer review only - http://bmjopen.bmj.com/site/about/guidelines.xhtml

communicated to the participant as soon as possible. Participants must be re-consented to the most current version of the ICF(s) during their participation in the study.

Any new information which becomes available, which might affect the participant's willingness to continue participating in the trial will be communicated to the participant as soon as possible and participants must be re-consented where an updated ICF(s) might impact on their decision to remain in the study.

Registration:

Following informed consent, the participant will be registered on the INNODIA central database using de-identifiable information only and a participant ID generated. All identifiable information such as full name, contact details and date of birth will be registered locally following local policies and regulations. Participant eligibility for INNODIA Master protocol will be recorded at this stage as well as gender and ethnicity.

Screening and baseline assessments for those who are eligible and have consented:

The screening and baseline visit should be carried out within less than 6 weeks of the date of first insulin injection. Trial specific assessments will only be conducted after participants have given written informed consent (IC) and must be in place before the participant initiates fasting prior to the screening visit. Study procedures and their timing are summarized in Figure 2.

Assessments performed at screening and baseline are as follows: Demographics (age, gender, ethnicity), date of T1D diagnosis (date of first insulin dose), HbA1c at diagnosis, daily insulin regimen at time of visit, blood glucose at time of visit, physical examination (including height and weight), medical history, diabetes care, concomitant medication, including vaccinations in last 6 weeks, family medical history, ECG and vital signs. Additionally, for women of childbearing potential, if applicable, a pregnancy test will be performed according to local requirements (urine pregnancy test or serum pregnancy test). Blood will be collected for the following screening assessments: Fasting C-peptide, autoantibodies (Glutamic acid decarboxylase antibodies-GADA, Insulin auto-antibodies-IAA, IA-2 antibodies-IA-2A or Zinc transporter 8 antibody ZnT8A), Safety lab (incl. full blood count (FBC), complete metabolic profile (CMP)) and HIV, Hepatitis B and C.

At the same visit, the following INNODIA baseline samples will be collected from all screened participants: DNA extraction, HbA1c, Omics, ß cell killing assay, whole blood RNA, microRNA (plasma omics), immune cells (PBMC), urine (omics, including microbiome analysis), stool (omics, including microbiome and metabolome analysis).

Following review of the laboratory results from the screening samples by the local medical team, participants will be declared eligible or non-eligible for the clinical trial. If any inclusion criteria are answered no or any exclusion criteria are answered yes, the subject is a screening failure. For screening failures, the screening failure form in the electronic case report form (eCRF) must be completed with the reason for not continuing in the trial. Re-sampling or re-screening is not allowed if the subject has failed one of the inclusion criteria or meets one of the exclusion criteria related to laboratory parameters. However, if a lab test at the screening visit is inconclusive a re-test can be performed. The repeat test results must be available for evaluating the subject's eligibility before randomisation. Eligible participants will be invited for the randomisation visit (V0) and asked to attend the visit fasting (from midnight). Non-eligible participants will be informed of the results of the screening visit and explained the reason for non-eligibility and invited to join the INNODIA longitudinal study.

Samples collected in the study as part of the INNODIA Clinical Trial Master Protocol will be stored and analysed as described in the Master Protocol and outlined in the online supplemental information (see Ver-A-T1D Study Protocol Paper v1.1 25 July 2024-SUPPLEMENTARY MATERIAL). Additional samples collected that are in the same nature, for example samples from additional

For peer review only - http://bmjopen.bmj.com/site/about/guidelines.xhtml

MMTT or for additional immune cell studies, will be stored and analysed according to the INNODIA Clinical Trial Master Protocol .

Randomisation and blinding:

The trial is double-blind, randomisation is carried out for all eligible participants using a web-based platform (Randomizer®) at Medical University of Graz. At the randomisation visit (Visit 0) participants meeting all inclusion criteria and none of the exclusion criteria will be assigned a unique participant ID number and centrally randomised to one of the two parallel treatment groups in a 2:1 (verapamil 360 mg : placebo) titrated from: Day 0 to Week 4, 120 mg once daily; Week 4 to Week 8, 240 mg once daily; Week 8 to Month 12, 360 mg once daily. Placebo (matching verapamil 360 mg) mg will be titrated in the same manner. Trial participants and research teams are blinded to the treatment group for the duration of the trial. The double blinding will be achieved by providing verapamil identical placebo tablets.

The randomisation software is programmed with blind-breaking instructions. In case of an emergency, an investigator has the responsibility for determining if unblinding of a participants' treatment assignment is warranted. Participant safety must always be the first consideration in making such a determination. If the investigator decides that unblinding is warranted, the investigator should make every effort to contact the sponsor and medical monitor prior to unblinding a participant's treatment assignment unless this could delay emergency treatment of the participant. If a participant's treatment assignment is unblinded, the sponsor must be notified within 24 hours after breaking the blind. The date and reason that the blind was broken must be recorded in the source documentation and eCRF, as applicable. When the code is broken, the treatment allocation will be accessible to the investigator and the Trial Management Group. If the code has been broken the subject must be withdrawn from the trial and a withdrawal session must be completed in the eCRF.

Trial participants attend the randomisation visit fasted and have a 120-minute mixed meal tolerance test (MMTT) with Ensure Plus for measuring C-peptide and glucose as a measurement of beta cell response. Additional assessments include physical examination, vital signs and HbA1c. Capillary glucose and Dry Blood Spot (DBS) will be collected at home pre and 60 minutes after consumption of EsurePlus, monthly, for the full 12 months follow-up for DBS C-peptide measurement. Participants will be set up with a Continuous Glucose Monitor (CGM) and handed out a patient diary before leaving the clinical research facility.

Subsequent assessments: Follow-up visits 1 and 2:

The schematic representation of assessments at study visits can be found in online supplemental information (see Ver-A_T1D Table 3 SUPPLEMENTARY MATERIAL). This table details assessments at all follow-up visits. Participants are assessed for adverse events (AEs), withdrawal criteria, concomitant medication including vaccination, safety lab, ECG, vital signs, pregnancy test (if applicable), DBS, Investigational Medicinal Product (IMP) dispensing, dose titration to 240 mg at visit 1 and 360 mg at visit 2, CGM and patient diary reviews, diabetes care, Patient Reported Outcomes (PROMs), fasting C-peptide and HbA1c.

Subsequent assessments: Follow-up visits 3-6:

AE, withdrawal criteria, concomitant medication including vaccination, safety lab, ECG, DBS, IMP dispensing, CGM and patient diary review, diabetes care, vital signs, pregnancy test (if applicable), physical examination (height, weight). Additional INNODIA assessments include family medical history, MMTT (incl. fasting C-peptide and blood glucose), HbA1c, Blood ß-cell killing, Blood (omics), mirco RNA (plasma omics), immune cells (PBMC), urine (biomarkers) and stool (microbiome, metabolome).

For peer review only - http://bmjopen.bmj.com/site/about/guidelines.xhtml

Women of childbearing potential are required to use adequate contraception for the duration of the trial and for 7 days after the completion of last treatment (Visit 6). This includes Intrauterine Device (IUD), hormonal based contraception (pill, contraceptive injection or implant etc), barrier contraception (condom or occlusive cap e.g., diaphragm or cervical cap with spermicide), true abstinence (where this is in accordance with the participants preferred and usual lifestyle). Men are required to use adequate contraception for the entire duration of the trial and for 7 days after the completion of the last treatment. This includes barrier contraception (condom and spermicide) or true abstinence (where this is in accordance with the participants preferred and usual lifestyle).

Subsequent assessments: Phone visits 1-3:

Phone visits 1, 2 and 3 occur at 1 week ±2 days, 5 weeks ±2 days and 9 weeks ±2 days post treatment start. AEs, withdrawal and criteria and concomitant medication including vaccinations are recorded.

Long-term assessment: Follow-up visit 7:

At 24 months participants will be assessed for adverse events (AEs), diabetes care and safety lab. Additional INNODIA assessments include MMTT (incl. fasting C-peptide and blood glucose), HbA1c, autoantibodies, blood ß-cell killing, blood (omics), whole blood RNA, RNA (plasma omics), immune cells (PBMC), urine (biomarkers) and stool (microbiome, metabolome).

End of trial participation:

A participant is considered to have completed the study if he/she has completed all phases of the study including the last visit. The end of the study is defined as the date of the last visit of the last participant in the study in the trial globally. Participants will be expected to continue normal standard of care during the trial period and following their participation in the trial.

Early discontinuation/withdrawal of participants:

Participants may terminate participation in the study at any time. An investigator can stop the participation of a participant after consideration of the benefit/risk ratio. Possible reasons are (i) Serious Adverse Events (SAEs); (ii) Treatment emergent side effects, that do not allow dose escalation to 240 mg verapamil or placebo; (iii) Non-compliance with the study protocol; (iv) Technical grounds (e.g., patient moves) or (v) Early termination at the request of the Chief Investigator/ Principal Investigator or Co-Investigator.

Participants may withdraw without necessarily giving a reason, without any personal disadvantage and without affecting their usual patient care. Withdrawal and permission to retain samples and data already collected will be documented in the eCRF. Withdrawal by an investigator and the permission to retain sample and data already collected will be clearly documented in the eCRF and will not affect usual patient care. In rare instances, it may be necessary for a participant to permanently discontinue (definitive discontinuation) study intervention. If study intervention is definitively discontinued, the participant will remain in the study to be evaluated for follow-up assessments.

A participant will be considered lost to follow-up if he or she repeatedly fails to return for scheduled visits and is unable to be contacted by the study site. The following actions must be taken if a participant fails to return to the clinic for a required study visit: The site must attempt to contact the participant and reschedule the missed visit as soon as possible and counsel the participant on the importance of maintaining the assigned visit schedule and ascertain whether the participant wishes to and/or should continue in the study. Before a participant is deemed lost to follow up, the investigator or designee must make every effort to regain contact with the participant (where possible, 2 telephone calls or local equivalent methods). These contact attempts should be documented in the participant's medical record. Should the participant continue to be unreachable, they will be considered to have withdrawn from the study. Participants who are withdrawn will not be replaced.

For peer review only - http://bmjopen.bmj.com/site/about/guidelines.xhtml

Verapamil 120 mg preparation, dose and administration:

Verapamil is an L-type calcium channel blocker, that has been approved by the US Food and Drug Administration (FDA) and the European Medicine Agency (EMA).

Participants of the trial randomised to verapamil will receive verapamil 120 mg tablets at the following visits: V0, V1, V2, V3, V4, V5. Instruction on oral administration will happen at each visit. Participants will be instructed to take all IMP dose once daily at approximately the same time. Participants having mild side effects like dizziness or hypotension may be advised to take it in the evening before sleep. Female participants are instructed to not dose IMP before a urine pregnancy test has been ruled out.

All participants will initiate 120 mg verapamil or 120 mg placebo treatment on the day of randomisation. As the target dose is 360 mg verapamil or placebo, the dose will be escalated in increments of 120 mg verapamil or placebo every month until 360 mg verapamil or placebo has been reached. In cases where participants suffer intolerable verapamil side effects related to the dose escalation it is acceptable to maintain the current verapamil dose and postpone escalation by 1 month. If 360 mg verapamil or placebo is not tolerated due to side effects, the dose can be reduced to 240 mg verapamil or placebo, which is the lowest acceptable dose. In cases where 240 mg verapamil or placebo is not tolerated, the subject must be withdrawn.

The investigator or designee must confirm appropriate temperature conditions have been maintained during transit for all study medication received and any discrepancies are reported and resolved before use of the study medication. Only participants enrolled in the study may receive study medication and only authorized site staff may supply or administer study medication. All study medications must be stored in a secure, environmentally controlled, and monitored (manual or automated) area in accordance with the labelled storage conditions with access limited to the investigator and authorized site staff. The investigator or designee must confirm appropriate temperature conditions have been maintained during transit for all study medication received and any discrepancies are reported and resolved before use of the study medication.

Further guidance and information for the final disposition of unused study interventions are provided in the pharmacy manual online supplemental information (see Ver-A-T1D Pharmacy Manual_Version 4.0).

Placebo:

Participants randomised to placebo will receive placebo tablets identical to verapamil that will be labelled as required per country requirement, labels will be blinded and provided centrally by the sponsor, Medical University of Graz (MUG).

Known drug reactions and interaction with other therapies:

Drug-drug interactions:

These known drug-drug interactions, selected for relevance of the Ver-A-T1D trial, see DRUGBANK Online for a complete list.

- Atorvastatin The serum concentration of Verapamil can be increased when it is combined with Atorvastatin.
- Dasiglucagon Verapamil may increase the hypotensive activities of Dasiglucagon.
- Fenofibrate The metabolism of Fenofibrate can be decreased when combined with Verapamil.
- Fluvastatin The metabolism of Fluvastatin can be decreased when combined with Verapamil.
- Gemfibrozil The metabolism of Verapamil can be decreased when combined with Gemfibrozil.

For peer review only - http://bmjopen.bmj.com/site/about/guidelines.xhtml

- Insulin The risk or severity of hypoglycaemia can be increased when Verapamil is combined with Insulin.
- Lovastatin The risk or severity of myopathy and rhabdomyolysis can be increased when Verapamil is combined with Lovastatin.
- Magnesium Magnesium can cause a decrease in the absorption of Verapamil resulting in a reduced serum concentration and potentially a decrease in efficacy.
- Pravastatin The serum concentration of Pravastatin can be increased when it is combined with Verapamil.
- Rosuvastatin The metabolism of Rosuvastatin can be decreased when combined with Verapamil.
- Simvastatin The risk or severity of myopathy and rhabdomyolysis can be increased when Verapamil is combined with Simvastatin.

Regarding interaction with HMG-CoA reductase inhibitors (statins) via the CYP3A4 pathway, Rosuvastatin, Pravastatin and Fluvastatin are labelled as "non-3A4 substrate", thus have only minimal metabolism via the Cytochrome P450 system.[22, 23]

Advice on SARS-CoV-2/COVID-19 for the Ver-A-T1D trial:

Patients may be exposed to the risk of COVID-19 transmission and infection in relation to site visits if an outbreak is ongoing in the country concerned at the time of trial conduct. The risk of COVID-19 transmission in relation to site visits is overall considered to be low. To minimize the risk the following measures may be taken if appropriate:

- The number of physical on-site visits has been limited to the extent possible.
- On-site visits will be well-prepared and as short as possible. Physical contact between study participants and site staff will be limited to the extent possible, and protective measures will be implemented (mouth and nose protectors will be used by both site staff and study participants)
- Before entering the clinic, subjects will have a body temperature check and a symptom screening (coughing, shortness of breath, fever).

The use of a SARS-CoV-2 vaccine in patients treated with Verapamil 120 mg has not been studied.

Given the risk posed by COVID-19 during the pandemic, however, decisions regarding the use of any vaccination, including approved / authorized for use SARS-CoV-2 vaccines, in patients treated with Verapamil 120 mg should be made at the discretion of the investigator using their best clinical judgment and after careful consideration of risk benefit factors for the patient. The investigator must consult the vaccine product label for further information regarding associated risks and precautions, and also guidance from local regulatory agencies. Hypersensitivity events have been reported in association with certain vaccines, in close temporal relation to the application.

Applicable information regarding an individual's receipt of vaccination(s) must be documented in the participant's source documents and each administration date of the vaccine (each time) recorded as a concomitant medication in the eCRF. Any possible related adverse events from the vaccination should be reported according to the Adverse Event/Serious Adverse Event reporting guidance and to the appropriate manufacture, according to local practice.

The sites must assess this situation on an ongoing basis and must provide real time feedback to the sponsor if there is the potential to impact clinical research operations or if conditions at the site have the potential to impact the ability to monitor either the safety of participants or the scientific integrity of study(ies) at the site.

Assessment of diabetes and appropriate attention to the standard of care treatment will be provided throughout the trial. It is therefore concluded that the potential benefits from the trial will outweigh the potential risks for the Verapamil 120 mg as well as placebo treated patients. Based on

For peer review only - http://bmjopen.bmj.com/site/about/guidelines.xhtml

the risk assessment, the evaluation of COVID-19 and the implemented measures, the residual risk for study participants is considered low.

Concomitant treatments:

Concomitant medications will be assessed and recorded at each trial and phone visit. Participants will continue their current insulin treatment after they have been randomised and it is preferred that participants continue the same type of insulin treatment throughout the trial. Participants will be trained in diabetes self-care including carbohydrate counting before and at randomisation and whenever needed during the trial to achieve the most optimal diabetes control according to local standard of care. During the trial participants will receive insulin treatment to achieve metabolic control according to the local insulin titration guideline. Bolus and/or basal insulin can be stopped or paused at all times during the trial at the discretion of the investigator. The participant's need for bolus insulin will be documented in the eCRF.

During the MMTT no rapid or short-acting insulin will be given, the use of rapid acting insulin is acceptable up to 2 hours before the MMTT and the use of short-acting insulin up to 6 hours before the MMTT, to correct hyperglycaemia. Long-acting insulin and basal rates on an insulin pump will not be discontinued during the MMTT. During the DBS home collection short or rapid acting insulin should not be used until the end of the collection.

Any permitted medication or vaccine (including over the counter or prescription medicines, vitamins, and/or herbal supplements) that the subject is receiving at the time of enrolment or receives during the study are recorded along with, reason for use, dates of administration including start and end dates and dosage information (dose and frequency). The use of noninsulin pharmaceuticals that affect glycaemic control, alpha-blockers, beta-blockers, cardiac glycosides, antiarrhytmics, ivabradine, lithium, sulfinpyrazone, almotriptan and acetylsalecylic acid are prohibited for the trial duration. Concomitant medication known for inducing or inhibiting CYP3A4 and/or glycoprotein-P metabolism are also prohibited.

Compliance with trial treatment:

Compliance with study intervention will be assessed at each visit by the investigator or designee and is assessed by counting returned tablets during the site visits and documented in the source documents and eCRF. Deviation(s) from the prescribed dosage regimen are recorded in the eCRF. A record of the number of study tablets dispensed and taken by each participant is maintained and reconciled with study drug accountability and compliance records. Treatment start and stop dates, including dates for treatment delays and/or dose reductions will also be recorded in the eCRF.

Missed and unscheduled visits:

If a visit is missed every effort is made to ensure information is collected and participants will be invited for the next scheduled visit according to the visit schedule. An unscheduled visit can be scheduled at any time at the discretion of the investigator, e.g. in case additional blood samples must be performed for safety reasons. This should be reported on the unscheduled visit form in the eCRF stating the reason for the visit. If the subject attends the clinic due to re-sampling of visit-related assessments, including MMTT, this is not considered an unscheduled visit. The date of the assessments for a specific visit must be updated in the eCRF accordingly. Likewise, coming to the site for additional trial products or ancillary supplies is not considered as an unscheduled visit.

Evaluation of adverse events (AEs):

The sponsor expects that adverse events are recorded from the point of informed consent regardless of whether a participant has yet received a medicinal product. Individual adverse events should be evaluated by the investigator. This includes the evaluation of its seriousness, and any relationship between the investigational medicinal product(s) and/or concomitant therapy and the adverse event (causality). Additional information on the definitions for assessments of safety in Ver-

For peer review only - http://bmjopen.bmj.com/site/about/guidelines.xhtml

A-T1D can be found in online supplemental information (see Ver-A-T1D Study Protocol Paper v1.1 22 July 2024-SUPPLEMENTARY MATERIAL).

Seriousness is assessed against the criteria outlined in online supplemental information (see Ver-A-T1D Study Protocol Paper v1.1 22 July 2024-SUPPLEMENTARY MATERIAL). This defines whether the event is an adverse event (AE), serious adverse event (SAE) or a serious adverse reaction (SAR). Assessment of causality is categorised as: (1) Definitely: A causal relationship is clinically/biologically certain. This is therefore an Adverse Reaction (AR); (2) Probable: A causal relationship is clinically / biologically highly plausible and there is a plausible time sequence between onset of the AE and administration of the investigational medicinal product and there is a reasonable response on withdrawal. This is therefore an Adverse Reaction; (3) Possible: A causal relationship is clinically / biologically plausible and there is a plausible time sequence between onset of the AE and administration of the investigational medicinal product. This is therefore an Adverse Reaction; (4) Unlikely: A causal relation is improbable and another documented cause of the AE is most plausible. This is therefore an Adverse Event; (5) Unrelated: A causal relationship can be definitely excluded and another documented cause of the AE is most plausible. This is therefore an Adverse Event. Unlikely and Unrelated causalities are considered not to be IMP related. Definitely, Probable and Possible causalities are considered to be IMP related. A pre-existing condition must not be recorded as an AE or reported as an SAE unless the condition worsens during the trial and meets the criteria for reporting or recording in the appropriate section of the eCRF.

All events should be graded for severity according to the NCI-CTCAE Toxicity Criteria (V.5.0). AEs and ARs are recorded in the medical notes and the appropriate section of the eCRF at all phone and site visits. SAEs and SARs are be reported to the sponsor as detailed below.

Expected Adverse Events/Serious Adverse Events (AE/SAE):

The following are (S)AEs that could be reasonably expected for this trial population during the trial: (1) Hypoglycaemia and (2) Diabetic Ketoacidosis. These events must be recorded in the eCRF. Episodes not fulfilling the criteria for an SAE are not to be reported as AEs. If one of the above-mentioned episodes fulfils the criteria for an SAE then in addition to the above, an SAE form must also be filled in. The events are exempt from being reported as SAEs only if the causalities are not considered to be trial drug related.

Reporting serious adverse events:

Adverse events and adverse reactions should be recorded in the medical notes and the appropriate section of the eCRF and/or AE/AR log. Serious Adverse Events and Serious Adverse Reactions should be reported to the sponsor. Each Principal Investigator needs to record all adverse events and report serious adverse events to the Chief Investigator using the trial specific SAE form within 24 hours of their awareness of the event. The Chief Investigator is responsible for ensuring the assessment of all SAEs for expectedness and relatedness is completed and the onward notification of all SAEs to the sponsor immediately but not more than 24 hours of first notification. The sponsor has to keep detailed records of all SAEs reported to them by the trial team.

The Chief Investigator is also responsible for prompt reporting of all serious adverse event findings to the competent authority of each concerned member state if they could: (1) adversely affect the health of participants, (2) impact the conduct of the trial, (3) alter the risk to benefit ratio of the trial, or (4) alter the competent authority's authorisation to continue the trial in accordance with Directive 2001/20/EC. SAEs are reported to the Chief Investigator at MUG.

Reporting of Suspected Unexpected Serious Adverse Reactions (SUSARs):

All suspected adverse reactions related to an investigational medicinal product (the tested IMP and comparators) which occur in the concerned trial, and that are both unexpected and serious (SUSARs) are subject to expedited reporting. The sponsor delegates the responsibility of notification of

For peer review only - http://bmjopen.bmj.com/site/about/guidelines.xhtml

SUSARs to the Chief Investigator. The Chief Investigator must report all the relevant safety information previously described, to the Sponsor, Competent authorities in the concerned member states and Ethics Committee in the concerned member states. The Chief Investigator shall inform all investigators concerned of relevant information about SUSARs that could adversely affect the safety of participants.

All parties must be notified of fatal or life-threatening SUSARs as soon as possible but no later than 7 calendar days after the trial team and sponsor has first knowledge of the minimum criteria for expedited reporting. In each case relevant follow-up information should be sought and a report completed as soon as possible. It should be communicated to all parties within an additional 8 calendar days. Non-fatal, non-life-threatening SUSARs and safety issues must be reported to all parties as soon as possible but no later than 15 calendar days after first knowledge of the minimum criteria for expedited reporting. Further relevant follow-up information should be given as soon as possible. Information on the final description and evaluation of an adverse reaction report may not be available within the required time frames for reporting. For regulatory purposes, initial expedited reports should be submitted within the time limits as soon as the minimum following criteria are met: (1) a suspected investigational medicinal product, (2) an identifiable participant (e.g. trial participant code number), (3) an adverse event assessed as serious and unexpected, and for which there is a reasonable suspected causal relationship and (4) an identifiable reporting source. When available and applicable a unique clinical trial identification (EudraCT number or in case of non-European Community trials the sponsor's trial protocol code number) and a unique case identification (i.e. sponsor's case identification number) should also be reported.

In case of incomplete information at the time of initial reporting, all the appropriate information for an adequate analysis of causality should be actively sought from the reporter or other available sources. Further available relevant information should be reported as follow-up reports. In certain cases, it may be appropriate to conduct follow-up of the long-term outcome of a particular reaction. Electronic reporting is the expected method for expedited reporting of SUSARs to the competent authority. The format and content as defined by the competent authority should be adhered to.

Pregnancy Reporting:

All pregnancies within the trial in female trial participants will be collected after the start of study intervention and until 7 days after the last dose and should be reported to the Chief Investigator and the sponsor using the relevant pregnancy reporting form within 14 days of notification. Details of pregnancies in female participants will be collected after the first trial-related activity after obtaining informed consent and until pregnancy outcome. If a pregnancy is reported in a female participant, the investigator should inform the Chief Investigator and sponsor within 14 calendar days of learning of the pregnancy and pregnancy outcome should be documented in the participant's medical record. Participants will be followed to determine the outcome of the pregnancy. The investigator will report information on the participant and the pregnancy outcome until the new born infant is one month of age in accordance with European Medicines Agency (EMA).[24] Abnormal pregnancy outcome (e.g. spontaneous abortion, foetal death, stillbirth, congenital anomalies and ectopic pregnancy) is considered an SAE.

Collection of pregnancy information - Female participants who become pregnant will adhere to the following steps:

- Investigator will collect pregnancy information on any female participant, who becomes pregnant while participating in this trial.
- Information will be recorded on the appropriate form and submitted to the Chief Investigator and sponsor within 14 calendar days of learning of a participant's pregnancy.
- Participant will be followed to determine the outcome of the pregnancy. The investigator will collect follow-up information on participant and neonate, which will be forwarded to the

For peer review only - http://bmjopen.bmj.com/site/about/guidelines.xhtml

sponsor. Generally, follow-up will not be required for longer than 1 month beyond the delivery date.

- Any termination of pregnancy will be reported, regardless of foetal status (presence or absence of anomalies) or indication for procedure.
- While pregnancy itself is not considered to be an AE or SAE, any pregnancy complication or elective termination of a pregnancy will be reported as an AE or SAE.
- A spontaneous abortion is always considered to be an SAE and will be reported as such.
- Any SAE occurring because of a post-trial pregnancy which is considered possibly/probably related to the trial product by the investigator will be reported to the sponsor.

Any female participant who becomes pregnant while participating in the trial will discontinue trial product.

Toxicity Management – Emergency Procedures:

Verapamil has a vasodilating action on the vascular system. Toxic effects occur usually after a delay of 1 to 5 hours following ingestion. The main cardiovascular symptoms are: bradycardia and atrioventricular block (in 82% of cases) hypotension and cardiogenic shock (in 78% of cases) cardiac arrest (in 18% of cases). AV-Block 1st degree is treated as outlined in the online supplemental information (see Ver-A-T1D Study Protocol Paper v1.1 22 July 2024-SUPPLEMENTARY MATERIAL). Pulmonary edema may occur. Impairment of consciousness and seizures may occur and are related to a low cardiac output. Nausea and vomiting may be observed. Metabolic acidosis due to shock and hyperglycaemia may occur. Verapamil is a calcium channel blocker and inhibits the entry of calcium through calcium channels into cardiovascular cells. Verapamil reduces the magnitude of the calcium current entry and decreases the rate of recovery of the channel. Verapamil decreases peripheral vascular and coronary resistance but it is a less potent vasodilator than nifedipine. In contrast, its cardiac effects are more prominent than those of nifedipine. At doses necessary to produce arterial vasodilatation, verapamil has much greater negative chronotropic, dromotropic and inotropic effects than nifedipine. At toxic doses, calcium channel inhibition by verapamil results in three principal effects: hypotension due to arterial vasodilatation, cardiogenic shock secondary to a negative inotropic effect, bradycardia and atrio-ventricular block. The therapeutic effects of verapamil on hypertension and angina pectoris are due to arterial systemic and coronary vasodilatation. The antiarrhythmic activity of verapamil is due to a delay in impulse transmission through the AV node by a direct action. Toxicity may occur after ingestion of 1 g. verapamil was tested on human peripheral lymphocytes in vitro using micronucleus (MN) test. The MN frequencies showed increase after all treatment. The results of FISH analysis suggest that Verapamil , separately or combined with ritodrine, shows to a larger extent aneugenic than clastogenic effect. Verapamil hydrochloride may increase blood alcohol (ethanol) concentrations and prolong its effects.

Toxicity Management – Mild to Moderate Toxicity:

Patients who have asymptomatic bradycardia can be admitted and observed with telemetry if judged reasonable by the investigator. Obtain peripheral intravenous access and monitor ECG. Mild hypotension may only require treatment with intravenous fluid administration.

Toxicity Management – Severe Toxicity:

Patients with bradycardia and hypotension require standard advanced cardiac life support (ACLS) treatment. Place a central line and consider placement of an arterial line. Standard first line treatment includes atropine for bradycardia although in a serious poisoning it is rarely effective. High dose insulin and dextrose have been effective in animal studies and multiple case reports in patients with hypotension refractory to other modalities and should be considered early in patients with significant hypotension. Use intravenous calcium in severe poisonings although in these cases, beneficial effects of calcium infusion (calcium chloride is preferred) may be very minimal or short-lived. Repeat bolus doses or a continuous intravenous infusion are often needed. Standard

For peer review only - http://bmjopen.bmj.com/site/about/guidelines.xhtml

vasopressors should be administered to maintain blood pressure. Lipid emulsion has been successful in animal studies and several case report of patients with hypotension refractory to other therapies. Intravenous glucagon has been used with variable success. In a patient whose hemodynamic status continues to be refractory despite the treatment described above, extracorporeal membrane oxygenation or cardiopulmonary bypass should be considered. Treat seizures with IV benzodiazepines; barbiturates or propofol may be needed if seizures persist or recur. AV-Block 1st degree is treated as per Figure 3.

Storage and Analysis of Samples:

Samples collected in the study as part of the INNODIA Clinical Trial Master Protocol will be stored and analysed as described in the Master Protocol. Additional samples collected that are in the same nature, for example samples from additional MMTT or for additional immune cell studies, will be stored and analysed according to the INNODIA Clinical Trial Master Protocol[20].

STATISTICS OVERVIEW:

The trial is a multi-centre, randomised, double-blind, placebo-controlled trial in subjects with T1D within 6 weeks of diagnosis. A total sample size of 120 participants will be randomised 2:1 between 360mg verapamil and placebo. The primary endpoint of interest is the area under the stimulated C-peptide response curve over the first two hours of a mixed meal tolerance test (MMTT) after 12 months therapy compared to placebo.

One interim analysis will be performed using data available when approximately 50 participants have been randomised to determine whether the trial should be stopped for futility.

All analyses will be performed on an Intention-to-treat (ITT) approach that will include all randomised participants irrespective of protocol compliance.

EVALUATION OF RESULTS (DEFINITIONS AND RESPONSE/EVALUATION OF OUTCOME MEASURES):

Statistical Methods for Primary Analyses:

All model assumptions will be checked via graphical means such as plotting residuals versus dose and fitted values. We will transform our primary outcome, AUC C-pep value to ln(AUC C-pep+1) as recommended by . The transformed AUC C-pep value is assumed to be normally distributed; this distributional assumption will be assessed using a Q-Q plot and whether the residuals of the model deviate from a straight line. If the residuals are not normally distributed, then the outcome will be transformed to improve the assumption. If no transformation is available, then non-parametric methods will be used.

The primary endpoint, the area under the C-peptide curve over the first two hours (using all available measurements within the first 2 hours) of a mixed meal tolerance test (AUC C-pep) at 12 months (after transformation AUC C-pep →ln(AUC C-pep +1)) will be analysed using a linear mixed model at the end of the trial. The model will have fixed effects of treatment and time and the random effect will be participant ID. Additionally autocorrelations will be included within participants and ideally an unstructured matrix will be fitted stratified by treatment group, however, if the data do not allow such complexity then an AR(1) autocorrelation pattern will be estimated. The contrast of interest is the mean difference in AUC C-pep between verapamil 360mg and placebo at 12 months.

The transformed AUC C-pep value is assumed to be normally distributed and this distributional assumption will be assessed using a Q-Q plot and whether the residuals of the model deviate from a straight line. Additionally, departures from normality will be assessed by using normality tests, like for instance the Shapiro-Wilk test. If model assumptions are violated for the AUC C-pep →ln(AUC C-pep +1) values, then log- or square root transformations will be applied. If none of these transformations yields normally distributed residuals, then treatments will be compared by means of non-parametric methods using the change from baseline as dependent variable.

For peer review only - http://bmjopen.bmj.com/site/about/guidelines.xhtml

Statistical Methods for Secondary Analyses:

The secondary endpoints will also be analysed via a mixed effects models with fixed effects of treatment and time and the random effect will be participant ID. If required the models may include additional covariates which may be potential factors that are confounding the relationship between treatment and outcomes.

Subgroup analyses will be considered for a select list of potential covariates, the subgroup treatment effect will be analysed using an interaction test and additional factors will be included in the model to conduct this test.

A detailed statistical analysis plan (SAP) will be completed before the final database lock and will be based on top of the INNODIA Master SAP within the INNODIA clinical trial network (www.innodia.eu).

Interim analyses:

The interim analysis should be carried out after 10 months from the start of the trial.

As with the primary analysis, the endpoint, the area under the C-peptide curve over the first two hours of a mixed meal tolerance test (AUC-C-pep) will be analysed using a mixed linear model. The model will have fixed effects of treatment and time and the random effect will be participant ID. Additionally autocorrelations will be included within participants and ideally an unstructured matrix will be fitted stratified by treatment group, however, if the data do not allow such complexity, then an AR(1) autocorrelation pattern will be estimated. The analysis will be an intention to treat analysis. The contrast of interest is the mean difference in AUC-C-pep between verapamil 360mg and placebo at 6 months as there will be no one who has completed the 12-month follow-up visit at 10 months. The statistical test will be the z-test and the trial will be recommended to stop if the z-statistics is less than -0.5 i.e. where treatment is marginally worse than placebo.

Given a recruitment rate of 5 participants per month the interim analysis at 10 months should have 15 people with 3 months of follow-up data, 15 people with 6 months of follow-up data and 15 people with 9 months of follow-up data. Different recruitment rates will alter the operating characteristics of the trial but the type 1 error at the final analysis is controlled but power may vary. If recruitment is faster then the timing of the interim analysis will be re-assessed, if there is sufficient information the interim may proceed earlier than 10 months.

Model assumptions will be checked via graphical means such as plotting residuals versus dose and fitted values. The AUC-C-pep is assumed to be normally distributed, this distributional assumption will be assessed using a Q-Q plot and whether the residuals of the model deviate from a straight line. If the residuals are not normally distributed then the outcome will be transformed to improve the assumption.

Number of participants to be enrolled - Sample size calculation:

From the randomised, double-blind, placebo-controlled phase 2 clinical trial the SD for the AUC C-peptide endpoint after a MMTT over 2 hours at 12 months was 0.27 nmol/L/min as per[14]. With this SD, 90% power, 5% significance level then 40 participants on the control arm and 80 on the treatment arm will be needed to detect a change of 0.18 nmol/L/min in C-peptide. All tests are for superiority tests and the tests are two-sided tests.

Criteria for the premature termination of the trial:

The sponsor designee/INNODIA reserves the right to close the study site or terminate the study at any time for any reason at the sole discretion of the sponsor. Study sites will be closed upon study completion. A study site is considered closed when all required documents and study supplies have been collected and a study-site closure visit has been performed.

For peer review only - http://bmjopen.bmj.com/site/about/guidelines.xhtml

The investigator may initiate study-site closure at any time, provided there is reasonable cause and sufficient notice is given in advance of the intended termination.

Reasons for the early closure of a study site by the sponsor or investigator may include but are not limited to:

- Failure of the investigator to comply with the protocol, the requirements of the IRB/IEC or local health authorities, the sponsor's procedures, or GCP guidelines
- Inadequate recruitment of participants by the investigator
- Discontinuation of further study intervention development

If the study is prematurely terminated or suspended, the sponsor shall promptly inform the investigators, the IECs/IRBs, the regulatory authorities, and any contract research organization(s) used in the study of the reason for termination or suspension, as specified by the applicable regulatory requirements. The investigator shall promptly inform the subject and should assure appropriate subject therapy and/or follow-up.

Procedure to account for missing or spurious data:

All participants who are randomised will be included in this analysis and the model will have fixed effects for time and dose and participant is a random effect. All available measurements over time will be included in the analysis and an unstructured autocorrelation will be estimated for each dose level if sufficient data. The estimates assume that the missing data are missing at random. If the missing data are non-ignorable then a sensitivity analysis will be performed.

The secondary endpoints will also be analysed using a mixed effects model similar to the one described for the primary outcome. Again, model assumptions and distributional assumptions will be inspected graphically.

Definition of the end of the trial:

The end of the trial is defined as the date of the last visit of the last participant in the trial.

Data management and eCRF:

All data will be transferred into an electronic Case Report Form (eCRF) which will be anonymised. All trial data in the eCRF must be extracted from and be consistent with the relevant source documents. The eCRFs must be completed, dated and signed by the investigator or designee in a timely manner. It remains the responsibility of the investigator for the timing, completeness, legibility and accuracy of the eCRF pages. The eCRF will be accessible to trial coordinators, data managers, the investigators, clinical trial monitors, auditors and inspectors as required.

All subject data relating to the trial will be recorded on eCRFs. The investigator is responsible for verifying that data entries are accurate and correct by electronically signing the eCRF.

Corrections to the eCRF data may be made by the investigator or the investigator's delegated staff. An audit trail will be maintained in the eCRF application containing as a minimum: the old and the new data, identification of the person entering the data, date and time of the entry and reason for the correction. If corrections are made by the investigator's delegated staff after the date when the investigator signed the eCRF, the eCRF must be signed and dated again by the investigator.

The investigator must be able to access his/her trial documents without involving the sponsor in any way. If applicable, electronic CRF and other subject data will be provided in an electronic readable format to the investigator before access is revoked to the systems supplied by the sponsor. Site-specific CRFs and other subject data (in an electronic readable format or as paper copies or prints) must be retained by the trial site. If the provided electronic data (e.g. the CD-ROM) is not readable during the entire storage period, the investigator can request a new copy. A copy of all data will be stored by the sponsor.

For peer review only - http://bmjopen.bmj.com/site/about/guidelines.xhtml

Data will be collected using INNODIA (e)CRFs. Suitably qualified personnel designated by the PI and listed on the delegation of responsibility log will be responsible for completing the eCRF. Each clinical centre will be responsible for managing collected data and for generating and resolving data queries.

Source Data:

Source documents provide evidence for the existence of the participant and substantiate the integrity of the data collected. Source documents are filed at the investigator's site. Data reported on the Source Data Form or entered in the eCRF that are transcribed from source documents must be consistent with the source documents or the discrepancies must be explained. The investigator may need to request previous medical records or transfer records, depending on the study. Also, current medical records must be available.

To enable peer review, monitoring, audit and/or inspection the investigator must agree to keep records of all participating participants (sufficient information to link records e.g., eCRFs, hospital records and samples), all original signed informed consent forms and copies of the eCRF in an electronic readable format .

Definition of what constitutes source data can be found in a source document agreement at each trial site. There will only be one source document defined at any time for any data element.

Data Protection and Participant Confidentiality:

All investigators and trial site staff involved in this trial must comply with the requirements of the Data Protection Act 1998, GDPR (EU) 2016/679, local data protection laws and Trust Policy with regards to the collection, storage, processing, transfer and disclosure of personal information and will uphold the Act's core principles.

- Participants will be assigned a unique study identifier as agreed with the sponsor. Any participant records or datasets that are transferred to the sponsor will contain the identifier only; participant names or any information which would make the participant identifiable will not be transferred.
- The participant must be informed that his/her personal study-related data will be used by the sponsor in accordance with local data protection law. The level of disclosure must also be explained to the participant.
- The participant must be informed that his/her medical records may be examined by Clinical Quality Assurance auditors or other authorized personnel appointed by the sponsor, by appropriate IEC members, and by inspectors from regulatory authorities.
- Data may also be sent out to non- European countries.

Protocol Compliance and Breaches of GCP:

Prospective, planned deviations or waivers to the protocol are not allowed and must not be used. All participating sites must ensure that any substantial amendment is approved before implementation by an accredited EC.

However, deviations from the protocol should be avoided. If deviations do occur, the investigator must inform the monitor and the implications of the deviation must be reviewed and discussed. Protocol deviations must be adequately documented on the relevant forms and reported to the Chief Investigator and sponsor immediately.

Deviations must be documented and explained in a protocol deviation by stating the reason, date, and the action(s) taken. Some deviations, for which corrections are not possible, can be acknowledged and confirmed via edit checks in the eCRF or via listings from the protocol deviation forms.

Deviations from the protocol which are found to occur repeatedly will not be accepted and will require immediate action and could potentially be classified as a serious breach. Any

For peer review only - http://bmjopen.bmj.com/site/about/guidelines.xhtml

potential/suspected serious breaches of GCP must be reported immediately to the sponsor without any delay.

Monitoring, trial documentation, archiving, audit & inspection:

The Trial Master File (TMF) will be kept up to date by the coordinating centre and each participating site will be responsible for maintaining their Investigator Site Files (ISF). These files need to be complete at the end of the trial and archived for 25 years. No records may be destroyed or transferred to another location or party without written notification of the sponsor during the retention period.

The sponsor will be responsible for archiving the TMF. Other participating sites will be responsible for archiving their ISF. Records and documents including source data will be stored at each participating site. The investigator must be able to access his/ her trial documents without involving the sponsor in any way. If applicable, electronic CRF and other subject data will be provided in an electronic readable format to the investigator before access is revoked to the systems supplied by the sponsor.

All essential and trial documentation will be securely archived after the last analysis of the study data has been completed and the final study report has been submitted to the relevant bodies.

The investigator must make all trial documentation and related records available should an MHRA or EMA inspection or any regulatory authority inspection occur. Should a monitoring visit or audit be requested, the investigator must make the trial documentation and source data available to the sponsor's representative. All participant data must be handled and treated confidentially.

The sponsor's monitoring frequency will be determined by an initial risk assessment performed prior to the start of the trial. A detailed monitoring plan will be generated detailing the frequency and scope of the monitoring for the trial. Throughout the course of the trial, the risk assessment will be reviewed and the monitoring frequency adjusted as necessary. The scope and frequency of the monitoring will be determined by the risk assessment and detailed in the Monitoring Plan for the study.

ETHICS AND DISSEMINATION:

Ethical committee review:

Before the start of the trial and upon implementation of any amendment approvals of the trial protocol, protocol amendments, informed consent forms and other relevant documents e.g., advertisements and general practitioner (GP) information letters if applicable were obtained from the research ethics committee (REC). Ethics approval was sought from the following ethics committees: Medical University of Graz Ethics Committee (ID: 32-664 ex 19/20), Commissie voor Medische Ethiek ZNA, p/a ZNA Koningin Paola Kinderziekenhuis Antwerpen (ID: 5494), Comité de Protection des Personnes Est-II, CHRU – Hôpital Saint Jacques (ID: 21.01.26.73506), Comitato Etico dell' IRCCS Ospedale S.Raffaele di Milano (ID: 9/05/22), Comitato Etico Regione Toscana – Area Vasta Sud Est (ID: 19709), Medizinische Hochschule Hannover Ethikkommission (Nr. 9465_AMG_mono_2020), Medizinische Hochschule Hannover Ethikkommission und Ethikkommission der Landesärztekammer Baden-Württemberg (Nr. 9465_AMG_M_2020) and NHS Health Research Authority, London – City & East Research Ethics Committee (REC reference: 20/LO/1295). Thus, all procedures were conducted in compliance with the ethical standards established by the institutional ethics and research committees. All participants provided written informed consent prior to enrolment in the study.

All correspondence with the REC is retained in the Trial Master File/Investigator Site File and annual reports are submitted to the REC in accordance with national requirements. It is the Chief Investigator's responsibility to produce the annual reports as required.

Regulatory Compliance:

For peer review only - http://bmjopen.bmj.com/site/about/guidelines.xhtml

The trial will not commence until a Clinical Trial Authorisation (CTA) is obtained from the applicable regulatory authorities. The protocol and trial conduct will comply with the Medicines for Human Use (Clinical Trials) Regulations 2004 and any relevant amendments. Regulatory authorities will receive the clinical trial application, protocol amendments, reports on SAEs, and the clinical trial report according to national requirements.

Development Safety Update Reports (DSURs) will be submitted to the regulatory authorities in accordance with national requirements. It is the Chief Investigators responsibility to produce the annual reports as required.

Protocol Amendments:

Protocol amendments must be reviewed and agreement received from the sponsor for all proposed amendments prior to submission to the HRA, REC and/or MHRA.

The only circumstance in which an amendment may be initiated prior to HRA, REC and/or MHRA approval is where the change is necessary to eliminate apparent, immediate risks to the participants (Urgent Safety Measures). In this case, accrual of new participants will be halted until the HRA, REC and/or MHRA approval has been obtained.

In the event of an important safety measure, the Principal Investigator or suitable qualified delegate at the participating site will be informed within 48 hours by the Chief Investigator or suitable qualified member of the study team.

Peer Review:

This study protocol has been peer reviewed by the sponsor, trial management group and Principal Statistician.

Declaration of Helsinki and Good Clinical Practice (GCP):

The trial will be performed in accordance with the spirit and the letter of the declaration of Helsinki, the conditions and principles of Good Clinical Practice, the protocol and applicable local regulatory requirements and laws.

GCP Training:

All trial staff must hold evidence of appropriate GCP training or undergo GCP training prior to undertaking any responsibilities on this trial. This training should be updated every 2 years or in accordance with your Trust's policy.

Authorisation of Participating Sites:

Prior to initiating a participating site, the following documentation will be in place: 1) Investigator Site File, 2) Ethics approval from each country in addition and following home country approval, 3) Competent Authority approval, 4) All relevant local institutional approvals (e.g. local hospital institution), 5) Signed participating site agreement when required, 6) Insurance statement, 7) Protocol signed and dated by PI, 8) Confirmation of receipt of investigator's brochure by PI, 9) Patient Information leaflets including informed consent form and any other study material for participants to be provided in English and translated to home country language, 10) Delegation of Responsibility and Signature Log, 11) PI signed and dated CV, 12) Signed and dated CVs from everyone listed on the delegation of responsibility log, 13) GCP certificate from PI and everyone listed on the delegation of responsibility log, 14) Final eCRF, 15) Study Manual and SOPs, 16) Signed Source Data Verification Agreement Form (SDVAF) and 17) Local laboratory accreditation (or equivalent) and reference ranges for the protocol-specified parameters.

Procedure for initiating/opening a new site:

The study manager and/or monitor will organize the initiation meeting on behalf of the CI and invite all the participating site study members. The CI or delegate, study manager and/or monitor and PI

For peer review only - http://bmjopen.bmj.com/site/about/guidelines.xhtml

will present throughout the meeting. The PI's legal responsibilities will be listed in the Participating Site Agreement, if applicable, but each recruiting site will have a nominated PI who will be expected to:

- Read the protocol and agree to follow it and future amended protocols in accordance with ICH Good Clinical Practice guidelines, legal and regulatory requirements.
- Providing oversight of the conduct of the trial at the site and adherence to requirements of ICH guidelines, the IRB/IEC, and all other applicable local regulations
- Provide written summaries of the status of the trial in accordance with the requirements, policies, and procedures established by the IRB/IEC and/or regulatory authorities
- Notify the IRB/IEC of SAEs or other significant safety findings as required by IRB/IEC procedures
- Ensuring submission of the clinical trial report (CTR) synopsis to the IRB/IEC
- Attend initiation meeting and subsequent study meetings or delegate to suitable qualified team member
- Adhere to safety reporting timelines
- Have overall responsibility of data collection and responsibility of maintaining ISF
- Be thoroughly familiar with the appropriate use of the investigational product(s), as described in the protocol, in the current Investigator's Brochure, in the product information and in other information sources provided by the sponsor.
- Permit monitoring and auditing by the sponsor, and inspection by the appropriate regulatory authority(ies).
- Maintain a list of appropriately qualified persons to whom the investigator has delegated significant trial-related duties.

Sponsorship, Financial & Insurance:

The trial is sponsored by Medical University of Graz.

The trial will be funded by JDRF International and the Innovative Medicines Initiative 2 Joint Undertaking under grant agreement No 115797 (INNODIA) and No 945268 (INNODIA HARVEST). This Joint Undertaking receives support from the Union's Horizon 2020 research and innovation programme, "EFPIA", "JDRF" and "The Leona M. and Harry B. Helmsley Charitable Trust".

The CE-marked CGM devices are provided by DexCom Inc. (USA) and supported by IMI2-JU under grant No 945268 (INNODIA HARVEST).

Medical University of Graz will accept full financial liability for harm caused to participants in the clinical trial caused through the negligence of its employees and honorary contract holders. There are no specific arrangements for compensation should a participant be harmed through participation in the trial, but no-one has acted negligently.

Medical University of Graz will arrange insurance for negligent harm caused as a result of protocol design and for non-negligent harm arising through participation in the clinical trial.

Participants or their legal representatives of this study will not receive any payment for participating in this study, however, all reasonable travel costs incurred whilst travelling to the recruiting centre for each study visit will be reimbursed to the participant or legal representative by the coordinating centre.

Publications policy:

Ownership of the data arising from this study are owned by the beneficiary/ beneficiaries of the INNODIA Harvest consortium who generated them. On completion of the study the data will be analysed and tabulated and a Final Study Report prepared. Participating local investigators will have no rights to publish any of the study data without the permission of the Chief Investigator.

For peer review only - http://bmjopen.bmj.com/site/about/guidelines.xhtml

As outlined in the Consortium agreement each INNODIA partner (participant) has a maximum of 30 days to approve a publication or submit an objection after they have received the draft version in writing to the Coordination Team (publication@innodia.eu). If no response is gathered by day 30, then approval is assumed to be granted.

Nevertheless, the Beneficiaries acknowledge that some kind of publications may require shorter approval times due to given submission timelines:

Type of communication	Period for approval	Reminder sent out after	Approval required from
Full research paper	30 days	20 days	All INNODIA and ITC partners
Abstracts/ Posters	7 days	5 days	
Press releases*	5 days	--	
Public communication	5 days	--	

*Where national media releases are made, key messages and INNODIA researchers mentioned in the release should be circulated in English for approval.

In case of exceptional urgency, the Coordination team can grant permission to submit an abstract or a manuscript sub condition, meaning that the manuscript or abstract will have to be withdrawn from the review and publication process in case an INNODIA beneficiary objects.

Participants and legal representatives will be notified of the outcome of this study by a specifically designated newsletter, after the study has been published.

TRIAL STATUS:

Ver-A-T1D closed to recruitment on , 3 May 2024. Date of first enrolment was 8th February, 2021 in MUG. Ver-A-T1D received regulatory and ethics approval in Graz from the Ethics Committee of the Medical University of Graz on 24th August, 2020. Regulatory approval has also been granted by the Austrian competent authority in 11th February, 2021. Planned last patient last visit (LPLV) is 20 May 2025 and final reporting due May 2026.

DATA STATEMENT:

Data access:

No data are associated with this article. No data are associated with this article. Data will be available in accordance with the data sharing plan and can be found in the online supplemental information (Ver-A-T1D_Data Sharing Plan_18.09.2024).

Extended data:

This project contains the following extended data:

1) Ver-A-T1D Informed Consent Version 5.0 11-Mar-2022.pdf (UK PIS, ICF and consent forms)
2) Ver-A-T1D Pharmacy Manual_Version 4.0.doc

REPORTING GUIDELINES:

SPIRIT checklist for ` A randomised, double-blind, placebo controlled, parallel group, multi-centre trial in adult subjects with newly diagnosed type 1 diabetes mellitus investigating the effect of Verapamil on preservation of beta-cell function (Ver-A-T1D)'[21].

AUTHOR CONTRIBUTIONS:

For peer review only - http://bmjopen.bmj.com/site/about/guidelines.xhtml

Writing – Original Draft Preparation: Wych J

Conceptualisation – Pieber TR; Dayan C; Mander AP; Mathieu C

Funding Acquisition – Pieber TR; Dayan C; Mander AP; Mathieu C

Methodology – Mander AP; Pieber TR; Dayan, C

Writing, Review & Editing – Pieber TR; Dayan C; Mander AP; Mathieu C ; Brunner, M; Stenson, R; Chmura PJ; Danne, T; *Wych J.*

Project Administration – Brunner M.

Pieber TR acted as guarantor.

COMPETING INTERESTS STATEMENT:

JW, MB, PJC, RS, TD, AM, CD, CM and TRP have no competing interests.

FUNDING STATEMENT:

This project has received funding from the Innovative Medicines Initiative 2 Joint Undertaking under grant agreement No 115797 (INNODIA) and No 945268 (INNODIA HARVEST). This Joint Undertaking receives support from the Union's Horizon 2020 research and innovation programme, "EFPIA", "JDRF" and "The Leona M. and Harry B. Helmsley Charitable Trust". The IMP is supplied by Medical University of Graz. The CE-marked CGM devices are provided by DexCom Inc. (USA) and supported by IMI2-JU under grant No 945268 (INNODIA HARVEST). Any dissemination of results must indicate that it reflects only the author's view and that the JU is not responsible for any use that may be made of the information it contains.

Any dissemination of results must indicate that it reflects only the author's view and that the JU is not responsible for any use that may be made of the information it contains.

REFERENCES:

1. DiMeglio LA, Evans-Molina C, Oram RA. Type 1 diabetes. Lancet. 2018;391(10138):2449-62.
2. Atkinson MA, Eisenbarth GS, Michels AW. Type 1 diabetes. Lancet. 2014;383(9911):69-82.
3. Sørensen JS, Johannesen J, Pociot F, Kristensen K, Thomsen J, Hertel NT, et al. Residual β-Cell function 3-6 years after onset of type 1 diabetes reduces risk of severe hypoglycemia in children and adolescents. Diabetes Care. 2013;36(11):3454-9.
4. Nathan DM, Genuth S, Lachin J, Cleary P, Crofford O, Davis M, et al. The effect of intensive treatment of diabetes on the development and progression of long-term complications in insulin-dependent diabetes mellitus. N Engl J Med. 1993;329(14):977-86.
5. Lachin JM, McGee P, Palmer JP. Impact of C-peptide preservation on metabolic and clinical outcomes in the Diabetes Control and Complications Trial. Diabetes. 2014;63(2):739-48.
6. Allen LA, Dayan CM. Immunotherapy for type 1 diabetes. Br Med Bull. 2021;140(1):76-90.
7. Zhou R, Tardivel A, Thorens B, Choi I, Tschopp J. Thioredoxin-interacting protein links oxidative stress to inflammasome activation. Nat Immunol. 2010;11(2):136-40.
8. Eissa LD, Ghobashy WA, El-Azab MF. Inhibition of thioredoxin-interacting protein and inflammasome assembly using verapamil mitigates diabetic retinopathy and pancreatic injury. Eur J Pharmacol. 2021;901:174061.
9. Domingues A, Jolibois J, Marquet de Rougé P, Nivet-Antoine V. The Emerging Role of TXNIP in Ischemic and Cardiovascular Diseases; A Novel Marker and Therapeutic Target. Int J Mol Sci. 2021;22(4).
10. Chen J, Saxena G, Mungrue IN, Lusis AJ, Shalev A. Thioredoxin-interacting protein: a critical link between glucose toxicity and beta-cell apoptosis. Diabetes. 2008;57(4):938-44.

For peer review only - http://bmjopen.bmj.com/site/about/guidelines.xhtml

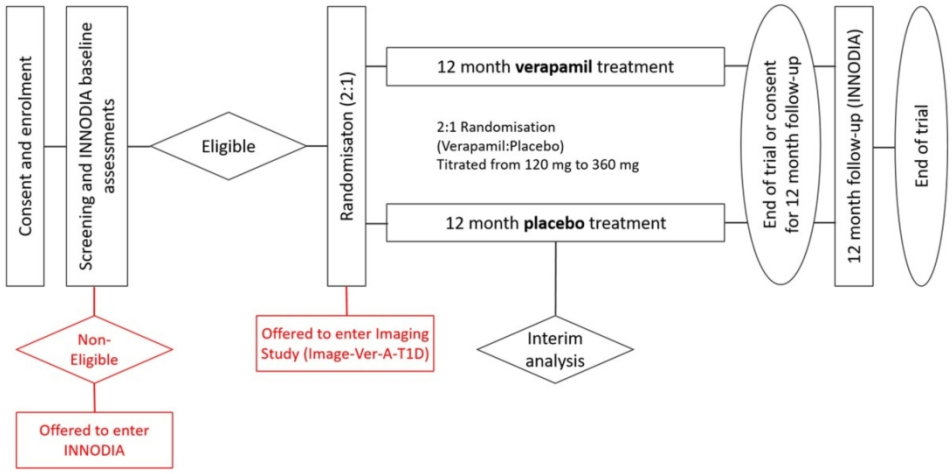
11. Chen J, Hui ST, Couto FM, Mungrue IN, Davis DB, Attie AD, et al. Thioredoxin-interacting protein deficiency induces Akt/Bcl-xL signaling and pancreatic beta-cell mass and protects against diabetes. Faseb j. 2008;22(10):3581-94.
12. Chen J, Cha-Molstad H, Szabo A, Shalev A. Diabetes induces and calcium channel blockers prevent cardiac expression of proapoptotic thioredoxin-interacting protein. Am J Physiol Endocrinol Metab. 2009;296(5):E1133-9.
13. Cao X, He W, Pang Y, Cao Y, Qin A. Redox-dependent and independent effects of thioredoxin interacting protein. Biol Chem. 2020;401(11):1215-31.
14. Ovalle F, Grimes T, Xu G, Patel AJ, Grayson TB, Thielen LA, et al. Verapamil and beta cell function in adults with recent-onset type 1 diabetes. Nat Med. 2018;24(8):1108-12.
15. Xu G, Grimes TD, Grayson TB, Chen J, Thielen LA, Tse HM, et al. Exploratory study reveals far reaching systemic and cellular effects of verapamil treatment in subjects with type 1 diabetes. Nat Commun [Internet]. 2022 2022/03//; 13(1):[1159 p.].
16. Forlenza GP, McVean J, Beck RW, Bauza C, Bailey R, Buckingham B, et al. Effect of Verapamil on Pancreatic Beta Cell Function in Newly Diagnosed Pediatric Type 1 Diabetes: A Randomized Clinical Trial. JAMA. 2023;329(12):990-9.
17. Yin T, Kuo SC, Chang YY, Chen YT, Wang KK. Verapamil Use Is Associated With Reduction of Newly Diagnosed Diabetes Mellitus. J Clin Endocrinol Metab. 2017;102(7):2604-10.
18. Cooper-Dehoff R, Cohen JD, Bakris GL, Messerli FH, Erdine S, Hewkin AC, et al. Predictors of development of diabetes mellitus in patients with coronary artery disease taking antihypertensive medications (findings from the INternational VErapamil SR-Trandolapril STudy [INVEST]). Am J Cardiol. 2006;98(7):890-4.
19. Xu G, Chen J, Jing G, Shalev A. Preventing β-cell loss and diabetes with calcium channel blockers. Diabetes. 2012;61(4):848-56.
20. Dunger DB, Bruggraber SFA, Mander AP, Marcovecchio ML, Tree T, Chmura PJ, et al. INNODIA Master Protocol for the evaluation of investigational medicinal products in children, adolescents and adults with newly diagnosed type 1 diabetes. Trials. 2022;23(1):414.
21. Chan A-W TJ, Gøtzsche PC, Altman DG, Mann H, Berlin J, Dickersin K, Hróbjartsson A, Schulz KF, Parulekar WR, Krleža-Jerić K, Laupacis A, Moher D. SPIRIT 2013 Explanation and Elaboration: Guidance for protocols of clinical trials. BMJ. 2013;346:e7586.
22. Kostapanos MS, Milionis HJ, Elisaf MS. Rosuvastatin-associated adverse effects and drug-drug interactions in the clinical setting of dyslipidemia. Am J Cardiovasc Drugs. 2010;10(1):11-28.
23. Rowan CG, Brunelli SM, Munson J, Flory J, Reese PP, Hennessy S, et al. Clinical importance of the drug interaction between statins and CYP3A4 inhibitors: a retrospective cohort study in The Health Improvement Network. Pharmacoepidemiol Drug Saf. 2012;21(5):494-506.
24. Agency EM. Guideline on the exposure to medicinal products during pregnancy: Need for postauthorisation data 2005.

Figure 1 Ver-A-T1D Trial Design

Figure 2 Ver-A-T1D Trial Flow Chart

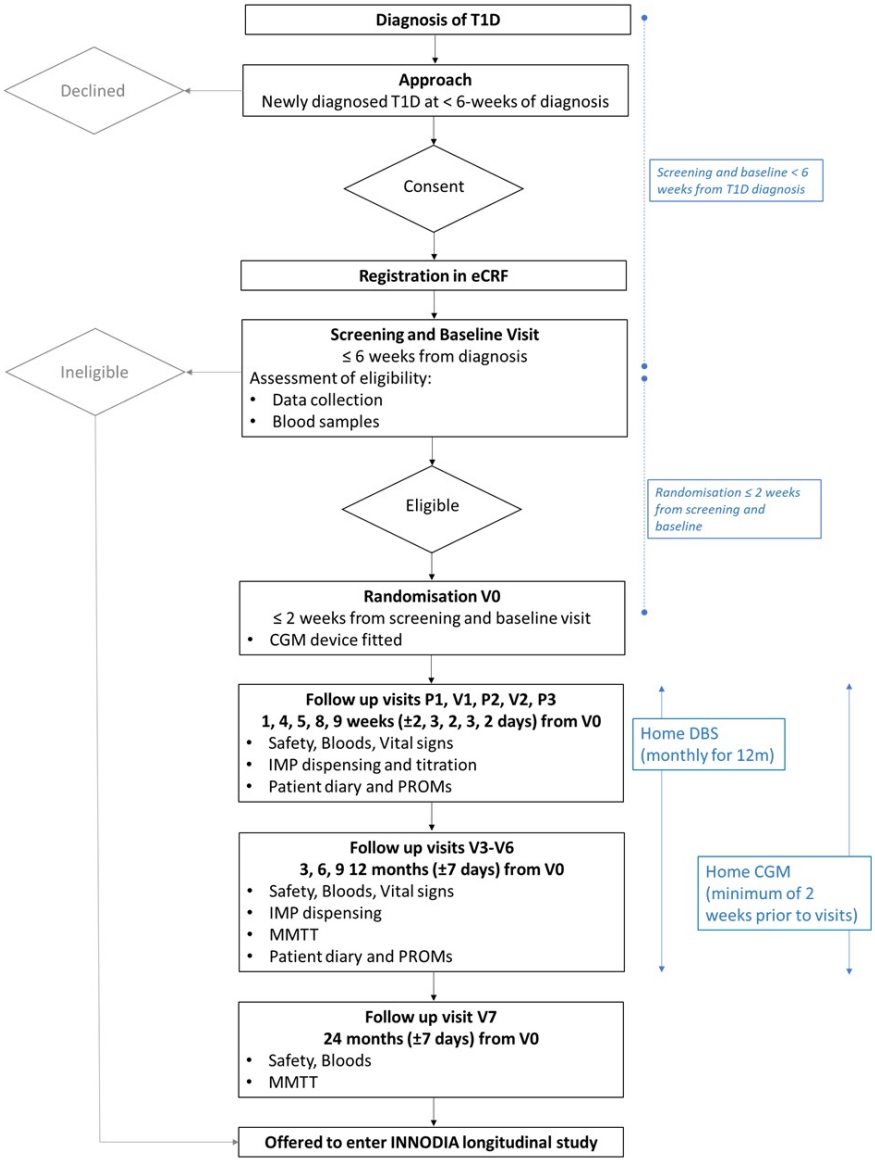
Figure 3 Ver-A-T1D AV-Block Management

For peer review only - http://bmjopen.bmj.com/site/about/guidelines.xhtml



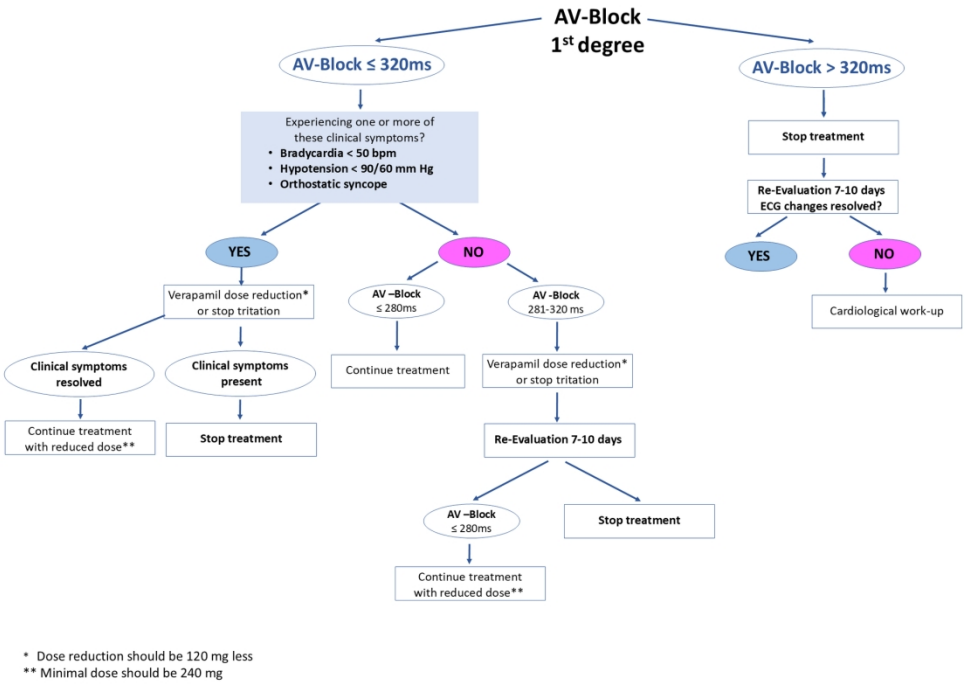
Ver-A-T1D Trial Design

173x97mm (300 x 300 DPI)



Ver-A-T1D Trial Flow Chart

83x113mm (290 x 290 DPI)



Ver-A-T1D AV-Block Management

173x121mm (300 x 300 DPI)

Table 3. Schematic representation of assessments at study visits.

Trial period	**Consent and enrolment**	**Screening and baseline assessment**	**Randomisation**	**Treatment**									**Observation**
Visit type (C: Clinic, P: Phone contact)	**C**	**C**	**C**	**P**	**C**	**P**	**C**	**P**	**C**	**C**	**C**	**C**	**C**
Visit number		**V-1**	**V0**	**P1**	**V1**	**P2**	**V2**	**P3**	**V3**	**V4**	**V5**	**V6**	**V7**
Visit number INNODIA backbone		INN V1							INN V2	INN V3		INN V4	INN V5
Timeline		**<6 weeks from diagnosis[b]**	**Day 0 (≤2 weeks from V-1)**	**Week 1**	**Week 4**	**Week 5**	**Week 8**	**Week 9**	**Month 3**	**Month 6**	**Month 9**	**Month 12**	**Month 24**
Visit window (days)				**±2**	**±3**	**±2**	**±3**	**±2**	**±7**	**±7**	**±7**	**±7**	**±7**
Assessment													
Informed consent	x[a]	x[a]										x	
Randomisation			x										
Attend visit fasting		x	x		x		x		x	x	x	x	x
In/exclusion criteria		x											
Demographic		x											
Medical history/ concomitant illness		x											
Family medical history[c]		x	x						x	x		x	
Concomitant medication incl. vaccinations		x	x	x	x	x	x	x	x	x	x	x	
Diabetes care (Insulin regimen)[c]		x	x		x		x		x	x	x	x	x
Physical examination (incl. height, weight)		x	x						x	x		x	
ECG		x			x		x		x	x	x	x	
Vital signs		x	x		x		x		x	x	x	x	
HIV, Hepatitis B and C		x											
Autoantibodies		x										x	x
Fasting C-peptide, Blood glucose[i]		x	x		x		x		x	x	x	x	x
DNA extraction		x											
HbA1c		x	x		x		x		x	x	x	x	x
Immune cells (PBMC)		x							x	x		x	x
Blood (omics)		x							x	x	x	x	x
Blood (beta-cell killing)		x							x	x	x	x	x
Whole blood RNA		x										x	x
microRNA (plasma omics)		x							x	x	x	x	x
Urine (biomarkers)		x							x	x		x	x
Stool (microbiome, metabolome)		x							x	x		x	x
Safety lab (incl. FBC, CMP)		x			x		x		x	x	x	x	x
MMTT			x						x	x	x	x	x
IMP dispensing			x		x		x		x	x	x		
IMP dose (mg SR once daily)			**120**	**120**	**240**	**240**	**360**	**360**	**360**	**360**	**360**	**360**	
Drug accountability			x		x		x		x	x	x	x	
Withdrawal criteria			x	x	x	x	x	x	x	x	x	x	
Adverse events assessment			x	x	x	x	x	x	x	x	x	x	x
Handout and instruct in CGM, DBS,			x										

For peer review only - http://bmjopen.bmj.com/site/about/guidelines.xhtml

Trial period	**Consent and enrolment**	**Screening and baseline assessment**	**Randomisation**	**Treatment**								**Observation**
Visit type (C: Clinic, P: Phone contact)	**C**	**C**	**C**	**P**	**C**	**P**	**C**	**P**	**C**	**C**	**C**	**C**	**C**
Visit number		**V-1**	**V0**	**P1**	**V1**	**P2**	**V2**	**P3**	**V3**	**V4**	**V5**	**V6**	**V7**
Visit number INNODIA backbone		INN V1							INN V2	INN V3		INN V4	INN V5
Timeline		**<6 weeks from diagnosis[b]**	**Day 0 (≤2 weeks from V-1)**	**Week 1**	**Week 4**	**Week 5**	**Week 8**	**Week 9**	**Month 3**	**Month 6**	**Month 9**	**Month 12**	**Month 24**
Visit window (days)				**±2**	**±3**	**±2**	**±3**	**±2**	**±7**	**±7**	**±7**	**±7**	**±7**
Assessment													
patient diary and pregnancy test (if applicable)													
CGM data download (Review CGM)					x		x		x	x	x	x	
Review of patient diary					x		x		x	x	x	x	
Pregnancy test[d]		x	x		x		x		x	x	x	x	
PROMs[e]					x					x		x	
Home measurements[f]:													
Home DBS for C-Peptide (monthly)			x		x		x		x	x	x	x	
CGM[g]			x				**Readings done 2 weeks prior to each visit**						
Home Pregnancy test[h]			x		x		x		x	x	x	x	

Footnotes:

[a]Written informed consent must be in place before the participant initiates fasting prior to the screening visit. Any trial specific assessments must be conducted only after participants have given written informed consent.
[b]Diagnosis date is defined as date of first insulin injection.
[c]Familiy medical history and diabetes care information should be updated at the given visits
[d]Urine human chorionic gonadotropin (hCG) pregnancy test (as needed for women of childbearing potential or per local requirements)
[e]PROMs: HFS and DTSQs will be assessed at V1, V4, V6. DTSQc will be assessed at V6. ADDQoL will be assessed at V4, V6.
[f]Capillary glucose and DBS will be collected at home pre and 60 min post consumption of EnsurePlus, monthly, for the full 12 months follow-up, for DBS C-peptide measurement.
[g]Glucose monitor to be used constantly if possible but patient advised to wear sensors for 2 weeks prior to visits as a minimum.
[h]Subjects will be instructed to perform the test at home if no site visit is planned according to local requirements. In case a menstrual period is missed or if pregnancy is suspected at any time during the trial, a urine pregnancy test should be performed. The subjects should be instructed to not dose trial product before urine pregnancy test has been ruled out.
[i]At visits where participants have a MMTT, no extra fasting C-peptide samples or blood glucose samples must be taken.

For peer review only

Supplementary information – Ver-A-T1D Protocol appendix

Legal status of the investigational medical product (IMP)/ placebo:

Verapamil SR is an L-type calcium channel blocker, that has been approved by the US Food and Drug Administration (FDA) and the European Medicine Agency (EMA).

Supply of IMP/ Placebo

IMP supply to sites will be overseen by the Medical University of Graz and distributed by ABF Pharmaceutical Services GmbH, Vienna. Upon initial authorisation by the sponsor, an initial supply will be sent to sites; supplies thereafter will be requested and distributed as detailed in the pharmacy manual.

Accountability of the trial treatment:

The investigator, institution, or the head of the medical institution (where applicable) is responsible for study medication accountability, reconciliation, and record maintenance (receipt, reconciliation, and final disposition records). Only participants enrolled in the study may receive IMPs and only authorised site staff may supply or administer study intervention. Used and unused study medication will be destroyed at site after written confirmation from the sponsor. Destruction of IMPs will be documented and carried out according to local procedures after accountability is finalised and reconciled by the monitor.

Definitions for assessment of safety in Ver-A-T1D:

Clinical assessment of severity is classified as Mild, the participant is aware of the event or symptom, but the event or symptom is easily tolerated, Moderate, the participant experiences sufficient discomfort to interfere with or reduce his or her usual level of activity or Severe, significant impairment of functioning; the subject is unable to carry out usual activities and / or the participant's life is at risk from the event.

Recording of all adverse events starts from the point of informed consent regardless of whether a participant has yet received a medicinal product. Any untoward medical occurrence in a participant or clinical trial participant administered a medicinal product and which does not necessarily have a causal relationship with this treatment. An adverse event can therefore be any unfavourable and unintended sign (including an abnormal laboratory finding), symptom, or disease temporally associated with the use of an investigational medicinal product, whether or not considered related to the investigational medicinal product.

The IDMC will assess safety from reported adverse events and will have the right to suspend or stop the trial at any point for safety concern. The trial may be suspended by the chief investigator and/or the sponsor following SUSAR.

Adverse reaction to an investigational medicinal product (AR) is an untoward and unintended response to an investigational medicinal product related to any dose administered. All adverse events judged by either the reporting investigator or the sponsor as having a reasonable causal relationship to a medicinal product qualify as adverse reactions. The expression reasonable causal relationship means to convey in general that there is evidence or argument to suggest a causal relationship.

Unexpected adverse reaction is an adverse reaction, the nature, or severity of which is not consistent with the applicable reference safety information (RSI) (e.g. summary of product characteristics

For peer review only - http://bmjopen.bmj.com/site/about/guidelines.xhtml

(SmPC) for an authorised product). When the outcome of the adverse reaction is not consistent with the applicable RSI this adverse reaction should be considered as unexpected. The term "severe" is often used to describe the intensity (severity) of a specific event. This is not the same as "serious," which is based on participant /event outcome or action criteria.

Serious adverse event or serious adverse reaction (SAE / SAR) is any untoward medical occurrence that at any dose:

- results in death
- is life-threatening
- requires hospitalisation or prolongation of existing inpatients´ hospitalisation
- results in persistent or significant disability or incapacity
- is a congenital anomaly or birth defect
- is an important medical event - Some medical events may jeopardise the participant or may require an intervention to prevent one of the above characteristics/ consequences. Such events (hereinafter referred to as 'important medical events') should also be considered as 'serious'

Life-threatening in the definition of a serious adverse event or serious adverse reaction refers to an event in which the participant was at risk of death at the time of event; it does not refer to an event which hypothetically might have caused death if it were more severe.

Suspected Unexpected Serious Adverse Reaction (SUSAR) is a serious adverse reaction, the nature and severity of which is not consistent with the information set out in the Reference Safety Information. All expected Adverse Reactions are listed in the latest MHRA approved version of the RSI. This must be used when making a determination as to the expectedness of the adverse reaction. If the adverse reaction meets the criteria for seriousness, this must be reported as per section.

A list of medical events that defines which reactions are expected for the IMP within a given trial and thus determining which serious adverse reactions (SARs) require expedited reporting. The RSI is contained in a clearly identified section (section 4.8) of the Summary of Product Characteristics (SmPC).

Procedures for the management of AV-Block are outlines in Figure 1.

Study Samples:

Ver-A-T1D will utilise the INNODIA consortium established SOPs for sample collection, shipments, storage and analysis. All Ver-A-T1D sample shipments from participating sites to central laboratories will be recorded via the eCRF. Samples sent to central laboratories will be pseudo-anonymised. The following central INNODIA consortium laboratories will be used for analysis and storage of Ver-A-T1D biological samples: 1) Core Biochemical Assay Laboratory (CBAL) at the Cambridge University Hospitals NHS Foundation Trust, UK led by Mr Keith Burling, 2) Paediatric Diabetes Research Group (PEDIA) Laboratory at the University of Helsinki, Helsinki, Finland led by Prof Mikael Knip, 3) Peter Gorer Department of Immunobiology at the School of Immunology and Microbial Sciences, King's College London, Guy's Hospital, London, UK led by Dr Tim Tree, 4) Diabetes and Autoimmunity Research (DeAR) Lab at the Institut Cochin, INSERM U1016, Paris, France led by Prof Roberto Mallone, 5) Diabetes Research Lab at the Leiden University Medical Centre, Leiden, The Netherlands led by Prof Bart Roep, 6) Centre for Regenerative Therapies Dresden at the Technische Universität Dresden, Dresden, Germany led by Prof Ezio Bonifacio, 7) Department of Medical Sciences, Surgery and Neurosciences at the University of Siena, Siena, Italy led by Dr Guido Sebastiani, 8)

For peer review only - http://bmjopen.bmj.com/site/about/guidelines.xhtml

JDRF/Welcome Trust Diabetes and Inflammation Laboratory at the University of Oxford, Oxford, UK led by Prof John Todd with 2)-7) being INNODIA immune hubs. The Ver-A-T1D Trial Manual details sample collection, processing and shipment requirements in more detail.

All other samples collected for exploratory studies (blood, urine and stool for Omics analysis) will be processed locally at participating sites according to the respective INNODIA SOPs and stored locally in <-69°C in freezers with temperature monitoring until shipped in batches to the University of Cambridge. Until required for exploratory analysis, samples will be sorted and stored by the University of Cambridge, at the University of Cambridge or at the National Institute of Health Research National Biosample Centre. When requested, samples will be sent to selected analytical laboratories. At every location, samples will be kept at <-69°C in freezers with temperature monitoring. For transport, samples will be shipped on dry ice. All shipments will be recorded in the INNODIA data warehouse which tracks the location of the samples (Table 1).

Toxicology and normal standard of care samples:

Samples collected in the trial that are part of the normal standard of care or for screening/safety (for example HbA1c, FBC, biochemistry, HIV, hepatitis and SARS-CoV-2 serology and PCR) will be analysed locally by the local hospital accredited laboratory and samples discarded once analysed as per normal local protocols.

Mixed Meal Tolerance Test (MMTT) measurements:

At baseline and at 3, 6-, 9-, 12- and 24-months trial participants will have an initial 120-minute MMTT, during which blood will be collected for measuring glucose and C-peptide. The MMTT will be performed according to the following protocol. Long-acting insulins or basal rates (in case of using an insulin pump) will be continued. The use of rapid-acting insulin is acceptable up to 2 hours before the MMTT and the use of short-acting insulin up to 6 hours before the MMTT to correct hyperglycaemia. The test will be only performed if the glucose level is between 4 and 11.1 mmol/l.

Participants will be given 6 ml/kg of Ensure Plus meal solution (up to a maximum of 360 ml) orally which needs to be ingested within 10 minutes. Blood samples for the measurement of C-peptide and glucose will be collected 10 minutes prior to the meal (-10 mins), at the time of ingestion (0 minutes), and at 15, 30, 60, 90 and 120 minutes thereafter. Participants who are not able to tolerate Ensure Plus will be advised to eat a standardised breakfast with a defined content of carbohydrates, proteins and lipids, which will be the same for all visits during the study.

If the glucose level at t=120 minutes is >8 mmol/l, a subcutaneous insulin correction dose will be given, either via injection or pump, according to the participant's own insulin sensitivity factor. If the glucose level at t=120 is >14 mmol/l, ketones will be tested by finger prick. If ketones are >0.6 mmol/l, glucose and ketones will be repeated until ketones have decreased <0.6 mmol/l and the participant can be discharged from the clinical centre.

Dried Blood Spot (DBS) measurements:

The first DBS and blood glucose measurements will be carried out in parallel with the MMTT. Only the first DBS is collected on-site (V0). Following the baseline DBS test, fasted participants will be requested to collect DBS samples and record capillary blood glucose measurements at home, collection will be monthly. Each time, a blood glucose measurement will need to be recorded and a DBS sample collected, immediately before and 60 min after starting a liquid meal (Ensure Plus) solution (replacing breakfast), whilst omitting their morning/pre-breakfast insulin.

For peer review only - http://bmjopen.bmj.com/site/about/guidelines.xhtml

Continuous Glucose Monitoring (CGM):

Dexcom G6 devices will be provided by Dexcom for use in Ver-A-T1D (use Dexcom Order Form). Blood glucose variability will be studied through subcutaneous glucose variation, using data de-rived from glucose monitoring for the 2 weeks prior to each clinic visit. All participants will be provided with a continuous glucose monitoring system (Dexcom G6) during visit V0. Suitable training will be provided to the participants so they can place the device and collect data at home. Only the Dexcom G6 can be used for the trial assessments.

Training will be provided to site staff on how the device is to be used in Ver-A-T1D. This training should be recorded on a training log. Trained individuals may then be added to the Log of Staff Delegation. The Dexcom G6 device is commercially available and User Guides from the manufacturer are provided with each kit in the local language. Please refer to these documents for additional in-formation on how to apply the Dexcom G6. Data will be downloaded in the Clarity software from the receiver by the trial team once 14 days of home CGM is complete.

Patient diary:

The participants will be provided with a diary at visit V0 and at all subsequent visits as applicable. The participants should be trained in the correct use of the diary. Detailed instructions are outlined in the patient diary itself. Mean daily insulin use will be calculated over 7 consecutive days during the 2 weeks preceding all visits and participants will be asked to record all insulin usage in their diary during those 2 weeks. This value will be calculated in units of IU/kg/day and combine doses of all different types of insulin administered over this study period. Where data from consecutive days are not available, the three days closest together will be used.

The investigator or delegate should review the diary during the in-house visits. Completed diaries will be collected at each in-house visit and filed in the participant's study records. New diaries should be handed out (in sufficient quantity to cover longer intervals between the study vis-its) to the participants whenever the previous one is collected or completed by the participants. The patient diary is version controlled and must be approved by the local or national ethics committee prior to implementation. The patient diary must be kept as they are source data.

For peer review only

For peer review only - http://bmjopen.bmj.com/site/about/guidelines.xhtml

Table 1. Study Sample storage and analysis methods

Sample For	Sample	Before analysis	Analysis	Storage after analysis
Screening eligibility criteria	Random plasma C-peptide	Plasma collected for C-peptide analysis will be sent on dry ice to University of Cambridge	CBAL	Samples will be kept at <-69°C in freezers with temperature monitoring by University of Cambridge
	Diabetes-related autoantibodies (GADA, IAA, IA-2A or ZnT8A)	Serum will be sent for analysis fresh within 24 hours to the PEDIA Laboratory (Helsinki, Finland)	PEDIA Laboratory	Samples will be kept at <-69°C in freezers with temperature monitoring by the PEDIA Laboratory
Primary outcome	AUC stimulated C-peptide over first 2h of MMTT at 12 months follow-up	Plasma collected for C-peptide analysis will be sent on dry ice to the University of Cambridge, where they will be stored until analysis at <-69°C in freezers with temperature monitoring	Analysis in batches CBAL	Before and after analysis, samples will be kept at <-69°C in freezers with temperature monitoring by University of Cambridge
Secondary outcomes	AUC stimulated C-peptide over first 2h of MMTT at baseline, 3, 6 and 12-months follow-up	Plasma collected for C-peptide analysis will be sent on dry ice to the University of Cambridge, where they will be stored until analysis at <-69°C in freezers with temperature monitoring	Analysis in batches by CBAL	Samples will be stored at <-69°C in freezers with temperature monitoring by University of Cambridge
	DBS C-peptide at observed times	DBS cards collected for C-peptide analysis will be stored locally at participating sites (frozen <-69°C) until shipment on dry ice to the University of Cambridge	Analysis by CBAL	After analysis by CBAL, samples will be stored by the University of Cambridge
	HbA1c (all time points)	Whole blood collected for HbA1c measurement will be sent to local hospital accredited laboratory routinely performing this analysis as standard of care	Analysis by local hospital accredited laboratory. HbA1c results will be entered into the eCRF by participating sites.	Samples will be discarded after analysis as per normal local protocols

For peer review only - http://bmjopen.bmj.com/site/about/guidelines.xhtml

Sample For	Sample	Before analysis	Analysis	Storage after analysis
	T1D-associated autoantibodies at baseline and 12 months	Serum will be sent for analysis fresh within 24 hours to the PEDIA Laboratory	Analysis by the PEDIA Laboratory	After analysis samples will be kept at <-69°C in freezers with temperature monitoring by the INNODIA central laboratory by the PEDIA Laboratory
Exploratory studies	Biomarkers related to immunological changes and β-cell death/ survival	Whole blood will be sent fresh following collection to an INNODIA immune hub	Fresh blood immune assays and PBMC isolation performed by INNODIA immune hubs	Isolated PBMCs will be stored in liquid nitrogen by an INNODIA immune hubs
	Diabetes-related genotyping	Blood cells collected for genotyping will be stored locally at participating sites (frozen <-69°C) until shipment on dry ice to the University of Cambridge where they will be further forwarded to the genotyping lab for DNA extraction and analysis	JDRF/Welcome Trust Diabetes and Inflammation Laboratory	Remaining cells and extracted DNA samples will be stored at <-69°C in freezers with temperature monitoring by JDRF/Welcome Trust Diabetes and Inflammation Laboratory

For peer review only

For peer review only - http://bmjopen.bmj.com/site/about/guidelines.xhtml

Pharmacy Manual

General Information
&
Drug Preparation Instructions

A randomised, double-blind, placebo controlled, parallel group, multi-centre trial in adult subjects with newly diagnosed type 1 diabetes mellitus investigating the effect of Verapamil SR on preservation of beta-cell function (Ver-A-T1D)

Verapamil SR in Adults with Type 1 Diabetes (Ver-A-T1D)

Trial phase: 2

For peer review only

Document History:

Version	Date	Description of change
1.0	26-JAN-2021	Original Version
2.0	15-FEB-2021	Update of “Central Contacts” section; phone numbers added Section 3.4 Randomisation process has been updated: “For the randomisation procedure only the last 4 digits of the Subject ID (generated by eCRF) must be entered” Section 3.5 “Viewing Randomisations” and Section 3.6 “Editing Randomisations” added. Section 3.7 “Accessing Online Help” added.
3.0	22-Feb-2021	Pharmacy Manual Signature Page: Name of IMP Manager changed. Section 4.2.3 “Storage of IMP”: The requirement of temperature logging during transfer from one long-term storage location to another has been specified. Section 4.8 “Relabelling” added. Appendix 1 Ver-A-T1D_Clinical trial prescription: Time of collection added. Appendix 3 Ver-A-T1D_List of applicable documents: Full name of the documents added. The forms “Ver-A-T1D_Clinical trial prescription” and “Ver-A-T1D_Temperature protocol_ambient storage” must be used only if there is no local equivalent available.
4.0	01-Jun-2022	Pharmacy Manual Signature Page: Name of IMP Manager changed. Update of “Central Contacts” section: UK coordinator changed, phone numbers added Update of “Central Contact” section Changed IMP Manager to IMP Management: email address changed and deleted the name of the IMP manager Update of “Central Contact” section Phone number for Randomizer, Emergency unblinding added Table 1 “Trial Flow Chart” updated Figure 12 “Label booklet cover page example” updated The “Treatment Code” section updated Figure 15 changed “Treatment Code” in “ Example Treatment Code” and updated the figure In all the sections the word Manager is changed to Management The number of Ver-A-T1D_Clinical trial prescription appendix has changed from 2 to 1 The number of “Summary of Product Characteristic” appendix has changed from 3 to 2. The number of “Ver-A-T1D_List of applicable documents “appendix has changed from 4 to 3

For peer review only

Pharmacy Manual Signature Page

Authored by:	Name, Job Title Dr. Cristiana M. L. Di Giuro, IMP Manager	Date, Signature
Approved by:	Name, Job Title Martina Brunner, Clinical Trial Manager	Date, Signature
Approved by:	Name, Job Title Prof. Thomas Pieber, MD, Chief Investigator	Date, Signature

For peer review only

This Pharmacy Manual is designed to contain instructions and information not provided in the study protocol. If any information in this manual contradicts the protocol, *the protocol takes precedence*.

The pharmacy manual must be read in conjunction with the current Study Protocol and Study Reference Manual.

The Pharmacy Manual, Standard Operating Procedures (SOPs) and Logs are version controlled. Printed copies should be checked for validity at all time.

For peer review only

For peer review only - http://bmjopen.bmj.com/site/about/guidelines.xhtml

Central contacts	
Ver-A-T1D Study Management	
Sponsor	Medical University of Graz, Austria
Chief Investigator	Professor Thomas Pieber Department of Internal Medicine Medical University of Graz, Austria thomas.pieber@medunigraz.at Telephone: +43 316 385 82834
Trial Manager	Martina Brunner Center of Medical Research, Clinical Trials Unit Medical University of Graz, Austria martina.brunner@medunigraz.at Telephone: +43 (0)316 385 72841
Co-Chief Investigator (UK)	Professor Colin Dayan Cardiff University School of Medicine Heath Park, Cardiff CF14 4XN, UK DayanCM@cardiff.ac.uk Telephone: +44 2920 742182
Coordinator (UK)	Rhiân Evans Clinical Trials Co-ordinator Cardiff University School of Medicine Heath Park, Cardiff CF14 4XN Ver-A-T1D@cardiff.ac.uk Telephone: +44 (0) 7792 175 271
IMP Management, Unblinded person	ver-a-t1d-orders@medunigraz.at Telephone: +43 (0)316 385 72841 or +43 (0)316 385 72800
Randomizer, Emergency unblinding	ver-a-t1d@medunigraz.at Telephone: +43 (0)316 385 72841 or +43 (0)316 385 72800

For peer review only

IMP labelling, storage, QP release and distribution	ABF Pharmaceutical Services GmbH Brunner Strasse 63/18-19 1230 Wien, Austria order@abf-pharma.com Julia.Koycheva@abf-pharma.com (PM) Telephone +43 676 897 11 55 59 Katarina.kytkova@abf-pharma.com (backup PM) Telephone +43 676 897 11 55 32

For peer review only

Table of Contents

For peer review only

Abbreviations

AE/AR	Adverse event/Adverse reaction
CI	Chief Investigator
eCRF	Electronic case report form
EMA	European Medicines Agency
EudraCT	European clinical trials database
FDA	Food and Drug Administration
GCP	Good clinical practice
IB	Investigator´s brochure
ICF	Informed consent form
IMP	Investigational medicinal product
INNODIA	An innovative approach towards understanding and arresting Type 1 diabetes
ISF	Investigator site file
LOS_DOT	Log of Staff Delegation of Tasks
PI	Principal Investigator
RS	Reference safety information
SAE/SAR	Serious adverse event/Serious adverse reaction
SmPC	Summary of Product Characteristic
SOP	Standard operating procedure
SR	Sustained release
SUSAR	Suspected unexpected serious adverse reaction
Ver-A-T1D	Verapamil SR in Adults with Type 1 Diabetes

For peer review only

List of tables

List of figures

For peer review only

1. Protocol Overview

This trial is a multi-centre, randomised, double-blind, placebo-controlled trial testing the efficacy of 360 mg verapamil SR administered orally once daily (titrated over the first 3 months from 120 mg to 360 mg) on protection of stimulated C-peptide decline in subjects with diagnosis of T1D within 6 weeks of diagnosis. Participants will be allocated to treatment or placebo in a 2:1 ratio (verapamil SR:placebo). The duration of the trial with 52 weeks of exposure of 360 mg verapamil SR administered orally once daily (titrated over the first 3 months from 120 mg to 360 mg) has been chosen to align with the regulatory requirements from FDA and EMA.

40 participants on the control arm and 80 on the experimental arm (total of 120 subjects) are expected to complete the trial. We plan to randomise 138 participants in this trial (2:1 ratio) to compensate for an estimated drop-out rate of 15%.

The trial duration for the participants will be approximately 24 months, consisting of screening, randomisation, 12 months treatment period and an additional 12 months INNODIA follow-up.

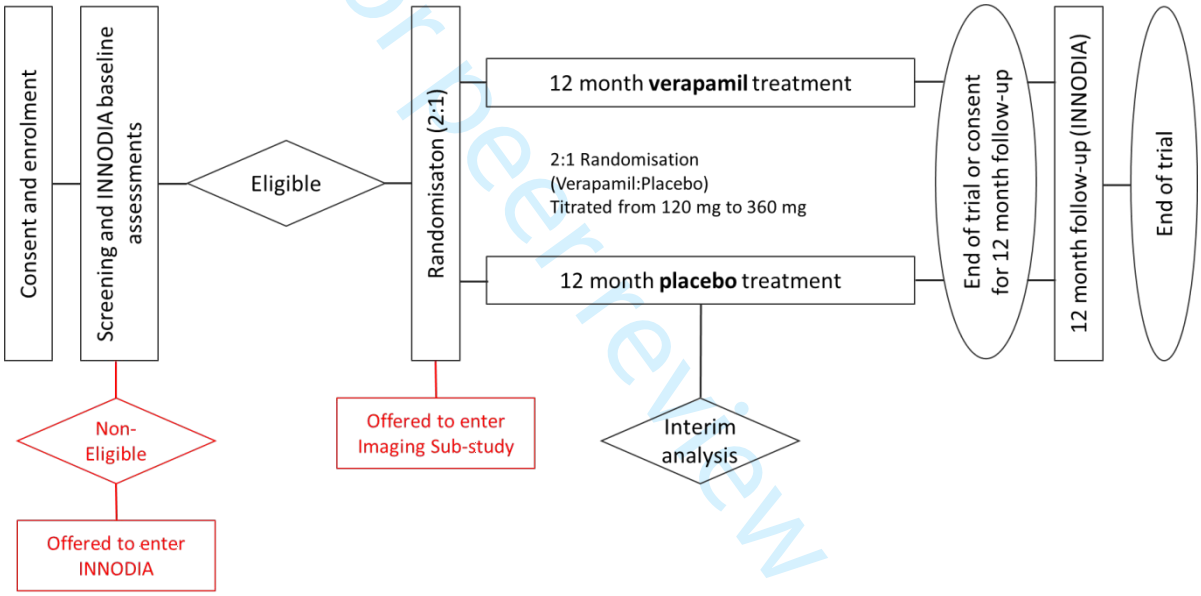


Figure 1: Trial Flow Chart

2. Summary of Responsibilities

2.1. Sponsor & IMP Management

The Medical University of Graz is the sponsor of this study. The sponsor is responsible for providing IMP and supporting documentation to the site.

The IMP management coordinates the supply of the study drug to each participating site. Contact details of the IMP management are available on the contact list.

2.2. Site Personnel

The site personnel, who can be either a pharmacist or study nurse/ coordinator or treating physician, delegated to manage IMP is responsible for the day-to-day activities involved in the IMP management including but not limited to:

For peer review only - http://bmjopen.bmj.com/site/about/guidelines.xhtml

- Receipt
- Storage
- Temperature monitoring
- Preparation
- Administration of IMPs to patients
- Accountability
- Destruction/ return of IMP
- Blinded archiving (Pharmacy File/Investigator Site File)

The site personnel is required to maintain adequate records of the IMP management and to ensure that copies are on file.

2.3. Principal Investigator

The PI maintains the overall responsibility of the study at his/her site to include delegation and oversight of IMP. The PI is responsible for ensuring all personnel involved in IMP receipt, storage, preparation and administration are trained, authorized and delegated on the Site Signature/Delegation Log.

The PI is responsible for ensuring the IMP is administered only to those patients under his or her personal supervision, or the supervision of a sub-investigator who has been appropriately trained and delegated, who meet the protocol requirements for IMP administration.

3. Subject Screening and Randomisation

3.1. Screening

At the screening visit, the local clinical trial team at each site will allocate a participant trial ID using the online eCRF. This ID number indicates which site this participant has been recruited from and stays with the participant for the duration of the study.
Once eligibility is confirmed, participants will be invited to the randomisation visit, where the randomisation session will be carried out.

3.2. Randomisation

The randomisation session will be carried out by the investigator and/or delegated site staff for all eligible subjects using a web-based platform (Randomizer®):

https://www.randomizer.at/random/login

To access the web-based randomisation system for the first time, you have to create a new user account by following the steps described in the **section "**Registration in Randomizer®".
In case a new study member needs to be provided with an account, they can request one by emailing the central coordination team: ver-a-t1d@medunigraz.at. Prior to access being granted, you must be authorized for this task by the Principal Investigator on the LOS_DOT Log. When a staff member leaves the trial, please request for their account to be deactivated by emailing the central coordination team: ver-a-t1d@medunigraz.at.

3.3. Registration in Randomizer®

To register in the Randomizer®, a new user account must be created. This must be done only once, before you first log in to the system.

To register:

1. Start your web browser and go to: https://www.randomizer.at/random/

For peer review only - http://bmjopen.bmj.com/site/about/guidelines.xhtml

2. Click "Register now!":

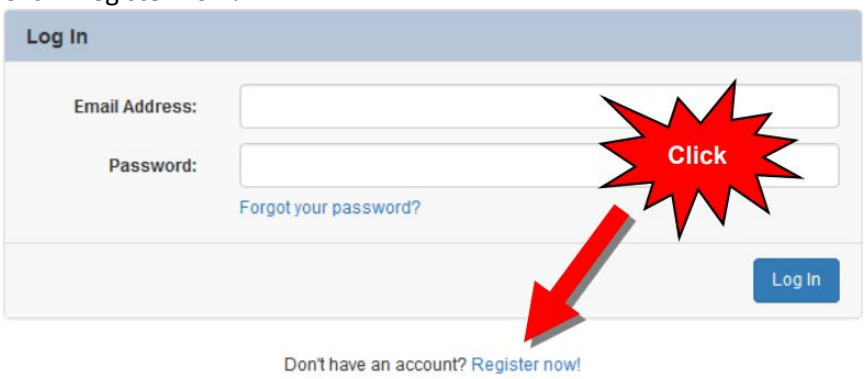


Figure 2: Randomizer® „Register now“

3. On the next page, fill in your personal details in the form shown (all fields marked with an asterisk (*) are mandatory), and choose a password. You will need your password later when you log in. To ensure that you entered your e-mail address and your password correctly, you must confirm this data by entering it again. Once the form has been completed, click Register.

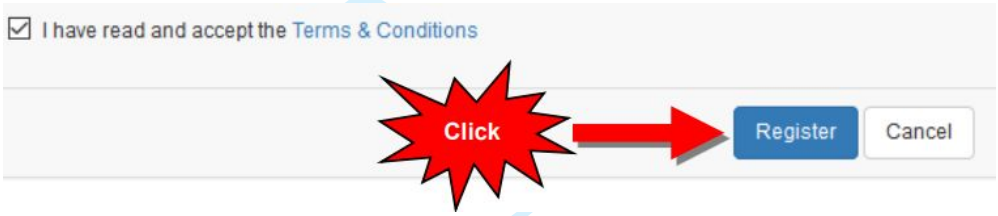


Figure 3: Randomizer® Registration

4. Your email address must now be confirmed. To do this, the Randomizer sends an auto-generated e-mail to the address provided during the registration process. The email with the subject Randomizer: Email Address Verification contains instructions on how to proceed, as well as a link that must be clicked in order for you to confirm your email address. Click on the link provided.

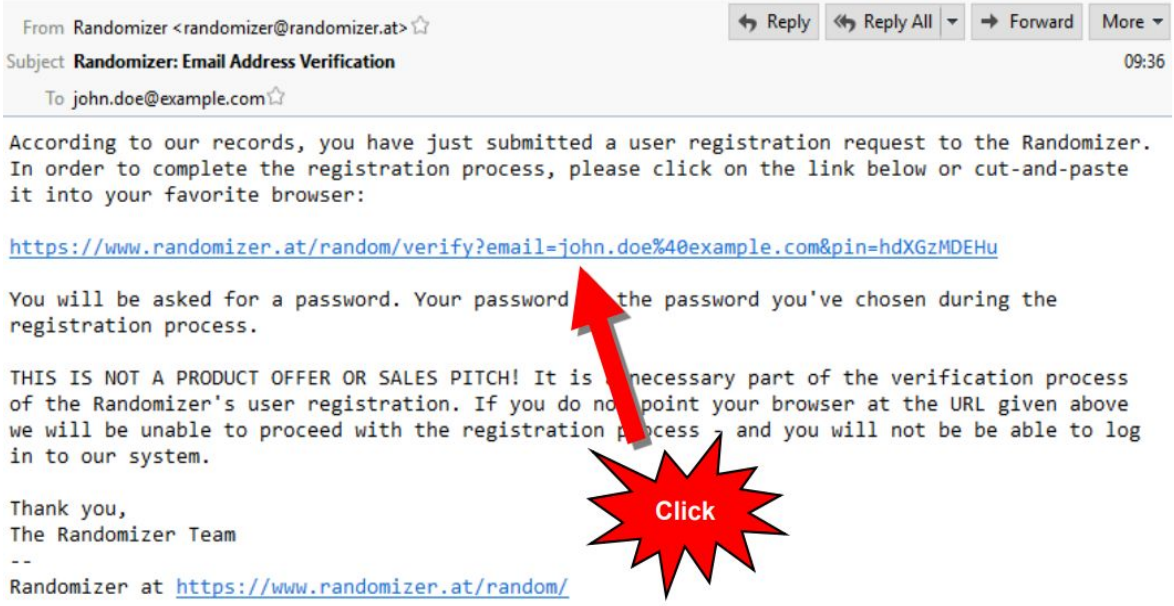


Figure 4: E-Mail confirmation link

5. After clicking the link, your web browser will open a new page titled Email Address Verification. In the form shown, the Email Address and PIN fields are already completed. Enter the password you provided during the registration process into the Password field and click “Verify Address”.

Figure 5: E-Mail verification

6. This completes the registration process. You will receive a confirmation email shortly with the subject Randomizer: Registration Confirmation.

3.4. Randomisation process

The randomisation should be performed:

- After the Principal Investigator (PI) or delegated investigator has reviewed the baseline data and confirmed the participant to be suitable for randomisation.
- PI or delegated investigator must complete the Checklist Ver-A-T1D Subject Identification Code list.
- The review should be documented in the source data (see **section 11** Data Management).
- Before the participant is due to receive their first study medication, allowing sufficient time for treatment preparation
- Randomise the participant according to the description below.

Randomisation

Perform randomisation online by following the next steps:

1.) Login on the web-based platform (Randomizer®) with your personal login data (https://www.randomizer.at/random/login)

2.) After you have logged in, you will see the Ver-A-T1D trial, if you have been granted access to it.

3.) Select the Ver-A-T1D trial by clicking on it, the name of the trial and your role will appear in the yellow bar on the top of the page

4.) Select “Randomise” from the menu bar on the left side of the page

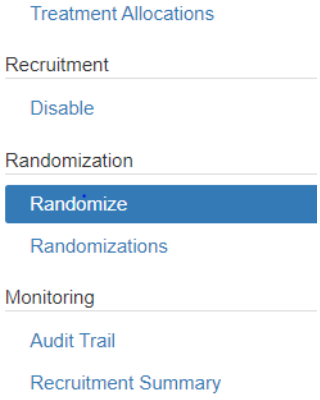


Figure 6: Randomizer® „menu bar“

For peer review only - http://bmjopen.bmj.com/site/about/guidelines.xhtml

A window with your site code and site name, where you can enter the unique subject-ID and additional comments if needed, shows up:

a. In the first row, usually you will be able to see the site code and name of your Site, in case it is different, please choose your site by clicking on the arrow
b. Enter the **last 4 digits of the subject-ID** (generated by the eCRF) in the subject-ID field
c. And finally, click "Randomise"

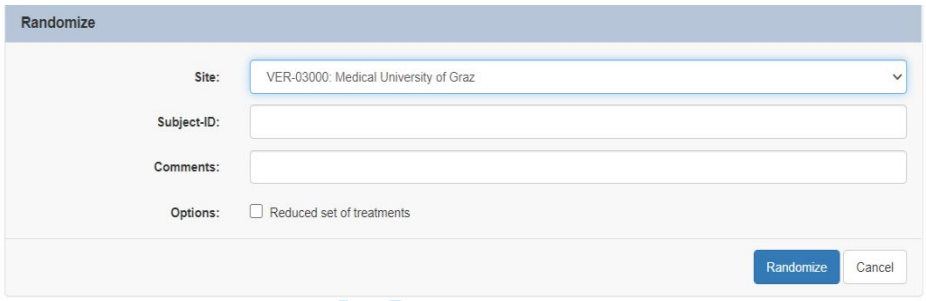


Figure 7: Site code

Participant randomisation (example)

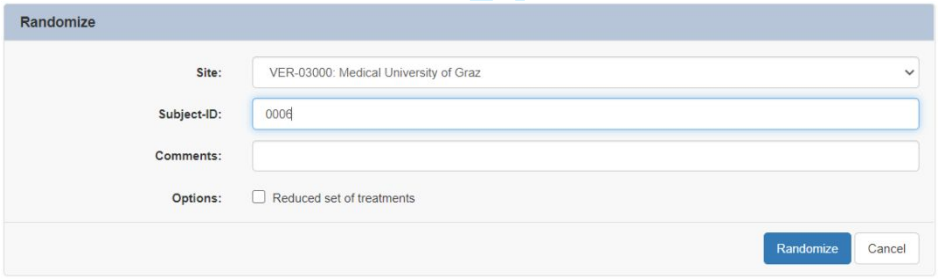


Figure 8: Subject-ID

A summary of the participant's data including the randomisation result is shown next

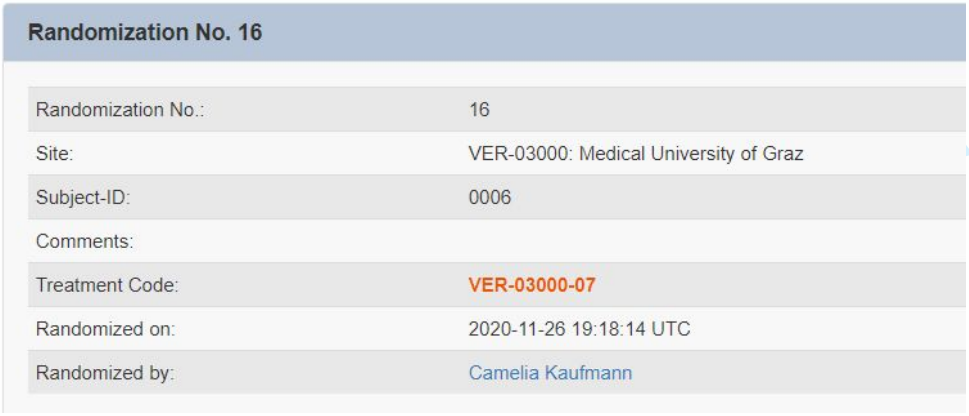


Figure 9: Summary of the participant's data

The randomisation result should be printed and filed in the ISF/ Pharmacy File.
Note: it is always possible to go back to see the randomisation result if not printed right away.

If a pharmacy department is involved, notification of the subject ID and treatment code will be made to the local pharmacy by email (e.g. send the printed page of the randomisation result). Additionally, if applicable, the local study team will send a trial prescription to their pharmacy department (Appendix 1).

For peer review only - http://bmjopen.bmj.com/site/about/guidelines.xhtml

3.5. Viewing Randomisations

To display the list of randomizations, choose the "Randomizations" link from the menu. Click on the page numbers below the list to step back and forward between pages, use the "Page Size" drop-down menu to change the number of randomizations displayed per page. The list is sorted by randomization number, use the "Sort" drop-down menu to switch between ascending sort order (i.e. oldest randomizations first) and descending sort order (i.e. newest randomizations first) and the "Group" drop-down menu to select a grouping criterion. Rejected randomizations are shown as strike-through. To display full randomization details, click on the "Details" link in each row. To download the list of randomizations as CSV file click on the "Export" link in the upper or lower right corner of the list.

Figure 10: Illustration of viewing randomizations

For peer review only

Emergency unblinding

It may be necessary to break a single randomisation blinding in case of emergency. Participant safety must always be the first consideration in making such a determination. The investigator decides if the unblinding of the randomisation of a participant has to be performed. The unblinding can be done by each study member, who has the right to perform randomisation, but only randomisations made by the user site can be unblinded.

To unblind a randomisation:

1.) First display the list of randomisations (using the "Randomisations" link from the menu)

2.) In the row corresponding to the randomisation to unblind, click on the "Unblind" link

3.) Enter a reason why you want to break the randomisation's blinding

4.) Confirm the operation by entering your password

5.) And finally, click on the "Unblind" button

The randomisation details, including the treatment name, will be displayed and users subscribed to unblind notifications will be notified.

If the code has been broken:

1.) The subject must be withdrawn from the trial and a withdrawal session must be completed in the eCRF

2.) The sponsor must be notified within 24 hours after breaking the blind ver-a-t1d@medunigraz.at

3.6. Editing Randomisations

To deal with data input errors and post-randomization exclusions (for example, when ineligible subjects are mistakenly randomized into a trial), the Randomizer offers a limited set of options for randomization modification. Using the “Edit” link in the list of randomizations – only available to users with the access right to edit randomizations – a randomization´s subject identification, comments and randomization tag can be changed, a randomization can be rejected, or, in double-blind trials, a replacement code can be requested.

Rejection means that the randomization remains in the database but is ignored when computing imbalance scores for further randomizations. A replacement code is a treatment code that maps to the same treatment as the code already allocated.

To modify a randomization click on the “Edit” link in the corresponding row in the list of randomizations. Then choose the type of modification to perform, enter the new data (if you are changing the randomization subject identification, comments or tag) and the reason why you want to modify the randomization. Finally, confirm the modification by entering your password and click “Save”. The updated randomization details will be displayed and users subscribed to modification notifications will be notified.

3.7. Accessing Online Help

To access the Randomizer online help after logging in, click on the "Help" link on the bottom of each page (and additionally, if you are logged in, in the upper right corner of each page). Online help is displayed in its own browser window, so make sure that your browser's popup blockers are set to allow popups for the Randomizer website.

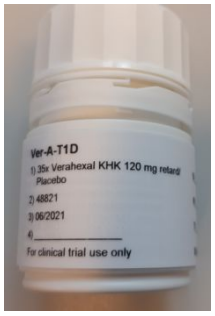
NOTE: For any questions or need of assistance regarding the Randomizer®, contact the central coordination team of the study: ver-a-t1d@medunigraz.at

For peer review only - http://bmjopen.bmj.com/site/about/guidelines.xhtml

4. Investigational Medicinal Product (IMP)

This section provides instruction for site and/or pharmacy staff involved in handling the IMP.

4.1. Introduction to IMP

	Test product	Placebo product
Name	Verapamil SR 120 mg (trade name: VeraHEXAL KHK 120 mg retard)	Placebo
Dosage form	Tablet	Tablet
Route of administration	Oral	Oral
Strength	120 mg	N/A
Packaging	Study intervention is provided in HDPE bottles. Each bottle is labelled with booklet labels including applicable text in the local languages and according to local requirements. Labels are blinded.  	
Content of each bottle	1 bottle contains 35 tablets	
Identifier	Each bottle is uniquely numbered within the trial with a Treatment Code.	
Storage requirements	Store between +15 °C to +25 °C, tightly closed.	

4.2. IMP Distribution

4.2.1. Initial shipment

The sponsor is responsible for providing IMP and supporting documentation to the site.
For supply questions to sponsor please e-mail to: Ver-A-T1D-Orders@medunigraz.at

The initial shipment of IMP will take place after all essential documents necessary for IMP release have been collected.
Initial shipment of IMP will be executed once the Regulatory Green Light (RGL) has been issued by the sponsor after site initiation.

For peer review only - http://bmjopen.bmj.com/site/about/guidelines.xhtml

The initial quantities of trial supplies are calculated based on the provided recruitment estimation from each site. Please note that these are expected quantities and changes may occur.
Maintaining sufficient stock of IMP at site is managed by the sites, the monitor and the IMP management.
Remain in frequent contact with your monitor and the IMP management during the recruitment and the treatment period of the trial, as the sponsor may need to change the supply strategy. Subject recruitment information is used to plan and calculate supplies and secure the resupply on an ongoing basis.
Please remember to inform Ver-A-T1D-Orders@medunigraz.at of the need for resupply at least four weeks in advance.

The IMP will be supplied by sponsor's distribution designee ABF Pharmaceutical Services GmbH (Brunner-Straße 63/18-19, 1230 Vienna, Austria). IMP will be shipped by **World Courier** to the site in validated shippers including a temperature monitoring device.

IMPORTANT: Shipments will be dispatched by ABF Pharmaceutical Services GmbH (ABF) only on **Monday, Tuesday** and **Wednesday.**

4.2.2. IMP receipt at site/pharmacy

The site/pharmacy must complete inventory and reconciliation of all IMP shipments as soon as the IMP is delivered to site. IMP cannot be administered until the inventory and product quality check is performed and verified.

IMP will be shipped and stored at ambient conditions (+15°C to +25°C). Each shipment of IMP to site contains a temperature monitoring device (TT Logger) and a Delivery note/Packing list (Ver-A-T1D_Delivery Note).

World Courier keeps the transport box and collects the TT logger after the delivery. ABF will receive the logger read-outs from the courier via e-mail. Site does not need to read out the logger. The temperature read-outs will be provided from ABF to site and should be filed appropriately in the ISF/ Pharmacy File. IMP from shipment should not be used until the temperature read-out has been received by site.

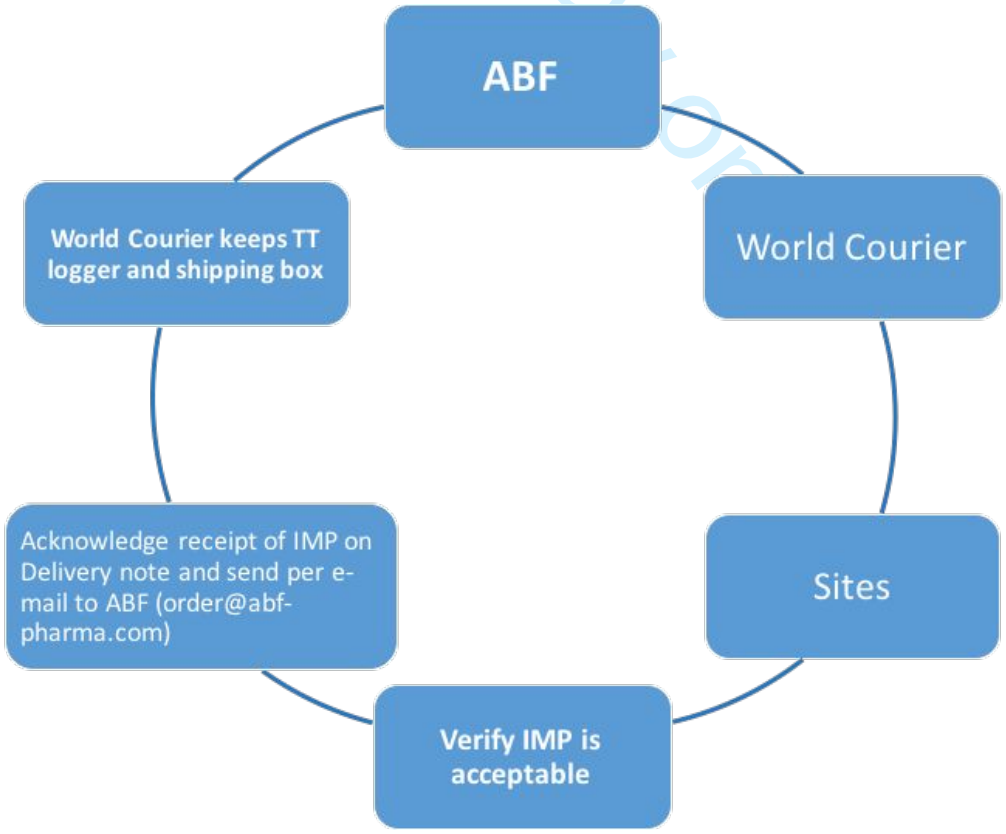


Figure 11: IMP distribution

For peer review only - http://bmjopen.bmj.com/site/about/guidelines.xhtml

The following must be done upon receipt of the IMP:

1	***SITE to investigate and verify:*** • Is it the right IMP and is the content correct (Batch numbers, quantities, treatment codes) as noted on shipping delivery note/packing list? • Has the IMP been received properly without any issues and undamaged? • Has the IMP been shipped at +15°C to +25°C?
2	***Temperature monitoring devise (TT logger):*** The temperature monitoring device (TT logger) will be stopped by Courier. Check for any alarm notifications should be performed. Transport box and logger will be returned to World Courier. Note: ABF will receive the logger read-outs from World Courier and provide to site and sponsor for filing purposes. In case any temperature deviations occur during the shipment the following steps must be followed: • Quarantine the product as temporarily unavailable, mark them visible and assign with **"IMP in QRT - received out of range"** and store in ambient temperature monitoring area. • **Contact ABF via email order@abf-pharma.com immediately and provide the completed and signed Delivery note.** • Please arrange with the IMP management Ver-A-T1D-Orders@medunigraz.at in case urgent supplies are required, as a shipment will NOT be raised automatically.
3	Acknowledge receipt by signing the shipment documents and email to ABF order@abf-pharma.com
4	Move the trial product to the dedicated storage facility.
5	Complete inventory documentation properly and file copies of all applicable documents in the appropriate section of the Investigator Site File or Pharmacy File.

If there are any discrepancies discovered upon receipt of the IMP, or if there is evidence of breakage, compromised storage conditions or product tampering:

- ABF/Sponsor must be promptly notified.
- The IMP must be quarantined and stored within +15°C to +25°C until further instructions are given.
- Any correspondence between the site/pharmacy personnel and the IMP supplier/ sponsor concerning compromised storage conditions upon delivery to the site must be documented and maintained with other accountability documentation in the Investigator Site File or Pharmacy File.

4.2.3. Storage of IMP

IMP must be stored in dedicated area with sufficient space, separated from marketed products and any returned trial products.
The trial products must be stored in a place with restricted access, for authorized personnel only.

For peer review only - http://bmjopen.bmj.com/site/about/guidelines.xhtml

The temperature during storage must be monitored using a temperature monitoring device or system. For a min/max thermometer, a copy of the handwritten log is to be reviewed, dated, signed and filed. For a continuous monitoring system, a monthly copy of the loggings is to be reviewed, dated, signed and filed.

If transfer between different long-term storage locations is required, the transfer time must be documented and the IMP must be transferred in an insulated box. Temperature logging is necessary if the transfer time exceeds 15 minutes. **Note:** This does not include the transfer from e.g. pharmacies to the ward on the day of IMP dispensing to the patients where no temperature logging is necessary.

4.2.4. Temperature Requirements for IMP

IMP must be stored at ambient temperature (+15°C to +25°C). The temperature should be monitored by recording actual, minimum, and maximum temperatures using a calibrated temperature monitoring device or system. The temperature should be evaluated and documented at least on working days on a temperature log. This log must be included in the Investigator Site File upon study termination.

Detailed instructions regarding appropriate temperature maintenance are described in the Summary of Product Characteristics (SmPC) (Appendix -2) and the Investigator's Brochure (IB). Temperature control must be maintained from the time of receipt of IMP until the product has been dispensed to the patient or is deemed no longer usable, unless otherwise specified in the protocol or by the sponsor.

- IMP must be maintained at temperatures between +15°C to +25°C.
- The IMP must not be frozen.
- The site/ pharmacy should have a system or procedure for identifying and alerting personnel when proper temperature storage conditions have been compromised.
- Temperature conditions must be monitored as evidenced by documentation on the study-specific logs (), data logger or site/pharmacy-specific logs that have previously approved for use in the study.
- Devices used to monitor temperature should be calibrated, within expiry date and correctly placed where IMP is stored.
- Calibration records should be provided to the site monitor for review.

4.2.5. Temperature Excursions

If storage conditions have been compromised (e.g. temperature excursions) or if there is any suspicion that IMP has not been stored properly, the following actions must be taken:

- **Contact the IMP manager and the site monitor immediately**
  - Complete Temperature Deviation Form:
    - Site name and number, responsible investigator
    - Description of the deviation (including the severity and the duration for the deviation), batch number, expiry number, treatment code, amount affected – and send the Temperature Deviation Form) to the sponsor by e-mail: Ver-A-T1D-Orders@medunigraz.at
  - Clearly mark and quarantine the compromised IMP; maintain it under appropriate storage conditions until further notice
  - Document the occurrence and action to be taken in a telephone contact or email summary of the discussion. File the correspondence with the IMP accountability documentation.

The sponsor will determine, based on the severity and length of temperature excursion, if the IMP can still be used. **The quarantine IMP is not to be used unless written documentation granting approval of usage is received from the sponsor.**

For peer review only

Expired/unused IMP must be separated from used IMP and placed in quarantine at +15°C to +25°C until monitor has verified drug accountability and sponsor has approved that the expired/unused IMP can be destroyed at the site or returned to ABF.

4.3. IMP preparation/dispensing

After completion of the randomisation session, perform the IMP preparation and dispensing.
The timing of clinical activities must be managed so that when the investigator has performed the randomisation of the patient, the responsible site/ pharmacy personnel will dispense/prepare the IMP. A second responsible site/ pharmacy personnel should perform a double check of proper dispensing/ preparation of IMP.

Before dispensing, ensure that:

1. trial ID is correct on the trial product label(s) and the study medication is not expired.
2. **site No. (e.g. VER-3000)**, **Physician's name**, **subject No. (last 4 digits)** and the **visit number** is **entered manually** on the labels.
3. the treatment code stated on the label(s) corresponds to the correct subject number.
4. the study medication has been stored according to the correct temperature requirements.
5. For pharmacies, sign and date the prescription (if applicable).

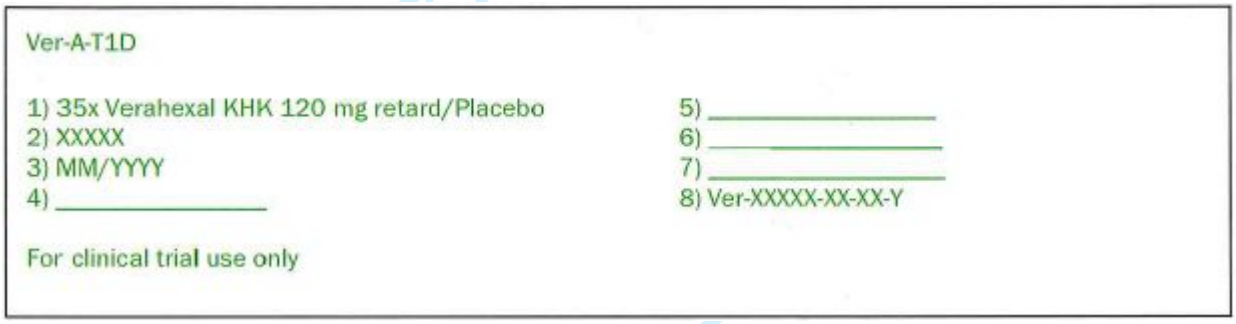


Figure 12: Label booklet cover page example (Line 4, 5, 6, 7 must be entered manually)

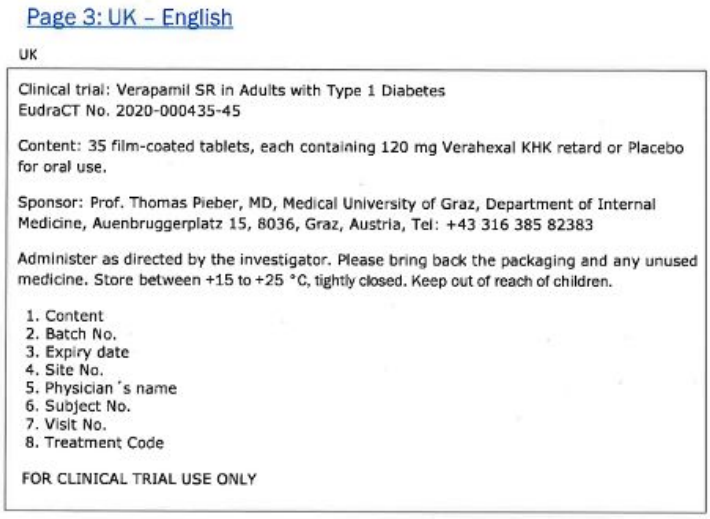


Figure 13: Label booklet text, example UK-English

For peer review only - http://bmjopen.bmj.com/site/about/guidelines.xhtml

Figure 14: Label booklet (page 2) contents list

For peer review only

4.3.1. Dispensing of IMP

IMP must only be dispensed by authorized and trained staff only. Study participants will be dosed as per the table below.

Table 1: IMP Trial Flow Chart

Trial period	**Consent and enrolment**	**Screening and baseline assessment**	**Randomisation**	**Treatment**								
Visit type (C: Clinic, P: Phone contact)	**C**	**C**	**C**	**P**	**C**	**P**	**C**	**P**	**C**	**C**	**C**	**C**
Visit number		**V-1**	**V0**	**P1**	**V1**	**P2**	**V2**	**P3**	**V3**	**V4**	**V5**	**V6**
Time line		**<6 weeks from diagnosis[b]**	**Day 0 (≤2 weeks from V-1)**	**Week 1**	**Week 4**	**Week 5**	**Week 8**	**Week 9**	**Month 3**	**Month 6**	**Month 9**	**Month 12**
Visit window (days)				**±2**	**±3**	**±2**	**±3**	**±2**	**±7**	**±7**	**±7**	**±7**
IMP dispensing			x		x		x		x	x	x	
IMP dose (once daily)			**120 mg**	**120 mg**	**240 mg**	**240 mg**	**360 mg**	**360 mg**	**360 mg**	**360 mg**	**360 mg**	**360 mg**
Amount of bottles to be dispensed*			**1**		**2**		**3**		**9**	**9**	**9**	
Drug accountability			x		x		x		x	x	x	x

*The IMP is provided in bottles. 1 bottle contains 35 tablets. For IMP dispensing the treatment regimen given in the table below, must be followed.
There are 6 dispensing visits: V0, V1, V2, V3, V4, V5.

For peer review only - http://bmjopen.bmj.com/site/about/guidelines.xhtml

Table 2: Treatment Regimen

	VeraHEXAL KHK 120 mg retard	Placebo
Frequency	Once daily	Once daily
Route of administration	Oral	Oral
Ingestion time	Morning or evening	Morning or evening
Titration regimen**	120 mg from week 1-4 240 mg from week 5-8 360 mg from week 9-52	120 mg placebo from week 1-4 240 mg placebo from week 5-8 360 mg placebo from week 9-52
Packaging form	35 tablets per bottle	
Dose formulation and unit dose strength	Tablet 120 mg	N/A

** In case of intolerable IMP side effects related to the dose escalation it is acceptable to maintain current IMP dose and postpone escalation by 1 month. If 360 mg IMP is not tolerated due to side effects, the dose can be reduced to 240 mg, which is considered to be the lowest acceptable dose. If 240 mg IMP is not tolerated, the subject must be withdrawn.

NOTE:

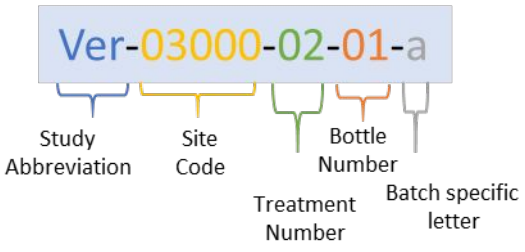
- Participants must be instructed in how to take the study medication.
- Participants must be informed labelling information should be kept intact as the information is needed for documentation purposes after return of the product.
- Participants should be instructed to return all used, partly used and unused trial products, including empty packaging material for drug accountability.

Document the dispensing of the trial product in the Subject Drug Accountability log and Stock Sheet.

Treatment Code

The Treatment Code (see example below) on the label consists of the abbreviation of the study code, site code, Treatment number, bottle number (1-33) and an additional batch specific letter. The Treatment number is assigned through the randomization and it is not the same number as the subject ID.[1]

Figure 15: Example Treatment Code



[1] Please check correct code

For peer review only - http://bmjopen.bmj.com/site/about/guidelines.xhtml

4.4. IMP accountability and return

Accountability of IMP must be documented from the time of initial IMP receipt to final disposition of IMP at the site. The Drug Accountability Log and the Stock Sheet must be accurate and up to date and maintained throughout the course of the study.
In case the pharmacy/site prefers to use their own templates, a template log should be provided before the start of the study. The monitor will confirm if all necessary information is captured, will seek for approval with the Sponsor.

The monitor will be responsible to review drug accountability and administration, to assess if all IMP handling procedures have been performed according to study protocol.

Collect returned (used and unused) trial products. Perform drug accountability for used, returned, damaged and expired trial products in the subject drug accountability log. Compliance will be assessed by counting the returned tablets and documenting data in subject drug accountability log. Trial products not returned should be accounted for as 'Lost'.

Used trial product, returned trial product, expired or damaged trial product can be stored at room temperature (no temperature control) and must be stored separately from trial products available for dispensing until reconciled by the monitor.

At site closure, drug accountability must be performed for all remaining trial products present at site.

4.5. IMP destruction

Before destruction, all received trial products must be accounted for by site staff and reconciled by the monitor.
Trial products must be destroyed in agreement and after written confirmation with the sponsor only. Destruction of trial products can be performed on an on-going basis, unless other agreements have been made with the monitor according to local procedures. Destruction of products must be documented.

4.6. IMP recall

In the case of IMP recall, specific procedures for return of IMP will be conducted in compliance with the Sponsor or IMP depot's (ABF) instructions.

4.7. Requesting IMP supplies

Study drug will be shipped to the study sites regularly throughout the study, as needed, based upon actual and anticipated use and expiry of the study drug. There will be an anticipated 1 – 3 site shipments throughout the trial conduct.
The pharmacist or designee should contact the IMP management for any questions related to IMP supply.

NOTE: Maintaining sufficient stock of IMP at site is managed by the sites, the monitor and the IMP management. Remain in frequent contact with your monitor and the IMP management (Ver-A-T1D-Orders@medunigraz.at) during the recruitment and the treatment period of the trial, as the sponsor may need to change the supply strategy. Subject recruitment information is used to plan and calculate supplies and secure the re-supply on an on-going basis.
Please remember to inform Ver-A-T1D-Orders@medunigraz.at of the need for re-supply in due time.

For peer review only - http://bmjopen.bmj.com/site/about/guidelines.xhtml

4.8. **Relabelling**

The stock may require relabelling due to extension of shelf-life. This process will require completion at the site pharmacy with labels provided as below.

ABF will provide the new labels and send them to the Trial Sites. The sponsor will provide a trial specific SOP (including form for logging the relabelling). The site pharmacy needs to return any unused labels, together with the completed and signed relabelling form to the sponsor, to confirm the relabelling has been completed.

For peer review only

5. APPENDICES

Appendix 1 Ver-A-T1D_Clinical trial prescription

A randomised, double-blind, placebo controlled, parallel group, multi-centre trial in adult sub-jects with newly diagnosed type 1 diabetes mellitus investigating the effect of Verapamil SR on preservation of beta-cell function (Ver-A-T1D)

Clinical Trial Prescription
(Ver-A-T1D)

Principal Investigator: _____

(attach addressograph)
Subject name:

Hospital no:

Address:

DOB:

Subject study ID: _____

Visit number: _____

Please dispense _____ (number of bottles) of VeraHEXAL KHK 120 mg retard or Placebo.

Doctor's signature: _____ Date: _____ Ext: _____

Doctor's name *(please print)* _____

FOR PHARMACY USE ONLY

Dispensed by: ……..…… Date: ……...……..

Checked by: ……..…….. Date: ……...……...

Collected/received by: ..... (name) Signature: .....

Role: ..... Date: ..... & Time: .....

Please retain and file in pharmacy site file

For peer review only - http://bmjopen.bmj.com/site/about/guidelines.xhtml

Appendix2: SmPC of VeraHEXAL

English translation of the SmPC of VeraHEXAL approved in Germany[1]

SUMMARY OF PRODUCT CHARACTERISTICS

1. NAME OF THE MEDICINAL PRODUCT

VeraHEXAL® 40 mg film-coated tablets
VeraHEXAL® 80 mg film-coated tablets
VeraHEXAL® 120 mg film-coated tablets
VeraHEXAL® 120 mg retard hard capsules, retarded
VeraHEXAL® 180 mg retard hard capsules, retarded
VeraHEXAL® 240 mg retard hard capsules, retarded
VeraHEXAL® KHK 120 mg retard retard tablets
VeraHEXAL® RR 240 mg retard retard tablets

Verapamil hydrochloride

2. QUALITATIVE AND QUANTITATIVE COMPOSITION

VeraHEXAL 40
1 film-coated tablet contains 40 mg verapamil hydrochloride
Excipient with known effect: lactose monohydrate

VeraHEXAL 80
1 film-coated tablet contains 80 mg verapamil hydrochloride
Excipient with known effect: lactose monohydrate

VeraHEXAL 120
1 film-coated tablet contains 120 mg verapamil hydrochloride
Excipient with known effect: lactose monohydrate

VeraHEXAL 120 mg retard
1 retarded-release hard capsule contains 120 mg verapamil hydrochloride
Excipient with known effect: sucrose

VeraHEXAL 180 mg retard
1 retarded-release hard capsule contains 180 mg verapamil hydrochloride
Excipient with known effect: sucrose

VeraHEXAL 240 mg retard
1 retarded-release hard capsule contains 240 mg verapamil hydrochloride
Excipient with known effect: sucrose

VeraHEXAL KHK 120 mg retard
1 retard tablet contains 120 mg verapamil hydrochloride
Excipient with known effect: lactose monohydrate

VeraHEXAL RR 240 mg retard
1 retarded tablet contains 240 mg verapamil hydrochloride
Excipient with known effect: lactose monohydrate

For a full list of excipients, see section 6.1

[1] German Federal Institute for Drugs and Medical Devices (BfArM). VeraHEXAL® [Fachinformation, 13. 10. 2016]. Accessed 2 December 2020. Available from https://www.pharmnet-bund.de

Page 1 of 19

3. PHARMACEUTICAL FORM

VeraHEXAL 40/ -80/ -120
Film-coated tablets

VeraHEXAL 40 is a white, round, biconvex film-coated tablet.

VeraHEXAL 80 is a white, round, biconvex film-coated tablet, with a score line on one side. The film-coated tablet can be divided into equal doses.

VeraHEXAL 120 is a white, round, biconvex film-coated tablet, with a score line on one side. The score line is only to facilitate breaking for ease of swallowing and not to divide into equal doses.

VeraHEXAL 120 mg retard/ -180 mg retard/ - 240 mg retard
Hard capsule, retarded

VeraHEXAL 120 mg retard is a capsule with a pink-coloured cap and body, filled with white to yellowish pellets.

VeraHEXAL 180 mg retard is a capsule, one half transparent, the other reddish-brown, filled with white to yellowish pellets.

VeraHEXAL 240 mg retard is a capsule with a reddish-brown cap and body, filled with white to yellowish pellets.

VeraHEXAL KHK 120 mg retard/ - RR 240 mg retard
Retard tablets

VeraHEXAL KHK 120 mg retard is a beige to ochre, round retard tablet, with a score line on one side.
The score line is only to facilitate breaking for ease of swallowing and not to divide into equal doses.

VeraHEXAL RR 240 mg retard is a green, oblong, slightly biconvex retard tablet, with a score line on both sides.
The retard tablet can be divided into equal doses.

4. CLINICAL PARTICULARS

4.1 Therapeutic indications

- Symptomatic coronary heart disease:
  - Chronic stable angina pectoris (angina of effort)
  - Unstable angina pectoris (crescendo angina, angina at rest)
  - Vasospastic angina pectoris (Prinzmetal's angina, variant angina)
  - Angina pectoris in post myocardial infarction status in patients without cardiac insufficiency, when beta blockers are not indicated.
- Heart rate disorders in:
  - paroxysmal supraventricular tachycardia
  - atrial fibrillation/atrial flutter with fast AV conduction (except in WPW syndrom or Lown Ganong Levine syndrome, see section 4.3).
- Hypertension

4.2 Posology and method of administration

<u>Posology</u>

For peer review only - http://bmjopen.bmj.com/site/about/guidelines.xhtml

Verapamil hydrochloride, the active substance of VeraHEXAL, should be dosed on an individual basis, depending on the severity of the disease. Long-standing clinical experience shows that the average dose in almost all indications is between 240 mg and 360 mg daily.

A daily dose of 480 mg should not be exceeded as long-term therapy. It may be increased for a short period.

Unless otherwise prescribed, the following dosage guidelines apply:

POSOLOGY	**VeraHEXAL 40** **VeraHEXAL 80** **VeraHEXAL 120** Film-coated tablets	**VeraHEXAL 120 mg retard** **VeraHEXAL 180 mg retard** Hard capsule, retarded **VeraHEXAL KHK 120 mg retard** Retard tablets	**VeraHEXAL 240 mg retard** Hard capsule, retarded **VeraHEXAL RR 240 mg retard** Retard tablets
Adults and adolescents weighing over 50 kg			
Coronary heart disease	**Recommended dosage:** [1,2] (120)–240–480 mg verapamil hydrochloride daily in 3 – 4 single doses	**Recommended dosage:** [3] 240–480 mg verapamil hydrochloride daily in 2 single doses	
Hypertension	**Recommended dosage:** [1,2] (120)–240–360 mg verapamil hydrochloride daily in 3 single doses	**Recommended dosage:** 240–480 mg verapamil hydrochloride daily in 2 single doses	**Recommended dosage:** 240–480 mg verapamil hydrochloride daily in 1 – 2 single doses (1 single dose in the morning; 1 additional single dose in the evening in case of inadequate efficacy)
Paroxysmal supraventricular tachycardia, atrial fibrillation/ atrial flutter	**Recommended dosage:** [1,2] (120)–240–480 mg verapamil hydrochloride daily in 3 – 4 single doses	**Recommended dosage:** [3] 240–480 mg verapamil hydrochloride daily in 2 single doses	
Children (only in the case of heart rate disorders)			
Older pre-school children up to 6 years of age	**Recommended dosage:** 80–120 mg verapamil hydrochloride daily in 2 – 3 single doses		
School children aged 6 – 14 years	**Recommended dosage:** [4] 80–360 mg verapamil hydrochloride daily in 2 – 4 single doses		

[1] The use of VeraHEXAL 40 is indicated in patients in whom adequate efficacy can already be expected at low doses (e.g. in patients with liver function disorders or elderly patients).
[2] VeraHEXAL 120 is indicated if adequate efficacy has not been achieved with lower doses (e.g. 240 mg verapamil hydrochloride daily).
[3] Vera HEXAL 240 retard/ - RR 240 retard is indicated if adequate efficacy has not been achieved with lower doses (e.g. 240 mg verapamil hydrochloride daily)
[4] VeraHEXAL 80/ -120 is indicated in school children if adequate efficacy has not been achieved with lower doses (e.g. 80 – 120 mg verapamil hydrochloride daily)

Children and adolescents

The safety and efficacy of verapamil retard tablets in children and adolescents has not been established. Data are not yet available.

For peer review only - http://bmjopen.bmj.com/site/about/guidelines.xhtml

For all pharmaceutical forms:

Impaired kidney function
The information currently available is described in section 4.4. Caution should be exercised when administering verapamil hydrochloride to patients with impaired kidney function. Strict monitoring is required.

Impaired liver function
In patients with impaired liver function, depending on the severity, the effect of verapamil hydrochloride is potentiated and prolonged because of delayed metabolism of the drug. Therefore, in such cases the dosage needs to be adjusted with special caution, starting with low doses (e.g. in patients with liver function disorders initially 2 to 3 times daily 40 mg verapamil hydrochloride, corresponding to 80 mg – 120 mg verapamil hydrochloride daily), see also section 4.4.

Method of administration

The product should be taken without sucking or chewing, with sufficient liquid (e.g. with 1 glass of water, no grapefruit juice!) preferably with or shortly after meals.

VeraHEXAL should not be taken in the lying position.

Verapamil hydrochloride can be used in patients with angina pectoris after myocardial infarction only 7 days after the acute myocardial event.

The duration of administration is not limited.

After long-term therapy, VeraHEXAL should not be discontinued abruptly but gradually decreased.

4.3 Contraindications

Verapamil should not be used in case of:

- Hypersensitivity (allergy) to the active substance verapamil hydrochloride or to any of the excipients of VeraHEXAL listed in section 6.1
- Cardiovascular shock
- Pronounced disturbances in stimulus conduction (e.g. second- and third-degree SA or AV block; except in patients with a pacemaker)
- Sick sinus syndrome (except in patients with a pacemaker)
- Heart failure with a reduced ejection fraction of less than 35% and/or pulmonary wedge pressure above 20 mmHg (unless secondary to supraventricular tachycardia which responds to verapamil)
- Atrial fibrillation/flutter and concomitant presence of an accessory bypass tract (e.g. WPW or Lown Ganong Levine syndromes). These patients are at greater risk of developing ventricular tachycardia, including ventricular fibrillation if verapamil is administered
- Concomitant administration of ivabradin (see section 4.5)

Beta blockers should not be administered intravenously at the same time as treatment with verapamil (except in intensive care medicine) (see also section 4.5).

For peer review only - http://bmjopen.bmj.com/site/about/guidelines.xhtml

4.4 Special warnings and precautions for use

Acute myocardial infarction
Use VeraHEXAL with caution in acute myocardial infarction with complications (bradycardia, hypotension and left heart failure).

Conduction disorders / first-degree AV block/bradycardia/asystole
Verapamil hydrochloride affects the AV and sinus nodes and prolongs AV conduction time. Use with caution as the onset of second- or third-degree AV block (contraindication) or unifascicular, bifascicular or trifascicular bundle branch block may warrant discontinuation of verapamil hydrochloride and the initiation of appropriate therapy, if required.

Verapamil hydrochloride affects AV and sinus nodes and can in rare cases trigger second- or third-degree AV block, bradycardia or, in extreme cases, asystole. This is more likely to occur in patients with sick sinus syndrome, which is more common in elderly patients.

Asystole in patients not suffering from sick sinus syndrome is usually of short duration (a few seconds or less) with a spontaneous return to AV nodal or normal sinus rhythm. If this does not occur promptly, appropriate therapy should be initiated without delay, also see section 4.8.

Antiarrhythmic agents, beta blockers and inhalation anaesthetics
Antiarrhythmic agents (e.g. flecainide, disopyramide), beta receptor blockers (e.g. metoprolol, propranolol) and inhalation anaesthetics may mutually potentiate the cardiovascular effects (severe AV block, substantial drop in heart rate, onset of heart failure, increased hypotension) if administered concomitantly with verapamil hydrochloride (see also section 4.5).

Asymptomatic bradycardia (36 bpm) was observed in one patient fitted with a wandering atrial pacemaker who received eye drops containing timolol (a beta blocker) and verapamil concomitantly.

Digoxin
Digoxin dose levels should be reduced if administered concomitantly with verapamil, also see section 4.5.

Heart failure
Heart failure patients with an ejection fraction higher than 35% should be compensated before starting verapamil treatment and adequately treated throughout.

HMG-CoA reductase inhibitors ("statines")
See section 4.5

Diseases with impaired neuromuscular transmission
Verapamil should be used with caution in the presence of diseases adversely affecting neuromuscular transmission (Myasthenia gravis, Lambert-Eaton syndrome, progressive Duchenne muscular dystrophy).

Hypotension
Particularly strict monitoring is required in the case of hypotension (less than 90 mmHg systolic).

Further information

Specific patient groups

For peer review only - http://bmjopen.bmj.com/site/about/guidelines.xhtml

Impaired kidney function
Although in comparison studies it has been reliably shown that impaired renal function in patients with terminal kidney failure has no influence on the pharmacokinetics of verapamil, individual case reports suggest that verapamil should be used only with caution and under careful supervision (ECG, blood pressure) in patients with impaired renal function.

Verapamil cannot be removed through haemodialysis.

Impaired liver function
Exercise caution when administering to patients with severely impaired liver function (see also section 4.2).

Additional for VeraHEXAL 40/- 80/- 120/- KHK 120 mg retard/- RR 240 mg retard
Patient with rare hereditary galactose intolerance, lactase deficiency or glucose-galactose malabsorption should not take VeraHEXAL 40/- 80/- 120/- KHK 120 mg retard and RR 240 mg retard.

Additional for VeraHEXAL 120 mg retard/- 180 mg retard/- 240 mg retard
Patient with rare hereditary fructose intolerance, glucose-galactose malabsorption or saccharase-isomaltase deficiency should not take VeraHEXAL 120 mg retard/- 180 mg retard and - 240 mg retard.

4.5 Interaction with other medicinal products and other forms of interaction

In-vitro studies have shown that verapamil hydrochloride is metabolised by cytochrome P450 isoenzymes CYP3A4, CYP1A2, CYP2C8, CYP2C9 and CYP2C18. Verapamil inhibits CYP3A4 and P-glycoprotein (P-gp).

Clinically significant interactions have been reported with CYP3A4 inhibitors, causing elevated verapamil hydrochloride plasma levels, while CYP3A4 inducers have lowered plasma levels of verapamil hydrochloride. Patients should therefore be monitored for drug interactions.

Potential pharmacokinetic interactions are listed in the following table:

Potential interactions, related to CYP P450		
Concomitant medication	**Potential effect on verapamil or concomitant medication**	**Comment**
Alpha blockers		
Prazosin	↑ prazosin c_{max} (~ 40%) no effect on half-life	Additive hypotensive effect
Terazosin	↑ terazosin AUC (~ 24%) and (25%)	
Antiarrhymics		
Flecainide	Minimal effect on flecainide plasma clearance (< ~ 10%); no effect on verapamil plasma clearance	Further information (see section 4.4 – Antiarrhythmics, beta receptor blockers and inhalation anaesthetics)
Quinidine	↑ (~ 35%) oral quinidine clearance	Hypotension Pulmonary oedema may develop in patients with hypertrophic obstructive cardiomyopathy
Amiodarone	Increase in amiodarone plasma levels	
Antiasthmatics		

For peer review only - http://bmjopen.bmj.com/site/about/guidelines.xhtml

Theophylline	Oral and systemic clearance ↓ by ~ 20%	Clearance reduction was less marked in smokers (~ 11%)
Anticonvulsants/antiepileptics		
Carbamazepine	Carbamazepine AUC ↑ (~ 46%) in refractory partial epilepsy patients	Increased carbamazepine levels
	Reduction in verapamil hydrochloride plasma levels	This may trigger carbamazepine side effects such as diplopia, headaches, ataxia or dizziness/drowsiness
Phenytoin	Verapamil plasma concentrations ↓	
Antidepressants		
Imipramine	Imipramine AUC ↑ (~ 15%)	No effect on the levels of the active metabolite, desipramine
	Increase in verapamil hydrochloride plasma levels	
Antidiabetics		
Glibenclamide	↑ glibenclamide c_{max} (~ 28%) and AUC (~ 26%)	
	Increase in verapamil hydrochloride plasma levels	
Anti-gout drugs		
Colchicine	↑ in colchicine AUC (~ 2.0-fold) and c_{max} (~ 1.3-fold)	Reduction in Colchicin des (concomitant administration of colchicine and verapamil hydrochloride is not recommended)
Anti-infectives		
Clarithromycin	Possible ↑ in verapamil levels	
Erythromycin	Possible ↑ in verapamil levels	
Rifampicin	↓ in verapamil AUC (~ 97%), c_{max} (~ 94%) and oral bioavailability (~ 92%) following oral administration of verapamil	Blood pressure lowering effect may be reduced
	No change in PK following intravenous administration of verapamil	
Telithromycin	Possible ↑ in verapamil levels	
Antineoplastics		
Doxorubicin	↑ in doxorubicin AUC (104%) and c_{max} (61%) following oral administration of verapamil	In patients with small cell lung cancer
	No significant changes in doxorubicin PK following intravenous verapamil administration	In patients with advanced tumours
Azole fungistatics		
Clotrimazole	Increase in verapamil hydrochloride plasma levels	
Ketoconazole	Increase in verapamil hydrochloride plasma levels	
Itraconazole	Increase in verapamil hydrochloride plasma levels	
Barbiturates		
Phenobarbital	↑ in clearance of oral verapamil (~ 5-fold)	
Benzodiazepines and other anxiolytics		
Buspirone	↑ in buspirone AUC and c_{max} (~ 3.4-fold)	
	Increase in verapamil hydrochloride plasma levels	

For peer review only - http://bmjopen.bmj.com/site/about/guidelines.xhtml

Midazolam	↑ in midazolam AUC (~ 3-fold) and c_{max} (~ 2-fold)	
	Increase in verapamil hydrochloride plasma levels	
Beta blockers		
Metoprolol	In patients with Angina pectoris ↑ in metoprolol AUC (~ 32.5%) and c_{max} (~ 41%)	See section 4.4
	Increase in verapamil hydrochloride plasma levels	
Propranolol	In patients with Angina pectoris ↑ in propranolol AUC (~ 65%) and c_{max} (~ 94%)	
	Increase in verapamil hydrochloride plasma levels	
Cardiac glycosides		
Digitoxin	↓ total clearance (~ 27%) and extrarenal clearance (~ 29%) of dogitoxin	
Digoxin	In healthy subjects: ↑ in digoxin c_{max} (~ 44 %), ↑ in digoxin $c_{12\,h}$ (~ 53%), ↑ in digoxin c_{ss} (~ 44%) and ↑ digoxin AUC (~ 50%)	Reduce the digoxin dose, see also section 4.4
H2 receptor antagonists		
Cimetidine	AUC of R- (~ 25%) and S-verapamil (~ 40%) with corresponding ↓ in R- and S-verapamil clearance	Cimetidine reduces verapamil clearance following intravenous verapamil administration
Immunologics/immunsuppressants		
Ciclosporin	↑ ciclosporin AUC, c_{ss}, c_{max} (~ 45 %)	
Everolimus	↑ in everolimus AUC (~ 3.5-fold) and c_{max} (~ 2.3-fold), ↑ in verapamil c_{trough} (~ 2.3-fold)	Concentration determination and dose adjustment of everolimus may be necessary
Sirolimus	↑ in sirolimus AUC (~ 2.2-fold); ↑ in S-verapamil AUC (~ 1.5-fold)	Concentration determination and dose adjustment of sirolimus may be necessary
Tacrolimus	Possible ↑ in tacrolimus levels	
Lipid-lowering agents/HMG-CoA reductase inhibitors		
Atorvastatin	Possible ↑ in atorvastatin levels ↑ in verapamil AUC (~ 43%)	For further information see below
Lovastatin	Possible ↑ in lovastatin levels ↑ in verapamil AUC (~ 63%) and c_{max} (~ 32%)	
Simvastatin	↑ in simvastatin AUC (~ 2.6-fold) and c_{max} (~ 4.6-fold)	
Serotonin receptor agonists		
Almotriptan	↑ in almotriptan AUC (~ 20%) and c_{max} (~ 24%)	
	Increase in verapamil hydrochloride plasma levels	
Uricosurics		
Sulfinpyrazone	↑ in verapamil oral clearance (~ 3-fold), ↓ bioavailability (~ 60%)	Blood pressure lowering effect may be reduced

For peer review only - http://bmjopen.bmj.com/site/about/guidelines.xhtml

	No change in PK with intravenous verapamil administration	
Other		
Grapefruit juice	↑ in AUC of R- (~ 49%) and S-verapamil (~ 37%) ↑ in c_{max} of R- (~ 75%) and S-verapamil (~ 51%)	Elimination half-life and renal clearance unaffected. Consumption of food and beverages containing grapefruit juice should be avoided during the administration of verapamil.
St. John's Wort	↓ in AUC of R- (~ 78%) and S-verapamil (~ 80%) with corresponding reduction in c_{max}	

Other interactions and additional information

HIV antiviral agents

Due to the inhibitory potential of some HIV antiviral agents such as ritonavir, verapamil plasma concentrations may increase. Caution should therefore be exercised and verapamil dose levels decreased, if necessary.

Similarly, verapamil hydrochloride may lead to an increase in the plasma levels of these medicinal products by affecting their metabolic degradation.

Lithium

Increased sensitivity to the effects of lithium (neurotoxicity) has been reported during concomitant administration of verapamil hydrochloride and lithium, with either no change or an increase in lithium levels.

The administration of verapamil has, however, also resulted in the lowering of serum lithium levels in patients receiving long-term oral lithium therapy. Patients receiving both active substances should therefore be strictly monitored.

Muscle relaxants

Both clinical and experimental animal data show that verapamil hydrochloride may potentiate the activity of muscle relaxants (Curare-type and depolarising). The dose of verapamil and/or of the muscle relaxant may have to be reduced when both are administered concomitantly.

Acetyl salicylic acid

Increased tendency to bleed.

Ethanol (alcohol)

Delayed ethanol degradation and increase of ethanol plasma levels, hence the effect of alcohol is potentiated by verapamil.

HMG-CoA reductase inhibitors (statins)

In patients who take verapamil, treatment with an HMG-CoA reductase inhibitor (e.g. simvastatin, atorvastatin or lovastatin) should start at the lowest possible dose and be up-titrated. If a treatment with verapamil is added to an existing therapy with HMG-CoA reductase inhibitors (e.g. simvastatin, atorvastatin or lovastatin), a reduction in the statin dose should be considered, with back-titration against the serum cholesterol concentration.

When verapamil and simvastatin at higher doses are used at the same time, the risk of myopathy/rhabdomyolysis increases. The simvastatin dose should be adjusted accordingly (see manufacturer's production information; see also section 4.4).

For peer review only - http://bmjopen.bmj.com/site/about/guidelines.xhtml

Fluvastatin, pravastatin and rosuvastatin are not metabolised through cytochrome P450 isoenzyme CYP3A4. An interaction with verapamil is less likely.

Antihypertensives, diuretics, vasodilators

Potentiation of the antihypertensive effect with the risk of excessive lowering of blood pressure.

Antiarrhythmics (e.g. flecainide, disopyramide), beta receptor blockers (e.g. metoprolol, propranolol), inhalation anaesthetics

Mutual potentiation of cardiovascular effects (severe AV block, substantial decrease in heart rate, onset of heart failure, marked hypotensive effect).

Beta receptor blockers should not be administered concomitantly via the intravenous route to patients during intravenous verapamil hydrochloride therapy (exception: intensive care medicine, see also section 4.3). The concomitant administration of intravenous verapamil hydrochloride and anti-adrenergic active substances may lead to an excessive lowering of blood pressure. The risk of these undesirable effects is increased following the concomitant administration of intravenous beta blockers or disopyramide with intravenous verapamil, especially in patients with pre-existing cardiovascular diseases such as severe cardiomyopathy, congestive heart failure or recent myocardial infarction, because both drug classes suppress myocardial contractility and AV conduction (see also section 4.8).

Concomitant use with **ivabradine** is contraindicated due to the additional heart rate-lowering effect of verapamil to ivabradine (see section 4.3)

Concomitant administration of verapamil and **dabigatran** probably increases blood concentrations of dabigatran. Caution should be exercised due to risk of bleeding. Dabigatran C_{max} and AUC increased following concomitant administration of oral verapamil and dabigatran etexilate (150 mg). The extent of these changes however differed depending on time of administration and pharmaceutical form of verapamil. Administration of retarded verapamil 240 mg potentiated the efficacy of dabigatran (increase in C_{max} by approx. 90% and AUC by approx. 70%).

Dabigatran C_{max} and AUC levels increased by about 180% and 150%, respectively, when a rapid-release formulation of verapamil 120 mg was administered one hour before a single dose of dabigatran etexilate. No significant interactions were observed when verapamil was administered 2 hours after dabigatran etexilate (C_{max} and AUC levels increased by approx. 10% and 20%, respectively).

Close clinical monitoring is recommended when verapamil is combined with dabigatran etexilate, especially in the event of bleeding and particularly in patients with mild to moderate renal impairment.

4.6 Fertility, pregnancy and lactation

Pregnancy

Verapamil hydrochloride can cross the placenta. The plasma concentration in the umbilical vein blood is 20 - 92% of the plasma concentration in the maternal blood. Insufficient experience exists with the use of verapamil hydrochloride during pregnancy. However, data on a limited number of orally treated pregnant women do not suggest a teratogenic effect of verapamil hydrochloride. Experimental animal studies have shown reproduction toxicity (see section 5.3).

Therefore, verapamil hydrochloride should not be taken in the first and second trimester of pregnancy. It should be taken in the third trimester of pregnancy only if there is a compelling indication, taking into account the risk for mother and child.

For peer review only - http://bmjopen.bmj.com/site/about/guidelines.xhtml

Lactation
Verapamil passes into breast milk (milk concentration approx. 23% of maternal plasma concentration).
Limited human data following oral administration have shown that the nursing infant takes in only a small amount of the active substance (0.1 – 1% of the maternal dose) and administration is therefore possibly compatible with breast-feeding.

A risk to newborn infants/nursing infants cannot be ruled out. However, because of the risk of severe side effects in the nursing infant, verapamil should be used during breast-feeding only if this is absolutely necessary for the well-being of the mother.

There is evidence that in individual cases verapamil can cause hyperprolactinaemia and galactorrhoea.

4.7 Effects on ability to drive and use machines

Treatment with verapamil requires regular medical supervision. As a result of individually occurring different reactions, the ability to react can be changed to the extent that the ability to take an active part in driving, operate machinery or work in situations without secure support is impaired. This applies to a greater extent at the start of treatment, when the dose is increased and when the preparation is changed, as well as in combination with alcohol. Verapamil may possibly increase blood alcohol levels and slow down its elimination, thereby potentiating the effects of alcohol.

4.8 Undesirable effects

The following adverse reactions of verapamil have been reported in clinical studies, post-marketing surveillance or phase IV clinical trials. They are listed below according to system organ class.
Frequencies of adverse reactions are categoriesed as follows:

Very common:	(≥ 1/10)
Common:	(≥ 1/100 to < 1/10)
Uncommon:	(≥ 1/1.000 to < 1/100)
Rare:	(≥ 1/10.000 to < 1/1.000)
Very rare:	(< 1/10.000)
Unknown:	(frequencies cannot be estimated from the available data)

The most commonly reported adverse reactions were headache, dizziness or drowsiness, gastrointestinal disorders (nausea, constipation and abdominal pain), furthermore bradycardia, tachycardia, palpitations, hypotension, flushes, peripheral oedema and fatigue.

Adverse reactions reported from clinical studies with verapamil and post-marketing observations

MedDRA system organ class	Common	Uncommon	Rare	Very rare	Unknown
Immune system disorders					Hypersensitivity

For peer review only - http://bmjopen.bmj.com/site/about/guidelines.xhtml

Nervous system disorders	Dizziness or drowsiness, headache, neuropathy		Paresthesia, tremor		Extrapyramidal symptoms, paralysis (tetraparesis)[1], cramps
Metabolism and nutrition disorders		Reduced glucose tolerance			Hyperkalaemia
Psychiatric disorders	Nervousness		Somnolence		
Ear and labyrinth disorders			Tinnitus		Vertigo
Cardiac disorders	Bradycardia, onset of heart failure or deterioration of pre-existing heart failure, excessive drop in blood pressure and/or orthostatic dysregulation	Palpitations, tachycardia			AV block (first-, second- and third-degree), heart failure, sinus arrest, sinus bradycardia, asystole
Vascular disorders	Flushes, hypotension				
Respiratory, thoracic and mediastinal disorders					Bronchospasms, dyspnoea
Gastrointestinal disorders	Constipation, Nausea	Abdominal pain	Vomiting		Abdominal discomfort, gingival hyperplasia; ileus
Hepatobiliary disorders		Probably allergy-induced hepatitis with a reversible increase in liver-specific enzymes			
Skin and subcutaneous tissue disorders	Erythromelalgia		Hyperhidrosis	Photodermatitis	Angioedema, Stevens-Johnson syndrome, erythema multiforme, alopecia, itching, pruritus, purpura, maculopapular exanthema, urticaria

For peer review only - http://bmjopen.bmj.com/site/about/guidelines.xhtml

Musculoskeletal and connective tissue disorders				Worsening of Myasthenia gravis, Lambert Eaton Syndrome and advanced Duchenne muscular dystrophy	Arthralgia, muscular weakness, myalgia
Renal and **urinary** disorders					Kidney failure
Reproductive system and breast disorders					Erectile dysfunction, galactorrhoea, gynaecomastia
General disorders and administration site conditions	Peripheral oedema	Fatigue			
Investigations					Increase in blood prolactin levels

[1] There has been a single post-marketing report of paralysis (tetraparesis) associated with the concomitant use of verapamil and colchicine. This may have been caused by colchicine crossing the blood-brain barrier due to CYP3A4 and P-gp inhibition by verapamil. Also see section 4.5.

Note
In patients with pacemakers, an increase in the pacing and sensing threshold under verapamil hydrochloride cannot be ruled out.

In the case of patients with pre-existing cardiovascular disorders such as severe cardiomyopathy, congestive heart failure or recent myocardial infarction, the risk of severe adverse reactions increased during concomitant administration of intravenous beta blockers or disopyramide together with intravenous verapamil, as both substance classes have a cardiodepressant effect (also see section 4.5).

Reporting of suspected adverse drug reactions
Reporting of suspected adverse reactions in the post-marketing phase is of major importance. This allows continuous monitoring of the risk-benefit ration of the medicinal product. Healthcare professionals are urged to report any suspected case of adverse reaction to

Bundesinstitut für Arzneimittel und Medizinprodukte
Abt. Pharmakovigilanz
Kurt-Georg-Kiesinger-Allee 3
D-53175 Bonn
Website: http://www.bfarm.de

4.9 Overdose

Symptoms of an overdose
Intoxication symptoms after poisoning with verapamil hydrochloride progress depending on the amount administered, the time when the detoxification measures are applied and the contractile functionality of the myocardium (age-related).

For peer review only - http://bmjopen.bmj.com/site/about/guidelines.xhtml

The following symptoms have been observed in case of severe intoxication: Severe reduction in blood pressure, cardiac insufficiency, bradycardic or tachycardic arrhythmia (e.g. junctional rhythm with AV dissociation and high-grade AV block) that can lead to cardiovascular shock and cardiac arrest.

Clouding of consciousness progressing to coma, hyperglycaemia, hypokalaemia, metabolic acidosis, hypoxia, cardiogenic shock with pulmonary oedema, impaired renal function and convulsions. Fatalities have occasionally been reported.

Therapeutic measures in the case of overdose
Priority treatment consists of detoxification and restoration of stable cardiovascular conditions.

Therapeutic measures depend on the time and type of administration, as well as the type and severity of intoxication symptoms.

In the case of intoxication with larger amounts of retarded-release preparations, it should be noted that the active substance can be released and absorbed in the intestine even longer than 48 hours after intake.

Gastric lavage is advisable after oral intoxication with verapamil hydrochloride, even later than 12 hours after intake, if no gastrointestinal motility (peristaltic sounds) is detectable. If intoxication with retarded-release preparations is suspected, comprehensive elimination measures are indicated, such as induced vomiting, removal of the contents of the stomach and the small intestine under endoscopic control, intestinal lavage, laxative, high enema.

Because verapamil hydrochloride cannot be dialysed, haemodialysis is not advisable, but haemofiltration and possibly plasmapheresis (high plasma protein binding of calcium antagonists) is recommended.

Usual intensive care resuscitation measures, such as extrathoracic heart massage, respiration, defibrillation or pacemaker therapy.

Specific measures
Elimination of cardiodepressive effects, hypotension and bradycardia.

Bradycardic arrhythmia is treated symptomatically with atropine and/or beta sympathomimetics (isoprenaline, orciprenaline); in the case of life-threatening bradycardic arrhythmia, temporary pacemaker therapy is required. Asystole should be treated with conventional methods including beta adrenergic stimulation (e.g. isoprenaline).

Calcium may be used as specific antidote, e.g. 10 – 20 ml of a 10% calcium gluconate solution administered intravenously (2.25 to 4.5 mmol), if necessary repeated or as continuous drip infusion (e.g. 5 mmol/hour).

Hypotension, as a result of cardiogenic shock and arterial vasodilation, is treated with dopamine (up to 25 µg per kg bodyweight per minute), dobutamine (up to 15µg per kg bodyweight per minute), epinephrine or norepinephrine. Dosage of these medicinal products is guided only by the effect achieved. The serum calcium level should be maintained at high-normal to slightly elevated. In the early stage, additional fluid substitution (Ringer's or sodium chloride solution) is necessary because of arterial vasodilation.

For peer review only - http://bmjopen.bmj.com/site/about/guidelines.xhtml

5. PHARMACOLOGICAL PROPERTIES

5.1 Pharmacodynamic properties

Pharmacotherapeutic group: Selective calcium channel blockers with direct cardiac effects, phenylalkylamine derivatives. ATC-Code: C08DA01

Verapamil hydrochloride belongs to the group of calcium channel blockers. These substances have an inhibiting effect on the calcium influx through muscle cell membranes.

Verapamil hydrochloride also acts as calcium antagonist on the smooth musculature, particularly in the area of the vessels and the gastrointestinal tract. The effect on the smooth vascular muscles manifests itself as vasodilation.

As a calcium antagonist, verapamil also has a distinct effect on the myocardium. The effect on the AV nodes manifests itself by lengthening of the conduction time. In the area of the working myocardium, it can result in a negative inotropic effect.

Verapamil hydrochloride causes a decrease in total peripheral resistance in humans, as a result of the vasodilation. There is no reflex increase in cardiac output. Accordingly, the blood pressure goes down.

5.2 Pharmacokinetic properties

Verapamil hydrochloride is a racemic mixture consisting of equal portions of the R- and the S-enantiomer. Verapamil is extensively metabolised. Norverapamil is one of 12 metabolites that can be identified in the urine, has 10 to 20% of the pharmacological activity of verapamil and accounts for 6% of the excreted active substance.

The steady state plasma concentrations of norverapamil and verapamil are similar. Steady state after multiple single daily dosing is reached after three to four days.

Absorption
Following oral administration, more than 90% of verapamil is rapidly absorbed from the small intestine. The mean systemic availability of the unchanged substance after a single dose of non-retarded verapamil is 22%, compared with approx. 32% with retarded verapamil, owing to a marked hepatic first-pass effect.

Bioavailability is about twice as high with repeated administration. Peak verapamil plasma levels are reached one to two hours after administration of non-retarded release verapamil compared with four to five hours after administration of retarded release verapamil. The peak plasma concentration of norverapamil is reached after one hour (non-retarded release) or after five hours (retarded release).

The presence of food has no effect on the bioavailability of verapamil.

Distribution
Verapamil is widely distributed throughout the body tissues, the volume of distribution ranging from 1.8 to 6.8 l/kg in healthy subjects. Plasma protein binding of verapamil is 90%.

Metabolism
Verapamil is extensively metabolised. In-vitro studies show that verapamil is metabolised by the cytochrome P450 isoenzymes CYP3A4, CYP1A2, CYP2C8, CYP2C9 and CYP2C18. In healthy men, orally administered verapamil undergoes extensive metabolism in the liver, with 12 metabolites having been identified, most of them only in trace amounts. The major part of

For peer review only - http://bmjopen.bmj.com/site/about/guidelines.xhtml

metabolites has been identified as various N and O-dealkylated degradation products of verapamil. Of these metabolites, only norverapamil has any appreciable pharmacological effect (about 20% of that of the parent substance), which was observed in a study with dogs.

Elimination
Following intravenous infusion, verapamil is rapidly eliminated bi-exponentially with a more rapid early distribution phase (half-life of about four minutes) and a slower terminal elimination phase (half-life of two to five hours).

Following oral administration, the elimination half-life of verapamil is three to seven hours.

About 50% of the dose administered is eliminated renally within 24 hours, and 70% within five days. Up to 16% of the dose is excreted in the faeces. About 3 to 4% of the renally excreted active substance is excreted in its unchanged form. The total clearance is nearly as high as the hepatic blood flow, which is about 1 l/h/kg (range: 0.7 to 1.3 l/h/kg).

There are major interindividual differences in clearance.

Special patient groups

Paediatric
Only limited data on pharmacokinetics in children and adolescents are available. After intravenous dosing, the mean half-life of verapamil was 9.17 hours and the mean clearance was 30 l/h compared with 70 l/h for an adult weighing 70 kg. Steady state plasma concentrations after oral dosing appear to be lower in children compared with those observed in adults.

Elderly patients
Aging may possibly affect the pharmacokinetic effects in hypertensive patients. The elimination half-life may be prolonged in elderly patients. The antihypertensive effect of verapamil was found not to be age-related.

Impaired kidney function
Impaired kidney function does not affect the pharmacokinetics of verapamil. This was shown in comparative studies in patients with end stage kidney failure and patients with healthy kidneys.

Verapamil and norverapamil cannot be removed by haemodialysis.

Impaired liver function
The half-life of verapamil is prolonged in patients with impaired liver function. This is due to the lower clearance of the orally ingested substance and the increased distribution volume.

5.3 Preclinical safety data

In-vitro and in-vivo studies showed no evidence of mutagenic effects of verapamil hydrochloride.

In a long-term study in rats no evidence of tumourigenic potential of verapamil hydrochloride was observed.

For peer review only - http://bmjopen.bmj.com/site/about/guidelines.xhtml

Embryotoxicity studies in rabbits and rats showed no evidence of a teratogenic potential, up to a daily dose of 15 mg/kg and 60 mg/kg. In rats however, embryocidal effects and retarded foetal growth (reduced weight of offspring) were observed at maternal-toxic levels.

6. PHARMACEUTICAL PARTICULARS

6.1 List of excipients

VeraHEXAL 40/- 80/- 120
- Microcrystalline cellulose
- Sodium carboxymethyl starch (typ A) (Ph.Eur.)
- Hypromellose
- Lactose monohydrate
- Magnesium stearate (Ph.Eur.)
- Maize starch
- Povidone (K 25)
- Highly dispersed silicium dioxide
- Titanium dioxid (E 171)

Additional for VeraHEXAL 40/- 80
- Hyprolose
- Macrogol 6000

Additional for VeraHEXAL 120
- Macrogol 4000

VeraHEXAL 120 mg retard/- 180 mg retard/- 240 mg retard
- Ethylcellulose
- Gelatine
- Magnesium stearat (Ph.Eur.)
- Maize starch
- Poly(methacrylic acid, ethyl acrylat)
- Povidon (K 30)
- Sucrose
- Talcum
- Triethyl citrate
- Purified water
- Iron(III) oxide (E 172)
- Titanium dioxide (E 171)

VeraHEXAL KHK 120 mg retard/- RR 240 mg retard
- Microcrystalline cellulose
- Hypromellose
- Lactose monohydrate
- Macrogol 4000
- Magnesium stearate (Ph.Eur.)
- Sodium alginate
- Povidon (K 25)
- Highly dispersed silicium dioxide

For peer review only - http://bmjopen.bmj.com/site/about/guidelines.xhtml

Additional for VeraHEXAL KHK 120 mg retard
- Iron(III)-hydroxide oxide (E 172)
- Titanium dioxide (E 171)

Additional for VeraHEXAL RR 240 mg retard
- Quinoline yellow (E 104)
- Indigo carmine (E 132)
- Titanium dioxide (E 171)

6.2 Incompatibilities

Not applicable

6.3 Shelf life

VeraHEXAL 40/- 80/- 120
5 years

VeraHEXAL 120 mg retard/- 180 mg retard/- 240 mg retard
3 years

VeraHEXAL KHK 120 mg retard/- RR 240 mg retard
24 months

6.4 Special precautions for storage

VeraHEXAL 80
This medicinal product requires no special storage conditions.

VeraHEXAL 40/- 120/- 120 mg retard/- 180 mg retard/- 240 mg retard/- KHK 120 mg retard/- RR 240 mg retard
Do not store above 30 °C.

VeraHEXAL KHK 120 mg retard/- RR 240 mg retard
Do not store above 25 °C.

6.5 Nature and contents of container

VeraHEXAL 40/- 80/- 120
Pack sizes of 30, 50 and 100 film-coated tablets

VeraHEXAL 120 mg retard/- 180 mg retard/- 240 mg retard
Pack sizes of 30, 50 and 100 hard capsules, retarded

VeraHEXAL KHK 120 mg retard/- RR 240 mg retard
Pack sizes of 30, 50 and 100 retard tablets

Not all pack sizes may be marketed.

6.6 Special precautions for disposal and other handling

Any unused medicinal product or waste material should be disposed of in accordance with

For peer review only - http://bmjopen.bmj.com/site/about/guidelines.xhtml

local requirements.

7. MARKETING AUTHORISATION HOLDER

Hexal AG
Industriestraße 25
83607 Holzkirchen
Telephone: +49 (0) 8024 908-0
Fax: +49 (0) 8024 908-1290
e-mail: medwiss@hexal.com

8. MARKETING AUTHORISATION NUMBER(S)

VeraHEXAL 40:	26214.00.00
VeraHEXAL 80:	7676.00.00
VeraHEXAL 120:	7676.01.00
VeraHEXAL 120 mg retard:	7721.00.01
VeraHEXAL 180 mg retard:	7721.01.01
VeraHEXAL 240 mg retard:	7721.02.01
VeraHEXAL KHK 120 mg retard:	33952.01.00
VeraHEXAL RR 240 mg retard:	33952.00.00

9. DATE OF FIRST AUTHORISATION/RENEWAL OF AUTHORISATION

VeraHEXAL 40:	29.04.2003
VeraHEXAL 80:	09.05.2003
VeraHEXAL 120:	09.05.2003
VeraHEXAL 120 mg retard:	29.04.2003
VeraHEXAL 180 mg retard:	09.12.2003
VeraHEXAL 240 mg retard:	29.04.2003
VeraHEXAL KHK 120 mg retard:	06.05.2003
VeraHEXAL RR 240 mg retard:	29.04.2003

10. DATE OF REVISION OF THE TEXT

August 2016

11. CLASSIFICATION FOR SUPPLY

Only available on prescription

For peer review only - http://bmjopen.bmj.com/site/about/guidelines.xhtml

Appendix 3: Ver-A-T1D_List of applicable documents

Name	Compulsory	To be used if no local equivalent available
Ver-A-T1D_Clinical trial prescription		✓
Ver-A-T1D_Subject Drug Accountability Log	✓	
Ver-A-T1D_Stock Sheet	✓	
Ver-A-T1D_Temperature protocol_ambient storage		✓
Ver-A-T1D_Temperature Deviation Form	✓	

For peer review only

Data Sharing Plan (Ver-A-T1D)

Will individual participant data be available (including data dictionaries)?	yes
What data in particular will be shared?	Individual participant data that underlie the results reported in this article after deidentification (text, tables, figures, and appendices).
What other documents will be available?	Study protocol
When will data be available ? (start and end dates)	Beginning after publication of the primary results papers reporting the prespecified endpoints described in the Statistical analysis plan. (no end date)
With whom?	Researchers who provide a methodologically sound proposal – and if needed an ethics approval for the project
For what types of analyses?	For research projects. To achieve aims in the approved proposal at the level of individual data including for meta-analyses
By what mechanism will data be made available?	Proposals should be directed to the Chief-Investigator (who may consult with other members of the trial team). To gain access, data requestors will need to sign a data access agreement. Data will be made available directly to the person requesting the data.

For peer review only

Clinical Trial Protocol

Trial Title:	A randomised, double-blind, placebo controlled, parallel group, multi-centre trial in adult subjects with newly diagnosed type 1 diabetes mellitus investigating the effect of Verapamil SR on preservation of beta-cell function (Ver-A-T1D)
Trial Short Title:	Verapamil SR in Adults with Type 1 Diabetes (Ver-A-T1D)
Trial Phase:	2
Protocol Number:	Ver-A-T1D
EudraCT Number:	2020-000435-45
Investigational Product:	Verapamil SR
Protocol Version:	V 8.0 (08-NOV-2021)

This protocol is following the INNODIA Master Protocol inside INNODIA platform.

Chief Investigator:	Prof. Thomas Pieber, MD
CI Address:	Medical University of Graz Department of Internal Medicine Auenbruggerplatz 15 A8036 Graz Austria
Telephone:	+43 316 385 82383
Co-Chief Investigator:	Prof. Colin Dayan, MD
CoCI Address:	Cardiff University School of Medicine Heath Park Cardiff CF14 4XN UK
Telephone:	+442920742182

For peer review only - http://bmjopen.bmj.com/site/about/guidelines.xhtml

Study Sponsor:	Medical University of Graz
SAE Reporting:	Prof. Thomas Pieber, MD Medical University of Graz Department of Internal Medicine Auenbruggerplatz 15 A8036 Graz Austria
Telephone:	+43 316 385 82383
E-Mail:	SAE-reporting@medunigraz.at

For peer review only

For peer review only - http://bmjopen.bmj.com/site/about/guidelines.xhtml

Document History:

Version	Date	Description of change
2.0	06-SEP-2019	Original Version
3.0	24-JAN-2020	EudraCT number added. Secondary outcome measures: Continous glucose monitoring (CGM) time in range (70-140 mg/dL, 3.9-7.8 mmol/L) added. Update of trial flow chart and flow chart of trial assessments. Implementation of SAE reporting email address. Section 2, Trial Management Group completed. Referencing to INNODIA protocol in section 8.7.3 deleted, Exploratory outcome measure has been implemented according to INNODIA protocol. Section 10.1.3, Drug supply has been added. Assessment of vital signs at screening visit added. Drug screen and alcohol breath test has been deleted at screening visit. Schedule of phone visit 1 and 2 updated (to one week (+/- 2 days) after first dose escalation) and additional phone visit 3 added. Sample size changed from 108 (36 participants in the control arm and 72 in the experimental arm) to 120 participants (40 participants in the control arm and 80 in the experimental arm). Number of subjects to be randomised increased to 138. Section 11.5.4, CGM data collection expanded to 14 days prior each clinic visit. Section 11.5.5, Record of hypoglycaemia added. Section 11.5.6, Diabetes care (Insulin regimen) added. Section 11.5.11, Patient diaries added. Term "Primary Co-Investigator" changed to "Co-Chief Investigator".
4.0	05-MAR-2020	Categorisation of hypoglycaemia added to Section 11.5.5. Interim analysis altered from 9 month to 10 month. EC "Active participation in another T1D treatment study in the previous 30 days" has been reformulated to "Use of any other investigational drug in the previous 30 days and/or intent on using any investigational drug for the duration of the trial" Update of trial flow chart. Email adress of Prof. Adrian Mander updated.

For peer review only - http://bmjopen.bmj.com/site/about/guidelines.xhtml

5.0	26-JUN-2020	Analysis of the fecal metabolome added. Reference to INNODIA Master protocol added. Section 11.5.4, upload and storage of encrypted CGM data using Dexcom Clarity software added. Tertiary objective "To compare between treatment arms and across the course of treatment the PROMs scores completed by participants" and tertiary outcome measures "DTSQ, ADDQoL, HypoFear questionnaires completed by participants" added. Section 11.5.9 Patient Reported Outcome Measures (PROMS) added. Section 11.5.12 Patient Diaries: precise definition of the information to be collected in the patient diaries. EC/IC numbering introduced. Precise definition of IC4 regarding diabetes-related autoantibodies to: "Must have at least one or more of the following diabetes-related autoantibodies present at screening: GADA, IA-2A and/or ZnT8A" History of liver insufficiency and renal insufficiency added to EC 8 and EC 9. EC: Concomittant use of alpha-blockers, beta-blockers, cardiac glycosides, antiarrhytmics, ivabradine, lithium, sulfinpyrazone, almotriptan, acetylsalecylic acid moved to section 10.3.3 Prohibited concomitant therapy. EC 14 added: "Concomittant medication known for inducing or inhibiting CYP3A4 and/or glycoprotein-P metabolism" EC 15 added: "Intake of grapefruit juice, licorice, St.John's Wort, cannabidiol, ginkgo biloba" EC 16 added: "Substrate intake of CYP3A4 and/or glycoprotein-P metabolism, as judged by the investigator"EC 17: severe left ventricular dysfunction, atrial flutter or atrial fibrillation in the presence of an accessory bypass tract (e.g. Wolff-Parkinson-White syndrome), hypertrophic cardiomyopathy, attenuated neuromuscular transmission (e.g. by myasthenia gravis, Lambert-Eaton syndrome, advanced Duchenne muscular dystrophy) added Section 11.5.7 Clincial Safety Laboratory Assessments: C reactive protein (CRP), High-density lipoprotein (HDL), low-density lipoprotein (LDL), total cholesterol, triglycerides, Estimated Glomerular Filtration Rate (eGFR) calculated by the central laboratory based on the creatinine value using the CKD-EPI equation added to list of clinical laboratory tests to be performed at the screening and baseline assessment.

For peer review only - http://bmjopen.bmj.com/site/about/guidelines.xhtml

		Section 13 Toxicity – Emergency Procedures: Information "Verapamil hydrochloride may increase blood alcohol (ethanol) concentrations and prolong its effects" added. Section 12.3 Excpected Adverse Events/ Serious Adverse Events (AE/SAE): Diabetic Ketoacidosis added to known side effects which will not be recorded as AE/AR.
6.0	23-JUL-2020	VER-A-T1D changed to Ver-A-T1D Time points for PROMs in section 11.5.9 and the flow chart for trial assemssments changed.
7.0	25-SEP-2020	IC 5 changed to "Must have fasting C-peptide levels ≥100 pmol/L measured at screening" EC 20 added: "Current use of ß-blockers" Update of trial flow chart: autoantibodies at V-1, V6, V7 only, DNA extraction at V-1 only, Blood (omics) to V5 added, Whole blood RNA at V-1, V6, V7 only, micro RNA (plasma omics) to V5 added, Safety lab from V0 removed, Foot line "i" added explaining C-peptide and blood glucose samples collection. 10.1 Treatment Summary: IMP packaging information removed. 11.3.1 Screening and baseline assessments (Visit V-1): Assessments listed in detail in accordance with the trial flow chart. 11.3.2 Participant Randomisation (Visit 0): Assessments listed in detail in accordance with the trial flow chart. Section 11.5: Maximum blood sample volume per visit (204 mls) added. Section 11.7: Collection of Fresh blood immune assays (FACs) removed from the Protocol-Required Exploratory INNODIA samples (assessments performed by the central laboratory/INNODIA) table. Section 11.5.9: Information about electronic version of PROMs as part of the eCRF added.Section 11.5.10: Moved before section 11.5.11 – no changes to the content. Section 11.5.11: Assessments listed in detail in accordance with the trial flow chart. Therefore Section "Innodia Assessments at time point Visit -1, Visit 3, Visit 4, Visit 6 removed. 11.6 Long-Term Follow-up Assessments: Assessments listed in detail in accordance with the trial flow chart. Section 4 Trials Synopsis updated according to protocol amendments.
7.2	29-JAN-2021	Trial Synopsis section "Procedures: End of Trial" has been updated and the wording changed to clearly define that the final visit is mandatory.

For peer review only - http://bmjopen.bmj.com/site/about/guidelines.xhtml

		Section 5: The Trial Flow Chart has been updated and the reference to the imaging study has been removed. Section 10.3.3: Reference to the SmPC for full details on potential drug-drug interactions in addition to the list provided included. Section 10.1.1: The rationale for the selected target dose of 360 mg once daily and the minimum target dose of 240 mg once daily has been added. Reference to the literature (Ovalle et al, 2018) has been made. Section 12.1.6 updated to clearly define the appropriate RSI for the study and the statement in section 12.6 Section 12.3 "Expected Adverse Events/Serious Adverse Events (AE/SAE)" updated to clarify in which case exempt from standard safety reporting is acceptable. Section 17.2 "Independent Data Monitoring Committee" has been added and aligned with the trial synopsis. The name Data Monitoring Committee (incl. the corresponding abbreviations) was changed to Independent Data Monitoring Committee.
8.0	08-NOV-2021	Fax number for SAE reporting deleted. Secondary outcome measures: Preproinsulin deleted and Insulin, Pro-IAPP and Proglucagon added. Visit 7 (Long-Term Follow-up Assessments): time window ±7 days changed to ±3 weeks. EC 14: Wording changed to "Concomitant medication known for significantly inducing or inhibiting CYP3A4 and/or glycoprotein-P metabolism. EC 18: "Incomplete branch block" added. Trial Synopsis: inconsistency of CGM read outs "2 weeks post visit" corrected to "2 weeks prior to visit". Section 9.2: EC 17 "Hypotension of less than 90mmHg systolic" corrected to "less than 100mmHg systolic". Section 5 Trial Flow Chart has been updated and the need of monthly performed pregnancy tests has been added to the foot note "h" of the trial flow chart. Section 7.1: Short description of the associated INNODIA study Image-Ver-A-T1D added. Note added that this section is a country specific section. Section 8.7.3 Inconsistency corrected, "Secondary outcome measure" on page 33 deleted and sentence added to the rationale of the trial design. Section 9.5 "Participant Withdrawal Criteria" has been updated and the following thresholds for heart rate and QT time prolongation were added to the participant withdrawal criteria:

For peer review only - http://bmjopen.bmj.com/site/about/guidelines.xhtml

		• Heart Rate 50-100 beats/min (normal QRS width): corrected QT interval (QTc Bazett) = QT/√(RR interval) > 500 ms • Heart Rate 50-100 beats/min, QRS bundle block (QRS width > 500ms): QRSwidth – 120 = x; QTc > 500ms + x Section 9.5 "Participant Withdrawal Criteria": Pregnancy and Intention of becoming pregnant added as withdrawal criteria Section 10.3.2 "Permitted concomitant therapy" has been updated and the use of antiarrhythmics drugs known to cause QTc interval prolongation with precaution only, has been implemented. A detailed list of antiarrhythmic agents has been added to this section. Section 10.3.3: The medical monitor should be contacted if uncertainty regarding the use of concomitant medication occurs. Section 10.3.3 Prohibited concomitant therapy: "Monoamine oxidase (MAO) inhibitors" added. Section 10.3.3 Prohibited concomitant therapy: Wording changed to "Furthermore, concomitant medication known for significantly inducing or inhibiting CYP3A4 or being predominantly degraded via CYP3A4 and/or glycoprotein-P metabolism must not be taken under Verapamil therapy". Section 11.3.1 and section 11.3.2: the correct timing of assessments has been described more clearly. Section 11.5.7 Clinical Safety Laboratory Assessments: the blood parameters % reticulocytes, blood urea nitrogen (BUN), direct bilirubin and urine parameters blood, bilirubin, urobilinogen, nitrite, leukocyte esterase deleted. Urine parameters erythrocytes and leucocytes added. The possibility of additional tests if determined necessary by the investigator or local regulations added. HbA1c removed from Table "Protocol-Required Exploratory INNODIA samples (assessments performed by the central laboratory/INNODIA)" Section 11.5.8 Mixed Meal Tolerance Test: Option to re-schedule visits if participants glucose levels are outside the accepted range added. The confirmation of eligibility before start of MMTT added. Section 11.5.8: Measurement of Pro-IAPP and Pro-glucagon levels on stored samples from the MMTT at a later timepoint added. Section 11.9 "Trial restrictions" has been updated and highly effective birth control methods for women of childbearing potential according to CFTG recommendations were implemented. Definition of women

For peer review only - http://bmjopen.bmj.com/site/about/guidelines.xhtml

		of childbearing potential has been added to the section. A country specific section for Belgium has been implemented and the use of condom with spermicide for men outlined as not acceptable for Belgium sites. Section 11.5.11 "Timing of assessments": "DBS" changed to "Collect DBS cards". Section 12.1.6 has been updated as follows and the appropriate RSI for the study was clearly defined: "The protocol RSI is contained in a clearly identified section (section 4.8) of the Summary of Product Characteristics (SmPC)." Section 12.5 has been updated and the described procedures aligned with the following regulatory requirements: SAEs must be reported from the investigator to the sponsor within 24 hours. The relatedness of a SAE with the study drug must be assessed by the investigator and the sponsor. Section 12.6.1 has been updated and the reporting of SUSARs clearly defined as sponsor responsibility. Section 15 has been updated. A definite strategy for handling of missing data has been predefined and statistical methods described in more detail. Section 17 updated and clearly outlined which committees are constituted. Section 24.3, Appendix 3 "Benefit-Risk Assessment" included.

For peer review only

For peer review only - http://bmjopen.bmj.com/site/about/guidelines.xhtml

1 Protocol Signatures:

I give my approval for the protocol entitled "A randomised, double-blind, placebo controlled, parallel group, multi-centre trial in adult subjects with newly diagnosed type 1 diabetes mellitus investigating the effect of Verapamil SR on preservation of beta-cell function (Ver-A-T1D)" dated 08-NOV-2021.

Chief Investigator

Name: Prof. Thomas Pieber, MD

Signature: _____

Date: _____

For peer review only

For peer review only - http://bmjopen.bmj.com/site/about/guidelines.xhtml

I give my approval for the protocol entitled "A randomised, double-blind, placebo controlled, parallel group, multi-centre trial in adult subjects with newly diagnosed type 1 diabetes mellitus investigating the effect of Verapamil SR on preservation of beta-cell function (Ver-A-T1D)" dated 08-NOV-2021.

Co-Chief Investigator

Name: Prof. Colin Dayan, MD

Signature: _____

Date: _____

For peer review only

For peer review only - http://bmjopen.bmj.com/site/about/guidelines.xhtml

Site Signatures

I have read the attached protocol entitled "A randomised, double-blind, placebo controlled, parallel group, multi-centre trial in adult subjects with newly diagnosed type 1 diabetes mellitus investigating the effect of Verapamil SR on preservation of beta-cell function (Ver-A-T1D)" dated 08-NOV-2021 and agree to abide by all provisions set forth therein.

I agree to comply with the conditions and principles of Good Clinical Practice as outlined in the European Clinical Trials Directives 2001/20/EC and 2005/28/EC, the Medicines for Human Use (Clinical Trials) Regulations 2004 (SI 2004/1031) and any subsequent amendments of the clinical trial regulations, the sponsor's SOPs, and other regulatory requirements as amended.

I agree to ensure that the confidential information contained in this document will not be used for any other purpose other than the evaluation or conduct of the clinical investigation without the prior written consent of the Sponsor.

Principal Investigator

Name: _____

Signature: _____

Date: _____

For peer review only

For peer review only - http://bmjopen.bmj.com/site/about/guidelines.xhtml

2 Trial Management Committee(s) and Protocol Contributors

Trial Management Group (TMG)		
Chief Investigator	Prof TR Pieber Medical University of Graz, Austria thomas.pieber@medunigraz.at	MUG
INNODIA Coordinator	Prof C Mathieu KU Leuven, Belgium chantal.mathieu@uzleuven.be	KUL
Co-Chief Investigator	Prof C Dayan Cardiff University, UK dayancm@cardiff.ac.uk	CU
Principal Statistician and INNODIA Chief Statistician	Prof A Mander Cardiff University, UK mandera@cardiff.ac.uk,	CU
INNODIA clinical collection coordinator	Dr S Bruggraber University of Cambridge, UK Sb2194@medschl.cam.ac.uk	UCAM
Trial Manager	M Brunner, MSc Medical University of Graz, Austria martina.brunner@medunigraz.at	MUG
INNODIA data management coordinator	P Jaroslaw Chmura Copenhagen University, Denmark piotr.chmura@cpr.ku.dk	UCPH
Collaborators		
Chair INNODIA Patient Advisory Committee	Olivier Arnaud JDRF international, France oarnaud@jdrf.org	PAC

For peer review only

For peer review only - http://bmjopen.bmj.com/site/about/guidelines.xhtml

Table of Contents

For Peer review only

For peer review only - http://bmjopen.bmj.com/site/about/guidelines.xhtml

For peer review only

For peer review only - http://bmjopen.bmj.com/site/about/guidelines.xhtml

3 Abbreviations

ADA	American Diabetes Association
ADDQoL	Audit of diabetes dependent quality of life
AE/AR	Adverse event/Adverse reaction
ALT	Alanine transaminase
AST	Aspartate aminotransferase
AUC	Area under the curve
BW	Body weight
CA	Competent authority
CGM	Continuous glucose monitoring
CMP	Complete metabolic profile
CRF	Case report form
CRP	C-reactive protein
CTIMP	Clinical trial of investigational medicinal product
COPD	Chronic obstructive pulmonary disease
DBS	Dried blood spot
DKA	Diabetic ketoacidosis
IDMC	Independent data monitoring committee
DSUR	Development safety update report
DTSQs	Diabetes treatment satisfaction questionnaire – status
DTSQc	Diabetes treatment satisfaction questionnaire - change
ECG	Electrocardiogram
EMA	European Medicines Agency
eGFR	Estimated glomerular filtration rate
FACS	Fluorescence-activated cell sorting
FBC	Full blood count
FDA	Food and Drug Administration
GADA	Glutamic acid decarboxylase antibodies
GP	General practitioner
GCP	Good Clinical Practice
HDL	High-density lipoprotein
HFS	Hypoglycaemia Fear Survey
HIV	Human immunodeficiency virus
HRA	Health research authority
IA-2A	Insulinoma-associated protein 2 autoantibody
IAA	Insulin autoantibodies
IB	Investigators brochure
ICF	Informed consent form
IMP	Investigational medicinal product
IWRS	Interactive Web Response System
LDL	Low-density lipoprotein
MHRA	Medicines and Healthcare products Regulatory Agency
MMTT	Mixed meal tolerance test
NA	Not applicable
NIMP	Non investigational medicinal product
PIS	Participant information sheet
PBMC	Peripheral blood mononuclear cells
PROMs	Patient reported outcome measures
Pro-IAPP	Pro - islet amyloid polypeptide
R&D	Research and Development
RA	Regulatory agency

For peer review only - http://bmjopen.bmj.com/site/about/guidelines.xhtml

REC	Research ethics committee
RSI	Reference safety information
SAE/SAR	Serious adverse event/Serious adverse reaction
SD	Standard deviation
SDVAF	Source Data Verification Agreement Form
SmPC	Summary of product characteristics
SR	Sustained release
SUSAR	Suspected unexpected serious adverse reaction
T1D	Type 1 diabetes mellitus
TMG	Trial Management Group
TSC	Trial Steering Committee
ZnT8A	Zinc transporter 8 autoantibody
TXNIP	Thioredoxin-interacting protein

For peer review only

For peer review only - http://bmjopen.bmj.com/site/about/guidelines.xhtml

4 Trial Synopsis

Title of clinical trial	A randomised, double-blind, placebo controlled, parallel group, multi-centre trial in adult subjects with newly diagnosed type 1 diabetes mellitus investigating the effect of Verapamil SR on preservation of beta-cell function (Ver-A-T1D)
Trial Short Title:	Verapamil SR in Adults with Type 1 Diabetes (Ver-A-T1D)
Trial Phase	2
Sponsor name	Medical University of Graz
EudraCT number	2020-000435-45
Medical condition or disease under investigation	Type 1 diabetes (T1D)
Purpose of clinical trial	To confirm the effect of 360mg Verapamil sustained release (SR) administered orally once daily (titrated over the first 3 months from 120 mg to 360 mg) on the preservation of beta-cell function measured as stimulated C-peptide after 12 months compared to placebo.
Primary objective	To determine the changes in stimulated C-peptide response during the first two hours of a mixed meal tolerance test (MMTT) at baseline and after 12 months for 360mg Verapamil SR administered orally once daily versus placebo.
Secondary objective (s)	To determine the effects of 360mg Verapamil SR administered orally once daily on fasting C-peptide and Dried Blood Spot (DBS) C-peptide measurements over time. To determine the effects of 360mg Verapamil SR administered orally once daily on HbA1c daily total insulin dose and continous glucose monitoring (CGM) time in range. To determine the effects of treatment on other biomarkers related to immunological changes and beta-cell death and survival in this population. To determine the effects of 360mg Verapamil SR administered orally once daily on safety (vital signs, ECG).
Tertiary objective (s)	To compare between treatment arms and across the course of treatment the PROMs scores completed by participants.
Trial Design	The trial is a multi-centre, randomised, double-blind, placebo-controlled trial in subjects with T1D within 6 weeks of diagnosis. The participants will be randomised in 2:1 between 360mg Verapamil SR and placebo administered orally

For peer review only - http://bmjopen.bmj.com/site/about/guidelines.xhtml

	once daily (titrated over the first 3 months from 120 mg to 360 mg). T1D patients aged ≥18 and <45 years will be eligible for recruitment within 6 weeks of diagnosis (defined as day of starting insulin therapy).
Trial Outcome Measures	Primary outcome measure: • The area under the stimulated C-peptide response curve over the first two hours of a mixed meal tolerance test (MMTT) after 12 months therapy compared to placebo Secondary outcome measures: • The area under the stimulated C-peptide response curve over the first two hours of a mixed meal tolerance test (MMTT) at 3, 6, 9 months • Proinsulin, Insulin, Pro-IAPP and Proglucagon secretion during the first two hours of a mixed meal tolerance test (MMTT) at baseline and 3, 6, 9 an 12 months • Fasting C-peptide after 12 months therapy compared to placebo • The DBS C-peptide measurements at all observation times • Change in HbA1c baseline to 12 months • Number of treatment emergent severe hypoglycaemic episodes. Severe hypoglycaemia denotes severe cognitive impairment requiring external assistance for recovery according to the American Diabetes Association (ADA) • Number of treatment emergent episodes of diabetic ketoacidosis (DKA) • Change in insulin requirements, baseline to 12 months as the daily total dose (three days average) in units per kg body weight (BW) • Change in T1D associated autoantibodies (GADA, IAA, IA-2A and ZnT8A) from baseline to 12 months • Continous glucose monitoring (CGM) time in range (70-140 mg/dL, 3.9-7.8 mmol/L) and (70-180 mg/dL, 3.9-10.0 mmol/L), time above range (>180 mg/dL, >10.0 mmol/L), time below range (<70 mg/dL, < 3.9 mmol/L) • The area under the stimulated C-peptide response curve over the first two hours of a mixed meal tolerance test (MMTT) at 24 months • Change in HbA1c baseline to 24 months • Change in insulin requirements, baseline to 24 months as the daily total dose (three days average) in units per kg BW Tertiary outcome measures:

For peer review only

For peer review only - http://bmjopen.bmj.com/site/about/guidelines.xhtml

	• DTSQ, ADDQoL, HypoFear questionnaires completed by participants
Sample Size	Participants will be allocated to treatment or placebo in a 2:1 ratio (verapamil SR:placebo). 120 subjects will be needed (40 participants in the control arm and 80 in the experimental arm) to achieve 90% power at 5% significance level to detect a change of 0.18 nmol/L/min in C-peptide AUC.
Summary of eligibility criteria	• Inclusion Criteria: 1. Have given written informed consent 2. Age ≥18 and <45 years at consent 3. Must have a diagnosis of T1D of within 6 weeks duration at screening (from date of the first insulin injection) 4. Must have at least one or more of the following diabetes-related autoantibodies present at screening: GADA, IA-2A and/or ZnT8A 5. Must have fasting C-peptide levels ≥100 pmol/L measured at screening 6. Be willing to comply with intensive diabetes management • Exclusion Criteria: 1. Be immunodeficient or have clinically significant chronic lymphopenia: Leukopenia (< 3,000 leukocytes /µL), neutropenia (<1,500 neutrophils/µL), lymphopenia (<800 lymphocytes/µL), or thrombocytopenia (<100,000 platelets/µL) 2. Have active signs or symptoms of acute infection at the time of screening 3. Be currently pregnant or lactating, or anticipate getting pregnant during the 12 months study period 4. Require use of immunosuppressive agents including chronic use of systemic steroids 5. Have evidence of current or past human immunodeficiency virus (HIV), Hepatitis B or Hepatitis C infection 6. Have any complicating medical issues or abnormal clinical laboratory results that may interfere with study conduct, or cause increased risk to include pre-existing cardiac disease, chronic obstructive pulmonary disease (COPD), sickle cell disease, neurological, or blood count abnormalities, as judged by the investigator 7. Have persistent history of malignancies other than skin 8. 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

For peer review only

For peer review only - http://bmjopen.bmj.com/site/about/guidelines.xhtml

	9. History of renal insufficiency or evidence of renal dysfunction with creatinine greater than 1.5 times the upper limit of normal 10. Current or ongoing use of non-insulin pharmaceuticals that affect glycaemic control within prior 7 days of screening 11. Use of any other investigational drug in the previous 30 days and/or intent on using any investigational drug for the duration of the trial 12. Current use of Verapamil or other calcium channel blockers 13. Known hypersensitivity to Verapamil or to any of its excipients 14. Concomitant medication known for significantlyinducing or inhibiting CYP3A4 and/or glycoprotein-P metabolism 15. Intake of grapefruit juice, licorice, St.John's Wort, cannabidiol, ginkgo biloba 16. Substrate intake of CYP3A4 and/or glycoprotein-P metabolism, as judged by the investigator 17. Hypotension (of less than 100mmHg systolic), sick sinus syndrome (except patients with a functioning artificial pacemaker), uncompensated heart failure or severe left ventricular dysfunction; marked bradycardia (less than 50 beats/minute), atrial flutter or atrial fibrillation in the presence of an accessory bypass tract (e.g. Wolff-Parkinson-White syndrome), hypertrophic cardiomyopathy, acute myocardial infarction, attenuated neuromuscular transmission (e.g. by myasthenia gravis, Lambert-Eaton syndrome, advanced Duchenne muscular dystrophy) 18. ECG second or third degree atrioventricular block; Incomplete branch block. 19. Any condition that in the investigator's opinion may adversely affect study participation or may compromise the study results. 20. Current use of ß-blockers.
Investigational medicinal product and dosage	Verapamil SR 360mg administered orally once daily (titrated over the first 3 months from 120 mg to 360 mg)
Comparator product(s)	Placebo
NIMPs	NA
Route(s) of administration	Oral
Maximum duration of treatment of a participant	12 months
Procedure: Approach, consent and enrolment	Potentially eligible individuals will be approached by health care professionals and/or local research teams

For peer review only - http://bmjopen.bmj.com/site/about/guidelines.xhtml

	during routine clinical appointment or by phone/e-mail if they have previously agreed that their personal details may be used for research studies purposes. Consent will be obtained in compliance with ICH-GCP, local regulatory and legal requirements from all potential participants approached once they have been given sufficient time to consider their participation in the study. Consent will include permission to retain contact details at the clinical site to enable us to inform participants of potential recall to future intervention/research studies. Following informed consent, the participant will be registered in the INNODIA central database using de-identifiable information only and a participant ID generated.
Procedures: screening and baseline assessment	**Visit V-1 (<6 weeks from diagnosis)** Participants will arrive fasted (from midnight). Blood will be collected for the following screening assessments: • Fasting C-peptide • Autoantibodies • Safety lab (incl. full blood count (FBC), complete metabolic profile (CMP)) • HIV, Hepatitis B and C Additionally, for women of childbearing potential, if applicable, a pregnancy test will be performed. At the same visit, the following information will be recorded: • Inclusion/ Exclusion criteria • Demographics (date of birth, gender, ethnicity) • Date of T1D diagnosis • HbA1c at diagnosis • Daily insulin regimen at time of visit • Blood glucose at time of visit • Physical examination (including height and weight) • Medical history • Diabetes care • Concomitant medication, including vaccinations in last 6 weeks • Family medical history • ECG, Vital signs Additionally, the following baseline samples will be collected: DNA extraction, HbA1c, omics, ß cell killing assay, whole blood RNA and circulating micro RNA (plasma omics), immune cells (PBMC) isolation. Urine and stools for omics will also be collected.

For peer review only - http://bmjopen.bmj.com/site/about/guidelines.xhtml

Procedures: randomisation	**Visit V0 (≤2 weeks from V-1)** Participants will arrive fasted (from midnight) and be assessed for adverse events, withdrawal criteria, family medical history, diabetes care, physical examination (incl. height and weight), vital signs, concomitant medication, HbA1c and pregnancy (if applicable). All participants will have a 120 minutes mixed meal tolerance test (MMTT) with EnsurePlus for measuring C-peptide and glucose as a measurement of beta cell response. Participants will be randomised to one of the two treatment groups, dispensed medication (verapamil SR 120mg or placebo) and receive instructions on frequency of administration (daily intake). Participants will be set up with a continuous glucose monitor (CGM) and handed out a patient diary before leaving the clinical research facility.
Procedures: treatment and follow-up period	Participants will have a total of 3 telephone visits and 7 visits at the trial site. Telephone visits are scheduled one week (+/- 2 days) after visit 0 respectively after each dose escalation at week 1 (P1), week 5 (P2) and week 9 (P3). Trial site visits are scheduled at week 4 (V1), week 8 (V2), month 3 (V3), month 6 (V4), month 9 (V5) and month 12 (V6) after treatment start. 12 months after active treatment a follow-up visit is planned at month 24 (V7). **Telephone visits (P1, P2, P3):** Adverse events, Withdrawal criteria, concomitant medication (including vaccination) will be recorded. **All trial site visits (V1-6)**: Participants will arrive fasted (from midnight). Adverse events, withdrawal criteria, vital signs, ECG, concomitant medication (including vaccination), diabetes care, CGM data for 2 weeks prior to the visit will be recorded and a pregnancy test performed (if applicable). Patient diary will be reviewed. Blood will be collected for safety lab (incl. FBC, CMP), Fasting C-peptide, HbA1c. **Visit 1 and 2**: Dose escalation of verapamil SR/placebo from 120 to 240 and 360 mg once daily. **Visit 3, 4 and 6:** Additional INNODIA Assessments, MMTT for beta cell function, **Home collection:** Additionally, capillary glucose and DBS will be collected at home pre and 60 min post consumption of EnsurePlus, monthly, for the full 12 months follow-up, for DBS C-peptide measurement.
Procedures: End of trial	Patients enrolled into this trial already receive the appropriate standard of care, and this care continues after the study. Participants finish the trial at the end

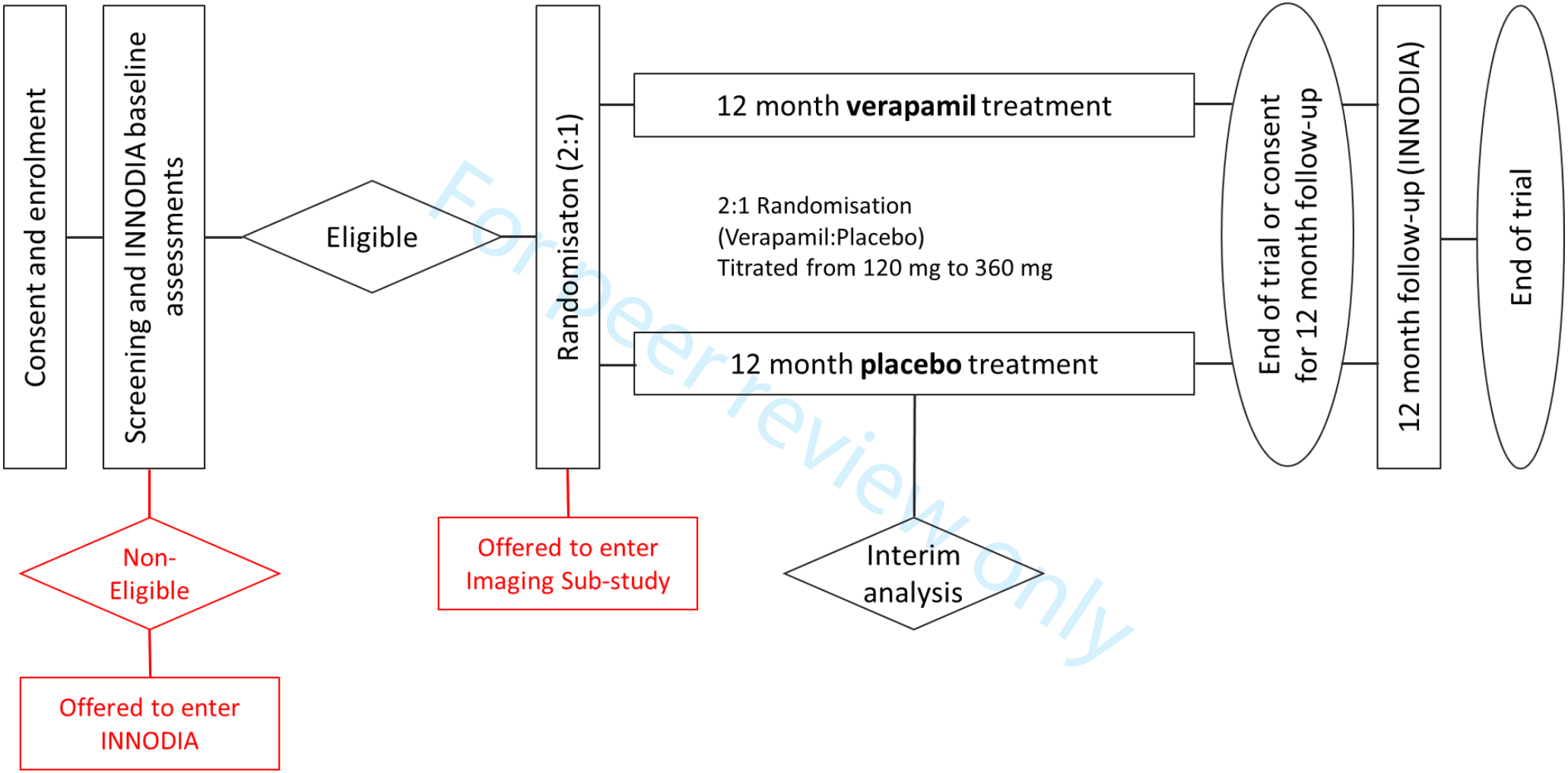
For peer review only - http://bmjopen.bmj.com/site/about/guidelines.xhtml

	of the last visit (V6) at 12 month post first treatment day (V0). Informed consent is sought upon joining the study to confirm that participants are happy to be contacted to inform them of study results and future intervention and research diabetes studies organised by INNODIA. After completion of treatment at 12 months from diagnosis, participants will continue for a further 12 months in the observation part of the study. This will involve 1 single visit 24 months from diagnosis (visit 8).
Procedure for interim analysis	As the trial progresses, a statistician, un-blinded, will analyse all the data available at time 10 months. A mixed effects model will be fitted with treatment and time as fixed effects and id as a random intercept. A wald test will be used on the differences of mean AUC MMTT C-peptide at 6 months between treated and control groups. If the Z-statistic is below -0.5 then the study will stop for futility (this is that the treatment is a little worse than control group at the 6 month time point).
Procedures for safety monitoring during trial	The IDMC will assess safety from reported adverse events and will have the right to suspend or stop the trial at any point for safety concern. The trial may be suspended by the chief investigator and/or the sponsor following SUSAR.
Criteria for withdrawal of participants	Participants may withdraw from the trial at their request at any time. Clinicians may also choose to withdraw participants if they feel it is in their best interests or if they have been unable to comply with the requirements of the trial.

For peer review only

For peer review only - http://bmjopen.bmj.com/site/about/guidelines.xhtml

5 Trial Flow Chart:



For peer review only

For peer review only - http://bmjopen.bmj.com/site/about/guidelines.xhtml

Flowchart for trial assessments

Trial period	Consent and enrolment	Screening and baseline assessment	Randomisation	Treatment									Observation
Visit type (C: Clinic, P: Phone contact)	**C**	**C**	**C**	**P**	**C**	**P**	**C**	**P**	**C**	**C**	**C**	**C**	**C**
Visit number		**V-1**	**V0**	**P1**	**V1**	**P2**	**V2**	**P3**	**V3**	**V4**	**V5**	**V6**	**V7**
Visit number INNODIA backbone		INN V1							INN V2	INN V3		INN V4	INN V5
Time line		**<6 weeks from diagnosis[b]**	**Day 0 (≤2 weeks from V-1)**	**Week 1**	**Week 4**	**Week 5**	**Week 8**	**Week 9**	**Month 3**	**Month 6**	**Month 9**	**Month 12**	**Month 24**
Visit window (days)				**±2**	**±3**	**±2**	**±3**	**±2**	**±7**	**±7**	**±7**	**±7**	**±3 weeks**
Assessment													
Informed consent	X[a]	X[a]										X	
Randomisation			X										
Attend visit fasting		X	X		X		X		X	X	X	X	X
In/exclusion criteria		X											
Demographic		X											
Medical history/ concomitant illness		X											
Family medical history[c]		X	X						X	X		X	
Concomitant medication incl. vaccinations		X	X	X	X	X	X	X	X	X	X	X	
Diabetes care (Insulin regimen)[c]		X	X		X		X		X	X	X	X	X
Physical examination (incl. height, weight)		X	X						X	X		X	
ECG		X			X		X		X	X	X	X	
Vital signs		X	X		X		X		X	X	X	X	
HIV, Hepatitis B and C		X											
Autoantibodies		X										X	X
Fasting C-peptide, Blood glucose[i]		X	X		X		X		X	X	X	X	X
DNA extraction		X											
HbA1c		X	X		X		X		X	X	X	X	X
Immune cells (PBMC)		X							X	X		X	X
Blood (omics)		X							X	X	X	X	X

For peer review only - http://bmjopen.bmj.com/site/about/guidelines.xhtml

Trial period	**Consent and enrolment**	**Screening and baseline assessment**	**Randomisation**	**Treatment**									**Observation**
Visit type (C: Clinic, P: Phone contact)	**C**	**C**	**C**	**P**	**C**	**P**	**C**	**P**	**C**	**C**	**C**	**C**	**C**
Visit number		**V-1**	**V0**	**P1**	**V1**	**P2**	**V2**	**P3**	**V3**	**V4**	**V5**	**V6**	**V7**
Visit number INNODIA backbone		INN V1							INN V2	INN V3		INN V4	INN V5
Time line		**<6 weeks from diagnosis[b]**	**Day 0 (≤2 weeks from V-1)**	**Week 1**	**Week 4**	**Week 5**	**Week 8**	**Week 9**	**Month 3**	**Month 6**	**Month 9**	**Month 12**	**Month 24**
Visit window (days)				**±2**	**±3**	**±2**	**±3**	**±2**	**±7**	**±7**	**±7**	**±7**	**±3 weeks**
Assessment													
Blood (beta-cell killing)		X							X	X	X	X	X
Whole blood RNA		X										X	X
microRNA (plasma omics)		X							X	X	X	X	X
Urine (biomarkers)		X							X	X		X	X
Stool (microbiome, metabolome)		X							X	X		X	X
Safety lab (incl. FBC, CMP)		X			X		X		X	X	X	X	X
MMTT			X						X	X	X	X	X
IMP dispensing			X		X		X		X	X	X		
IMP dose (mg SR once daily)			**120**	**120**	**240**	**240**	**360**	**360**	**360**	**360**	**360**	**360**	
Drug accountability			X		X		X		X	X	X	X	
Withdrawal criteria			X	X	X	X	X	X	X	X	X	X	
Adverse events assessment			X	X	X	X	X	X	X	X	X	X	X
Handout and instruct in CGM, DBS, patient diary and pregnancy test (if applicable)			X										
CGM data download (Review CGM)					X		X		X	X	X	X	
Review of patient diary					X		X		X	X	X	X	
Pregnancy test[d]		X	X		X		X		X	X	X	X	
PROMs[e]					X					X		X	
Home measurements[f]:													
Home DBS for C-Peptide (monthly)			X		X		X		X	X	X	X	
CGM[g]			X	**Readings done 2 weeks prior to each visit**									

For peer review only

For peer review only - http://bmjopen.bmj.com/site/about/guidelines.xhtml

Trial period	Consent and enrolment	Screening and baseline assessment	Randomisation	Treatment									Observation
Visit type (C: Clinic, P: Phone contact)	**C**	**C**	**C**	**P**	**C**	**P**	**C**	**P**	**C**	**C**	**C**	**C**	**C**
Visit number		**V-1**	**V0**	**P1**	**V1**	**P2**	**V2**	**P3**	**V3**	**V4**	**V5**	**V6**	**V7**
Visit number INNODIA backbone		INN V1							INN V2	INN V3		INN V4	INN V5
Time line		**<6 weeks from diagnosis[b]**	**Day 0 (≤2 weeks from V-1)**	**Week 1**	**Week 4**	**Week 5**	**Week 8**	**Week 9**	**Month 3**	**Month 6**	**Month 9**	**Month 12**	**Month 24**
Visit window (days)				**±2**	**±3**	**±2**	**±3**	**±2**	**±7**	**±7**	**±7**	**±7**	**±3 weeks**
Assessment													
Home Pregnancy test[h]			X		X		X		X	X	X	X	

Footnotes:

[a]Written informed consent must be in place before the participant initiates fasting prior to the screening visit. Any trial specific assessments must be conducted only after participants have given written informed consent.

[b]Diagnosis date is defined as date of first insulin injection.

[c]Familiy medical history and diabetes care information should be updated at the given visits

[d]Urine human chorionic gonadotropin (hCG) pregnancy test (as needed for women of childbearing potential or per local requirements)

[e]PROMs: HFS and DTSQs will be assessed at V1, V4, V6. DTSQc will be assessed at V6. ADDQoL will be assessed at V4, V6.

[f]Capillary glucose and DBS will be collected at home pre and 60 min post consumption of EnsurePlus, monthly, for the full 12 months follow-up, for DBS C-peptide measurement.

[g]Glucose monitor to be used constantly if possible but patient advised to wear sensors for 2 weeks prior to visits as a minimum.

[h]Subjects will be instructed to perform the test monthly at home if no site visit is planned according to local requirements. In case a menstrual period is missed or if pregnancy is suspected at any time during the trial, a urine pregnancy test should be performed.The subjects should be instructed to not dose trial product before urine pregnancy test has been ruled out.

[i]At visits where participants have a MMTT, no extra fasting C-peptide samples or blood glucose samples must be taken.

For peer review only

For peer review only - http://bmjopen.bmj.com/site/about/guidelines.xhtml

6 Introduction

6.1 Background

INNODIA is an Innovative Medicines Initiative consortium (IMI-2), established through Horizon 2020 initiative of the European Union, involving academic, industry and charitable partners. Recruitment to the INNODIA study is defined by the recruitment of subjects with a diagnosis of T1D identified within the first six weeks from diagnosis. INNODIA provides a standardised routine centralised assessment of critical immunological biological factors which determine the rate of progression of T1D with particular reference to declines in beta cell function and the potential impact of IMPs which could alter these trajectories.

7 Rationale for Trial

Type 1 diabetes mellitus (T1DM) is a disorder that arises following the selective autoimmune destruction of the insulin-producing beta-cells (1,2). A cure for T1DM would aim at ensuring that the necessary endogenous functional beta-cell mass required for adequate insulin production is preserved or increased. The Diabetes Control and Complications Trial have shown that even a small amount of preserved endogenous insulin production has beneficial effects in terms of outcome, overall glycaemic control and prevention of severe hypoglycaemia (3-5). Beta-cell destruction is considered to be mainly immune-mediated, and many efforts to stop or modify this destruction have focused on immunomodulatory, antigen-specific or anti-inflammatory interventions. Attempts to replace beta cells by pancreas or islet transplantation are associated with potentially severe side effects due to the necessary immunosuppression. Recently beta-cell protective or beta-cell regenerative approaches have gained wider attention, and pharmacological approaches to protect the patient's own insulin-producing beta cell mass have been proposed (6).

Verapamil is a L-type calcium channel blocker, has been approved by the US Food and Drug Administration and the European Medicine Agency and has been used as an antihypertensive compound for more than 3 decades. Several retrospective studies have reported that verapamil use is associated with a lower risk of developing type 2 diabetes (7,8). Recently it has been demonstrated that thioredoxin-interacting protein (TXNIP), a cellular redox regulator, is overexpressed during hyperglycaemia and induces beta-cell apoptosis (9). Furthermore, it has been reported that verapamil effectively lowers beta cell TXNIP expression in rodent beta cells and islets as well as in human islets, and thus promotes functional beta cell mass and prevents and even reverses overt diabetes (10). In a randomised double-blind placebo-controlled phase 2 clinical trial the efficacy and safety of oral verapamil added for 12 months to a standard insulin regimen in adult subjects with recent-onset T1D was assessed. Verapamil treatment, compared with placebo was well tolerated and associated with an improved mixed-meal-stimulated C-peptide area under the curve, a measure of endogenous beta cell function, at 3 and 12 months, as well as with a lower increase in insulin requirements and fewer hypoglycaemic events (6).

The aim of this trial is to confirm the effect of 360mg verapamil SR administered orally once daily (titrated over the first 3 months from 120 mg to 360 mg) on the preservation of stimulated C-peptide at 12 months compared to placebo.

7.1 Image-Ver-A-T1D

This section is relevant for sites in the following countries only:

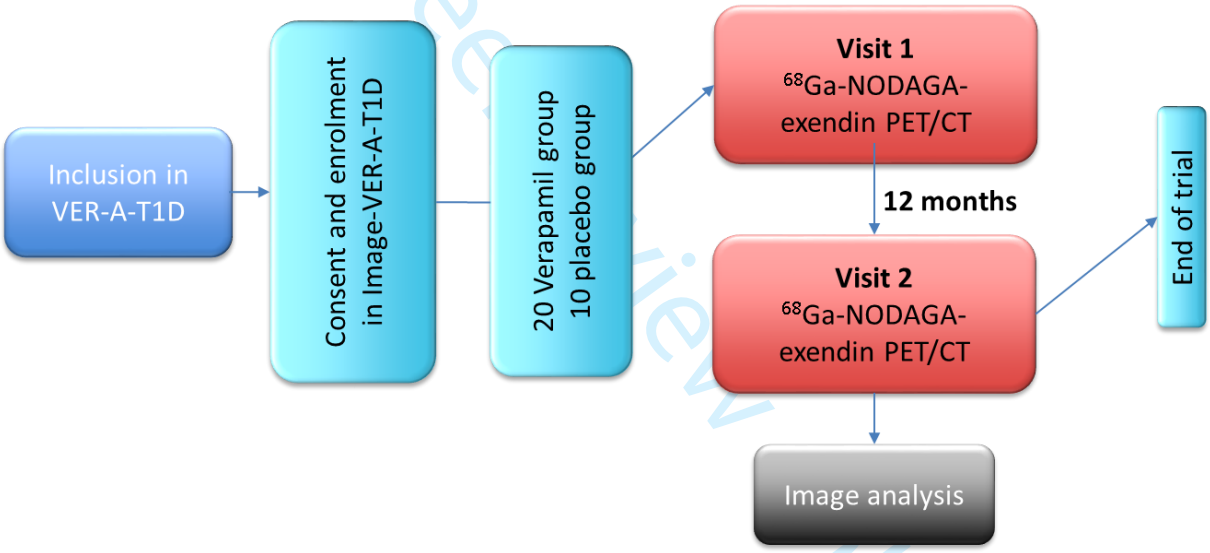
- Austria

For peer review only - http://bmjopen.bmj.com/site/about/guidelines.xhtml

- United Kingdom
- France

The Image-Ver-A-T1D trial is a multi-center imaging trial within INNODIA. The aim of this associated study is to investigate the effects of Verapamil treatment on preservation of the beta cell mass as visualized using 68Ga-NODAGA-Exendin-4 PET/CT compared to placebo at 12 months in adult subjects with newly diagnosed type 1 diabetes mellitus. The trial will include a total number of 30 participants that are already enrolled in the Ver-A-T1D trial. It will be conducted in specific PET/CT imaging sites selected by the sponsor of the trial. The sponsor of the Image-Ver-A-T1D study is Radboud University Medical Center (INNODIA partner). Participants that are enrolled in the Ver-A-T1D trial may be informed about the Image-Ver-A-T1D trial by the Ver-A-T1D study team before the randomisation visit. If participants express their interest, they will be offered to contact the imaging site where all the details will be discussed with the participants. Once they have been given sufficient time to consider their participation in the trial, consent will be obtained by the Image-Ver-A-T1D study team.
Participants will have a total of 2 imaging visits.

Image-Ver-A-T1D_**Trial flow chart**



Detailed study procedures will be provided in a separate Image-Ver-A-T1D study protocol in the relevant countries. Before the start of the trial or implementation of any amendment, approval of the trial protocol, protocol amendments, informed consent forms and other relevant documents from the research ethics committee (REC) and the competent health authority will be obtained.

8 Trial Design

8.1 Statement of Design

This is a multi-centre, randomised, double-blind, placebo-controlled trial testing the efficacy of 360mg verapamil SR administered orally once daily (titrated over the first 3 months from 120 mg to 360 mg) on protection of stimulated C-peptide decline in subjects with diagnosis of T1D within 6 weeks of diagnosis.

For peer review only - http://bmjopen.bmj.com/site/about/guidelines.xhtml

8.2 Rationale for trial design

The rationale for the trial design is to investigate the effect of 360mg verapamil SR administered orally once daily (titrated over the first 3 months from 120 mg to 360 mg) on preservation of beta-cell function compared to placebo at week 52 in adult subjects with newly diagnosed T1DM with residual beta-cell function. Participants will be allocated to treatment or placebo in a 2:1 ratio (verapamil SR:placebo). The duration of the trial with 52 weeks of exposure of 360mg verapamil SR administered orally once daily (titrated over the first 3 months from 120 mg to 360 mg) has been chosen to align with the regulatory requirements from FDA and EMA. The FDA and EMA guidelines advise that studies of products aimed at preservation of beta-cell function in recent-onset T1DM with remaining endogenous insulin reserve, should evaluate metabolic outcomes, such as stimulated C-peptide levels. Therefore, the MMTT stimulated $AUC_{0\text{-}2h}$ C-peptide concentration has been chosen as the primary efficacy parameter.

From the randomised, double-blind, placebo-controlled phase 2 clinical trial (6) the SD for the AUC C-peptide endpoint after a MMTT over 2 hours at 12 months was 0.27 nmol/L/min. With this SD, 90% power, 5% significance level then 40 participants on the control arm and 80 on the experimental arm will be needed to detect a change of 0.18 nmol/L/min in C-peptide. If the SD was much higher at 0.4 nmol/L/min then the size of treatment effect would change from a 0.18 nmol/L/min difference to a 0.27 nmol/L/min difference.

Clinical meaningful endpoints have been included such as number of treatment emergent severe hypoglycaemic episodes and change in insulin dose per day and HbA1c. Furthermore, other secondary end-points e.g. fasting values of C-peptide have been included to describe effect of treatments on the glucose metabolism and insulin usage and CGM parameters to evalulate effects on glycaemic variability.

The study also provides an opportunity to identify interventional strategies which in the future could be stratified by predicted rate of ß-cell decline and new discovery of critical biomarkers – an approach which will lead to personalised medicine.

A multi-centre and multinational design has been chosen to ensure that the results are applicable for subjects with different demographic characteristics.

8.3 Number of Centres

We plan to include all the sites who are part of the existing INNODIA clinical network and that are confirmed suitable for undertaking this specific study from the accreditation undertaken as part of INNODIA. However, in order to recruit the required number of participants, suitable INNODIA sites may work with their local existing network to identify and recruit potential participants. Additional sites in the UK that form part of the UK Type 1 Diabetes Immunotherapy Consortium and can perform studies to appropriate standards consistent with the INNODIA platform will also be considered.

8.4 Number of Participants

40 participants on the control arm and 80 on the experimental arm (total of 120 subjects) are expected to complete the trial. We plan to randomise 138 participants in this trial (2:1 ratio) to compensate for an estimated drop-out rate of 15%. We anticipate that we require approximately 230 participants to be screened (approximately 60% consent rate).

For peer review only - http://bmjopen.bmj.com/site/about/guidelines.xhtml

8.5 Participants Trial Duration

The trial duration will be approximately 24 months, consisting of screening, randomisation, 12 months treatment period and an additional 12 months INNODIA follow-up.

8.6 Trial Objectives

8.6.1 Primary objective

To determine the changes in stimulated C-peptide response during the first two hours of a mixed meal tolerance test (MMTT) at baseline and after 12 months for 360mg verapamil SR administered orally once daily versus placebo.

8.6.2 Secondary objective

- To determine the effects of 360mg verapamil SR administered orally once daily on fasting C-peptide and DBS C-peptide measurements over time
- To determine the effects of 360mg verapamil SR administered orally once daily on HbA1c, daily total insulin dose and CGM time in range
- To determine the effects of treatment on other biomarkers related to immunological changes and beta-cell death and survival in this population.
- To determine the effects of 360mg verapamil SR administered orally once daily on safety (vital signs, ECG)

8.6.3 Tertiary objective

- To compare between treatment arms and across the course of treatment the PROMs scores completed by participants

8.7 Trial Outcome Measures

8.7.1 Primary outcome measure

The area under the stimulated C-peptide response curve over the first two hours of a mixed meal tolerance test (MMTT) at 12 months follow-up compared to placebo

8.7.2 Secondary outcome measure

- The area under the stimulated C-peptide response curve over the first two hours of a mixed meal tolerance test (MMTT) at 3, 6, 9 months
- Proinsulin, Insulin, Pro-IAPP and Proglucagon secretion during the first two hours of a mixed meal tolerance test (MMTT) at baseline and 3, 6, 9 an 12 months
- Fasting C-peptide after 12 months therapy compared to placebo
- The DBS C-peptide measurements at all observation times
- Change in HbA1c baseline to 12 months
- Number of treatment emergent severe hypoglycaemic episodes. Severe hypoglycaemia denotes severe cognitive impairment requiring external assistance for recovery according to the American Diabetes Association (ADA)
- Number of treatment emergent episodes of diabetic ketoacidosis (DKA)
- Change in insulin requirements, baseline to 12 months as the daily total dose (three days average) in units per kg BW
- Change in T1D associated autoantibodies (GADA, IAA, IA-2A and ZnT8A) from baseline to 12 months
- CGM time in range (70-180 mg/dL, 3.9-10.0 mmol/L) and (70-140 mg/dL, 3.9-7.8 mmol/L), time above range (>180 mg/dL, >10.0 mmol/L), time below range (<70 mg/dL, < 3.9 mmol/L)
- The area under the stimulated C-peptide response curve over the first two hours of a mixed meal tolerance test (MMTT) at 24 months

For peer review only - http://bmjopen.bmj.com/site/about/guidelines.xhtml

- Change in HbA1c baseline to 24 months
- Change in insulin requirements, baseline to 24 months as the daily total dose (three days average) in units per kg BW

8.7.3 Tertiary outcome measure

DTSQ, ADDQoL, HypoFear questionnaires completed by participants.

9 Selection and withdrawal of participants

9.1 Inclusion Criteria

To be included in the trial the participant must:

1. Have given written informed consent
2. Age ≥18 and <45 at consent
3. Must have a diagnosis of T1D of within 6 weeks duration at screening (date of the first insulin injection)
4. Must have at least one or more of the following diabetes-related autoantibodies present at screening: GAD, IA-2 and/or zinc transporter antibodies
5. Must have fasting C-peptide levels ≥100 pmol/L measured at screening
6. Be willing to comply with intensive diabetes management

9.2 Exclusion Criteria

The presence of any of the following will preclude participant inclusion:

1. Be immunodeficient or have clinically significant chronic lymphopenia: Leukopenia (< 3,000 leukocytes /μL), neutropenia (<1,500 neutrophils/μL), lymphopenia (<800 lymphocytes/μL), or thrombocytopenia (<100,000 platelets/μL)
2. Have active signs or symptoms of acute infection at the time of screening
3. Be currently pregnant or lactating, or anticipate getting pregnant during the 12 months study period
4. Require use of immunosuppressive agents including chronic use of systemic steroids
5. Have evidence of current or past human immunodeficiency virus (HIV), Hepatitis B or Hepatitis C infection
6. Have any complicating medical issues or abnormal clinical laboratory results that may interfere with study conduct, or cause increased risk to include pre-existing cardiac disease, chronic obstructive pulmonary disease (COPD), sickle cell disease, neurological, or blood count abnormalities, as judged by the investigator
7. Have persistent history of malignancies other than skin
8. 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
9. History of renal insufficiency or evidence of renal dysfunction with creatinine greater than 1.5 times the upper limit of normal
10. Current or ongoing use of non-insulin pharmaceuticals that affect glycaemic control within prior 7 days of screening
11. Use of any other investigational drug in the previous 30 days and/or intent on using any investigational drug for the duration of the trial
12. Current use of Verapamil or other calcium channel blockers
13. Known hypersensitivity to Verapamil or to any of its excipients
14. Concomittant medication known for significantly inducing or inhibiting CYP3A4 and/or glycoprotein-P metabolism
15. Intake of grapefruit juice, licorice, St.John's Wort, cannabidiol, ginkgo biloba
16. Substrate intake of CYP3A4 and/or glycoprotein-P metabolism, as judged by the investigator

For peer review only - http://bmjopen.bmj.com/site/about/guidelines.xhtml

17. Hypotension (of less than 100mmHg systolic), sick sinus syndrome (except patients with a functioning artificial pacemaker), uncompensated heart failure or severe left ventricular dysfunction; marked bradycardia (less than 50 beats/minute), atrial flutter or atrial fibrillation in the presence of an accessory bypass tract (e.g. Wolff-Parkinson-White syndrome), hypertrophic cardiomyopathy, acute myocardial infarction, attenuated neuromuscular transmission (e.g. by myasthenia gravis, Lambert-Eaton syndrome, advanced Duchenne muscular dystrophy)
18. ECG second or third degree atrioventricular block; Incomplete branch block.
19. Any condition that in the investigator's opinion may adversely affect study participation or may compromise the study results.
20. Current use of ß-blockers.

9.3 Treatment Assignment and Randomisation Number

All patients screened for the trial will be assigned a unique participant ID number.

The trial is double-blind. A randomisation session will be carried out for all subjects using a web-based platform (Randomizer®) at Medical University of Graz. At the randomisation visit (Visit 0) subjects meeting all inclusion criteria and none of the exclusion criteria will be centrally randomised to one of the two parallel treatment groups in a 2:1 (verapamil SR:placebo) manner to:

- Verapamil SR 360 mg
  - from Day 0 to Week 4: 120 mg SR once daily
  - from Week 4 to Week 8: 240 mg SR once daily
  - from Week 8 to Month 12: 360 mg SR once daily
- Placebo (matching verapamil SR 360 mg) mg
  - from Day 0 to Week 4: 120 mg once daily
  - from Week 4 to Week 8: 240 mg once daily
  - from Week 8 to Month 12: 360 mg once daily

9.4 Method of Blinding

Trial participants and research teams will be blinded to the treatment group for the duration of the trial. The double blinding will be achieved by providing verapamil SR identical placebo tablets.

9.5 Participant Withdrawal Criteria

A participant may terminate participation in the study at any time without necessarily giving a reason and without any personal disadvantage and without affecting their usual patient care. Withdrawal and permission to retain samples and data already collected will be documented in the eCRF.

An investigator can stop the participation of a participant after consideration of the benefit/risk ratio. Possible reasons are:

- Serious adverse events
- Treatment emergent side effects, that do not allow dose escalation to 240 mg verapamil SR or placebo
- Heart Rate 50-100 beats/min (normal QRS width): corrected QT interval (QTc Bazett) = $QT/\sqrt{(RR\ interval)} > 500$ ms
- Heart Rate 50-100 beats/min, QRS bundle block (QRS width > 500ms): QRS width − 120 = x; QTc > 500ms + x
- Non-compliance with the study protocol
- Technical grounds (e.g. patient moves)

For peer review only - http://bmjopen.bmj.com/site/about/guidelines.xhtml

- Early termination at the request of the CI/PI or Co-investigator
- Pregnancy
- Intention of becoming pregnant

The reason for withdrawal by an investigator and the permission to retain sample and data already collected will be clearly documented in the eCRF. Withdrawal from the study will not affect usual patient care.

In rare instances, it may be necessary for a participant to permanently discontinue (definitive discontinuation) study intervention. If study intervention is definitively discontinued, the participant will remain in the study to be evaluated for follow-up assessments.

A participant will be considered lost to follow-up if he or she repeatedly fails to return for scheduled visits and is unable to be contacted by the study site.
The following actions must be taken if a participant fails to return to the clinic for a required study visit:

- The site must attempt to contact the participant and reschedule the missed visit as soon as possible and counsel the participant on the importance of maintaining the assigned visit schedule and ascertain whether or not the participant wishes to and/or should continue in the study.
- Before a participant is deemed lost to follow up, the investigator or designee must make every effort to regain contact with the participant (where possible, 2 telephone calls or local equivalent methods). These contact attempts should be documented in the participant's medical record.
- Should the participant continue to be unreachable, he/she will be considered to have withdrawn from the study.

Subjects who are withdrawn will not be replaced.

10 Trial Treatments

Verapamil SR is a L-type calcium channel blocker, has been approved by the US Food and Drug Administration (FDA) and the European Medicine Agency (EMA) and has been used as an antihypertensive compound for more than 3 decades. Verapamil SR effectively lowers beta cell TXNIP expression in rodent beta cells and islets as well as in human islets. This effect is based on the established mode of action of verapamil SR, blockade of L-type calcium channels and the resulting decrease in intracellular free calcium leading to inhibition of TXNIP transcription. In mouse models of diabetes, oral administration of verapamil SR promotes functional beta cell mass and prevents and even reverses overt diabetes. In addition, downregulation of TXNIP also improves beta cell function including insulin production and secretion. In a randomised, double-blind, placebo-controlled phase 2 clinical trial the efficacy and safety of oral verapamil SR added for 12 months to a standard insulin regimen in adult subjects with recent-onset T1D was assessed. Verapamil SR treatment, compared with placebo was well tolerated and associated with an improved mixed-meal-stimulated C-peptide area under the curve, a measure of endogenous beta cell function, at 3 and 12 months, as well as with a lower increase in insulin requirements and fewer hypoglycaemic events (6).

After oral administration verapamil SR is absorbed well (more than 90%) but undergoes extensive first-pass hepatic metabolism so that bioavailability is only 10–23%. Verapamil SR is metabolized to several active and inactive metabolites. Most of the metabolites are excreted in bile. The most common side effects of verapamil SR are dose dependent and include constipation, dizziness, nausea, low blood pressure, and headache. Other side effects seen include: edema, congestive heart failure, pulmonary edema, fatigue,

For peer review only - http://bmjopen.bmj.com/site/about/guidelines.xhtml

elevated liver enzymes, shortness of breath, low heart rate, atrioventricular block, rash and flushing.

10.1 Treatment Summary

ARM Name	verapamil SR	placebo
IMP Name	verapamil SR	placebo
Type	drug	drug
Dose Formulation	tablet	tablet
Unit Dose Strength(s)	120 mg SR	120 mg
Dosage Level(s)	from Day 0 to Week 4: 120 mg once daily from Week 4 to Week 8: 240 mg once daily from Week 8 to Month 12: 360 mg once daily	from Day 0 to Week 4: 120 mg once daily from Week 4 to Week 8: 240 mg once daily from Week 8 to Month 12: 360 mg once daily
Route of Administration	oral	oral
Use	experimental	placebo comparator
IMP and NIMP	IMP	IMP
Sourcing	Provided centrally by MUG	Provided centrally by MUG
Packaging and Labeling	Study intervention will be labeled as required per country requirement. Labels will be blinded.	Study intervention will be will be labeled as required per country requirement. Labels will be blinded.

10.1.1 Name and description of verapamil SR

Verapamil (ATC: C08DA01) is a L-type calcium channel blocker, has been approved by the US Food and Drug Administration (FDA) and the European Medicine Agency (EMA) and has been used as an antihypertensive compound for more than 3 decades. After oral administration verapamil is absorbed well (more than 90%) but undergoes extensive first-pass hepatic metabolism so that bioavailability is only 10–23%. Verapamil is metabolized to several active and inactive metabolites. Most of the metabolites are excreted in the bile.

Verapamil inhibits the entry of calcium into smooth muscle cells of the systemic and coronary arteries and in the cells of cardiac muscle and the intracardiac conduction system. Verapamil lowers peripheral vascular resistance with little or no reflex tachycardia. Its efficacy in reducing both raised systolic and diastolic blood pressure is thought to be primarily due to this mode of action. Due to the effect on the movement of calcium in the intracardiac conduction system, verapamil reduces automaticity, decreases conduction velocity and increases the refractory period. This may cause the following cardiovascular side effects: bradycardic arrhythmias such as sinus bradycardia, sinus arrest with asystole, 2nd and 3rd degree AV block, bradyarrhythmia in atrial fibrillation, palpitations, tachycardia, development or aggravation of heart failure, and hypotension. The most common non-cardiovascular side effects of verapamil are dose dependent and include constipation, dizziness, nausea, and headache, fatigue, elevated liver enzymes, rash and flushing.

Verapamil effectively lowers beta cell TXNIP expression in rodent beta cells and islets as well as in human islets. This effect is based on the established mode of action of verapamil, blockade of L-type calcium channels and the resulting decrease in intracellular

For peer review only - http://bmjopen.bmj.com/site/about/guidelines.xhtml

free calcium leading to inhibition of TXNIP transcription. In mouse models of diabetes, oral administration of verapamil promotes functional beta cell mass and prevents and even reverses overt diabetes. In addition, downregulation of TXNIP also improves beta cell function including insulin production and secretion. In a randomised double-blind placebo-controlled phase 2 clinical trial the efficacy and safety of oral verapamil added for 12 months to insulin therapy was assessed in 11 adult subjects with recent-onset T1D was assessed. Verapamil treatment, compared with placebo was well tolerated and associated with an improved mixed-meal-stimulated C-peptide area under the curve, a measure of endogenous beta cell function, at 3 and 12 months, as well as with a lower increase in insulin requirements and fewer hypoglycaemic events (6).

The target dose of 360 mg once daily and the minimum target dose of 240 mg was chosen according to the literature. The rationale for the selected target dose is based on the efficacy demonstrated in this trial. In this already published randomized, double-blind, placebo-controlled phase 2 clinical trial, the participants were randomly assigned to receive a once-daily oral dose of sustained-release verapamil (titrated over the first 3 months from 120 mg to 360 mg) or placebo for a total of 12 months in addition to their insulin therapy. This dose was chosen according to its demonstrated tolerability and effectiveness in terms of calcium-channel blockade and considering that the maximal recommended daily dose for verapamil is 480 mg(6).

10.1.2 Legal status

Verapamil SR is an L-type calcium channel blocker, that has been approved by the US Food and Drug Administration (FDA) and the European Medicine Agency (EMA).

10.1.3 Drug supply

IMP supply to sites will be overseen by the Medical University of Graz and distributed by ABF Pharmaceutical Services GmbH, Vienna. Upon initial authorisation by the sponsor, an initial supply will be sent to sites; supplies thereafter will be requested and distributed as detailed in the pharmacy manual.

10.1.4 Drug administration

All participants of the trial will receive verapamil 120 mg SR tablets or identical placebo tablets at the following visits: V0, V1, V2, V3, V4, V5. Instruction on oral administration will happen at each visit.

Subjects will be instructed to take all IMP dose once daily at approximately same time. Subjects having mild side effects like dizziness or hypotension may be advised to take it in the evening before the sleep. At each in-house visit, data of wearable monitor will be reviewed for safety. Female subjects should be instructed to not dose trial product before urine pregnancy test has been ruled out.

10.1.5 Initiation and escalation of verapamil SR/ placebo

All subjects will initiate 120 mg verapamil SR or 120 mg placebo treatment on the day of randomisation. As the target dose is 360 mg verapamil SR or placebo, the dose will be escalated in increments of 120 mg verapamil SR or placebo every month until 360 mg verapamil SR or placebo has been reached. In case of intolerable verapamil side effects related to the dose escalation it is acceptable to maintain current verapamil dose and postpone escalation by 1 month. If 360 mg verapamil SR or placebo is not tolerated due to side effects, the dose can be reduced to 240 mg verapamil SR or placebo, which is considered to be the lowest acceptable dose. If 240 mg verapamil SR or placebo is not tolerated, the subject must be withdrawn.

For peer review only - http://bmjopen.bmj.com/site/about/guidelines.xhtml

10.1.6 Procedures for monitoring treatment compliance

Compliance with study intervention will be assessed at each visit by the investigator or designee. Compliance will be assessed by counting returned tablets during the site visits and documented in the source documents and eCRF. Deviation(s) from the prescribed dosage regimen should be recorded in the eCRF.
A record of the number of study tablets dispensed to and taken by each participant must be maintained and reconciled with study drug accountability and compliance records. Treatment start and stop dates, including dates for treatment delays and/or dose reductions will also be recorded in the eCRF.

10.2 Non Investigational Medicinal Products

No non-investigational medicinal products will be used in the trial.

10.3 Concomitant Therapy

10.3.1 Insulin therapy

Subject will continue on their current insulin treatment after they have been randomised. It is preferred that subjects continue on the same type of insulin treatment throughout the trial. Subjects will be trained in diabetes self-care including carbohydrate counting before and at randomisation and whenever needed during the course of the trial in order to achieve the most optimal diabetes control according to local standard of care.

During the trial subjects will receive insulin treatment in order to achieve metabolic control according to the local insulin titration guideline. Bolus and/or basal insulin can be stopped or paused at all times during the trial at the discretion of the investigator. The subject's need for bolus insulin will be documented in the eCRF.

During the MMTT no rapid or short-acting insulin will be given. The use of rapid acting insulin is acceptable up to 2 hours before the MMTT and the use of short-acting insulin up to 6 hours before the test, to correct hyperglycaemia. Long-acting insulin and basal rates on an insulin pump will not be discontinued during the MMTT.

During the DBS home collection short or rapid acting insulin should not be used until the end of the collection.

10.3.2 Permitted concomitant therapy

Any medication or vaccine (including over-the-counter or prescription medicines, vitamins, and/or herbal supplements) that the subject is receiving at the time of enrollment or receives during the study must be recorded along with:

- Reason for use
- Dates of administration including start and end dates
- Dosage information including dose and frequency

The following antiarrhythmic drugs are known to cause QTc interval prolongation and must be used with precaution:

- Antiarrhythmic agents class Ia: Quinidine, Procainamide, Disopyramide, Ajmaline
- Antiarrhythmic agents class Ic: Encainide, Flecainide, Propafenone, Moricizine
- Antiarrhythmic agents class III: Amiodarone, Sotalol, Dronedarone, Ibutilide, Dofetilide, Vernakalant, Bretylium

10.3.3 Prohibited concomitant therapy

The use of noninsulin pharmaceuticals that affect glycaemic control, alpha-blockers, beta-blockers, cardiac glycosides, antiarrhytmics, ivabradine, lithium, sulfinpyrazone,

For peer review only - http://bmjopen.bmj.com/site/about/guidelines.xhtml

almotriptan, monoamine oxidase (MAO) inhibitors and acetylsalicylic acid will not be allowed for the trial duration. Furthermore, concomitant medication known for signifcantly inducing or inhibiting CYP3A4 or being predominantly degraded via CYP3A4 and/or glycoprotein-P metabolism must not be taken under Verapamil therapy.

For more information and full details on potential drug-drug interactions also consult the Summary of Product Characteristics for VeraHEXAL KHK 120 mg retard (SmPC of VeraHEXAL). Where there is uncertainty regarding the use of concomitant medication, cases should be referred to the medical monitor to resolve.

10.4 Emergency unblinding

The randomisation software will be programmed with blind-breaking instructions. In case of an emergency, an investigator has the responsibility for determining if unblinding of a participants' treatment assignment is warranted. Participant safety must always be the first consideration in making such a determination. If the investigator decides that unblinding is warranted, the investigator should make every effort to contact the sponsor and medical monitor prior to unblinding a participant's treatment assignment unless this could delay emergency treatment of the participant. If a participant's treatment assignment is unblinded, the sponsor must be notified within 24 hours after breaking the blind. The date and reason that the blind was broken must be recorded in the source documentation and eCRF, as applicable.

When the code is broken, the treatment allocation will be accessible to the investigator and the Trial Management Group. If the code has been broken the subject must be withdrawn from the trial and a withdrawal session must be completed in the eCRF.

10.5 Accountability and dispensing

10.5.1 Pharmacy responsibilities

The investigator or designee must confirm appropriate temperature conditions have been maintained during transit for all study medication received and any discrepancies are reported and resolved before use of the study medication.
Only participants enrolled in the study may receive study medication and only authorized site staff may supply or administer study medication. All study medications must be stored in a secure, environmentally controlled, and monitored (manual or automated) area in accordance with the labeled storage conditions with access limited to the investigator and authorized site staff.
Further guidance and information for the final disposition of unused study interventions are provided in the pharmacymanual.

10.5.2 Drug accountability

The investigator, institution, or the head of the medical institution (where applicable) is responsible for study medication accountability, reconciliation, and record maintenance (i.e. receipt, reconciliation, and final disposition records).

Only participants enrolled in the study may receive IMPs and only authorized site staff may supply or administer study intervention.

10.5.3 Returns and destruction

Used and unused study medication will be destroyed at site after written confirmation from the sponsor. Destruction of IMPs will be done according to local procedures after accountability is finalised and reconciled by the monitor. Destruction of products must be documented.

For peer review only - http://bmjopen.bmj.com/site/about/guidelines.xhtml

11 Procedures and assessments

Throughout the trial the investigator should ensure working in accordance with (ICH GCP) and local regulations. The investigator must ensure that trial procedures are performed as described in the protocol. Any discrepancies will result in protocol and/or GCP deviations and the investigator must take appropriate action to avoid recurrence of the detected discrepancies.
If deviations do occur, the investigator must inform the monitor and the implications of the deviation must be reviewed and discussed. Deviations must be documented and explained in a protocol deviation by stating the reason, date and the action(s) taken (if applicable).

The following sections describe the assessments and procedures that must be performed during this trial. The timing of the assessments and procedures are specified in the flow chart Section 5. The investigator must keep a subject screening log, a subject identification code list and a subject enrolment log. The subject screening log and subject enrolment log may be combined in one list. The investigator should keep a pre-screening log. In addition, the investigator must keep a log of staff and delegations of task(s) at the site. The investigator must sign the log of staff and the delegation of task(s) at site at the time of delegation.

11.1 Participant identification

Potentially eligible individuals will be approached by health care professionals and/or local research teams during routine clinical appointment. Other potential eligible individuals or parent /legal guardian will be approached by local research teams by phone if they have previously agreed that their personal details be used for research studies purposes.

The study will also be advertised by poster and flyers in diabetes clinics, on social media, for example Facebook and Twitter, via INNODIA or local sites own pages, on the INNODIA website, T1D UK Immunotherapy website and other diabetes related websites and via newspaper if applicable.

All potential individuals approached or that have contacted the research teams will be provided with a verbal explanation of the study and written information sheets. Once they have been given sufficient time to consider their participation in the study consent will be obtained.

11.2 Consent

The informed consent form must be approved by the local ethics committee and must be in compliance with GCP, local regulatory requirements and legal requirements. The investigator or designee must ensure that each trial participant, or his/her legally acceptable representative, is fully informed about the nature and objectives of the trial and possible risks associated with their participation.

The investigator or designee will obtain written informed consent from each participant or the participant's legally acceptable representative before any trial-specific activity is performed. The informed consent form used for this trial and any change made during the course of this trial, must be prospectively approved by the REC. The investigator will retain the original of each participant signed informed consent form and a copy will be provided to the participant.

Should a participant require a verbal translation of the trial documentation by a locally approved interpreter/translator, it is the responsibility of the individual investigator to use locally approved translators.

For peer review only - http://bmjopen.bmj.com/site/about/guidelines.xhtml

If the trial requires documentation in a different language (other than English) the translation and back translation documents need to be reviewed and approved by the sponsor prior to use. All sections of the approved documents must appear in the translation. The translated version must be appropriately dated and version controlled.

Any new information which becomes available, which might affect the participant's willingness to continue participating in the trial will be communicated to the participant as soon as possible. Participants must be re-consented to the most current version of the ICF(s) during their participation in the study.

11.2.1 Registration

Following informed consent, the participant will be registered on the INNODIA central database using de-identifiable information only and a participant ID generated. All identifiable information such as full name, contact details and date of birth will be registered locally following local policies and regulations.

Participant eligibility for INNODIA master protocol will be recorded at this stage as well as gender and ethnicity.

11.3 Screening evaluation and baseline assessment

11.3.1 Screening and baseline assessments (Visit V-1)

Trial specific assessments will only be conducted after participants have given written informed consent. Study procedures and their timing are summarized in the Flow Chart. The screening visit and baseline assessment (V-1) must be conducted within 6 weeks of diagnosis.

Blood will be collected for the following screening assessments:

- Fasting C-peptide
- Autoantibodies
- Safety lab (incl. full blood count (FBC), complete metabolic profile (CMP))
- HIV, Hepatitis B and C

Additionally, for women of childbearing potential, if applicable, a pregnancy test will be performed according to local requirements (urine pregnancy test or serum pregnancy test).

At the same visit, the following information will be recorded:

- Demographics (age, gender, ethnicity)
- Date of T1D diagnosis (date of first insulin dose)
- HbA1c at diagnosis
- Daily insulin regimen at time of visit
- Blood glucose at time of visit
- Physical examination (including height and weight)
- Medical history
- Diabetes care
- Concomitant medication, including vaccinations in last 6 weeks
- Family medical history
- ECG
- Vital signs

For peer review only - http://bmjopen.bmj.com/site/about/guidelines.xhtml

At the same visit, the following INNODIA baseline samples will be collected from all screened participants: DNA extraction, HbA1c, Omics, ß cell killing assay, Whole blood RNA, microRNA (plasma omics), Immune cells (PBMC), Urine (omics, including microbiome analysis), Stool (omics, including microbiome and metabolome analysis)

Following review of the laboratory results from the screening samples by the local medical team, participants will be declared eligible or non-eligible for the clinical trial.

If any inclusion criteria are answered no or any exclusion criteria are answered yes, the subject is a screening failure. For screening failures the screening failure form in the electronic case report form (eCRF) must be completed with the reason for not continuing in the trial.
Re-sampling or re-screening is NOT allowed if the subject has failed one of the inclusion criteria or meets one of the exclusion criteria related to laboratory parameters. However, if a lab test at the screening visit is inconclusive a re-test can be performed. The repeat test results must be available for evaluating the subject's eligibility before Visit 0.

- Eligible participants will be invited for the randomisation visit (V0) and asked to attend the visit fasting (from midnight).
- Non-eligible participants will be informed of the results of the screening visit and explained the reason for non-eligibility and invited to join the INNODIA observational study.

11.3.2 Participant Randomisation (Visit 0)

Participants will be assessed for adverse events, withdrawal criteria, family medical history, concomitant medication, diabetes care, vital signs, physical examination (incl. height, weight) , HbA1c and pregnancy test (if applicable).

Randomisation, baseline assessments and MMTT must be done only after the participant is deemed to be eligible for the visit. Eligible participants will be randomised into the verapamil SR or placebo arm and receive instructions on frequency of administration (daily intake). The randomisation visit must be performed within 2 weeks of the screening visit (V-1). The baseline MMTT, randomisation and first study drug administration should all be performed on the same day. The study drug should only be given AFTER completion of the MMTT. If the MMTT has to be rescheduled the randomisation and first dose of study drug should be delayed. The rescheduled randomisation visit should occur within 2 weeks and 3 days of the (V-1).

All participants will have a 120 minutes mixed meal tolerance test (MMTT) with Ensure Plus for measuring C-peptide and glucose as a measurement of beta cell response.

Participants will be set up with a continuous glucose monitor (CGM) and handed out a patient diary before leaving the clinical research facility.

11.4 Treatment

Verapamil SR 360mg orally administered daily (titrated over the first 3 months from 120 mg to 360 mg) versus placebo in a 2:1 manner.

11.5 Trial assessments

Study procedures and their timing are summarized in the Trial Flow Chart. Protocol waivers or exemptions are not allowed. Immediate safety concerns should be discussed

For peer review only - http://bmjopen.bmj.com/site/about/guidelines.xhtml

with the sponsor immediately upon occurrence or awareness to determine if the participant should continue or discontinue study treatment.

Adherence to the study design requirements, including those specified in the Trial Flow Chart, is essential and required for study conduct. All screening evaluations must be completed and reviewed to confirm that potential participants meet all eligibility criteria. The investigator will maintain a screening log to record details of all participants screened and to confirm eligibility or record reasons for screening failure, as applicable.

Procedures conducted as part of the participant's routine clinical management (e.g., blood count) and obtained before signing of the ICF may be utilized for screening or baseline purposes provided the procedures met the protocol-specified criteria and were performed within the time frame defined in the Trial Flow Chart.

Throughout the trial, a maximum of 3 ml per KG will be taken at each visit; no more than 204 mls per visit maximum.
Repeated or unscheduled samples may be taken for safety reasons or for technical issues with the samples.

11.5.1 Physical Examinations

At screening visit a complete physical examination will include, at a minimum, assessments of the cardiovascular, respiratory, gastrointestinal and neurological systems. Height and weight will also be measured and recorded.
A brief physical examination will take place at subsequent visits as jugded by the investigator. Investigators should pay special attention to clinical signs related to previous serious illnesses and possible withdrawal criteria.

11.5.2 Vital Signs

Body temperature (oral, tympanic or axillary, as per common site practice), pulse rate, and blood pressure will be assessed as outlined in the Trial Flow Chart. Blood pressure and pulse measurements will be assessed with a completely automated device. Manual techniques will be used only if an automated device is not available.

Blood pressure and pulse measurements should be preceded by at least 5 minutes of rest for the participant in a quiet setting without distractions (e.g. television, cell phones). Vital signs will be measured in a sitting position after 5 minutes rest and will include temperature, systolic and diastolic blood pressure, and pulse.

11.5.3 Electrocardiograms

Single 12-lead ECG will be obtained as outlined in the Trial Flow Chart using an ECG machine that automatically calculates the heart rate and measures PR, QRS, QT, and QTc intervals.

If a clinically significant finding is identified (including, but not limited to changes from baseline in PR interval, AV block) after enrollment, the investigator or qualified designee will determine if the participant can continue in the study and if any change in participant management is needed. This review of the ECG printed at the time of collection must be documented. Any new clinically relevant finding should be reported as an AE.

11.5.4 Continuous Glucose Monitoring (CGM)

Blood glucose variability will be studied through subcutaneous glucose variation, using data derived from glucose monitoring for the 2 weeks prior to each clinic visit (weeks 4, 8, month 3, 6, 9, 12).

For peer review only - http://bmjopen.bmj.com/site/about/guidelines.xhtml

All participants will be provided with a continuous glucose monitoring system (Dexcom G6) during visit V0. Suitable training will be provided to the participants so they can place the device and collect data at home.
Only the Dexcom G6 can be used for the trial assessments. Participants with other devices must agree to use the Dexcom G6 device for the two weeks prior to each visit to be eligible. Participants who already have a Dexcom G6 may continue to use it.

Participants are asked to wear a sensor for 2 weeks prior to each study visit and are advised to read their measurements at least 4-7 times a day to guide insulin dose adjustment. The sensor data will be downloaded by research staff or at home by participants at defined study visits. Participants are encouraged to use the sensors continuously outside of these 2 week periods to guide insulin adjustment and provide additional information. Each sensor can be used for 10 days before a new one is needed. Sufficient sensors will be given to participants at each study visit to cover until the next visit.

Encrypted glucose data from the sensor will be uploaded and stored in a cloud-based solution (Dexcom Clarity), an officially approved data storage and data preparation solution, where it remains available even after the study is completed.

11.5.5 Record/Categorisation of hypoglycaemia

Participants are advised to record in a trial diary any symptoms possibly related to hypoglycaemia (e.g. sweating, palpitations, confusion, requirement for external assistance for recovery, seizures, impairment or loss of consciousness) and their timing to allow us to compare to glucose readings with the glucose monitor data. A finger-prick blood glucose recording should be made and the result recorded in the diary any time hypoglycaemic symptoms occur, even if the glucose monitor sensor is also being worn.
The investigator should review the diary during the participant visit wherever possible to discuss any hypoglycaemic events documented. Clinical hypoglycaemic event rates will be calculated from records downloaded from the CGM device and the diary.

Categorisation of hypoglycaemic events will be done in two ways for analysis according to American Diabetes Assosciation (ADA) Guidelines (11,12).

1. **Level of Hypoglycaemia:**
   Level 1 - A glucose alert value of > 3.0 but ≤ 3.9 mmol/L (or less)
   Level 2 - A glucose level of ≤ 3.0 mmol/L - clinically important hypoglycaemia
   Level 3 - Severe hypoglycaemia, as defined by the ADA [12] denotes severe cognitive impairment requiring external assistance for recovery (see clinical characterisation below)

2. **Clinical characterisation:**

a. **Severe hypoglycaemia**. Severe hypoglycaemia is an event requiring assistance of another person to actively administer carbohydrates, glucagon, or take other corrective actions. Plasma glucose concentrations may not be available during an event, but neurological recovery following the return of plasma glucose to normal is considered sufficient evidence that the event was induced by a low plasma glucose concentration.
b. **Documented symptomatic hypoglycaemia**. Documented symptomatic hypoglycaemia is an event during which typical symptoms of hypoglycaemia are accompanied by a measured plasma glucose concentration < 3.9 mmol/L.

For peer review only - http://bmjopen.bmj.com/site/about/guidelines.xhtml

c. **Asymptomatic hypoglycaemia**. Asymptomatic hypoglycaemia is an event not accompanied by typical symptoms of hypoglycaemia but with a measured plasma glucose concentration < 3.9 mmol/L.
d. **Probable symptomatic hypoglycaemia**. Probable symptomatic hypoglycaemia is an event during which symptoms typical of hypoglycaemia are not accompanied by a plasma glucose determination but that was presumably caused by a plasma glucose concentration < 3.9 mmol/L

Hypoglycaemic events should be treated according to local clinical guidelines.

11.5.6 Diabetes care (Insulin regimen)

Mean daily insulin use will be calculated over 7 consecutive days during the 2 weeks preceding all visits and participants will be asked to record all insulin usage in their diary during those 2 weeks. This value will be calculated in units of IU/kg/day and combine doses of all different types of insulin administered over this study period. Where data from consecutive days are not available, the three days closest together will be used.

11.5.7 Clinical Safety Laboratory Assessments

Local laboratory will be used for safety lab evaluation.
See the list of clinical laboratory tests to be performed and the Trial Flow Chart for the timing and frequency.

The investigator must review the laboratory report, document this review, and record any clinically relevant changes occurring during the study in the AE section of the eCRF. The laboratory reports must be filed with the source documents. Clinically significant abnormal laboratory findings are those which are not associated with the underlying disease, unless judged by the investigator to be more severe than expected for the participant's condition.

All laboratory tests with values considered clinically significantly abnormal during participation in the study should be repeated until the values return to normal or baseline or are no longer considered clinically significant by the investigator or medical monitor.
If such values do not return to normal/baseline within a period of time judged reasonable by the investigator, the etiology should be identified and the sponsor notified.

Protocol-Required Safety Laboratory Assessments and Screening Assessments (performed by the local laboratory)

Laboratory Assessments	**Parameters**			
Hematology	Platelet Count Red blood cell (RBC) Count Hemoglobin Hematocrit	RBC Indices: MCV MCH	White blood cell (WBC) count with Differential: Neutrophils Lymphocytes Monocytes Eosinophils Basophils	
Clinical Chemistry[1]		Potassium	Aspartate Aminotransferase (AST)	Total bilirubin

For peer review only - http://bmjopen.bmj.com/site/about/guidelines.xhtml

Laboratory Assessments	Parameters			
	Creatinine	Sodium	Alanine Aminotransferase (ALT)	Total Protein
	Glucose	Calcium	Alkaline phosphatase	
Routine Urinalysis	• Specific gravity • pH, glucose, protein, erythrocytes, ketones, leucocytesby dipstick • Microscopic examination (if blood or protein is abnormal) • Urine human chorionic gonadotropin (hCG) pregnancy test (as needed for women of childbearing potential monthly per local requirements)[2]			
Other Screening Tests[3]	• Serology (HIV antibody, hepatitis B surface antigen [HBsAg], and hepatitis C virus antibody) • C reactive protein (CRP) • High-density lipoprotein (HDL), low-density lipoprotein (LDL), total cholesterol, triglycerides • Estimated Glomerular Filtration Rate (eGFR) calculated by the central laboratory based on the creatinine value using the CKD-EPI equation			

NOTES:
[1] All events of ALT ≥3 × upper limit of normal (ULN) and bilirubin ≥2 × ULN (>35% direct bilirubin) or ALT ≥3 × ULN or international normalized ratio (INR) >1.5 (if measured), which may indicate severe liver injury (possible Hy's Law), must be reported as an SAE.
[2] Local urine testing will be standard for the protocol unless serum testing is required by local regulation or IRB/IEC.
[3] At screening only.

Review of laboratory reports must be documented either on the document and/or in the subject's medical record.
The laboratory equipment may provide analyses not requested in the protocol but produced automatically in connection with the requested analyses according to specifications in the laboratory standard operating procedures. Such data will not be transferred to the trial documentation, but abnormal values will be reported to the investigator. The investigator must review all laboratory results for concomitant illnesses and AEs and report these according to this protocol.

Additional tests may be performed at any time during the trial as determined necessary by the investigator or required by local regulations.
If laboratory values from non-protocol specified laboratory assessments performed at the institution's local laboratory require a change in participant management or are considered clinically significant by the investigator (e.g., SAE or AE or dose modification), then the results must be recorded in the eCRF.

Subjects will be instructed to perform the following test monthly at home if no site visit is planned:

- Dried blood spot (DBS) for C-peptide
- Urine pregnancy test for women of childbearing potential (or as per local requirements)

Protocol-Required Exploratory INNODIA samples (assessments performed by the central laboratory/INNODIA)

For peer review only - http://bmjopen.bmj.com/site/about/guidelines.xhtml

Laboratory Assessments	Parameters
Blood	• C-peptide • Autoantibodies (GADA, IAA, IA-2A and ZnT8A) • DNA extraction • Omics • β cell killing assay • Whole blood RNA • Circulating microRNA (plasma omics) • Immune cells (PBMC)
Urinalysis	Omics, including microbiome analysis
Stool	Omics, including microbiome and metabolome analysis

11.5.8 Mixed Meal Tolerance Test (MMTT)

The MMTT will be performed according to the following protocol. Long-acting insulins or basal rates (in case of using an insulin pump) will be continued. The use of rapid-acting insulin is acceptable up to 2 hours before the MMTT and the use of short-acting insulin up to 6 hours before the MMTT to correct hyperglycaemia. Short-acting insulin can be used to up to 2 hours before the start of the MMTT to bring the glucose level into range. The test will be only performed if the glucose level is between 4 and 11.1 mmol/l at the start of the test. The eligibility of the participant for the MMTT should be in any case confirmed before visit specific assessments are started.

If it was necessary to correct hypoglycaemia after midnight the MMTT should be rescheduled. If the blood glucose level is outside the accepted range at the start of the test, the participant should treat accordingly and the visit should be abandoned and re-scheduled, if participant agrees.
Participants will be given 6 ml/kg of Ensure Plus meal solution (up to a maximum of 360 ml) orally which needs to be ingested within 10 minutes. Blood samples for the measurement of C-peptide and glucose will be collected 10 minutes prior to the meal (-10 mins), at the time of ingestion (0 minutes), and at 15, 30, 60, 90 and 120 minutes thereafter. Participants who are not able to tolerate Ensure Plus will be advised to eat a standardised breakfast with a defined content of carbohydrates, proteins and lipids, which will be the same for all visits during the study.

If the glucose level at t=120 minutes is >8 mmol/l, a subcutaneous insulin correction dose will be given, either via injection or pump, according to the participant's own insulin sensitivity factor. If the glucose level at t=120 is >14 mmol/l, ketones will be tested by finger prick. If ketones are >0.6 mmol/l, glucose and ketones will be repeated until ketones have decreased <0.6 mmol/l and the participant can be discharged from the clinical centre.

Proinsulin, Insulin, Pro-IAPP and Proglucagon levels will be measured on stored samples from the MMTT at a later timepoint.

11.5.9 Patient Reported Outcome Measures (PROMS)

Patients' quality of life will be assessed by participant-reported outcome measures (PROMs):

- the Diabetes Treatment Satisfaction Questionnaire – DTSQs, DTSQc
- the Audit of Diabetes Dependent Quality of Life - ADDQoL
- the Hypoglycaemia Fear Survey - HFS

For peer review only - http://bmjopen.bmj.com/site/about/guidelines.xhtml

Participants must complete DTSQs and HFS questionnaires at V1, V4 and V6. ADDQoL questionnaire must be completed at V4 and V6.
DTSQc questionnaire must be completed at V6 only.
The questionnaires will be provided electronically as part of the eCRF.

11.5.10 Patient diaries

The participants will be provided with a diary at Visit 0. The investigator or delegated will train the participants in the use of the diary according to the provided instructions.

The following information will be collected in the diaries:

- any illnesses, concomitant medications, severe hypoglycaemic events, hyperglycaemic events, pregnancy tests (if applicable) and insulin doses within the timeframes specified in the diary

The investigator or delegate should review the diary during the participant visit wherever possible.

11.5.11 Timing of assessments

Phone Visit 1 (1 week ±2 days post treatment start)

AE, Withdrawal criteria, Concomitant medication incl. vaccination

Visit 1 (4 weeks ±3 days post treatment start)

AE, Withdrawal criteria, Concomitant medication incl. vaccination, Safety Lab, ECG, Vital Signs, Pregnancy test (if applicable), Collect DBS cards, IMP dispensing, dose titration to 240 mg, Review CGM, Review patient diary, Diabetes care, PROMs, Fasting C-peptide, HbA1c, Hand out home measurement material

Phone Visit 2 (5 weeks ±2 days post treatment start)

AE, Withdrawal criteria, Concomitant medication incl. vaccination

Visit 2 (8 weeks ±3 days post treatment start)

AE, Withdrawal criteria, Concomitant medication incl. vaccination, Safety Lab, ECG, Vital Signs, Pregnancy test (if applicable), Collect DBS cards, IMP dispensing, dose titration to 360 mg, Review CGM, Review patient diary, Diabetes care, Fasting C-peptide, HbA1c, , Hand out home measurement material

Phone Visit 3 (9 weeks ±2 days post treatment start)

AE, Withdrawal criteria, Concomitant medication incl. vaccination

Visit 3 (3 months ±7 days post treatment start)

AE, Withdrawal criteria, Concomitant medication incl. vaccination, Safety Lab, ECG, Collect DBS cards, IMP dispensing, Review CGM, Review patient diary, Diabetes care, Vital Signs, Pregnancy test (if applicable), Physical examination (Height, weight), Hand out home measurement material, Additional INNODIA assessments: Family medical history, MMTT (incl. fasting C-peptide and blood glucose), HbA1c, Blood ß-cell killing, Blood (omics), mirco RNA (plasma omics), Immune cells (PBMC), Urine (biomarkers), Stool (microbiome, metabolome)

Visit 4 (6 months ±7 days post treatment start)

AE, Withdrawal criteria, Concomitant medication incl. vaccination, Safety Lab, ECG, Collect DBS cards, IMP dispensing, Review CGM, Review patient diary, Diabetes care, Vital Signs, Pregnancy test (if applicable), Physical examination (Height, weight), Hand

For peer review only - http://bmjopen.bmj.com/site/about/guidelines.xhtml

out home measurement material, Additional INNODIA assessments: Family medical history, MMTT (incl. fasting C-peptide and blood glucose), HbA1c, Blood ß-cell killing, Blood (omics), mirco RNA (plasma omics), Immune cells (PBMC), Urine (biomarkers), Stool (microbiome, metabolome), PROMs

Visit 5 (9 months ±7 days post treatment start)

AE, Withdrawal criteria, Concomitant medication incl. vaccination, Safety Lab, ECG, Collect DBS cards, IMP dispensing, Review CGM, Review patient diary, Diabetes care, Vital Signs, Pregnancy test (if applicable), Hand out home measurement material, Additional INNODIA assessments: MMTT (incl. fasting C-peptide and blood glucose), HbA1c, Blood ß-cell killing, Blood (omics), mirco RNA (plasma omics)

Visit 6 (12 months ±7 days post treatment start)

AE, Withdrawal criteria, Concomitant medication incl. vaccination, Safety Lab, ECG, Collect DBS cards, Review CGM, Review patient diary, Diabetes care, Vital Signs, Pregnancy test (if applicable), Physical examination (Height, weight), Additional INNODIA assessments: Family medical history, MMTT (incl. fasting C-peptide and blood glucose), HbA1c, Autoantibodies, Blood ß-cell killing, Blood (omics), Whole blood RNA, mirco RNA (plasma omics), Immune cells (PBMC), Urine (biomarkers), Stool (microbiome, metabolome), PROMs, Informed consent for Visit 7

11.6 Long-Term Follow-up Assessments

Visit 7 (24 months ± 3 weeks: INNODIA)
AE, Diabetes care, Safety Lab, Additional INNODIA assessments: MMTT (incl. fasting C-peptide and blood glucose), HbA1c, Autoantibodies, Blood ß-cell killing, Blood (omics), Whole blood RNA, mirco RNA (plasma omics), Immune cells (PBMC), Urine (biomarkers), Stool (microbiome, metabolome)

11.7 Missed visits and unscheduled visits

If a visit is missed every effort should be made to ensure information is collected at a telephone contact. Subjects will be invited for the next scheduled visit according to the visit schedule.

An unscheduled visit can be scheduled at any time at the discretion of the investigator, e.g. in case additional blood samples must be performed for safety reasons. This should be reported on the unscheduled visit form in the eCRF stating the reason for the visit.
If the subject attends the clinic due to re-sampling of visit-related assessments, including MMTT, this is not considered an unscheduled visit. The date of the assessments for a specific visit must be updated in the eCRF accordingly. Likewise, coming to the site for additional trial products or ancillary supplies is not considered as an unscheduled visit.

11.8 End of Trial Participation

A participant is considered to have completed the study if he/she has completed all phases of the study including the last visit.
The end of the study is defined as the date of the last visit of the last participant in the study in the trial globally.
Participants will be expected to continue normal standard of care during the trial period and following their participation in the trial.

11.9 Trial restrictions

Women of childbearing potential are required to use adequate contraception for the duration of the trial and for 7 days after the completion of last treatment (visit 6).

For peer review only - http://bmjopen.bmj.com/site/about/guidelines.xhtml

A woman is considered of childbearing potential (WOCBP), i.e. fertile, following menarche and until becoming postmenopausal unless permanently sterile. Permanent sterilisation methods include hysterectomy, bilateral salpingectomy and bilateral oophorectomy.

A postmenopausal state is defined as no menses for 12 months without an alternative medical cause. A high follicle stimulating hormone (FSH) level in the postmenopausal range may be used to confirm a postmenopausal state in women not using hormonal contraception or hormonal replacement therapy. However in the absence of 12 months of amenorrhea, a single FSH measurement is insufficient.

Women of childbearing potential are eligible to participate if they agree to use methods of contraception consistently and correctly as described as follows:

Highly effective contraceptive methods that are user dependent

Combined (oestrogen and progestogen containing) hormonal contraception associated with inhibition of ovulation:

- Oral
- Intravaginal
- Transdermal

Progestogen only hormonal contraception associated with inhibition of ovulation:

- Oral
- Injectable
- Implantable

Highly effective methods that are user independent

Implantable progestogen only hormonal contraception associated with inhibition of ovulation:

- Intrauterine device (IUD)
- Intrauterine hormone-releasing system (IUS)
- Bilateral tubal occlusion

Vasectomised partner

A vasectomised partner is a highly effective contraception method provided that the partner is the sole male sexual partner of the woman of childbearing potential and the absence of sperm has been confirmed. If not, an additional highly effective method of contraception should be used.

Sexual abstinence

Sexual abstinence is considered a highly effective method only if defined as refraining from heterosexual intercourse during the entire period of risk associated with the trial product. The reliability of sexual abstinence needs to be evaluated in relation to the duration of the trial and the preferred and usual lifestyle of the subject.

In certain cases, it is accepted to use double barrier methods [a condom combined with an occlusive cap (e.g. diaphragm) with/without the use of spermicide]. This should only be allowed in females:

- with known intolerance to the highly effective methods or where the use of any of the listed highly effective contraceptive measures are contraindicated in the individual subject, and/or
- if the risk of initiating treatment with a specific highly effective method outweighs the benefit for the female.

For peer review only - http://bmjopen.bmj.com/site/about/guidelines.xhtml

Justification for accepting double barrier method should be at the discretion of the investigator taking into consideration his/her knowledge about the female's concomitant illness, concomitant medication and observed AEs. The justification must be stated in the medical records.

Men are required to use adequate contraception for the entire duration of the trial and for 7 days after the completion of the last treatment. This includes:

- Barrier contraception (condom and spermicide)
- True abstinence (where this is in accordance with the participants preferred and usual lifestyle)

Country-specific requirements

Belgium:
Men, regardless of their fertility status, with non-pregnant women of childbearing potential (WOCBP) are required to use adequate contraception for the entire duration of the trial and for 7 days after the completion of the last treatment. This includes:

- True abstinence (where this is in accordance with the participants preferred and usual lifestyle)
- Condoms as well as 1 additional highly effective (less than 1% failure rate) method of contraception (such as combination oral contraceptives, implanted contraceptives, or intrauterine devices) or effective method of contraception (such as diaphragms with spermicide or cervical sponges).
- Condoms with spermicide are not acceptable.

12 Assessment of Safety

12.1 Definitions

12.1.1 Adverse event (AE)

Any untoward medical occurrence in a participant or clinical trial participant administered a medicinal product and which does not necessarily have a causal relationship with this treatment.
An adverse event can therefore be any unfavourable and unintended sign (including an abnormal laboratory finding), symptom, or disease temporally associated with the use of an investigational medicinal product, whether or not considered related to the investigational medicinal product.

Please note: Recording of all adverse events must start from the point of informed consent regardless of whether a participant has yet received a medicinal product.

12.1.2 Adverse reaction to an investigational medicinal product (AR)

All untoward and unintended responses to an investigational medicinal product related to any dose administered. All adverse events judged by either the reporting investigator or the sponsor as having a reasonable causal relationship to a medicinal product qualify as adverse reactions. The expression reasonable causal relationship means to convey in general that there is evidence or argument to suggest a causal relationship.

12.1.3 Unexpected adverse reaction

An adverse reaction, the nature, or severity of which is not consistent with the applicable reference safety information (RSI) (e.g. summary of product characteristics (SmPC) for an authorised product).
When the outcome of the adverse reaction is not consistent with the applicable RSI

For peer review only - http://bmjopen.bmj.com/site/about/guidelines.xhtml

this adverse reaction should be considered as unexpected.

The term "severe" is often used to describe the intensity (severity) of a specific event. This is not the same as "serious," which is based on participant /event outcome or action criteria.

12.1.4 Serious adverse event or serious adverse reaction (SAE / SAR)

Any untoward medical occurrence that at any dose:

- results in death
- is life-threatening
- requires hospitalisation or prolongation of existing inpatients´ hospitalisation
- results in persistent or significant disability or incapacity
- is a congenital anomaly or birth defect
- is an important medical event - Some medical events may jeopardise the participant or may require an intervention to prevent one of the above characteristics/ consequences. Such events (hereinafter referred to as 'important medical events') should also be considered as 'serious'

Life-threatening in the definition of a serious adverse event or serious adverse reaction refers to an event in which the participant was at risk of death at the time of event; it does not refer to an event which hypothetically might have caused death if it were more severe.

12.1.5 Suspected Unexpected Serious Adverse Reaction (SUSAR)

A serious adverse reaction, the nature and severity of which is not consistent with the information set out in the Reference Safety Information

12.1.6 Reference Safety Information (RSI)

A list of medical events that defines which reactions are expected for the IMP within a given trial and thus determining which serious adverse reactions (SARs) require expedited reporting.

The RSI is contained in a clearly identified section (section 4.8) of the Summary of Product Characteristics (SmPC).

12.2 Expected Adverse Reactions/Serious Adverse Reactions (AR /SARs)

All expected Adverse Reactions are listed in the latest MHRA approved version of the RSI as specified in section 12.1.6. This must be used when making a determination as to the expectedness of the adverse reaction. If the adverse reaction meets the criteria for seriousness, this must be reported as per section 12.5

12.3 Expected Adverse Events/Serious Adverse Events (AE/SAE)

The following events should not be reported as AEs:

- Non-serious hypoglycaemia as a result of the individual diabetes specific therapy is reported in the eCRF only instead of an AE form
- Non-serious Diabetic Ketoacidosis as a result of the individual diabetes specific therapy is reported in the eCRF only instead of an AE form

The following events can be expected as SAEs:

- Serious Hypoglycaemia
- Serious Diabetic Ketoacidosis

The above mentioned episodes fulfil the criteria for a SAE. In this case an AE and a SAE form must be filled in.

For peer review only - http://bmjopen.bmj.com/site/about/guidelines.xhtml

12.4 Evaluation of adverse events

The sponsor expects that adverse events are recorded from the point of informed consent regardless of whether a participant has yet received a medicinal product. Individual adverse events should be evaluated by the investigator. This includes the evaluation of its seriousness, and any relationship between the investigational medicinal product(s) and/or concomitant therapy and the adverse event (causality).

12.4.1 Assessment of seriousness

Seriousness is assessed against the criteria in section 12.1.4.This defines whether the event is an adverse event, serious adverse event or a serious adverse reaction

12.4.2 Assessment of causality

Definitely: A causal relationship is clinically/biologically certain. **This is therefore an Adverse Reaction**

Probable: A causal relationship is clinically / biologically highly plausible and there is a plausible time sequence between onset of the AE and administration of the investigational medicinal product and there is a reasonable response on withdrawal. **This is therefore an Adverse Reaction.**

Possible: A causal relationship is clinically / biologically plausible and there is a plausible time sequence between onset of the AE and administration of the investigational medicinal product. **This is therefore an Adverse Reaction.**

Unlikely: A causal relation is improbable and another documented cause of the AE is most plausible. **This is therefore an Adverse Event.**

Unrelated: A causal relationship can be definitely excluded and another documented cause of the AE is most plausible. **This is therefore an Adverse Event.**

Unlikely and Unrelated causalities are considered NOT to be trial drug related
Definitely, Probable and Possible causalities are considered to be trial drug related.

A pre-existing condition must not be recorded as an AE or reported as an SAE unless the condition worsens during the trial and meets the criteria for reporting or recording in the appropriate section of the eCRF.

12.4.3 Clinical assessment of severity

Mild: The participant is aware of the event or symptom, but the event or symptom is easily tolerated.

Moderate: The participant experiences sufficient discomfort to interfere with or reduce his or her usual level of activity.

Severe: Significant impairment of functioning; the subject is unable to carry out usual activities and / or the participant's life is at risk from the event.

12.4.4 Recording of adverse events

Adverse events and adverse reactions should be recorded in the medical notes and the appropriate section of the eCRF and/or AE/AR log. Serious Adverse Events and Serious Adverse Reactions should be reported to the sponsor as detailed in section 12.5.

12.5 Reporting serious adverse events

Each Principal Investigator needs to record all adverse events and report serious adverse events to the sponsorusing the trial specific SAE form within 24 hours of their awareness of the event.

The Investigator is responsible for ensuring the assessment of all SAEs for expectedness and relatedness is completed and the onward notification of all SAEs to the sponsor

For peer review only - http://bmjopen.bmj.com/site/about/guidelines.xhtml

immediately but not more than 24 hours of first notification. The investigator and the sponsor are obligated to assess the relationship between trial product and the occurrence of each SAE.
The sponsor has to keep detailed records of all SAEs reported to them by the trial team.

The sponsor is also responsible for prompt reporting of all serious adverse event findings to the competent authority of each concerned member state if they could:

- adversely affect the health of participants
- impact the conduct of the trial
- alter the risk to benefit ratio of the trial
- alter the competent authority's authorisation to continue the trial in accordance with Directive 2001/20/EC

The completed SAE form can be emailed. Details of where to report the SAE's can be found on the Ver-A-T1D SAE form and the front cover of the protocol.

12.6 Reporting of Suspected Unexpected Serious Adverse Reactions (SUSARs)

All suspected adverse reactions related to an investigational medicinal product (the tested IMP and comparators) which occur in the concerned trial, and that are both unexpected and serious (SUSARs) are subject to expedited reporting. Please see section 12.1.6 for the reference safety information to be used in this trial.

12.6.1 Who should report and whom to report to?

The investigator must report all the relevant safety information previously described, to thesponsor.
The sponsor must report all the relevant safety information previously described to the:

-
- Competent authorities in the concerned member states (eg MHRA)
- Ethics Committee in the concerned member states

The sponsor shall inform all investigators concerned of relevant information about SUSARs that could adversely affect the safety of participants.

12.6.2 When to report?

12.6.2.1 Fatal or life-threatening SUSARs

All parties listed in 12.6.1 must be notified as soon as possible but no later than **7 calendar days** after the trial team and sponsor has first knowledge of the minimum criteria for expedited reporting.
In each case relevant follow-up information should be sought and a report completed as soon as possible. It should be communicated to all parties within an additional **8 calendar days**.

12.6.2.2 Non-fatal and non-life-threatening SUSARs

All other SUSARs and safety issues must be reported to all parties listed in 12.6.1 as soon as possible but no later than **15 calendar days** after first knowledge of the minimum criteria for expedited reporting. Further relevant follow-up information should be given as soon as possible.

For peer review only - http://bmjopen.bmj.com/site/about/guidelines.xhtml

12.6.3 How to report?

12.6.3.1 Minimum criteria for initial expedited reporting of SUSARs

Information on the final description and evaluation of an adverse reaction report may not be available within the required time frames for reporting. For regulatory purposes, initial expedited reports should be submitted within the time limits as soon as the minimum following criteria are met:
a) a suspected investigational medicinal product
b) an identifiable participant (e.g. trial participant code number)
c) an adverse event assessed as serious and unexpected, and for which there is a reasonable suspected causal relationship
d) an identifiable reporting source

and, when available and applicable:
- an unique clinical trial identification (EudraCT number or in case of non-European Community trials the sponsor's trial protocol code number)
- an unique case identification (i.e. sponsor's case identification number)

12.6.3.2 Follow-up reports of SUSARs

In case of incomplete information at the time of initial reporting, all the appropriate information for an adequate analysis of causality should be actively sought from the reporter or other available sources. Further available relevant information should be reported as follow-up reports.
In certain cases, it may be appropriate to conduct follow-up of the long-term outcome of a particular reaction.

12.6.3.3 Format of the SUSARs reports

Electronic reporting is the expected method for expedited reporting of SUSARs to the competent authority. The format and content as defined by the competent authority should be adhered to.

12.7 Pregnancy Reporting

All pregnancies within the trial in female trial participant will be collected after the start of study intervention and until 7 days after the last dose and should be reported to the Chief Investigator and the sponsor using the relevant pregnancy reporting form within 14 days of notification.
Details of pregnancies in female subjects will be collected after the first-trial-related activity after obtaining informed consent and until pregnancy outcome. If a pregnancy is reported in female subjects, the investigator should inform the Chief Investigator and sponsor within 14 calendar days of learning of the pregnancy and should follow the procedures outlined in section 12.7.1. Pregnancy outcome should be documented in the subject's medical record. Abnormal pregnancy outcome (e.g. spontaneous abortion, foetal death, stillbirth, congenital anomalies and ectopic pregnancy) is considered an SAE. The investigator will report information on the subject and the pregnancy outcome until the newborn infant is one month of age in accordance with European Medicines Agency (EMA) (13). Information about the pregnancy and pregnancy outcome/health of the new-born infant has to be reported on paper pregnancy forms.

12.7.1 Collection of pregnancy information - Female subjects who become pregnant

- Investigator will collect pregnancy information on any female subject, who becomes
- pregnant while participating in this trial.

For peer review only - http://bmjopen.bmj.com/site/about/guidelines.xhtml

- Information will be recorded on the appropriate form and submitted to the Chief Investigator and sponsor within 14 calendar days of learning of a subject's pregnancy.
- Subject will be followed to determine the outcome of the pregnancy. The investigator will collect follow-up information on subject and neonate, which will be forwarded to the sponsor. Generally, follow-up will not be required for longer than 1 month beyond the delivery date.
- Any termination of pregnancy will be reported, regardless of foetal status (presence or absence of anomalies) or indication for procedure.
- While pregnancy itself is not considered to be an AE or SAE, any pregnancy complication or elective termination of a pregnancy will be reported as an AE or SAE.
- A spontaneous abortion is always considered to be an SAE and will be reported as such.
- Any SAE occurring as a result of a post-trial pregnancy which is considered possibly/probably related to the trial product by the investigator will be reported to the the sponsor.

Any female subject who becomes pregnant while participating in the trial will discontinue trial product.

13 Toxicity – Emergency Procedures

Verapamil SR has a vasodilating action on the vascular system. Toxic effects occur usually after a delay of 1 to 5 hours following ingestion. The main cardiovascular symptoms are: bradycardia and atrioventricular block (in 82% of cases) hypotension and cardiogenic shock (in 78% of cases) cardiac arrest (in 18% of cases). Pulmonary edema may occur. Impairment of consciousness and seizures may occur and are related to a low cardiac output. Nausea and vomiting may be observed. Metabolic acidosis due to shock and hyperglycaemia may occur. Verapamil SR is a calcium channel blocker and inhibits the entry of calcium through calcium channels into cardiovascular cells. Verapamil SR reduces the magnitude of the calcium current entry and decreases the rate of recovery of the channel. Verapamil SR decreases peripheral vascular and coronary resistance but it is a less potent vasodilator than nifedipine. In contrast, its cardiac effects are more prominent than those of nifedipine. At doses necessary to produce arterial vasodilatation, Verapamil SR has much greater negative chronotropic, dromotropic and inotropic effects than nifedipine. At toxic doses, calcium channel inhibition by Verapamil SR results in three principal effects: hypotension due to arterial vasodilatation, cardiogenic shock secondary to a negative inotropic effect, bradycardia and atrio-ventricular block. The therapeutic effects of Verapamil SR on hypertension and angina pectoris are due to arterial systemic and coronary vasodilatation. The antiarrhythmic activity of Verapamil SR is due to a delay in impulse transmission through the AV node by a direct action. Toxicity may occur after ingestion of 1 g. Verapamil SR was tested on human peripheral lymphocytes in vitro using micronucleus (MN) test. The MN frequencies showed increase after all treatment. The results of FISH analysis suggest that Verapamil SR, separately or combined with ritodrine, shows to a larger extent aneugenic than clastogenic effect. Verapamil hydrochloride may increase blood alcohol (ethanol) concentrations and prolong its effects.

13.1 Management of mild to moderate toxicity

Patients who have asymptomatic bradycardia can be admitted and observed with telemetry if jugded reasonable by the investigator. Obtain peripheral intravenous access and monitor ECG. Mild hypotension may only require treatment with intravenous fluid administration.

For peer review only - http://bmjopen.bmj.com/site/about/guidelines.xhtml

13.2 Management of severe toxicity

Patients with bradycardia and hypotension require standard advanced cardiac life support (ACLS) treatment. Place a central line and consider placement of an arterial line. Standard first line treatment includes atropine for bradycardia although in a serious poisoning it is rarely effective. High dose insulin and dextrose have been effective in animal studies and multiple case reports in patients with hypotension refractory to other modalities, and should be considered early in patients with significant hypotension. Use intravenous calcium in severe poisonings although in these cases, beneficial effects of calcium infusion (calcium chloride is preferred) may be very minimal or short-lived. Repeat bolus doses or a continuous intravenous infusion are often needed. Standard vasopressors should be administered to maintain blood pressure. Lipid emulsion has been successful in animal studies and several case report of patients with hypotension refractory to other therapies. Intravenous glucagon has been used with variable success. In a patient whose hemodynamic status continues to be refractory despite the treatment described above, extracorporeal membrane oxygenation or cardiopulmonary bypass should be considered. Treat seizures with IV benzodiazepines; barbiturates or propofol may be needed if seizures persist or recur.

14 Storage and Analysis of Samples

Samples collected in the study as part of the INNODIA Clinical Trial Master Protocol will be stored and analysed as described in the Master Protocol.

Additional samples collected that are in the same nature, for example samples from additional MMTT or for additional immune cell studies, will be stored and analysed according to the INNODIA Clinical Trial Master Protocol.

15 Statistics

The trial is a multi-centre, randomised, double-blind, placebo-controlled trial in subjects with T1D within 6 weeks of diagnosis. A total sample size of 120 participants will be randomised 2:1 between 360mg Verapamil SR and placebo. The primary endpoint of interest is the area under the stimulated C-peptide response curve over the first two hours of a mixed meal tolerance test (MMTT) after 12 months therapy compared to placebo.

One interim analysis will be perfomed using data available at approximately 10 months to determine whether the trial should be stopped for futility.

All analyses will be perfomed on an Intention-to-treat (ITT) approach that will include all randomised participants irrespective of protocol compliance.

15.1 Statistical methods

All model assumptions will be checked via graphical means such as plotting residuals versus dose and fitted values. We will transform our primary outcome, AUC C-pep value to ln(AUC C-pep+1) as recommended by [4]. The transformed AUC C-pep value is assumed to be normally distributed; this distributional assumption will be assessed using a Q-Q plot and whether the residuals of the model deviate from a straight line. If the residuals are not normally distributed, then the outcome will be transformed to improve the assumption. If no transformation is available, then non-parametric methods will be used.

For peer review only - http://bmjopen.bmj.com/site/about/guidelines.xhtml

15.1.1 Primary Analyses

The primary endpoint, the area under the C-peptide curve over the first two hours (using all available measurements within the first 2 hours) of a mixed meal tolerance test (AUC C-pep) at 12 months (after transformation AUC C-pep →ln(AUC C-pep +1)) will be analysed using a linear mixed model at the end of the trial. The model will have fixed effects of treatment and time and the random effect will be participant ID. Additionally autocorrelations will be included within participants and ideally an unstructured matrix will be fitted stratified by treatment group, however, if the data do not allow such complexity then an AR(1) autocorrelation pattern will be estimated. The contrast of interest is the mean difference in AUC C-pep between Verapamil SR 360mg and placebo at 12 months.

The transformed AUC Cpep value is assumed to be normally distributed and this distributional assumption will be assessed using a Q-Q plot and whether the residuals of the model deviate from a straight line. Additionally, departures from normality will be assessed by using normality tests, like for instance the Shapiro-Wilk test. If model assumptions are violated for the AUC C-pep →ln(AUC C-pep +1)values, then log- or square root transformations will be applied. If none of these transformations yields normally distributed residuals, then treatments will be compared by means of non-parametric methods using the change from baseline as dependent variable.

15.1.2 Secondary Analyses

The secondary endpoints will also be analysed via a mixed effects models with fixed effects of treatment and time and the random effect will be participant ID. If required the models may include additional covariates which may be potential factors that are confounding the relationship between treatment and outcomes.

Subgroup analyses will be considered for a select list of potential covariates, the subgroup treatment effect will be analysed using an interaction test and additional factors will be included in the model to conduct this test.

A detailed statistical analysis plan (SAP) will be completed before the final database lock inline with the INNODIA Master SAP.

15.2 Interim analyses

The interim analysis should be carried out after 10 months from the start of the trial.

As with the primary analysis, the endpoint, the area under the C-peptide curve over the first two hours of a mixed meal tolerance test (AUC-Cpep) will be analysed using a mixed linear model. The model will have fixed effects of treatment and time and the random effect will be participant ID. Additionally autocorrelations will be included within particpants and ideally an unstructured matrix will be fitted stratified by treatment group, however, if the data do not allow such complexity then an AR(1) autocorrelation pattern will be estimated. The analysis will be an intention to treat analysis. The contrast of interest is the mean difference in AUC-Cpep between Verapamil SR 360mg and placebo at **6 months** as there will be no one who has completed the 12 month follow-up visit at 10 months. The statistical test will be the z-test and the trial will be recommended to stop if the z-statistics is less than -0.5 i.e. where treatment is marginally worse than placebo.

Given a recruitment rate of 5 participants per month the interim analysis at 10 months should have 15 people with 3 months of follow-up data, 15 people with 6 months of follow-up data and 15 people with 9 months of follow-up data. Different recruitment rates will alter the operating characteristics of the trial but the type 1 error at the final analysis is controlled but power may vary. If recruitment is faster then the timing of the interim

For peer review only - http://bmjopen.bmj.com/site/about/guidelines.xhtml

analysis will be re-assessed, if there is sufficient information the interim may proceed earlier than 10 months.

Model assumptions will be checked via graphical means such as plotting residuals versus dose and fitted values. The AUC-Cpep is assumed to be normally distributed, this distributional assumption will be assessed using a Q-Q plot and whether the residuals of the model deviate from a straight line. If the residuals are not normally distributed then the outcome will be transformed to improve the assumption.

15.3 Number of Participants to be enrolled

From the randomised, double-blind, placebo-controlled phase 2 clinical trial (6) the SD for the AUC C-peptide endpoint after a MMTT over 2 hours at 12 months was 0.27 nmol/L/min. With this SD, 90% power, 5% significance level then 40 participants on the control arm and 80 on the treatment arm will be needed to detect a change of 0.18 nmol/L/min in C-peptide.

All tests are for superiority tests and the tests are two-sided tests.

15.4 Criteria for the premature termination of the trial

The sponsor designee/INNODIA reserves the right to close the study site or terminate the study at any time for any reason at the sole discretion of the sponsor. Study sites will be closed upon study completion. A study site is considered closed when all required documents and study supplies have been collected and a study-site closure visit has been performed.
The investigator may initiate study-site closure at any time, provided there is reasonable cause and sufficient notice is given in advance of the intended termination.
Reasons for the early closure of a study site by the sponsor or investigator may include but are not limited to:

- Failure of the investigator to comply with the protocol, the requirements of the IRB/IEC or local health authorities, the sponsor's procedures, or GCP guidelines
- Inadequate recruitment of participants by the investigator
- Discontinuation of further study intervention development

If the study is prematurely terminated or suspended, the sponsor shall promptly inform the investigators, the IECs/IRBs, the regulatory authorities, and any contract research organization(s) used in the study of the reason for termination or suspension, as specified by the applicable regulatory requirements. The investigator shall promptly inform the subject and should assure appropriate subject therapy and/or follow-up.

15.5 Procedure to account for missing or spurious data

If there are substantial missing data in the primary endpoint then a repeated measures mixed effects model will be used in the primary analysis. All participants who are randomised will be included in this analysis and the model will have fixed effects for time and dose and participant is a random effect. All available measurements over time will be included in the analysis and an unstructured autocorrelation will be estimated for each dose level if sufficient data. The estimates assume that the missing data are missing at random. If the missing data are non-ignorable then a sensitivity analysis will be performed.

The secondary endpoints will also be analysed using a mixed effects model similar to the one described above. Again model assumptions and distributional assumptions will be inspected graphically.

For peer review only - http://bmjopen.bmj.com/site/about/guidelines.xhtml

15.6 Definition of the end of the trial

The end of the trial is defined as the date of the last visit of the last subject in the trial.

16 Data handling and record keeping

16.1 eCRF

All data will be transferred into an electronic Case Report Form (eCRF) which will be anonymised. All trial data in the eCRF must be extracted from and be consistent with the relevant source documents. The eCRFs must be completed, dated and signed by the investigator or designee in a timely manner. It remains the responsibility of the investigator for the timing, completeness, legibility and accuracy of the eCRF pages. The eCRF will be accessible to trial coordinators, data managers, the investigators, clinical trial monitors, auditors and inspectors as required.

All subject data relating to the trial will be recorded on eCRFs. The investigator is responsible for verifying that data entries are accurate and correct by electronically signing the eCRF.

Corrections to the eCRF data may be made by the investigator or the investigator's delegated staff. An audit trail will be maintained in the eCRF application containing as a minimum: the old and the new data, identification of the person entering the data, date and time of the entry and reason for the correction. If corrections are made by the investigator's delegated staff after the date when the investigator signed the eCRF, the eCRF must be signed and dated again by the investigator.

The investigator must be able to access his/her trial documents without involving the sponsor in any way. If applicable, electronic CRF and other subject data will be provided in an electronic readable format to the investigator before access is revoked to the systems supplied by the sponsor. Site-specific CRFs and other subject data (in an electronic readable format or as paper copies or prints) must be retained by the trial site. If the provided electronic data (e.g. the CD-ROM) is not readable during the entire storage period, the investigator can request a new copy. A copy of all data will be stored by the sponsor.

16.2 Source Data

Source documents provide evidence for the existence of the participant and substantiate the integrity of the data collected. Source documents are filed at the investigator's site. Data reported on the Source Data Form or entered in the eCRF that are transcribed from source documents must be consistent with the source documents or the discrepancies must be explained. The investigator may need to request previous medical records or transfer records, depending on the study. Also, current medical records must be available.

To enable peer review, monitoring, audit and/or inspection the investigator must agree to keep records of all participating participants (sufficient information to link records e.g., eCRFs, hospital records and samples), all original signed informed consent forms and copies of the eCRF in an electronic readable format .

Definition of what constitutes source data can be found in a source document agreement at each trial site. There will only be one source document defined at any time for any data element.

For peer review only - http://bmjopen.bmj.com/site/about/guidelines.xhtml

16.3 Data Protection & Participant Confidentiality

All investigators and trial site staff involved in this trial must comply with the requirements of the Data Protection Act 1998, GDPR (EU) 2016/679, local data protection laws and Trust Policy with regards to the collection, storage, processing, transfer and disclosure of personal information and will uphold the Act's core principles.

- Participants will be assigned a unique study identifier as agreed with the sponsor. Any participant records or datasets that are transferred to the sponsor will contain the identifier only; participant names or any information which would make the participant identifiable will not be transferred.
- The participant must be informed that his/her personal study-related data will be used by the sponsor in accordance with local data protection law. The level of disclosure must also be explained to the participant.
- The participant must be informed that his/her medical records may be examined by Clinical Quality Assurance auditors or other authorized personnel appointed by the sponsor, by appropriate IEC members, and by inspectors from regulatory authorities.
- Data may also be sent out to non- European countries.

17 Independent Data Monitoring Committee/Trial Steering Committee

The day to day management of the trial is the responsibility of the trial management group (Section 2).

17.1 Trial Steering Committee

The sponsor will constitute a trial steering committee (TSC) to provide the overall supervision of the trial. The TSC will monitor the trial progress, the safety data, the critical efficacy endpoints and conduct and advise on scientific credibility. The TSC will ultimately carry the responsibility for deciding whether a trial needs to be stopped on grounds of safety or efficacy. The TSC may recommend unblinding of any data for further analysis.

The TSC will consider recommendations from the independent Data Monitoring Committee (IDMC). The TSC will decide whehter to modify the trial, or to seek additional data.

17.2 Independent Data Monitoring Committee

The IDMC charter will detail the purpose of this committee including: the description of the membership, terms of reference, roles, responsibilities, authority, decision-making and relationships of the IDMC for this trial. The charter will further include the timing of meetings, methods of providing information to and from the IDMC, frequency and format of meetings, statistical issues, and relationships with other committees. Briefly, it is planned that 1 interim analyses is undertaken during this trial and in light of these interim analyses and safety endpoints, the IDMC will advise the TSC of its recommendations regarding trial modification, continuation or termination of the trial. The IDMC charter will expand on the above.

18 Ethical & Regulatory considerations

This study will be conducted in accordance with the protocol and with the following:

- Consensus ethical principles derived from international guidelines including the Declaration of Helsinki (and amendments).
- Applicable ICH Good Clinical Practice (GCP) Guidelines.
- Applicable laws and regulations.

For peer review only - http://bmjopen.bmj.com/site/about/guidelines.xhtml

The protocol, protocol amendments, ICF, Investigator Brochure, and other relevant documents (e.g., advertisements) must be submitted to an Independent Ethics Committee (IEC) by the investigator and reviewed and approved by the IEC before the study is initiated.
Any amendments to the protocol will require IEC approval before implementation of changes made to the study design, except for changes necessary to eliminate an immediate hazard to study participants.
The investigator will be responsible for the following:

- Providing written summaries of the status of the study to the IEC annually or more frequently in accordance with the requirements, policies, and procedures established by the IEC.
- Notifying the IEC of SAEs or other significant safety findings as required by IEC procedures.
- Providing oversight of the conduct of the study at the site and adherence to ICH guidelines, the IEC, European regulation 2001/20/EC for clinical studies, and all other applicable local regulations.

18.1 Ethical committee review

Before the start of the trial or implementation of any amendment we will obtain approval of the trial protocol, protocol amendments, informed consent forms and other relevant documents e.g., advertisements and general practicioner (GP) information letters if applicable from the research ethics committee (REC). All correspondence with the REC will be retained in the Trial Master File/Investigator Site File.

Annual reports will be submitted to the REC in accordance with national requirements. It is the Chief Investigator's responsibility to produce the annual reports as required.

18.2 Informed Consent Process

- The investigator will explain the nature of the study to the participant and answer all questions regarding the study.
- Participants must be informed that their participation is voluntary. Participants will be required to sign a statement of informed consent that meets the requirements of local regulations, ICH guidelines, and the IEC or study centre.
- The medical record must include a statement that written informed consent was obtained before the participant was enrolled in the study and the date the written consent was obtained. The authorized person obtaining the informed consent must also sign the ICF.
- Participants must be re-consented where an updated ICF(s) might impact on their decision to remain in the study.
- A copy of the ICF(s) must be provided to the participant or the participant's legally authorized representative.

18.3 Regulatory Compliance

The trial will not commence until a Clinical Trial Authorisation (CTA) is obtained from the applicable regulatory authorities. The protocol and trial conduct will comply with the Medicines for Human Use (Clinical Trials) Regulations 2004 and any relevant amendments. Regulatory authorities will receive the clinical trial application, protocol amendments, reports on SAEs, and the clinical trial report according to national requirements.

For peer review only - http://bmjopen.bmj.com/site/about/guidelines.xhtml

Development Safety Update Reports (DSURs) will be submitted to the regulatory authorities in accordance with national requirements. It is the Chief Investigators responsibility to produce the annual reports as required.

18.4 Protocol Amendments

Protocol amendments must be reviewed and agreement received from the sponsor for all proposed amendments prior to submission to the HRA, REC and/or MHRA.

The only circumstance in which an amendment may be initiated prior to HRA, REC and/or MHRA approval is where the change is necessary to eliminate apparent, immediate risks to the participants (Urgent Safety Measures). In this case, accrual of new participants will be halted until the HRA, REC and/or MHRA approval has been obtained.

In the event of an important safety measue, the Principal Investigator or suitable qualified delegaten at the participating site will be informed within 48 hours by the Chief Investigator or suitable qualified member of the study team.

18.5 Peer Review

This study protocol has been peer reviewed by the sponsor, trial management group and Principal Statistican.

18.6 Declaration of Helsinki and Good Clinical Practice

The trial will be performed in accordance with the spirit and the letter of the declaration of Helsinki, the conditions and principles of Good Clinical Practice, the protocol and applicable local regulatory requirements and laws.

18.7 GCP Training

All trial staff must hold evidence of appropriate GCP training or undergo GCP training prior to undertaking any responsibilities on this trial. This training should be updated every 2 years or in accordance with your Trust's policy.

19 Sponsorship, Financial and Insurance

The trial is sponsored by Medical University of Graz.
The trial will be funded by JDRF International.
The CGM will be provided by Dexcom.

Medical University of Graz will accept full financial liability for harm caused to participants in the clinical trial caused through the negligence of its employees and honorary contract holders. There are no specific arrangements for compensation should a participant be harmed through participation in the trial, but no-one has acted negligently.

Medical University of Graz will arrange insurance for negligent harm caused as a result of protocol design and for non-negligent harm arising through participation in the clinical trial.

Participants or their legal representatives of this study will not receive any payment for participating in this study, however, all reasonable travel costs incurred whilst travelling to the recruiting centre for each study visit will be reimbursed to the participant or legal representative by the coordinating centre.

20 Monitoring, Audit & Inspection

The investigator must make all trial documentation and related records available should an MHRA inspection or any regulatory authority inspection occur. Should a monitoring

For peer review only - http://bmjopen.bmj.com/site/about/guidelines.xhtml

visit or audit be requested, the investigator must make the trial documentation and source data available to the sponsor's representative. All participant data must be handled and treated confidentially.

The sponsor's monitoring frequency will be determined by an initial risk assessment performed prior to the start of the trial. A detailed monitoring plan will be generated detailing the frequency and scope of the monitoring for the trial. Throughout the course of the trial, the risk assessment will be reviewed and the monitoring frequency adjusted as necessary.

The scope and frequency of the monitoring will be determined by the risk assessment and detailed in the Monitoring Plan for the study.

21 Protocol Compliance and Breaches of GCP

Prospective, planned deviations or waivers to the protocol are not allowed and must not be used.
All participating sites must ensure that any substantial amendment is approved before implementation by an accredited EC.

However, deviations from the protocol should be avoided. If deviations do occur, the investigator must inform the monitor and the implications of the deviation must be reviewed and discussed.
Protocol deviations must be adequately documented on the relevant forms and reported to the Chief Investigator and sponsor immediately.

Deviations must be documented and explained in a protocol deviation by stating the reason, date, and the action(s) taken. Some deviations, for which corrections are not possible, can be acknowledged and confirmed via edit checks in the eCRF or via listings from the protocol deviation forms.

Deviations from the protocol which are found to occur constantly again and again will not be accepted and will require immediate action and could potentially be classified as a serious breach.
Any potential/suspected serious breaches of GCP must be reported immediately to the sponsor without any delay.

22 Publications policy

Ownership of the data arising from this study resides with INNODIA. On completion of the study the data will be analysed and tabulated and a Final Study Report prepared. Participating local investigators will have no rights to publish any of the study data without the permission of the Chief Investigator.

As outlined in the Consortium agreement each INNODIA partner (participant) has a maximum of 30 days to approve a publication or submit an objection after he has received the draft version in writing to the Coordination Team (publication@innodia.eu). **If no response is gathered by day 30, then approval is assumed to be granted.**

Nevertheless, the Beneficiaries acknowledge that some kind of publications may require shorter approval times due to given submission timelines:

Type of communication	Period for approval	Reminder sent out after	Approval required from
Full research paper	30 days	20 days	

For peer review only - http://bmjopen.bmj.com/site/about/guidelines.xhtml

Abstracts/ Posters	7 days	5 days	All INNODIA and ITC partners
Press releases*	5 days	--	
Public communications	5 days	--	

*Where national media releases are made, key messages and INNODIA researchers mentioned in the release should be circulated in English for approval.

In case of exceptional urgency, the Coordination team can grant permission to submit an abstract or a manuscript *sub conditione*, meaning that the manuscript os abstract will have to be withdrawn from the review and publication process in case an INNODIA beneficiary objects.

Participants and legal representatives will be notified of the outcome of this study by a specifically designated newsletter, after the study has been published.

For peer review only

For peer review only - http://bmjopen.bmj.com/site/about/guidelines.xhtml

23 References

1. Atkinson MA, Eisenbarth GS, Michels AW. Type 1 diabetes. Lancet 2014; 383:69–82
2. DiMeglio LA, Evans-Molina C, Oram RA. Type 1 diabetes. Lancet 2018; 391:2449–62
3. Diabetes Control and Complications Trial Research Group. The effect of intensive treatment of diabetes on the development and progression of long-term complications in insulin-dependent diabetes mellitus. N Engl J Med 1993; 329:977–86
4. Lachin JM, McGee P, Palmer JP, Group DER. Impact of C-peptide preservation on metabolic and clinical outcomes in the Diabetes Control and Complications Trial. Diabetes 2014; 63:739-748
5. Sorensen JS, Johannesen J, Pociot F, Kristensen K, Thomsen J, Hertel NT, Kjaersgaard P, Brorsson C, Birkebaek NH. Danish Society for Diabetes in, Adolescence, Residual beta-Cell function 3-6 years after onset of type 1 diabetes reduces risk of severe hypoglycemia in children and adolescents. Diabetes Care 2013; 36:3454-3459
6. Ovalle F, Grimes T, Xu G, Patel AJ, Grayson TB, Thielen LA, Li P, Shalev A. Verapamil and beta cell function in adults with recent-onset type 1 diabetes. Nat Med 2018; 24:1108–1112
7. Yin T, Kuo SC, Chang YY, Chen YT, Wang KK. Verapamil use is associated with reduction of newly diagnosed diabetes mellitus. J. Clin. Endocrinol. Metab. 2017; 102:2604–2610
8. Cooper-Dehoff R, Cohen JD, Bakris GL, Messerli FH, Erdine S, Hewkin AC, Kupfer S, Pepine CJ, for the INVEST Investigators. Predictors of development of diabetes mellitus in patients with coronary artery disease taking antihypertensive medications (findings from the INternational Verapamil SR-Trandolapril Study [INVEST]). Am. J. Cardiol. 2006; 98:890–894
9. Chen J, Saxena G, Mungrue IN, Lusis AJ, Shalev A. Thioredoxininteracting protein: a critical link between glucose toxicity and beta cell apoptosis. Diabetes 2008; 57:938–944
10. Xu G, Chen J, Jing G, Shalev A. Preventing beta-cell loss and diabetes with calcium channel blockers. Diabetes 2012; 61:848–856
11. Seaquist ER, Anderson J, Childs B, Cryer P, Dagogo-Jack S, Fish L, Heller SR, Rodriguez H, Rosenzweig J, Vigersky R. Hypoglycemia and diabetes: a report of a workgroup of the American Diabetes Association and the Endocrine Society. Diabetes Care 2013; 36: 1384-1395
12. A.D.A. Workgroup on Hypoglycemia, Defining and reporting hypoglycemia in diabetes: a report from the American Diabetes Association Workgroup on Hypoglycemia. Diabetes Care 2005; 28: 1245-1249
13. Guideline on the exposure to medicinal products during pregnancy: Need for postauthorisation data (EMEA/CHMP/313666/2005). 2005.

24 Appendices

For peer review only - http://bmjopen.bmj.com/site/about/guidelines.xhtml

24.1 Appendix 1 - Trial Management / Responsibilities

The trial will be overseen by the Trial Management Committee.

Chief Investigator:	Prof. Thomas Pieber, MD
Address:	Medical University of Graz
	Department of Internal Medicine
	Auenbruggerplatz 15
	A8036 Graz, Austria
Telephone:	+43 316 385 82383
INNODIA Coordinator:	Prof. Chantal Mathieu, MD
Address:	UZ Leuven
	Herestraat 49
	3000 Leuven, Belgium
Telephone:	+32 1 634 6023
Co-Chief Investigator:	Prof. Colin Dayan, MD
Address:	Cardiff University School of Medicine
	Heath Park
	Cardiff CF14 4XN, UK
Telephone:	+44 29207 42182
INNODIA Chief Statistician:	Prof. Adrian Mander
Address:	Cardiff University
	Cardiff CF10 3SAT, UK
Telephone:	+44 29206 87472
Trial Manager:	Martina Brunner, MSc
Address:	Medical University of Graz
	Center of Medical Research, Clinical Trials Unit
	Stiftingtalstrasse 24
	A8010 Graz, Austria
Telephone:	+43 316 385 72841

24.1.1 Participant registration/ Randomisation procedure

Information on how to register participants can be found in section 11.2.1 of the protocol.

For peer review only - http://bmjopen.bmj.com/site/about/guidelines.xhtml

24.1.2 eCRF Completion & Data management

Data will be collected using INNODIA (e)CRFs. Suitably qualified personnel designated by the PI and listed on the delegation of responsibility log will be responsible for completing the eCRF. Each clinical centre will be responsible for managing collected data and for generating and resolving data queries.

24.1.3 Preparation & submission of amendments

The Chief Investigator will be responsible for the preparation and submission of all amendments in Austria (AUT). Each non-AUT site will be responsible for the preparation and submission of all amendments to the appropriate ethics committee. Protocol amendments must be reviewed and agreement received from the sponsor for all proposed amendments prior to submission to the relevant national regulatory authorities.

24.1.4 Preparation and submission of Annual Safety Report/Annual Progress Reports

The Chief Investigator will be responsible for the preparation and submission of annual safety reports and annual progress reports.

24.1.5 Data protection/ confidentiality

eCRFs will be stored in an electronic database in which the participant will be identified by a study specific number. The participant's name and any other identifying detail will be recorded separately and stored at each participating site linked only by the study number. This information will be collected with the participant's/ legal representative's consent to enable follow-up to be undertaken. The sponsor will be responsible for insuring that all data is held in compliance with current legislation surrounding data protection. See section 16.3 for further information.

24.1.6 Trial documentation & archiving

The Trial Master File (TMF) will be kept up to date by the coordinating centre and each participating site will be responsible for maintaining their Investigator Site Files (ISF). These files need to be complete at the end of the trial and archived for 25 years. No records may be destroyed or transferred to another location or party without written notification of the sponsor during the retention period.
The sponsor will be responsible for archiving the TMF. Other participating sites will be responsible for archiving their ISF. Records and documents including source data will be stored at each participating site. The investigator must be able to access his/ her trial documents without involving the sponsor in any way. If applicable, electronic CRF and other subject data will be provided in an electronic readable format to the investigator before access is revoked to the systems supplied by the sponsor.
All essential and trial documentation will be securely archived after the last analysis of the study data has been completed and the final study report has been submitted to the relevant bodies.

For peer review only - http://bmjopen.bmj.com/site/about/guidelines.xhtml

24.2 Appendix 2 – Authorisation of Participating Sites

24.2.1 Required Documentation

- Investigator Site File
- Ethics approval from each country in addition and following home country approval
- Competent Authority approval
- All relevant local institutional approvals (e.g. local hospital institution)
- Signed participating site agreement when required
- Insurance statement
- Protocol signed and dated by PI
- Confirmation of receipt of investigator's brochure by PI
- Patient Information leaflets including informed consent form and any other study material for participants to be provided in English and translated to home country language
- Delegation of Responsibility and Signature Log
- PI signed and dated CV
- Signed and dated CVs from everyone listed on the delegation of responsibility log
- GCP certificate from PI and everyone listed on the delegation of responsibility log
- Final eCRF
- Study Manual, Pharmacy and SOPs
- Signed Source Data Verification Agreement Form (SDVAF)
- Local laboratory accreditation (or equivalent) and reference ranges for the protocol-specified parameters

24.2.2 Procedure for initiating/opening a new site

The study manager and/or monitor will organize the initiation meeting on behalf of the CI and invite all the participating site study members. The CI or delegate, study manager and/or monitor and PI will present throughout the meeting.

24.2.3 Principal Investigator Responsibilities

The PI's legal responsibilities will be listed in the Participating Site Agreement, if applicable, but each recruiting site will have a nominated PI who will be expected to:

- Read the protocol and agree to follow it and future amendet protocols in accordance with ICH Good Clinical Practice guidelines, legal and regulatory requirements
- Providing oversight of the conduct of the trial at the site and adherence to requirements of ICH guidelines, the IRB/IEC, and all other applicable local regulations
- Provide written summaries of the status of the trial in accordance with the requirements, policies, and procedures established by the IRB/IEC and/or regulatory authorities
- Notify the IRB/IEC of SAEs or other significant safety findings as required by IRB/IEC procedures
- Ensuring submission of the clinical trial report (CTR) synopsis to the IRB/IEC
- Attend initiation meeting and subsequent study meetings or delegate to suitable qualified team member
- Adhere to safety reporting timelines
- Have overall responsibility of data collection and responsibility of maintaining ISF
- Be thoroughly familiar with the appropriate use of the investigational product(s), as described in the protocol, in the current Investigator's Brochure, in the product information and in other information sources provided by the sponsor.

For peer review only - http://bmjopen.bmj.com/site/about/guidelines.xhtml

- Permit monitoring and auditing by the sponsor, and inspection by the appropriate regulatory authority(ies).
- Maintain a list of appropriately qualified persons to whom the investigator has delegated significant trial-related duties.

For peer review only

For peer review only - http://bmjopen.bmj.com/site/about/guidelines.xhtml

24.3 Appendix 3 – Benefit-Risk Assessment

24.3.1 Risk assessment for the inclusion of subjects

Diabetes mellitus type 1 is a metabolic disorder, which affects more than 35 million people worldwide. The majority of the patients develop this disorder in childhood or adolescence. This is when the insulin-producing beta cells get completely or almost completely destroyed, which leads to a lifelong dependence on exogenous insulin. The number of patients diagnosed with T1D per year is increasing each year and is approaching epidemic levels in various countries (Gesundheitsbericht Diabetes 2019, page 124; published in diabetesDE, Kirchheim-Verlag, www.diabetesde.org).

In the planned phase 2 study, the effect of Verapamil SR (sustained release) on the maintenance of beta cell function will be investigated. The aim of this study is to confirm recent reports (from a limited number of subjects) showing that this approved antihypertensive drug may have benefits for people with newly diagnosed T1D. Verapamil SR has been utilized in medicine over 30 years for the treatment of high blood pressure. In a randomized, double-blind, placebo-controlled phase 2 clinical trial, the efficacy and safety of oral Verapamil SR application combined with the standard insulin treatment over 12 months, has already been investigated in adult subjects with recurrent T1D. The treatment with Verapamil SR was well tolerated compared to placebo and showed an improved beta cell function, measured and assessed by the area below the MMTT-stimulated C-peptide curve. Furthermore, a decreased need for insulin increase and a reduction of hypoglycemic events could be observed. Weeks and even months after the diagnosis of type 1 diabetes, up to 20% of the insulin-producing cells are still active. The Verapamil SR, used in the Ver-A-T1D study, may be able to protect these cells and maintain the endogen insulin production.

Socio-medical and health-economic factors also show the need for new treatment options for patients with type 1 diabetes. New treatment options could provide relief to the patients and their relatives. A novel therapy to maintain the beta cell function could significantly reduce the amount of insulin and blood sugar monitoring required several times a day as well as the associated stress. Due to these facts, it is essential to carry out studies with new therapeutic approaches for this patient population and consequently for their relatives who suggest a number of improvements concerning the course of the disease and, above all, the associated management.

The involved clinical trials sites have already carried out several phase 2 studies in the field of diabetes that have provided crucial knowledge and skills which has minimized the risk for subjects.

24.3.2 Risk assessment for IMP treatment

The risk for the subjects can be evaluated as low. A study by OVALLE et al. (2018) showed only mild side effects in adults during treatment with Verapamil SR and none of the subjects had to discontinue treatment with Verapamil nor was a dose reduction necessary. In the mentioned study, the subjects received Verapamil SR (or placebo) once a day, whereby the dose was increased over a period of 3 months from 120 mg to 360 mg, for a total duration of 12 months in addition to their insulin therapy. This dose was selected based on tolerability, efficacy, and the maximum daily dose of 480 mg Verapamil SR. The subjects were carefully monitored for any occurrence of hypotension, bradycardia, or ECG changes (prolongation of the PR or QT interval). The only adverse event that was observed with a higher incidence in subjects was constipation, one of the most common side effects of Verapamil SR. However, the reported symptoms were mild and did not require any medical treatment. Additionally, no severe hypoglycaemic episodes, which required help from other people, were observed. It is also important to mention, that Verapamil SR did not cause hypotension in any subjects. Furthermore, all subjects showed a normal heart rate during the study and the evaluation of the ECGs

For peer review only - http://bmjopen.bmj.com/site/about/guidelines.xhtml

showed that treatment with Verapamil SR did not lead to any changes in the QT or PR intervals.
The most common side effects (≥ 1/10 of patients) of Verapamil SR listed in the product information are dose-dependent and include constipation, dizziness, nausea, low heart rate, low blood pressure, hot flashes and peripheral edema. Furthermore, swelling around the ankle and other joints, headaches and tiredness (1/100- 1/10 patients; tiredness and exhaustion) can occur. Other less common side effects are arrhythmias (<1/10000 patients), congestive heart failure, pulmonary edema, increased liver enzymes and shortness of breath.
For risk minimization during the planned study, the subjects will be treated and followed up with under strict medical monitoring. The study treatment and medical monitoring are carried out by experienced medical specialists during the visits at the clinic and between the clinic visits by telephone. 3 telephone visits are planned to ascertain the concomitant medication and possible adverse events. In addition, the appropriately trained study team is available by telephone 24 hours a day via an emergency number. All subjects are informed in advance about the risks and treatment options during a detailed conversation and receive an emergency card with the relevant contact details of the study team.

OVALLE F, et al. Verapamil and beta cell function in adults with recent-onset type 1 diabetes. Nat Med 2018; 24:1108–12.

24.3.3 IMP independent risks

Regardless of the IMP, the following risks for study participants during the planned study are possible:

1. Infections and nerve damage from blood sampling and infusions
2. Inflammation and nerve damage caused by capillary blood sampling via finger prick for blood sugar measurement
3. Continuous glucose measurement (CGM)
4. Tolerance tests after a standardized meal

ad 1) Infections and nerve damage from blood sampling and infusions
Venous blood samples will be taken during the planned study. The injection site (local) may cause mild inflammation, hematoma and swelling or irritation / inflammation of the vein wall (phlebitis). In individual cases a systemic infection can develop as a result. In very rare cases, catheter insertion or blood sampling causes local nerve damage and as a rare side effect, chronic nerve damage.
The venous blood collection and the placement of indwelling cannulas are generally performed by trained doctors. Previous disinfection of the puncture site and the use of sterile materials as preventive measures are of course essential.
Finally, the risk of side effects or consequential damage from a venipuncture can be considered as low.

ad 2) Inflammation and nerve damage caused by capillary blood sampling via fingerprick for blood sugar measurement
Capillary blood sampling from the fingertip can cause pain, bruising, and in rare cases (1 of 1000) an infection. The procedure for capillary blood collection is also known beyond this study, as a common measure for the determination of blood sugar, necessary several times a day. The number of blood glucose measurements varies greatly between individuals in each diabetes clinic. Subjects with type 1 diabetes are already fully trained by a diabetes advisor about the procedure at the time of manifestation and thus informed about possible side effects and their preventive measures (washing hands beforehand, disinfecting of the puncture site, constantly changing the puncture site and lancet).

ad 3) Continuous glucose measurement

For peer review only - http://bmjopen.bmj.com/site/about/guidelines.xhtml

The device for continuous glucose measurement is inserted under the skin. This can cause slight pain or bruising and, in rare cases, an infection at the injection site of the sensors. Therefore, the skin must be thoroughly disinfected before each installation. In rare cases, wearing the glucose sensor or the plaster of the transmitter can cause skin irritation or inflammation. Hence, it is recommended not to wear the sensor for more than six days. Before receiving a device for continuous glucose measurement for the first time, patients will receive extensive theoretical and practical training in handling, risks and prevention of those risks. There will also be a corresponding instruction for the study participants

ad 4) Tolerance tests after a standardized meal
As part of the planned study, a standardized meal test with a nutritional drink (milkshake) will be carried out to measure the C-peptide level or the residual function of the ß-cells of the pancreas. In preparation for the test, the subjects are not allowed to eat or drink anything for up to 8 hours before the respective test, this may lead to hypoglycaemia in the morning hours. As a preventive measure, the subjects are informed in advance by the study doctor about insulin therapy that needs to be adapted in this regard. They will receive precise instructions on the correct insulin dosage needed. The use of the food supplement drink (milkshake) is not associated with any side effects, apart from the fact that the subjects may not enjoy the taste of the drink. However, there are different flavours available (strawberry, chocolate, vanilla) so the preferred flavour can be selected by the subject.

24.3.4 Anticipated Clinical Benefits

During this trial, it is expected that all study participants, including those randomised to placebo will benefit from participation through frequent contact with the trial site, where diabetes is monitored and treated following careful medical examinations. To ensure all study participants, including those receiving placebo have adequate glycaemic control, investigators are encouraged to optimise treatment with antidiabetic medications throughout the trial in accordance with local clinical practice. All study participants in this trial will receive trial product and CGM systems free of charge for the duration of the trial treatment period.

24.3.5 Benefit-Risk Assessment related to the COVID-19 pandemic

Patients may be exposed to the risk of COVID-19 transmission and infection in relation to site visits if an outbreak is ongoing in the country concerned at the time of trial conduct. The risk of COVID-19 transmission in relation to site visits is overall considered to be low. To minimize the risk as much as possible – dependent on the situation and requirements from regulatory authorities - the following measures may be taken if appropriate:

- The number of physical on-site visits has been limited to the extent possible.
- On-site visits will be well-prepared and as short as possible. Physical contact between study participants and site staff will be limited to the extent possible, and protective measures will be implemented (mouth and nose protectors will be used by both site staff and study participants)
- Before entering the clinic, subjects will have a body temperature check and a symptom screening (coughing, shortness of breath, fever).

The use of a SARS-CoV-2 vaccine in patients treated with Verapamil SR 120 mg has not been studied.

Given the risk posed by COVID-19 in the midst of this pandemic, however, decisions regarding the use of any vaccination, including approved / authorized for use SARS-CoV-2 vaccines, in patients treated with Verapamil SR 120 mg should be made at the discretion of the investigator using their best clinical judgment and after careful consideration of risk benefit factors for the patient.

For peer review only - http://bmjopen.bmj.com/site/about/guidelines.xhtml

The investigator must consult the vaccine product label for further information regarding associated risks and precautions, and also guidance from local regulatory agencies. Hypersensitivity events have been reported in association with certain vaccines, in close temporal relation to the application.

Applicable information regarding an individual's receipt of vaccination(s) must be documented in the participant's source documents and each administration date of the vaccine (each time) recorded as a concomitant medication in the eCRF. Any possible related adverse events from the vaccination should be reported according to the Adverse Event/Serious Adverse Event reporting guidance and to the appropriate manufacture, according to local practice.

The sponsor continues to closely monitor the global health crisis and to understand the impact to the conduct of the Ver-A-T1D trial. New or worsening outbreaks of COVID-19 are rapidly evolving, regional in nature, and have varying consequences to regional healthcare systems based upon a number of local factors, and thus are difficult to predict or monitor.
The sites must assess this situation on an ongoing basis and must provide real time feedback to the sponsor if there is the potential to impact clinical research operations or if conditions at the site have the potential to impact the ability to monitor either the safety of participants or the scientific integrity of study(ies) at the site.

24.3.6 Risk and benefit conclusion

Assessment of diabetes and appropriate attention to the standard of care treatment will be provided throughout the trial. It is therefore concluded that the potential benefits from the trial will outweigh the potential risks for the Verapamil SR 120 mg as well as placebo treated patients.

Based on the risk assessment, the evaluation of COVID-19 and the implemented measures, the residual risk for study participants is considered low.

For peer review only

For peer review only - http://bmjopen.bmj.com/site/about/guidelines.xhtml

Reporting checklist for protocol of a clinical trial.

Based on the SPIRIT guidelines.

Instructions to authors

Complete this checklist by entering the page numbers from your manuscript where readers will find each of the items listed below.

Your article may not currently address all the items on the checklist. Please modify your text to include the missing information. If you are certain that an item does not apply, please write "n/a" and provide a short explanation.

Upload your completed checklist as an extra file when you submit to a journal.

In your methods section, say that you used the SPIRITreporting guidelines, and cite them as:

Chan A-W, Tetzlaff JM, Gøtzsche PC, Altman DG, Mann H, Berlin J, Dickersin K, Hróbjartsson A, Schulz KF, Parulekar WR, Krleža-Jerić K, Laupacis A, Moher D. SPIRIT 2013 Explanation and Elaboration: Guidance for protocols of clinical trials. BMJ. 2013;346:e7586

For peer review only

		Reporting Item	Page Number
Administrative information			
Title	#1	Descriptive title identifying the study design, population, interventions, and, if applicable, trial acronym	1
Trial registration	#2a	Trial identifier and registry name. If not yet registered,	1

		name of intended registry	
Trial registration: data set	#2b	All items from the World Health Organization Trial Registration Data Set	1-32
Protocol version	#3	Date and version identifier	1
Funding	#4	Sources and types of financial, material, and other support	31-32
Roles and responsibilities: contributorship	#5a	Names, affiliations, and roles of protocol contributors	1, 31-32
Roles and responsibilities: sponsor contact information	#5b	Name and contact information for the trial sponsor	1
Roles and responsibilities: sponsor and funder	#5c	Role of study sponsor and funders, if any, in study design; collection, management, analysis, and interpretation of data; writing of the report; and the decision to submit the report for publication, including whether they will have ultimate authority over any of these activities	31-32
Roles and responsibilities: committees	#5d	Composition, roles, and responsibilities of the coordinating centre, steering committee, endpoint adjudication committee, data management team, and other individuals or groups overseeing the trial, if	9-10

For peer review only

		applicable (see Item 21a for data monitoring committee)	
Introduction			
Background and rationale	#6a	Description of research question and justification for undertaking the trial, including summary of relevant studies (published and unpublished) examining benefits and harms for each intervention	4-5
Background and rationale: choice of comparators	#6b	Explanation for choice of comparators	5-6
Objectives	#7	Specific objectives or hypotheses	6-8
Trial design	#8	Description of trial design including type of trial (eg, parallel group, crossover, factorial, single group), allocation ratio, and framework (eg, superiority, equivalence, non-inferiority, exploratory)	9-10
Methods: Participants, interventions, and outcomes			
Study setting	#9	Description of study settings (eg, community clinic, academic hospital) and list of countries where data will be collected. Reference to where list of study sites can be obtained	9-10
Eligibility criteria	#10	Inclusion and exclusion criteria for participants. If	10-11

For peer review only

		applicable, eligibility criteria for study centres and individuals who will perform the interventions (eg, surgeons, psychotherapists)	
Interventions: description	#11a	Interventions for each group with sufficient detail to allow replication, including how and when they will be administered	11-14
Interventions: modifications	#11b	Criteria for discontinuing or modifying allocated interventions for a given trial participant (eg, drug dose change in response to harms, participant request, or improving / worsening disease)	18-23
Interventions: adherance	#11c	Strategies to improve adherence to intervention protocols, and any procedures for monitoring adherence (eg, drug tablet return; laboratory tests)	20-21
Interventions: concomitant care	#11d	Relevant concomitant care and interventions that are permitted or prohibited during the trial	18-19
Outcomes	#12	Primary, secondary, and other outcomes, including the specific measurement variable (eg, systolic blood pressure), analysis metric (eg, change from baseline, final value, time to event), method of aggregation (eg, median, proportion), and time point for each outcome. Explanation of the clinical relevance of chosen efficacy and harm outcomes is strongly recommended	6-8
Participant timeline	#13	Time schedule of enrolment, interventions (including any run-ins and washouts), assessments, and visits for	12-17

For peer review only

		participants. A schematic diagram is highly recommended (see Figure)	
Sample size	#14	Estimated number of participants needed to achieve study objectives and how it was determined, including clinical and statistical assumptions supporting any sample size calculations	25-26
Recruitment	#15	Strategies for achieving adequate participant enrolment to reach target sample size	6
Methods: Assignment of interventions (for controlled trials)			
Allocation: sequence generation	#16a	Method of generating the allocation sequence (eg, computer-generated random numbers), and list of any factors for stratification. To reduce predictability of a random sequence, details of any planned restriction (eg, blocking) should be provided in a separate document that is unavailable to those who enroll participants or assign interventions	16-17
Allocation concealment mechanism	#16b	Mechanism of implementing the allocation sequence (eg, central telephone; sequentially numbered, opaque, sealed envelopes), describing any steps to conceal the sequence until interventions are assigned	16-17
Allocation:	#16c	Who will generate the allocation sequence, who will	16-17

For peer review only

implementation		enrol participants, and who will assign participants to interventions	
Blinding (masking)	#17a	Who will be blinded after assignment to interventions (eg, trial participants, care providers, outcome assessors, data analysts), and how	16-17
Blinding (masking): emergency unblinding	#17b	If blinded, circumstances under which unblinding is permissible, and procedure for revealing a participant's allocated intervention during the trial	9, 16-17
Methods: Data collection, management, and analysis			
Data collection plan	#18a	Plans for assessment and collection of outcome, baseline, and other trial data, including any related processes to promote data quality (eg, duplicate measurements, training of assessors) and a description of study instruments (eg, questionnaires, laboratory tests) along with their reliability and validity, if known. Reference to where data collection forms can be found, if not in the protocol	26-27 (see extended data)
Data collection plan: retention	#18b	Plans to promote participant retention and complete follow-up, including list of any outcome data to be collected for participants who discontinue or deviate from intervention protocols	6-9, 17-18, 20-21

For peer review only

Data management	#19	Plans for data entry, coding, security, and storage, including any related processes to promote data quality (eg, double data entry; range checks for data values). Reference to where details of data management procedures can be found, if not in the protocol	26-28
Statistics: outcomes	#20a	Statistical methods for analysing primary and secondary outcomes. Reference to where other details of the statistical analysis plan can be found, if not in the protocol	24-25
Statistics: additional analyses	#20b	Methods for any additional analyses (eg, subgroup and adjusted analyses)	25
Statistics: analysis population and missing data	#20c	Definition of analysis population relating to protocol non-adherence (eg, as randomised analysis), and any statistical methods to handle missing data (eg, multiple imputation)	26
Methods: Monitoring			
Data monitoring: formal committee	#21a	Composition of data monitoring committee (DMC); summary of its role and reporting structure; statement of whether it is independent from the sponsor and competing interests; and reference to where further details about its charter can be found, if not in the protocol. Alternatively, an explanation of why a DMC is not needed	9-10

For peer review only

Data monitoring: interim analysis	#21b	Description of any interim analyses and stopping guidelines, including who will have access to these interim results and make the final decision to terminate the trial	25
Harms	#22	Plans for collecting, assessing, reporting, and managing solicited and spontaneously reported adverse events and other unintended effects of trial interventions or trial conduct	21-24
Auditing	#23	Frequency and procedures for auditing trial conduct, if any, and whether the process will be independent from investigators and the sponsor	28
Ethics and dissemination			
Research ethics approval	#24	Plans for seeking research ethics committee / institutional review board (REC / IRB) approval	28
Protocol amendments	#25	Plans for communicating important protocol modifications (eg, changes to eligibility criteria, outcomes, analyses) to relevant parties (eg, investigators, REC / IRBs, trial participants, trial registries, journals, regulators)	29
Consent or assent	#26a	Who will obtain informed consent or assent from potential trial participants or authorised surrogates, and how (see Item 32)	14-15

For peer review only

Consent or assent: ancillary studies	#26b	Additional consent provisions for collection and use of participant data and biological specimens in ancillary studies, if applicable	na
Confidentiality	#27	How personal information about potential and enrolled participants will be collected, shared, and maintained in order to protect confidentiality before, during, and after the trial	27
Declaration of interests	#28	Financial and other competing interests for principal investigators for the overall trial and each study site	30, 32
Data access	#29	Statement of who will have access to the final trial dataset, and disclosure of contractual agreements that limit such access for investigators	31
Ancillary and post trial care	#30	Provisions, if any, for ancillary and post-trial care, and for compensation to those who suffer harm from trial participation	30
Dissemination policy: trial results	#31a	Plans for investigators and sponsor to communicate trial results to participants, healthcare professionals, the public, and other relevant groups (eg, via publication, reporting in results databases, or other data sharing arrangements), including any publication restrictions	30-31
Dissemination policy: authorship	#31b	Authorship eligibility guidelines and any intended use of professional writers	30-31
Dissemination policy:	#31c	Plans, if any, for granting public access to the full	31

For peer review only

reproducible research		protocol, participant-level dataset, and statistical code	

Appendices

Informed consent materials	#32	Model consent form and other related documentation given to participants and authorised surrogates	31 (see extended data)
Biological specimens	#33	Plans for collection, laboratory evaluation, and storage of biological specimens for genetic or molecular analysis in the current trial and for future use in ancillary studies, if applicable	15-16, 29-30 (see extended data)

Notes:

- 8: 6-8, 18-20, 35
- 13: 8-12, 31-32, 35-36
- 18b: 6-7, 12, 20-21, 24
- 32: 26 (see extended data)
- 33: 10, 24, 33-34 (see extended data) The SPIRIT Explanation and Elaboration paper is distributed under the terms of the Creative Commons Attribution License CC-BY-NC. This checklist was completed on 18. July 2024 using https://www.goodreports.org/, a tool made by the EQUATOR Network in collaboration with Penelope.ai

For peer review only

~~A Randomised, Double-blind, Placebo Controlled, Parallel Group, Multi-centre Trial in Adult Subjects with Newly Diagnosed Type 1 Diabetes Mellitus Investigating the Effect of Verapamil on Preservation of Beta-cell Function (Ver-A-T1D)~~

Investigating the effect of verapamil on preservation of beta-cell function in adults with newly diagnosed type 1 diabetes mellitus (Ver-A-T1D): protocol for a randomised, double-blind, placebo-controlled, parallel-group, multi-centre trial

AUTHOR LIST: Julie Wych[1*], Martina Brunner[2], Rachel Stenson[3], Piotr Jaroslaw Chmura[4], Thomas Danne[5], Adrian Mander[1], Chantal Mathieu[6], Colin Dayan[3], Thomas R. Pieber[2]

SHORT TITLE: Diabetes and Endocrinology Protocol

~~**SPONSOR**: Medical University of Graz, Department of Internal Medicine, Division of Endocrinology and Diabetology, Austria~~

~~**SPONSOR NUMBER**: Ver-A-T1D~~

~~**CENTRAL COORDINATION**: Medical University of Graz, Department of Internal Medicine, Division of Endocrinology and Diabetology, Austria (ver-a-t1d@medunigraz.at)~~

~~**EUDRACT NUMBER**: 2020-000435-45~~

~~**CLINICALTRIALS.GOV IDENTIFIER**: NCT04545151~~

~~**PROTOCOL VERSION**: Version 8.0; dated November 08, 2021~~

~~**CHIEF INVESTIGATOR AND ADDRESS**: Professor Thomas R. Pieber, MD. Medical University of Graz, Department of Internal Medicine, Division of Endocrinology and Diabetology, Austria, Auenbruggerplatz 15, A8036 Graz, Austria.~~

AFFILIATIONS:

1) Centre for Trials Research, College of Biomedical and Life Sciences, Cardiff University, Cardiff, UK

2) Medical University of Graz, Department of Internal Medicine, Division of Endocrinology and Diabetology, Austria

3) Cardiff University School of Medicine, Cardiff University, Cardiff, UK

4) Novo Nordisk Foundation Center for Protein Research, University of Copenhagen, Copenhagen, Denmark

5) Department of General Paediatrics, Endocrinology/Diabetology and Clinical Research, Auf der Bult Hospital for Children and Adolescents, Hannover Medical School, Germany

6) Katholieke Universiteit Leuven/ Universitaire Ziekenhuizen Leuven, Belgium

CORRESPONDING AUTHOR* Julie Wych (wychj@cardiff.ac.uk)

KEY WORDS: Type 1 diabetes, Phase 2, Adults, Beta-cell function, C-peptide, Verapamil 360 mg.

WORD COUNT: 12,699~~736~~ (excluding title page, abstract, references, figures, tables, acknowledgements)

ABSTRACT:

Introduction: Type 1 diabetes mellitus (T1DM) is a disorder that arises following the selective autoimmune destruction of the insulin-producing beta-cells. Beta-cell protective or beta-cell regenerative approaches have gained wider attention, and pharmacological approaches to protect the patient's own insulin-producing beta cell mass have been proposed. Verapamil is a L-type calcium channel blocker that has been reported to effectively lowers beta cell TXNIP expression in

For peer review only - http://bmjopen.bmj.com/site/about/guidelines.xhtml

rodent beta cells and islets as well as in human islets, and thus promotes functional beta cell mass. **Methods and analysis**: The trial is a multi-centre, randomised, double-blind, placebo-controlled trial in participants with T1DM, investigating the effect of Verapamil on preservation of beta-cell function (Ver-A-T1D). A total of 120 participants will be randomised 2:1 between 360mg Verapamil and placebo administered orally once daily. T1DM patients aged ≥18 and <45 years will be eligible for recruitment within 6 weeks of diagnosis (defined as day of starting insulin therapy). The primary objective will be to determine the changes in stimulated C-peptide response during the first two hours of a mixed meal tolerance test (MMTT) at baseline and after 12 months for 360mg Verapamil administered orally once daily versus placebo. Secondary objectives include the effects of 360mg Verapamil on 1) fasting C-peptide, 2) Dried Blood Spot (DBS) C-peptide, 3) HbA1c, 4) daily total insulin dose, 5) time in range by intermittent continuous glucose monitoring (CGM) measures, 6) other biomarkers related to immunological changes and beta-cell death and 6) safety (vital signs, ECG). ***Ethics and dissemination***: Ethics approval was sought from the research ethics committee (REC) of all participating countries. All participants provided written informed consent before joining the study. Ver-A-T1D received first regulatory and ethical approvals in Austria. The publication policy is set in the INNODIA grant agreement (www.innodia.eu).

TRIAL REGISTRATION

Sponsor: Medical University of Graz, Department of Internal Medicine, Division of Endocrinology and Diabetology, Austria

Sponsor Number: Ver-A-T1D

Central Coordination: Medical University of Graz, Department of Internal Medicine, Division of Endocrinology and Diabetology, Austria (ver-a-t1d@medunigraz.at)

EudraCT Number: 2020-000435-45

ClinicalTrials.gov Identifier: NCT04545151

Protocol Version: Version 8.0; dated November 08, 2021

Chief Investigator and Address: Professor Thomas R. Pieber, MD. Medical University of Graz, Department of Internal Medicine, Division of Endocrinology and Diabetology, Austria, Auenbruggerplatz 15, A8036 Graz, Austria.

ARTICLE SUMMARY:

Strengths and limitations of this study:

- ~~Prior evidence of efficacy and safety in this condition~~
- ~~Established safety profile for IMP~~
- ~~Alignment to a standard evaluation of efficacy and mechanistic outcomes~~
- ~~Large clinical infrastructure to support recruitment and study integrity across the European Union and the UK~~
- The investigational agent is a repurposed product with a well-established safety profile from over 50 years of use in different indications and if effective could be available at low cost.
- In contrast to previous treatments developed to alter the disease course in this autoimmune condition, the agent targets the beta cell rather than the immune system directly and hence has the potential to be used in future in combination with immune modulatory interventions.
- The trial is based on a master protocol with standard efficacy and mechanistic outcomes which has been designed to form the basis of a future platform trial of combined interventions.
- A limitations of the study is that it does not include children, which comprise around 40% of the newly diagnosed type 1 diabetes population.

For peer review only - http://bmjopen.bmj.com/site/about/guidelines.xhtml

- The study will not establish the durability of the intervention since it only spans one year of treatment.

LIST OF ABBREVIATIONS:

ADA: American Diabetes Association

ADDQoL: Audit of Diabetes-Dependent Quality of Life

AE: Adverse event

AR: Adverse reaction

ALT: Alanine transaminase

AST: Aspartate aminotransferase

AUC: Area under the curve

BW: Body weight

CA: Competent authority

CI: Chief investigator

CGM: Continuous glucose monitoring

eCRF: Electronic case report form

CRP: C-reactive protein

CTIMP: Clinical trial of investigational medicinal product

COPD: Chronic obstructive pulmonary disease

DBS: Dry blood spot

DTSQc: Diabetes Treatment Satisfaction Questionnaire change

DTSQs: Diabetes Treatment Satisfaction Questionnaire status

ECG: Electrocardiogram

EMA: European Medicines Agency

eGFR: Estimated glomerular filtration rate

FACS: Fluorescence-activated cell sorting

FBC: Full blood count

FDA: Food and Drug Administration

GADA: Glutamic acid decarboxylase antibodies

GDPR: General data protection regulations

GCP: Good Clinical Practice

HbA1c: Glycated haemoglobin

HDL: High-density lipoprotein

HFS: Hypoglycaemia Fear Survey

HIV: Human immunodeficiency virus

HRA: Health research authority

For peer review only - http://bmjopen.bmj.com/site/about/guidelines.xhtml

IA-2A: IA-2 antibodies

IAA: Insulin auto-antibodies

IB: Investigators brochure

IC: Informed consent

ICF: Informed consent form / informed assent form

IDMC: Independent data monitoring committee

IEC: Independent ethics committee

IMP: Investigational medicinal product

INNODIA consortium: An innovative approach towards understanding and arresting Type 1 diabetes consortium (www.innodia.eu)

INNODIA longitudinal study: An innovative approach towards understanding and arresting Type 1 diabetes longitudinal study (ClinicalTrials.gov: NCT03936634), part of the INNODIA consortium

ISF: Investigator Site File

ITT: Intention to treat

LDL: Low-density lipoprotein

MHRA: Medicines and Healthcare products Regulatory Agency

MMTT: Mixed meal tolerance test

MUG: Medical University of Graz

NA: Not applicable

NIMP: Non investigational medicinal product

PAC: Patient Advisory Committee

PBMC: Peripheral blood mononuclear cell

PI: Principal investigator

PIS: Participant information sheet

PROMs: Patient Reported Outcome Measures

PSF: Pharmacy site file

R&D: Research and Development

RA: Regulatory agency

REC: Research ethics committee

RSI: Reference safety information

SAE: Serious adverse event

SAR: Serious adverse reaction

SAP: Statistical analysis plan

SARS-CoV-2: Severe Acute Respiratory Syndrome CoronaVirus-2

SD: Standard deviation

SDVAF: Source Data Verification Agreement Form

For peer review only

For peer review only - http://bmjopen.bmj.com/site/about/guidelines.xhtml

SmPC: Summary of product characteristics

SOP: Standard operating procedure

SR: Sustained release

SUSAR: Suspected unexpected serious adverse reaction

T1D: Type 1 diabetes

TMF: Trial master file

TMG: Trial management group

TSC: Trial steering committee

ZnT8A: Zinc transporter 8 antibody

TXNIP: Thioredoxin-interacting protein

INTRODUCTION:

Background:

INNODIA is an Innovative Medicines Initiative consortium (IMI-2), established through Horizon 2020 initiative of the European Union, involving academic, industry and charitable partners. Recruitment to this INNODIA study is defined by the recruitment of subjects with a diagnosis of T1D identified within the first six weeks from diagnosis. INNODIA provides a standardised routine centralised assessment of critical immunological biological factors which determine the rate of progression of T1D with reference to declines in beta cell function and the potential impact of IMPs which could alter these trajectories.

Rationale for the trial:

Type 1 diabetes mellitus (T1DM) is a disorder that arises following the selective autoimmune destruction of the insulin-producing beta-cells.[1, 2] A cure for T1DM would aim at ensuring that the necessary endogenous functional beta-cell mass required for adequate insulin production is preserved or increased. The Diabetes Control and Complications Trial has shown that even a small amount of preserved endogenous insulin production has beneficial effects in terms of outcome, overall glycaemic control and prevention of severe hypoglycaemia.[3-5] Beta-cell destruction is considered to be mainly immune-mediated, and many efforts to stop or modify this destruction have focused on immunomodulatory, antigen-specific or anti-inflammatory interventions.[6] Attempts to replace beta cells by pancreas or islet transplantation are associated with potentially severe side effects due to the necessary immunosuppression. Recently beta-cell protective or beta-cell regenerative approaches have gained wider attention, and pharmacological approaches to protect the patient's own insulin-producing beta cell mass have been proposed.[6]

Pharmacokinetics & pharmacodynamics of Verapamil:

Verapamil (ATC: C08DA01) is a L-type calcium channel blocker that has been used as an antihypertensive compound for more than 3 decades and approved by the US Food and Drug Administration (FDA) and the European Medicine Agency (EMA). Verapamil effectively lowers beta cell Thioredoxin-interacting protein (TXNIP) expression in rodent beta cells and islets as well as in human islets. This effect is based on the established mode of action of verapamil , blockade of L-type calcium channels and the resulting decrease in intracellular free calcium leading to inhibition of TXNIP transcription. In mouse models of diabetes, oral administration of verapamil promotes functional beta cell mass and prevents and even reverses overt diabetes. In addition, downregulation of TXNIP also improves beta cell function including insulin production and secretion.[7-13] In a randomised, double-blind, placebo-controlled phase 2 clinical trial the efficacy and safety of oral verapamil added for 12 months to a standard insulin regimen in adult subjects with

For peer review only - http://bmjopen.bmj.com/site/about/guidelines.xhtml

recent-onset T1D was assessed. Verapamil treatment, compared with placebo was well tolerated and associated with an improved mixed-meal-stimulated C-peptide area under the curve, a measure of endogenous beta cell function, at 3 and 12 months, as well as with a lower increase in insulin requirements and fewer hypoglycaemic events.[14] Two year follow-up of this study has since been published suggesting a continued effect[15] and the beneficial effect on C-peptide preservation has been replicated in a study in children and adolescents.[16]

Several retrospective studies have reported that verapamil use is associated with a lower risk of developing type 2 diabetes.[17, 18] Recently it has been demonstrated that thioredoxin-interacting protein (TXNIP), a cellular redox regulator, is overexpressed during hyperglycaemia and induces beta-cell apoptosis.[10] As verapamil effectively lowers beta cell TXNIP expression in rodent beta cells and islets as well as in human islets, it therefore promotes functional beta cell mass and prevents and even reverses overt diabetes.[19]

Verapamil inhibits the entry of calcium into smooth muscle cells of the systemic and coronary arteries and in the cells of cardiac muscle and the intracardiac conduction system. Verapamil lowers peripheral vascular resistance with little or no reflex tachycardia. Its efficacy in reducing both raised systolic and diastolic blood pressure is thought to be primarily due to this mode of action. Due to the effect on the movement of calcium in the intracardiac conduction system, verapamil reduces automaticity, decreases conduction velocity and increases the refractory period. This may cause the following cardiovascular side effects: bradycardic arrhythmias such as sinus bradycardia, sinus arrest with asystole, 2nd and 3rd degree AV block, bradyarrhythmia in atrial fibrillation, palpitations, tachycardia, development or aggravation of heart failure, and hypotension.

After oral administration verapamil is absorbed well (more than 90%) but undergoes extensive first-pass hepatic metabolism so that bioavailability is only 10–23%. Verapamil is metabolized to several active and inactive metabolites. Most of the metabolites are excreted in bile. The most common side effects of verapamil are dose dependent and include constipation, dizziness, nausea, low blood pressure, and headache. Other side effects seen include: edema, congestive heart failure, pulmonary edema, fatigue, elevated liver enzymes, shortness of breath, low heart rate, atrioventricular block, rash and flushing.

The target dose of 360 mg once daily and the minimum target dose of 240 mg was chosen according to the study of Ovalle et al.[14] In this already published randomized, double-blind, placebo-controlled phase 2 clinical trial, the participants were randomly assigned to receive a once-daily oral dose of sustained-release verapamil (titrated over the first 3 months from 120 mg to 360 mg) or placebo for a total of 12 months in addition to their insulin therapy. This dose was chosen according to its demonstrated tolerability and effectiveness in terms of calcium-channel blockade and considering that the maximal recommended daily dose for verapamil is 480 mg. The rationale for the selected target dose in the current trial is based on the efficacy demonstrated in this trial.[14]

The Ver-A-T1D trial is run using the INNODIA Master Protocol within the INNODIA clinical trial network (www.INNODIA.eu).[20] The aim of this trial is to confirm the effect of 360mg verapamil administered orally once daily (titrated over the first 3 months from 120 mg to 360 mg) on the preservation of stimulated C-peptide at 12 months compared to placebo.

METHODS AND ANALYSIS:

Objectives:

The primary objective of Ver-A-T1D is to determine the changes in stimulated C-peptide response during the first two hours of a mixed meal tolerance test (MMTT) at baseline and after 12 months for 360mg verapamil administered orally once daily versus placebo in adult people with new onset T1D. The secondary objectives are to determine the effect of 360mg verapamil administered orally once daily on 1) fasting C-peptide and DBS C-peptide measurements, 2) HbA1c, 3) daily total insulin dose, 4) CGM time in range over time, 5) to determine the effects of treatment on other biomarkers

For peer review only - http://bmjopen.bmj.com/site/about/guidelines.xhtml

related to immunological changes and beta-cell death and survival in this population, and 6) to determine the effects of 360mg verapamil administered orally once daily on safety (vital signs, ECG). The tertiary objective will compare between treatment arms and across the course of treatment the PROMs scores completed by participants. Table 1 reports the specific trial objectives and related outcome measures.

SPIRIT reporting guidelines were used for this protocol.[21]

For peer review only

For peer review only - http://bmjopen.bmj.com/site/about/guidelines.xhtml

Table 1: Study objectives and outcomes.

Objectives	Outcome measures	Timepoints(s) of evaluation of outcome measure
Primary Objective		
1) To determine the changes in stimulated C-peptide response during the first two hours of a mixed meal tolerance test (MMTT) at baseline and after 12 months for 360mg Verapamil SR administered orally once daily versus placebo.	1) The area under the stimulated C-peptide response curve over the first two hours of a mixed meal tolerance test (MMTT) for the verapamil 360 mg and placebo arms	1) 12 months
Secondary Objectives		
2) ~~To determine the effects of 360mg Verapamil SR administered orally once daily on fasting C-peptide~~ To determine the effects of 360mg Verapamil SR administered orally once daily on fasting C-peptide and Dried Blood Spot (DBS) C-peptide measurements over time.	2) Fasting C-peptide after 12 months therapy compared to placebo and home DBS for C-peptide	2) Baseline, 1, 2, 3, 6, 9 and 12 months
3) ~~To determine the effects of 360mg Verapamil SR administered orally once daily on dried Blood Spot (DBS) C-peptide measurements over time.~~ To determine the effects of 360mg Verapamil SR administered orally once daily on HbA1c, daily total insulin dose and continuous glucose monitoring (CGM) time in range.	3) ~~Home DBS for C-peptide~~ Change in HbA1c baseline to 12 months, change in HbA1c baseline to 12 month, change in insulin requirements, baseline to 12 months as the daily total dose (three days average) in units per kg body weight (BW), continuous glucose monitoring (CGM) time in range (70-140 mg/dL, 3.9-7.8 mmol/L) and (70-180 mg/dL, 3.9-10.0 mmol/L), time above range (>180 mg/dL, >10.0 mmol/L), time below range (<70 mg/dL, < 3.9 mmol/L)	3) Baseline and monthly from 1-12 months
4) ~~To determine the effects of 360mg Verapamil SR administered orally once daily on HbA1c~~ To determine the effects of treatment on other biomarkers related to immunological	~~4) Change in HbA1c baseline to 12 months~~	~~4) Baseline, 1, 2, 3, 6, 9 and 12 months~~ 4)

For peer review only - http://bmjopen.bmj.com/site/about/guidelines.xhtml

changes and beta-cell death and survival in this population		
5) ~~To determine the effects of 360mg Verapamil SR administered orally once daily on daily total insulin dose~~ To determine the effects of 360mg Verapamil SR administered orally once daily on safety (vital signs, ECG)	~~5) Change in insulin requirements, baseline to 12 months as the daily total dose (three days average) in units per kg body weight (BW)~~ 5) Systolic blood pressure (mmHg), Diastolic blood pressure (mmHg), Pulse (bpm), ECG	5) Baseline, 1, 2, 3, 6, 9 and 12 months
6) ~~Continuous glucose monitoring (CGM) time in range.~~	6) ~~Continuous glucose monitoring (CGM) time in range (70-140 mg/dL, 3.9-7.8 mmol/L) and (70-180 mg/dL, 3.9-10.0 mmol/L), time above range (>180 mg/dL, >10.0 mmol/L), time below range (<70 mg/dL, < 3.9 mmol/L)~~	~~6) Baseline, 1, 2, 3, 6, 9 and 12 months~~
7) ~~To determine the effects of 360mg Verapamil SR administered orally once daily on safety (vital signs, ECG).~~	8) ~~Systolic blood pressure (mmHg), Diastolic blood pressure (mmHg), Pulse (bpm), ECG~~	~~7) Baseline, 1, 2, 3, 6, 9 and 12 months~~
Tertiary Objective		
~~8)~~6)To compare between treatment arms and across the course of treatment the PROMs scores completed by participants.	~~9)~~6)DTSQ, ADDQoL, HypoFear questionnaires ~~completed~~	~~9)~~6)HFS & DTSQ at 1, 6 and 12 months ADDQoL at 6 and 12 months

For peer review only

For peer review only - http://bmjopen.bmj.com/site/about/guidelines.xhtml

Study Summary:

Ver-A-T1D is a multi-centre, randomised, double-blind, placebo-controlled trial testing the efficacy of 360mg verapamil administered orally once daily (titrated over the first 3 months from 120 mg to 360 mg) on protection of stimulated C-peptide decline in subjects with diagnosis of T1D within 6 weeks of diagnosis. The Ver-A-T1D trial design is shown in Figure 1.

A multi-centre and multinational design has been chosen to ensure that the results are applicable for participants with different demographic characteristics. All sites are part of the existing INNODIA clinical network and are confirmed suitable for undertaking this specific study from the accreditation undertaken as part of INNODIA. However, to recruit the required number of participants, suitable INNODIA sites may work with their local existing network to identify and recruit potential participants. Additional sites in the UK that form part of the UK Type 1 Diabetes Research Consortium and can perform studies to appropriate standards consistent with the INNODIA platform will also be considered.

Further details on participating sites can be obtained from the Ver-A-T1D Coordinating team contact (ver-a-t1d@medunigraz.at) and via the INNODIA web page (innodia.eu - Clinical Trials).

Trial participants, Study Design and Oversight:

The aim is to randomise 138 participants in this trial to two arms, namely verapamil and placebo in a 2:1 allocation ratio, that will compensate for an estimated drop-out rate of 15%. It is anticipated that approximately 230 participants will be required to be screened (approximately 60% consent rate), with 40 participants on the control arm and 80 on the experimental arm (a total of 120 subjects) are expected to complete the trial.

The rationale for the trial design is to investigate the effect of 360mg verapamil administered orally once daily (titrated over the first 3 months from 120 mg to 360 mg) on preservation of beta-cell function compared to placebo at week 52 in adult subjects with newly diagnosed T1DM with residual beta-cell function. The duration of the trial with 52 weeks of exposure of 360mg verapamil administered orally once daily (titrated over the first 3 months from 120 mg to 360 mg) has been chosen to align with the regulatory requirements from FDA and EMA. The FDA and EMA guidelines advise that studies of products aimed at preservation of beta-cell function in recent-onset T1DM with remaining endogenous insulin reserve, should evaluate metabolic outcomes, such as stimulated C-peptide levels. Therefore, the MMTT stimulated AUC0-2h C-peptide concentration has been chosen as the primary efficacy outcome.

The day-to-day management of the trial is the responsibility of the trial management group. The Chief Investigator will be responsible for the preparation and submission of annual safety reports and annual progress reports.

Trial Steering Committee (TSC):

The sponsor will constitute a Trial Steering Committee (TSC) to provide the overall supervision of the trial. The TSC will monitor the trial progress, the safety data, the critical efficacy endpoints and conduct and advise on scientific credibility. The TSC will ultimately carry the responsibility for deciding whether a trial needs to be stopped on grounds of safety or efficacy. The TSC may recommend unblinding of any data for further analysis.

The TSC will consider recommendations from the Independent Data Monitoring Committee (IDMC). The TSC will decide whether to modify the trial, or to seek additional data.

Independent Data Monitoring Committee (IDMC):

The IDMC charter will detail the purpose of this committee including: the description of the membership, terms of reference, roles, responsibilities, authority, decision-making and relationships of the IDMC for this trial. The charter will further include the timing of meetings, methods of

For peer review only - http://bmjopen.bmj.com/site/about/guidelines.xhtml

providing information to and from the IDMC, frequency and format of meetings, statistical issues, and relationships with other committees. Briefly, it is planned that one interim analysis will be undertaken during this trial and considering these interim analyses and safety endpoints, the IDMC will advise the TSC of its recommendations regarding trial modification, continuation or termination of the trial. The IDMC charter will expand on the above.

Trial Management Group (TMG):

The TMG comprise investigators and individuals closely involved in running of the trial. The TMG aims to meet more frequently than the TSC to ensure that all practical details of the trial are progressing well.

Patient and Public Involvement statement:

A clear priority of INNODIA is to keep the needs and concerns of patients with Type 1 Diabetes at the centre of the project. Ver-A-T1D involvement of patients is organized by a Patient Advisory Committee (PAC). The specific activities of the PAC are to advise the Management Board of INNODIA on areas including informed consent, clinical protocol review and relationships with regulatory authorities. In addition, the PAC members act as T1D ambassadors, helping to communicate results to the wider public across 15 European countries.

More information can be found at the INNODIA webpage (https://www.innodia.eu/pac/).

Inclusion and exclusion criteria:

Table 2 lists the study's inclusion and exclusion criteria. Potential participants may not enter the trial if any of the exclusion criteria listed in Table 2 apply.

Table 2: Eligibility criteria.

Inclusion Criteria
1. Have given written informed consent 2. Age ≥18 and <45 years at consent 3. Must have a diagnosis of T1D of within 6 weeks duration at screening (from date of the first insulin injection) 4. Must have at least one or more of the following diabetes-related autoantibodies present at screening: GADA, IA-2A and/or ZnT8A 5. Must have fasting C-peptide levels ≥100 pmol/L measured at screening 6. Be willing to comply with intensive diabetes management
Exclusion Criteria
1. Be immunodeficient or have clinically significant chronic lymphopenia: Leukopenia (< 3,000 leukocytes /µL), neutropenia (<1,500 neutrophils/µL), lymphopenia (<800 lymphocytes/µL), or thrombocytopenia (<100,000 platelets/µL) 2. Have active signs or symptoms of acute infection at the time of screening 3. Be currently pregnant or lactating, or anticipate getting pregnant during the 12 months study period 4. Require use of immunosuppressive agents including chronic use of systemic steroids 5. Have evidence of current or past human immunodeficiency virus (HIV), Hepatitis B or Hepatitis C infection 6. Have any complicating medical issues or abnormal clinical laboratory results that may interfere with study conduct, or cause increased risk to include pre-existing cardiac disease, chronic obstructive pulmonary disease (COPD), sickle cell disease, neurological, or blood count abnormalities, as judged by the investigator 7. Have persistent history of malignancies other than skin

For peer review only - http://bmjopen.bmj.com/site/about/guidelines.xhtml

8. 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
9. History of renal insufficiency or evidence of renal dysfunction with creatinine greater than 1.5 times the upper limit of normal
10. Current or ongoing use of non-insulin pharmaceuticals that affect glycaemic control within prior 7 days of screening
11. Use of any other investigational drug in the previous 30 days and/or intent on using any investigational drug for the duration of the trial
12. Current use of Verapamil or other calcium channel blockers
13. Known hypersensitivity to Verapamil or to any of its excipients
14. Concomitant medication known for inducing or inhibiting CYP3A4 and/or glycoprotein-P metabolism
15. Intake of grapefruit juice, liquorice, St. John's Wort, cannabidiol, ginkgo biloba
16. Substrate intake of CYP3A4 and/or glycoprotein-P metabolism, as judged by the investigator
17. Hypotension (of less than 100mmHg systolic), sick sinus syndrome (except patients with a functioning artificial pacemaker), uncompensated heart failure or severe left ventricular dysfunction; marked bradycardia (less than 50 beats/minute), atrial flutter or atrial fibrillation in the presence of an accessory bypass tract (e.g. Wolff-Parkinson-White syndrome), hypertrophic cardiomyopathy, acute myocardial infarction, attenuated neuromuscular transmission (e.g. by myasthenia gravis, Lambert-Eaton syndrome, advanced Duchenne muscular dystrophy)
18. ECG second or third degree atrioventricular block
19. Any condition that in the investigator's opinion may adversely affect study participation or may compromise the study results.
20. Current use of ß-blockers.

Trial procedures:

The study procedures are reported in detail in online supplemental information (see Ver-A_T1D Table 3 SUPPLEMENTARY MATERIAL)~~Table 3~~ and the trial flow chart is shown in Figure 2. The trial duration will be approximately 24 months, consisting of screening, randomisation, 12 months treatment period and an additional 12 months INNODIA follow-up.

For peer review only

For peer review only - http://bmjopen.bmj.com/site/about/guidelines.xhtml

Table 3. Schematic representation of assessments at study visits.

Trial period	**Consent and enrolment**	**Screening and baseline assessment**	**Randomisation**	**Treatment**									**Observation**
Visit type (C: Clinic, P: Phone contact)	**C**	**C**	**C**	**P**	**C**	**P**	**C**	**P**	**C**	**C**	**C**	**C**	**C**
Visit number		**V-1**	**V0**	**P1**	**V1**	**P2**	**V2**	**P3**	**V3**	**V4**	**V5**	**V6**	**V7**
Visit number INNODIA backbone		INN V1							INN V2	INN V3		INN V4	INN V5
Timeline		**<6 weeks from diagnosis[b]**	**Day 0 (≤2 weeks from V-1)**	**Week 1**	**Week 4**	**Week 5**	**Week 8**	**Week 9**	**Month 3**	**Month 6**	**Month 9**	**Month 12**	**Month 24**
Visit window (days)				**±2**	**±3**	**±2**	**±3**	**±2**	**±7**	**±7**	**±7**	**±7**	**±7**
Assessment													
Informed consent	x[a]	x[a]										x	
Randomisation			x										
Attend visit fasting		x	x		x		x		x	x	x	x	x
In/exclusion criteria		x											
Demographic		x											
Medical history/ concomitant illness		x											
Family medical history[c]		x	x						x	x		x	
Concomitant medication incl. vaccinations		x	x	x	x	x	x	x	x	x	x	x	
Diabetes care (Insulin regimen)[c]		x	x		x		x		x	x	x	x	x
Physical examination (incl. height, weight)		x	x						x	x		x	
ECG		x			x		x		x	x	x	x	
Vital signs		x	x		x		x		x	x	x	x	
HIV, Hepatitis B and C		x											
Autoantibodies		x										x	x
Fasting C-peptide, Blood glucose[i]		x	x		x		x		x	x	x	x	x
DNA extraction		x											
HbA1c		x	x		x		x		x	x	x	x	x
Immune cells (PBMC)		x							x	x		x	x
Blood (omics)		x							x	x	x	x	x
Blood (beta-cell killing)		x							x	x	x	x	x
Whole blood RNA		x										x	x
microRNA (plasma omics)		x							x	x	x	x	x
Urine (biomarkers)		x							x	x		x	x
Stool (microbiome, metabolome)		x							x	x		x	x
Safety lab (incl. FBC, CMP)		x			x		x		x	x	x	x	x
MMTT			x						x	x	x	x	x
IMP dispensing			x		x		x		x	x	x		
IMP dose (mg SR once daily)			**120**	**120**	**240**	**240**	**360**	**360**	**360**	**360**	**360**	**360**	
Drug accountability			x		x		x		x	x	x	x	

For peer review only - http://bmjopen.bmj.com/site/about/guidelines.xhtml

Trial period	Consent and enrolment	Screening and baseline assessment	Randomisation	Treatment									Observation
Visit type (C: Clinic, P: Phone contact)	C	C	C	P	C	P	C	P	C	C	C	C	C
Visit number		V-1	V0	P1	V1	P2	V2	P3	V3	V4	V5	V6	V7
Visit number INNODIA backbone		INN V1							INN V2	INN V3		INN V4	INN V5
Timeline		<6 weeks from diagnosis[b]	Day 0 (≤2 weeks from V-1)	Week 1	Week 4	Week 5	Week 8	Week 9	Month 3	Month 6	Month 9	Month 12	Month 24
Visit window (days)				±2	±3	±2	±3	±2	±7	±7	±7	±7	±7
Assessment													
Withdrawal criteria			x	x	x	x	x	x	x	x	x	x	
Adverse events assessment			x	x	x	x	x	x	x	x	x	x	x
Handout and instruct in CGM, DBS, patient diary and pregnancy test (if applicable)			x										
CGM data download (Review CGM)					x		x		x	x	x	x	
Review of patient diary					x		x		x	x	x	x	
Pregnancy test[d]		x	x		x		x		x	x	x	x	
PROMs[e]					x					x		x	
Home measurements[f]:													
Home DBS for C-Peptide (monthly)			x		x		x		x	x	x	x	
CGM[g]			x				Readings done 2 weeks prior to each visit						
Home Pregnancy test[h]			x		x		x		x	x	x	x	

Footnotes:

[a]Written informed consent must be in place before the participant initiates fasting prior to the screening visit. Any trial specific assessments must be conducted only after participants have given written informed consent.

[b]Diagnosis date is defined as date of first insulin injection.

[c]Familiy medical history and diabetes care information should be updated at the given visits

[d]Urine human chorionic gonadotropin (hCG) pregnancy test (as needed for women of childbearing potential or per local requirements)

[e]PROMs: HFS and DTSQs will be assessed at V1, V4, V6. DTSQc will be assessed at V6. ADDQoL will be assessed at V4, V6.

[f]Capillary glucose and DBS will be collected at home pre and 60 min post consumption of EnsurePlus, monthly, for the full 12 months follow-up, for DBS C-peptide measurement.

[g]Glucose monitor to be used constantly if possible but patient advised to wear sensors for 2 weeks prior to visits as a minimum.

[h]Subjects will be instructed to perform the test at home if no site visit is planned according to local requirements. In case a menstrual period is missed or if pregnancy is suspected at any time during the trial, a urine pregnancy test should be performed. The subjects should be instructed to not dose trial product before urine pregnancy test has been ruled out.

[i]At visits where participants have a MMTT, no extra fasting C-peptide samples or blood glucose samples must be taken.

For peer review only

For peer review only - http://bmjopen.bmj.com/site/about/guidelines.xhtml

Throughout the trial investigators work in accordance with (ICH GCP) and local regulations and ensure that trial procedures are performed as described in the protocol. Any discrepancies that result in protocol and/or GCP deviations, the investigator takes appropriate action to avoid recurrence of the detected discrepancies. If deviations do occur, the investigator must inform the monitor and the implications of the deviation must be reviewed and discussed. Deviations are documented and explained in a protocol deviation by stating the reason, date and the action(s) taken (if applicable).

The timing of the assessments and procedures are specified in the trial flow chart (Figure 2) and detailed in online supplemental information (see Ver-A_T1D Table 3 SUPPLEMENTARY MATERIAL)~~Table 3~~. A subject screening log, a subject identification code list and a subject enrolment log are kept by the investigator and may be combined in one list. Additional logs kept include a pre-screening log and staff and delegations of task(s) at sites. The investigator signs off the log of staff and the delegation of task(s) at site at the time of delegation. Protocol waivers or exemptions are not allowed. Immediate safety concerns should be discussed with the sponsor immediately upon occurrence or awareness to determine if the participant should continue or discontinue study treatment.

Adherence to the study design requirements, including those specified in the Trial Flow Chart (Figure 2), is essential and required for study conduct. All screening evaluations must be completed and reviewed to confirm that potential participants meet all eligibility criteria. The investigator will maintain a screening log to record details of all participants screened and to confirm eligibility or record reasons for screening failure, as applicable. Procedures conducted as part of the participant's routine clinical management (e.g., blood count) and obtained before signing of the ICF may be utilized for screening or baseline purposes provided the procedures met the protocol-specified criteria and were performed within the time frame defined in the Trial Flow Chart (Figure 2). Throughout the trial, a maximum of 3 ml per Kg of blood will be taken at each visit; no more than 204 ml per visit maximum. Repeated or unscheduled samples may be taken for safety reasons or for technical issues with the samples.

Participants who fail to satisfy eligibility criteria may be offered participation in the INNODIA longitudinal study (Figures 1 & 2).

Participant identification:

Potentially eligible individuals are approached by health care professionals and/or local research teams during routine clinical appointment. The study is also advertised by poster and flyers in diabetes clinics, on social media, for example Facebook and Twitter, via INNODIA or local sites own pages, on the INNODIA website, UK T1D Research Consortium website and other diabetes related websites and via newspaper if applicable. All potential individuals approached or that have contacted the research teams are provided with a verbal explanation of the study and written information sheets. Once they have been given sufficient time to consider their participation in the study consent will be obtained.

Informed consent:

The informed consent form (ICF) has been approved by the local ethics committee and complies with GCP, local regulatory requirements and legal requirements and can be found in the online supplemental information (see Ver-A-T1D Informed Consent Version 5.0 11-Mar-2022). The investigator or designee must ensure that each trial participant, or their legally acceptable representative, is fully informed about the nature and objectives of the trial and possible risks associated with their participation. The investigator or designee will obtain written informed consent from each participant or the participant's legally acceptable representative before any trial-specific activity is performed. The ICF used for this trial and any change made during the trial, must be

For peer review only - http://bmjopen.bmj.com/site/about/guidelines.xhtml

prospectively approved by the Research Ethics Committee (REC). The investigator will retain the original of each participant signed ICF and a copy will be provided to the participant.

Informed consent (IC) is sought upon joining the study to confirm that participants are happy to be contacted to inform them of study results and future intervention and research diabetes studies organised by INNODIA. After completion of treatment at 12 months from diagnosis, participants will continue for a further 12 months in the observation part of the study. This will involve a single visit 24 months from randomisation. During IC, the investigator will explain the nature of the study to the participant and answer all questions regarding the study. Participants must be informed that their participation is voluntary and will be required to sign a statement of informed consent that meets the requirements of local regulations, ICH guidelines, and the Independent Ethics Committee (IEC) or study centre. The medical record must include a statement that written informed consent was obtained before the participant was enrolled in the study and the date the written consent was obtained. The authorized person obtaining the informed consent must also sign the ICF. A copy of the ICF(s) must be provided to the participant or the participant's legally authorized representative.

Where participants require a verbal translation of the trial documentation by a locally approved interpreter/translator, it is the responsibility of the individual investigator to use locally approved translators. If the trial requires documentation in a different language (other than English) the translation and back translation documents need to be reviewed and approved by the sponsor prior to use with all sections of the approved documents must appear in the translation. The translated version must be appropriately dated and version controlled. Any new information that becomes available, that might affect the participant's willingness to continue participating in the trial will be communicated to the participant as soon as possible. Participants must be re-consented to the most current version of the ICF(s) during their participation in the study.

Any new information which becomes available, which might affect the participant's willingness to continue participating in the trial will be communicated to the participant as soon as possible and participants must be re-consented where an updated ICF(s) might impact on their decision to remain in the study.

Registration:

Following informed consent, the participant will be registered on the INNODIA central database using de-identifiable information only and a participant ID generated. All identifiable information such as full name, contact details and date of birth will be registered locally following local policies and regulations. Participant eligibility for INNODIA M~~m~~aster protocol will be recorded at this stage as well as gender and ethnicity.

Screening and baseline assessments for those who are eligible and have consented:

The screening and baseline visit should be carried out within less than 6 weeks of the date of first insulin injection. Trial specific assessments will only be conducted after participants have given written informed consent (IC) and must be in place before the participant initiates fasting prior to the screening visit. Study procedures and their timing are summarized in Figure 2.

Assessments performed at screening and baseline are as follows: Demographics (age, gender, ethnicity), date of T1D diagnosis (date of first insulin dose), HbA1c at diagnosis, daily insulin regimen at time of visit, blood glucose at time of visit, physical examination (including height and weight), medical history, diabetes care, concomitant medication, including vaccinations in last 6 weeks, family medical history, ECG and vital signs. Additionally, for women of childbearing potential, if applicable, a pregnancy test will be performed according to local requirements (urine pregnancy test or serum pregnancy test). Blood will be collected for the following screening assessments: Fasting C-peptide, autoantibodies (Glutamic acid decarboxylase antibodies-GADA, Insulin auto-antibodies-IAA, IA-2 antibodies-IA-2A or Zinc transporter 8 antibody ZnT8A), Safety lab (incl. full blood count (FBC), complete metabolic profile (CMP)) and HIV, Hepatitis B and C.

For peer review only - http://bmjopen.bmj.com/site/about/guidelines.xhtml

At the same visit, the following INNODIA baseline samples will be collected from all screened participants: DNA extraction, HbA1c, Omics, ß cell killing assay, whole blood RNA, microRNA (plasma omics), immune cells (PBMC), urine (omics, including microbiome analysis), stool (omics, including microbiome and metabolome analysis).

Following review of the laboratory results from the screening samples by the local medical team, participants will be declared eligible or non-eligible for the clinical trial. If any inclusion criteria are answered no or any exclusion criteria are answered yes, the subject is a screening failure. For screening failures, the screening failure form in the electronic case report form (eCRF) must be completed with the reason for not continuing in the trial. Re-sampling or re-screening is not allowed if the subject has failed one of the inclusion criteria or meets one of the exclusion criteria related to laboratory parameters. However, if a lab test at the screening visit is inconclusive a re-test can be performed. The repeat test results must be available for evaluating the subject's eligibility before randomisation. Eligible participants will be invited for the randomisation visit (V0) and asked to attend the visit fasting (from midnight). Non-eligible participants will be informed of the results of the screening visit and explained the reason for non-eligibility and invited to join the INNODIA longitudinal study.

Samples collected in the study as part of the INNODIA Clinical Trial Master Protocol will be stored and analysed as described in the Master Protocol and outlined in the online supplemental information (see Ver-A-T1D Study Protocol Paper v1.1 25 July 2024-SUPPLEMENTARY MATERIAL). Additional samples collected that are in the same nature, for example samples from additional MMTT or for additional immune cell studies, will be stored and analysed according to the INNODIA Clinical Trial Master Protocol .

Randomisation and blinding:

The trial is double-blind, randomisation is carried out for all eligible participants using a web-based platform (Randomizer®) at Medical University of Graz. At the randomisation visit (Visit 0) participants meeting all inclusion criteria and none of the exclusion criteria will be assigned a unique participant ID number and centrally randomised to one of the two parallel treatment groups in a 2:1 (verapamil 360 mg : placebo) titrated from: Day 0 to Week 4, 120 mg once daily; Week 4 to Week 8, 240 mg once daily; Week 8 to Month 12, 360 mg once daily. Placebo (matching verapamil 360 mg) mg will be titrated in the same manner. Trial participants and research teams are blinded to the treatment group for the duration of the trial. The double blinding will be achieved by providing verapamil identical placebo tablets.

The randomisation software is programmed with blind-breaking instructions. In case of an emergency, an investigator has the responsibility for determining if unblinding of a participants' treatment assignment is warranted. Participant safety must always be the first consideration in making such a determination. If the investigator decides that unblinding is warranted, the investigator should make every effort to contact the sponsor and medical monitor prior to unblinding a participant's treatment assignment unless this could delay emergency treatment of the participant. If a participant's treatment assignment is unblinded, the sponsor must be notified within 24 hours after breaking the blind. The date and reason that the blind was broken must be recorded in the source documentation and eCRF, as applicable. When the code is broken, the treatment allocation will be accessible to the investigator and the Trial Management Group. If the code has been broken the subject must be withdrawn from the trial and a withdrawal session must be completed in the eCRF.

Trial participants attend the randomisation visit fasted and have a 120-minute mixed meal tolerance test (MMTT) with Ensure Plus for measuring C-peptide and glucose as a measurement of beta cell response. Additional assessments include physical examination, vital signs and HbA1c. Capillary glucose and Dry Blood Spot (DBS) will be collected at home pre and 60 minutes after consumption of EsurePlus, monthly, for the full 12 months follow-up for DBS C-peptide measurement. Participants

For peer review only - http://bmjopen.bmj.com/site/about/guidelines.xhtml

will be set up with a Continuous Glucose Monitor (CGM) and handed out a patient diary before leaving the clinical research facility.

Subsequent assessments: Follow-up visits 1 and 2:

The schematic representation of assessments at study visits can be found in online supplemental information (see Ver-A_T1D Table 3 SUPPLEMENTARY MATERIAL). This table~~Table 3~~ details assessments at all follow-up visits. Participants are assessed for adverse events (AEs), withdrawal criteria, concomitant medication including vaccination, safety lab, ECG, vital signs, pregnancy test (if applicable), DBS, Investigational Medicinal Product (IMP) dispensing, dose titration to 240 mg at visit 1 and 360 mg at visit 2, CGM and patient diary reviews, diabetes care, Patient Reported Outcomes (PROMs), fasting C-peptide and HbA1c.

Subsequent assessments: Follow-up visits 3-6:

AE, withdrawal criteria, concomitant medication including vaccination, safety lab, ECG, DBS, IMP dispensing, CGM and patient diary review, diabetes care, vital signs, pregnancy test (if applicable), physical examination (height, weight). Additional INNODIA assessments include family medical history, MMTT (incl. fasting C-peptide and blood glucose), HbA1c, Blood ß-cell killing, Blood (omics), mirco RNA (plasma omics), immune cells (PBMC), urine (biomarkers) and stool (microbiome, metabolome).

Women of childbearing potential are required to use adequate contraception for the duration of the trial and for 7 days after the completion of last treatment (Visit 6). This includes Intrauterine Device (IUD), hormonal based contraception (pill, contraceptive injection or implant etc), barrier contraception (condom or occlusive cap e.g., diaphragm or cervical cap with spermicide), true abstinence (where this is in accordance with the participants preferred and usual lifestyle). Men are required to use adequate contraception for the entire duration of the trial and for 7 days after the completion of the last treatment. This includes barrier contraception (condom and spermicide) or true abstinence (where this is in accordance with the participants preferred and usual lifestyle).

Subsequent assessments: Phone visits 1-3:

Phone visits 1, 2 and 3 occur at 1 week ±2 days, 5 weeks ±2 days and 9 weeks ±2 days post treatment start. AEs, withdrawal and criteria and concomitant medication including vaccinations are recorded.

Long-term assessment: Follow-up visit 7:

At 24 months participants will be assessed for adverse events (AEs), diabetes care and safety lab. Additional INNODIA assessments include MMTT (incl. fasting C-peptide and blood glucose), HbA1c, autoantibodies, blood ß-cell killing, blood (omics), whole blood RNA, RNA (plasma omics), immune cells (PBMC), urine (biomarkers) and stool (microbiome, metabolome).

End of trial participation:

A participant is considered to have completed the study if he/she has completed all phases of the study including the last visit. The end of the study is defined as the date of the last visit of the last participant in the study in the trial globally. Participants will be expected to continue normal standard of care during the trial period and following their participation in the trial.

Early discontinuation/withdrawal of participants:

Participants may terminate participation in the study at any time. An investigator can stop the participation of a participant after consideration of the benefit/risk ratio. Possible reasons are (i) Serious Adverse Events (SAEs); (ii) Treatment emergent side effects, that do not allow dose escalation to 240 mg verapamil or placebo; (iii) Non-compliance with the study protocol; (iv) Technical grounds (e.g., patient moves) or (v) Early termination at the request of the Chief Investigator/ Principal Investigator or Co-Investigator.

For peer review only - http://bmjopen.bmj.com/site/about/guidelines.xhtml

Participants may withdraw without necessarily giving a reason, without any personal disadvantage and without affecting their usual patient care. Withdrawal and permission to retain samples and data already collected will be documented in the eCRF. Withdrawal by an investigator and the permission to retain sample and data already collected will be clearly documented in the eCRF and will not affect usual patient care. In rare instances, it may be necessary for a participant to permanently discontinue (definitive discontinuation) study intervention. If study intervention is definitively discontinued, the participant will remain in the study to be evaluated for follow-up assessments.

A participant will be considered lost to follow-up if he or she repeatedly fails to return for scheduled visits and is unable to be contacted by the study site. The following actions must be taken if a participant fails to return to the clinic for a required study visit: The site must attempt to contact the participant and reschedule the missed visit as soon as possible and counsel the participant on the importance of maintaining the assigned visit schedule and ascertain whether the participant wishes to and/or should continue in the study. Before a participant is deemed lost to follow up, the investigator or designee must make every effort to regain contact with the participant (where possible, 2 telephone calls or local equivalent methods). These contact attempts should be documented in the participant's medical record. Should the participant continue to be unreachable, they will be considered to have withdrawn from the study. Participants who are withdrawn will not be replaced.

Verapamil 120 mg preparation, dose and administration:

Verapamil is an L-type calcium channel blocker, that has been approved by the US Food and Drug Administration (FDA) and the European Medicine Agency (EMA).

Participants of the trial randomised to verapamil will receive verapamil 120 mg tablets at the following visits: V0, V1, V2, V3, V4, V5. Instruction on oral administration will happen at each visit. Participants will be instructed to take all IMP dose once daily at approximately the same time. Participants having mild side effects like dizziness or hypotension may be advised to take it in the evening before sleep. Female participants are instructed to not dose IMP before a urine pregnancy test has been ruled out.

All participants will initiate 120 mg verapamil or 120 mg placebo treatment on the day of randomisation. As the target dose is 360 mg verapamil or placebo, the dose will be escalated in increments of 120 mg verapamil or placebo every month until 360 mg verapamil or placebo has been reached. In cases where participants suffer intolerable verapamil side effects related to the dose escalation it is acceptable to maintain the current verapamil dose and postpone escalation by 1 month. If 360 mg verapamil or placebo is not tolerated due to side effects, the dose can be reduced to 240 mg verapamil or placebo, which is the lowest acceptable dose. In cases where 240 mg verapamil or placebo is not tolerated, the subject must be withdrawn.

The investigator or designee must confirm appropriate temperature conditions have been maintained during transit for all study medication received and any discrepancies are reported and resolved before use of the study medication. Only participants enrolled in the study may receive study medication and only authorized site staff may supply or administer study medication. All study medications must be stored in a secure, environmentally controlled, and monitored (manual or automated) area in accordance with the labelled storage conditions with access limited to the investigator and authorized site staff. The investigator or designee must confirm appropriate temperature conditions have been maintained during transit for all study medication received and any discrepancies are reported and resolved before use of the study medication.

Further guidance and information for the final disposition of unused study interventions are provided in the pharmacy manual online supplemental information (see Ver-A-T1D Pharmacy Manual_Version 4.0~~_final~~).

For peer review only - http://bmjopen.bmj.com/site/about/guidelines.xhtml

Placebo:

Participants randomised to placebo will receive placebo tablets identical to verapamil that will be labelled as required per country requirement, labels will be blinded and provided centrally by the sponsor, Medical University of Graz (MUG).

Known drug reactions and interaction with other therapies:

Drug-drug interactions:

These known drug-drug interactions, selected for relevance of the Ver-A-T1D trial, see DRUGBANK Online for a complete list.

- Atorvastatin The serum concentration of Verapamil can be increased when it is combined with Atorvastatin.
- Dasiglucagon Verapamil may increase the hypotensive activities of Dasiglucagon.
- Fenofibrate The metabolism of Fenofibrate can be decreased when combined with Verapamil.
- Fluvastatin The metabolism of Fluvastatin can be decreased when combined with Verapamil.
- Gemfibrozil The metabolism of Verapamil can be decreased when combined with Gemfibrozil.
- Insulin The risk or severity of hypoglycaemia can be increased when Verapamil is combined with Insulin.
- Lovastatin The risk or severity of myopathy and rhabdomyolysis can be increased when Verapamil is combined with Lovastatin.
- Magnesium Magnesium can cause a decrease in the absorption of Verapamil resulting in a reduced serum concentration and potentially a decrease in efficacy.
- Pravastatin The serum concentration of Pravastatin can be increased when it is combined with Verapamil.
- Rosuvastatin The metabolism of Rosuvastatin can be decreased when combined with Verapamil.
- Simvastatin The risk or severity of myopathy and rhabdomyolysis can be increased when Verapamil is combined with Simvastatin.

Regarding interaction with HMG-CoA reductase inhibitors (statins) via the CYP3A4 pathway, Rosuvastatin, Pravastatin and Fluvastatin are labelled as “non-3A4 substrate”, thus have only minimal metabolism via the Cytochrome P450 system.[22, 23]

Advice on SARS-CoV-2/COVID-19 for the Ver-A-T1D trial:

Patients may be exposed to the risk of COVID-19 transmission and infection in relation to site visits if an outbreak is ongoing in the country concerned at the time of trial conduct. The risk of COVID-19 transmission in relation to site visits is overall considered to be low. To minimize the risk the following measures may be taken if appropriate:

- The number of physical on-site visits has been limited to the extent possible.
- On-site visits will be well-prepared and as short as possible. Physical contact between study participants and site staff will be limited to the extent possible, and protective measures will be implemented (mouth and nose protectors will be used by both site staff and study participants)
- Before entering the clinic, subjects will have a body temperature check and a symptom screening (coughing, shortness of breath, fever).

The use of a SARS-CoV-2 vaccine in patients treated with Verapamil 120 mg has not been studied.

For peer review only - http://bmjopen.bmj.com/site/about/guidelines.xhtml

Given the risk posed by COVID-19 during the pandemic, however, decisions regarding the use of any vaccination, including approved / authorized for use SARS-CoV-2 vaccines, in patients treated with Verapamil 120 mg should be made at the discretion of the investigator using their best clinical judgment and after careful consideration of risk benefit factors for the patient. The investigator must consult the vaccine product label for further information regarding associated risks and precautions, and also guidance from local regulatory agencies. Hypersensitivity events have been reported in association with certain vaccines, in close temporal relation to the application.

Applicable information regarding an individual's receipt of vaccination(s) must be documented in the participant's source documents and each administration date of the vaccine (each time) recorded as a concomitant medication in the eCRF. Any possible related adverse events from the vaccination should be reported according to the Adverse Event/Serious Adverse Event reporting guidance and to the appropriate manufacture, according to local practice.

The sites must assess this situation on an ongoing basis and must provide real time feedback to the sponsor if there is the potential to impact clinical research operations or if conditions at the site have the potential to impact the ability to monitor either the safety of participants or the scientific integrity of study(ies) at the site.

Assessment of diabetes and appropriate attention to the standard of care treatment will be provided throughout the trial. It is therefore concluded that the potential benefits from the trial will outweigh the potential risks for the Verapamil 120 mg as well as placebo treated patients. Based on the risk assessment, the evaluation of COVID-19 and the implemented measures, the residual risk for study participants is considered low.

Concomitant treatments:

Concomitant medications will be assessed and recorded at each trial and phone visit. Participants will continue their current insulin treatment after they have been randomised and it is preferred that participants continue the same type of insulin treatment throughout the trial. Participants will be trained in diabetes self-care including carbohydrate counting before and at randomisation and whenever needed during the trial to achieve the most optimal diabetes control according to local standard of care. During the trial participants will receive insulin treatment to achieve metabolic control according to the local insulin titration guideline. Bolus and/or basal insulin can be stopped or paused at all times during the trial at the discretion of the investigator. The participant's need for bolus insulin will be documented in the eCRF.

During the MMTT no rapid or short-acting insulin will be given, the use of rapid acting insulin is acceptable up to 2 hours before the MMTT and the use of short-acting insulin up to 6 hours before the MMTT, to correct hyperglycaemia. Long-acting insulin and basal rates on an insulin pump will not be discontinued during the MMTT. During the DBS home collection short or rapid acting insulin should not be used until the end of the collection.

Any permitted medication or vaccine (including over the counter or prescription medicines, vitamins, and/or herbal supplements) that the subject is receiving at the time of enrolment or receives during the study are recorded along with, reason for use, dates of administration including start and end dates and dosage information (dose and frequency). The use of noninsulin pharmaceuticals that affect glycaemic control, alpha-blockers, beta-blockers, cardiac glycosides, antiarrhytmics, ivabradine, lithium, sulfinpyrazone, almotriptan and acetylsalecylic acid are prohibited for the trial duration. Concomitant medication known for inducing or inhibiting CYP3A4 and/or glycoprotein-P metabolism are also prohibited.

Compliance with trial treatment:

Compliance with study intervention will be assessed at each visit by the investigator or designee and is assessed by counting returned tablets during the site visits and documented in the source

For peer review only - http://bmjopen.bmj.com/site/about/guidelines.xhtml

documents and eCRF. Deviation(s) from the prescribed dosage regimen are recorded in the eCRF. A record of the number of study tablets dispensed and taken by each participant is maintained and reconciled with study drug accountability and compliance records. Treatment start and stop dates, including dates for treatment delays and/or dose reductions will also be recorded in the eCRF.

Missed and unscheduled visits:

If a visit is missed every effort is made to ensure information is collected and participants will be invited for the next scheduled visit according to the visit schedule. An unscheduled visit can be scheduled at any time at the discretion of the investigator, e.g. in case additional blood samples must be performed for safety reasons. This should be reported on the unscheduled visit form in the eCRF stating the reason for the visit. If the subject attends the clinic due to re-sampling of visit-related assessments, including MMTT, this is not considered an unscheduled visit. The date of the assessments for a specific visit must be updated in the eCRF accordingly. Likewise, coming to the site for additional trial products or ancillary supplies is not considered as an unscheduled visit.

Evaluation of adverse events (AEs):

The sponsor expects that adverse events are recorded from the point of informed consent regardless of whether a participant has yet received a medicinal product. Individual adverse events should be evaluated by the investigator. This includes the evaluation of its seriousness, and any relationship between the investigational medicinal product(s) and/or concomitant therapy and the adverse event (causality). Additional information on the definitions for assessments of safety in Ver-A-T1D can be found in online supplemental information (see Ver-A-T1D Study Protocol Paper v1.1 22 July 2024-SUPPLEMENTARY MATERIAL).

Seriousness is assessed against the criteria outlined in online supplemental information (see Ver-A-T1D Study Protocol Paper v1.1 22 July 2024-SUPPLEMENTARY MATERIAL). This defines whether the event is an adverse event (AE), serious adverse event (SAE) or a serious adverse reaction (SAR). Assessment of causality is categorised as: (1) Definitely: A causal relationship is clinically/biologically certain. This is therefore an Adverse Reaction (AR); (2) Probable: A causal relationship is clinically / biologically highly plausible and there is a plausible time sequence between onset of the AE and administration of the investigational medicinal product and there is a reasonable response on withdrawal. This is therefore an Adverse Reaction; (3) Possible: A causal relationship is clinically / biologically plausible and there is a plausible time sequence between onset of the AE and administration of the investigational medicinal product. This is therefore an Adverse Reaction; (4) Unlikely: A causal relation is improbable and another documented cause of the AE is most plausible. This is therefore an Adverse Event; (5) Unrelated: A causal relationship can be definitely excluded and another documented cause of the AE is most plausible. This is therefore an Adverse Event. Unlikely and Unrelated causalities are considered not to be IMP related. Definitely, Probable and Possible causalities are considered to be IMP related. A pre-existing condition must not be recorded as an AE or reported as an SAE unless the condition worsens during the trial and meets the criteria for reporting or recording in the appropriate section of the eCRF.

All events should be graded for severity according to the NCI-CTCAE Toxicity Criteria (V.5.0). AEs and ARs are recorded in the medical notes and the appropriate section of the eCRF at all phone and site visits. SAEs and SARs are be reported to the sponsor as detailed below.

Expected Adverse Events/Serious Adverse Events (AE/SAE):

The following are (S)AEs that could be reasonably expected for this trial population during the trial: (1) Hypoglycaemia and (2) Diabetic Ketoacidosis. These events must be recorded in the eCRF. Episodes not fulfilling the criteria for an SAE are not to be reported as AEs. If one of the above-mentioned episodes fulfils the criteria for an SAE then in addition to the above, an SAE form must also be filled in. The events are exempt from being reported as SAEs only if the causalities are not considered to be trial drug related.

For peer review only - http://bmjopen.bmj.com/site/about/guidelines.xhtml

Reporting serious adverse events:

Adverse events and adverse reactions should be recorded in the medical notes and the appropriate section of the eCRF and/or AE/AR log. Serious Adverse Events and Serious Adverse Reactions should be reported to the sponsor. Each Principal Investigator needs to record all adverse events and report serious adverse events to the Chief Investigator using the trial specific SAE form within 24 hours of their awareness of the event. The Chief Investigator is responsible for ensuring the assessment of all SAEs for expectedness and relatedness is completed and the onward notification of all SAEs to the sponsor immediately but not more than 24 hours of first notification. The sponsor has to keep detailed records of all SAEs reported to them by the trial team.

The Chief Investigator is also responsible for prompt reporting of all serious adverse event findings to the competent authority of each concerned member state if they could: (1) adversely affect the health of participants, (2) impact the conduct of the trial, (3) alter the risk to benefit ratio of the trial, or (4) alter the competent authority's authorisation to continue the trial in accordance with Directive 2001/20/EC. SAEs are reported to the Chief Investigator at MUG.

Reporting of Suspected Unexpected Serious Adverse Reactions (SUSARs):

All suspected adverse reactions related to an investigational medicinal product (the tested IMP and comparators) which occur in the concerned trial, and that are both unexpected and serious (SUSARs) are subject to expedited reporting. The sponsor delegates the responsibility of notification of SUSARs to the Chief Investigator. The Chief Investigator must report all the relevant safety information previously described, to the Sponsor, Competent authorities in the concerned member states and Ethics Committee in the concerned member states. The Chief Investigator shall inform all investigators concerned of relevant information about SUSARs that could adversely affect the safety of participants.

All parties must be notified of fatal or life-threatening SUSARs as soon as possible but no later than 7 calendar days after the trial team and sponsor has first knowledge of the minimum criteria for expedited reporting. In each case relevant follow-up information should be sought and a report completed as soon as possible. It should be communicated to all parties within an additional 8 calendar days. Non-fatal, non-life-threatening SUSARs and safety issues must be reported to all parties as soon as possible but no later than 15 calendar days after first knowledge of the minimum criteria for expedited reporting. Further relevant follow-up information should be given as soon as possible. Information on the final description and evaluation of an adverse reaction report may not be available within the required time frames for reporting. For regulatory purposes, initial expedited reports should be submitted within the time limits as soon as the minimum following criteria are met: (1) a suspected investigational medicinal product, (2) an identifiable participant (e.g. trial participant code number), (3) an adverse event assessed as serious and unexpected, and for which there is a reasonable suspected causal relationship and (4) an identifiable reporting source. When available and applicable a unique clinical trial identification (EudraCT number or in case of non-European Community trials the sponsor's trial protocol code number) and a unique case identification (i.e. sponsor's case identification number) should also be reported.

In case of incomplete information at the time of initial reporting, all the appropriate information for an adequate analysis of causality should be actively sought from the reporter or other available sources. Further available relevant information should be reported as follow-up reports. In certain cases, it may be appropriate to conduct follow-up of the long-term outcome of a particular reaction. Electronic reporting is the expected method for expedited reporting of SUSARs to the competent authority. The format and content as defined by the competent authority should be adhered to.

Pregnancy Reporting:

All pregnancies within the trial in female trial participants will be collected after the start of study intervention and until 7 days after the last dose and should be reported to the Chief Investigator and

For peer review only - http://bmjopen.bmj.com/site/about/guidelines.xhtml

the sponsor using the relevant pregnancy reporting form within 14 days of notification. Details of pregnancies in female participants will be collected after the first trial-related activity after obtaining informed consent and until pregnancy outcome. If a pregnancy is reported in a female participant, the investigator should inform the Chief Investigator and sponsor within 14 calendar days of learning of the pregnancy and pregnancy outcome should be documented in the participant's medical record. Participants will be followed to determine the outcome of the pregnancy. The investigator will report information on the participant and the pregnancy outcome until the new born infant is one month of age in accordance with European Medicines Agency (EMA).[24] Abnormal pregnancy outcome (e.g. spontaneous abortion, foetal death, stillbirth, congenital anomalies and ectopic pregnancy) is considered an SAE.

Collection of pregnancy information - Female participants who become pregnant will adhere to the following steps:

- Investigator will collect pregnancy information on any female participant, who becomes pregnant while participating in this trial.
- Information will be recorded on the appropriate form and submitted to the Chief Investigator and sponsor within 14 calendar days of learning of a participant's pregnancy.
- Participant will be followed to determine the outcome of the pregnancy. The investigator will collect follow-up information on participant and neonate, which will be forwarded to the sponsor. Generally, follow-up will not be required for longer than 1 month beyond the delivery date.
- Any termination of pregnancy will be reported, regardless of foetal status (presence or absence of anomalies) or indication for procedure.
- While pregnancy itself is not considered to be an AE or SAE, any pregnancy complication or elective termination of a pregnancy will be reported as an AE or SAE.
- A spontaneous abortion is always considered to be an SAE and will be reported as such.
- Any SAE occurring because of a post-trial pregnancy which is considered possibly/probably related to the trial product by the investigator will be reported to the sponsor.

Any female participant who becomes pregnant while participating in the trial will discontinue trial product.

Toxicity Management – Emergency Procedures:

Verapamil has a vasodilating action on the vascular system. Toxic effects occur usually after a delay of 1 to 5 hours following ingestion. The main cardiovascular symptoms are: bradycardia and atrioventricular block (in 82% of cases) hypotension and cardiogenic shock (in 78% of cases) cardiac arrest (in 18% of cases). AV-Block 1st degree is treated as outlined in the online supplemental information (see Ver-A-T1D Study Protocol Paper v1.1 22 July 2024-SUPPLEMENTARY MATERIAL). Pulmonary edema may occur. Impairment of consciousness and seizures may occur and are related to a low cardiac output. Nausea and vomiting may be observed. Metabolic acidosis due to shock and hyperglycaemia may occur. Verapamil is a calcium channel blocker and inhibits the entry of calcium through calcium channels into cardiovascular cells. Verapamil reduces the magnitude of the calcium current entry and decreases the rate of recovery of the channel. Verapamil decreases peripheral vascular and coronary resistance but it is a less potent vasodilator than nifedipine. In contrast, its cardiac effects are more prominent than those of nifedipine. At doses necessary to produce arterial vasodilatation, verapamil has much greater negative chronotropic, dromotropic and inotropic effects than nifedipine. At toxic doses, calcium channel inhibition by verapamil results in three principal effects: hypotension due to arterial vasodilatation, cardiogenic shock secondary to a negative inotropic effect, bradycardia and atrio-ventricular block. The therapeutic effects of verapamil on hypertension and angina pectoris are due to arterial systemic and coronary vasodilatation. The antiarrhythmic activity of verapamil is due to a delay in impulse transmission through the AV node by a direct action. Toxicity may occur after ingestion of 1 g. verapamil was

For peer review only - http://bmjopen.bmj.com/site/about/guidelines.xhtml

tested on human peripheral lymphocytes in vitro using micronucleus (MN) test. The MN frequencies showed increase after all treatment. The results of FISH analysis suggest that Verapamil , separately or combined with ritodrine, shows to a larger extent aneugenic than clastogenic effect. Verapamil hydrochloride may increase blood alcohol (ethanol) concentrations and prolong its effects.

Toxicity Management – Mild to Moderate Toxicity:

Patients who have asymptomatic bradycardia can be admitted and observed with telemetry if judged reasonable by the investigator. Obtain peripheral intravenous access and monitor ECG. Mild hypotension may only require treatment with intravenous fluid administration.

Toxicity Management – Severe Toxicity:

Patients with bradycardia and hypotension require standard advanced cardiac life support (ACLS) treatment. Place a central line and consider placement of an arterial line. Standard first line treatment includes atropine for bradycardia although in a serious poisoning it is rarely effective. High dose insulin and dextrose have been effective in animal studies and multiple case reports in patients with hypotension refractory to other modalities and should be considered early in patients with significant hypotension. Use intravenous calcium in severe poisonings although in these cases, beneficial effects of calcium infusion (calcium chloride is preferred) may be very minimal or short-lived. Repeat bolus doses or a continuous intravenous infusion are often needed. Standard vasopressors should be administered to maintain blood pressure. Lipid emulsion has been successful in animal studies and several case report of patients with hypotension refractory to other therapies. Intravenous glucagon has been used with variable success. In a patient whose hemodynamic status continues to be refractory despite the treatment described above, extracorporeal membrane oxygenation or cardiopulmonary bypass should be considered. Treat seizures with IV benzodiazepines; barbiturates or propofol may be needed if seizures persist or recur. AV-Block 1st degree is treated as per Figure 3.

Storage and Analysis of Samples:

Samples collected in the study as part of the INNODIA Clinical Trial Master Protocol will be stored and analysed as described in the Master Protocol. Additional samples collected that are in the same nature, for example samples from additional MMTT or for additional immune cell studies, will be stored and analysed according to the INNODIA Clinical Trial Master Protocol[20].

STATISTICS OVERVIEW:

The trial is a multi-centre, randomised, double-blind, placebo-controlled trial in subjects with T1D within 6 weeks of diagnosis. A total sample size of 120 participants will be randomised 2:1 between 360mg verapamil and placebo. The primary endpoint of interest is the area under the stimulated C-peptide response curve over the first two hours of a mixed meal tolerance test (MMTT) after 12 months therapy compared to placebo.

One interim analysis will be performed using data available when approximately 50 participants have been randomised to determine whether the trial should be stopped for futility.

All analyses will be performed on an Intention-to-treat (ITT) approach that will include all randomised participants irrespective of protocol compliance.

EVALUATION OF RESULTS (DEFINITIONS AND RESPONSE/EVALUATION OF OUTCOME MEASURES):

Statistical Methods for Primary Analyses:

All model assumptions will be checked via graphical means such as plotting residuals versus dose and fitted values. We will transform our primary outcome, AUC C-pep value to ln(AUC C-pep+1) as recommended by . The transformed AUC C-pep value is assumed to be normally distributed; this distributional assumption will be assessed using a Q-Q plot and whether the residuals of the model deviate from a straight line. If the residuals are not normally distributed, then the outcome will be

For peer review only - http://bmjopen.bmj.com/site/about/guidelines.xhtml

transformed to improve the assumption. If no transformation is available, then non-parametric methods will be used.

The primary endpoint, the area under the C-peptide curve over the first two hours (using all available measurements within the first 2 hours) of a mixed meal tolerance test (AUC C-pep) at 12 months (after transformation AUC C-pep →ln(AUC C-pep +1)) will be analysed using a linear mixed model at the end of the trial. The model will have fixed effects of treatment and time and the random effect will be participant ID. Additionally autocorrelations will be included within participants and ideally an unstructured matrix will be fitted stratified by treatment group, however, if the data do not allow such complexity then an AR(1) autocorrelation pattern will be estimated. The contrast of interest is the mean difference in AUC C-pep between verapamil 360mg and placebo at 12 months.

The transformed AUC C-pep value is assumed to be normally distributed and this distributional assumption will be assessed using a Q-Q plot and whether the residuals of the model deviate from a straight line. Additionally, departures from normality will be assessed by using normality tests, like for instance the Shapiro-Wilk test. If model assumptions are violated for the AUC C-pep →ln(AUC C-pep +1) values, then log- or square root transformations will be applied. If none of these transformations yields normally distributed residuals, then treatments will be compared by means of non-parametric methods using the change from baseline as dependent variable.

Statistical Methods for Secondary Analyses:

The secondary endpoints will also be analysed via a mixed effects models with fixed effects of treatment and time and the random effect will be participant ID. If required the models may include additional covariates which may be potential factors that are confounding the relationship between treatment and outcomes.

Subgroup analyses will be considered for a select list of potential covariates, the subgroup treatment effect will be analysed using an interaction test and additional factors will be included in the model to conduct this test.

A detailed statistical analysis plan (SAP) will be completed before the final database lock and will be based on top of the INNODIA Master SAP within the INNODIA clinical trial network (www.innodia.eu).

Interim analyses:

The interim analysis should be carried out after 10 months from the start of the trial.

As with the primary analysis, the endpoint, the area under the C-peptide curve over the first two hours of a mixed meal tolerance test (AUC-C-pep) will be analysed using a mixed linear model. The model will have fixed effects of treatment and time and the random effect will be participant ID. Additionally autocorrelations will be included within participants and ideally an unstructured matrix will be fitted stratified by treatment group, however, if the data do not allow such complexity, then an AR(1) autocorrelation pattern will be estimated. The analysis will be an intention to treat analysis. The contrast of interest is the mean difference in AUC-C-pep between verapamil 360mg and placebo at 6 months as there will be no one who has completed the 12-month follow-up visit at 10 months. The statistical test will be the z-test and the trial will be recommended to stop if the z-statistics is less than -0.5 i.e. where treatment is marginally worse than placebo.

Given a recruitment rate of 5 participants per month the interim analysis at 10 months should have 15 people with 3 months of follow-up data, 15 people with 6 months of follow-up data and 15 people with 9 months of follow-up data. Different recruitment rates will alter the operating characteristics of the trial but the type 1 error at the final analysis is controlled but power may vary. If recruitment is faster then the timing of the interim analysis will be re-assessed, if there is sufficient information the interim may proceed earlier than 10 months.

For peer review only - http://bmjopen.bmj.com/site/about/guidelines.xhtml

Model assumptions will be checked via graphical means such as plotting residuals versus dose and fitted values. The AUC-C-pep is assumed to be normally distributed, this distributional assumption will be assessed using a Q-Q plot and whether the residuals of the model deviate from a straight line. If the residuals are not normally distributed then the outcome will be transformed to improve the assumption.

Number of participants to be enrolled - Sample size calculation:

From the randomised, double-blind, placebo-controlled phase 2 clinical trial the SD for the AUC C-peptide endpoint after a MMTT over 2 hours at 12 months was 0.27 nmol/L/min as per[14]. With this SD, 90% power, 5% significance level then 40 participants on the control arm and 80 on the treatment arm will be needed to detect a change of 0.18 nmol/L/min in C-peptide. All tests are for superiority tests and the tests are two-sided tests.

Criteria for the premature termination of the trial:

The sponsor designee/INNODIA reserves the right to close the study site or terminate the study at any time for any reason at the sole discretion of the sponsor. Study sites will be closed upon study completion. A study site is considered closed when all required documents and study supplies have been collected and a study-site closure visit has been performed.

The investigator may initiate study-site closure at any time, provided there is reasonable cause and sufficient notice is given in advance of the intended termination.

Reasons for the early closure of a study site by the sponsor or investigator may include but are not limited to:

- Failure of the investigator to comply with the protocol, the requirements of the IRB/IEC or local health authorities, the sponsor's procedures, or GCP guidelines
- Inadequate recruitment of participants by the investigator
- Discontinuation of further study intervention development

If the study is prematurely terminated or suspended, the sponsor shall promptly inform the investigators, the IECs/IRBs, the regulatory authorities, and any contract research organization(s) used in the study of the reason for termination or suspension, as specified by the applicable regulatory requirements. The investigator shall promptly inform the subject and should assure appropriate subject therapy and/or follow-up.

Procedure to account for missing or spurious data:

All participants who are randomised will be included in this analysis and the model will have fixed effects for time and dose and participant is a random effect. All available measurements over time will be included in the analysis and an unstructured autocorrelation will be estimated for each dose level if sufficient data. The estimates assume that the missing data are missing at random. If the missing data are non-ignorable then a sensitivity analysis will be performed.

The secondary endpoints will also be analysed using a mixed effects model similar to the one described for the primary outcome. Again, model assumptions and distributional assumptions will be inspected graphically.

Definition of the end of the trial:

The end of the trial is defined as the date of the last visit of the last participant in the trial.

Data management and eCRF:

All data will be transferred into an electronic Case Report Form (eCRF) which will be anonymised. All trial data in the eCRF must be extracted from and be consistent with the relevant source documents. The eCRFs must be completed, dated and signed by the investigator or designee in a timely manner. It remains the responsibility of the investigator for the timing, completeness, legibility and accuracy

For peer review only - http://bmjopen.bmj.com/site/about/guidelines.xhtml

of the eCRF pages. The eCRF will be accessible to trial coordinators, data managers, the investigators, clinical trial monitors, auditors and inspectors as required.

All subject data relating to the trial will be recorded on eCRFs. The investigator is responsible for verifying that data entries are accurate and correct by electronically signing the eCRF.

Corrections to the eCRF data may be made by the investigator or the investigator's delegated staff. An audit trail will be maintained in the eCRF application containing as a minimum: the old and the new data, identification of the person entering the data, date and time of the entry and reason for the correction. If corrections are made by the investigator's delegated staff after the date when the investigator signed the eCRF, the eCRF must be signed and dated again by the investigator.

The investigator must be able to access his/her trial documents without involving the sponsor in any way. If applicable, electronic CRF and other subject data will be provided in an electronic readable format to the investigator before access is revoked to the systems supplied by the sponsor. Site-specific CRFs and other subject data (in an electronic readable format or as paper copies or prints) must be retained by the trial site. If the provided electronic data (e.g. the CD-ROM) is not readable during the entire storage period, the investigator can request a new copy. A copy of all data will be stored by the sponsor.

Data will be collected using INNODIA (e)CRFs. Suitably qualified personnel designated by the PI and listed on the delegation of responsibility log will be responsible for completing the eCRF. Each clinical centre will be responsible for managing collected data and for generating and resolving data queries.

Source Data:

Source documents provide evidence for the existence of the participant and substantiate the integrity of the data collected. Source documents are filed at the investigator's site. Data reported on the Source Data Form or entered in the eCRF that are transcribed from source documents must be consistent with the source documents or the discrepancies must be explained. The investigator may need to request previous medical records or transfer records, depending on the study. Also, current medical records must be available.

To enable peer review, monitoring, audit and/or inspection the investigator must agree to keep records of all participating participants (sufficient information to link records e.g., eCRFs, hospital records and samples), all original signed informed consent forms and copies of the eCRF in an electronic readable format .

Definition of what constitutes source data can be found in a source document agreement at each trial site. There will only be one source document defined at any time for any data element.

Data Protection and Participant Confidentiality:

All investigators and trial site staff involved in this trial must comply with the requirements of the Data Protection Act 1998, GDPR (EU) 2016/679, local data protection laws and Trust Policy with regards to the collection, storage, processing, transfer and disclosure of personal information and will uphold the Act's core principles.

- Participants will be assigned a unique study identifier as agreed with the sponsor. Any participant records or datasets that are transferred to the sponsor will contain the identifier only; participant names or any information which would make the participant identifiable will not be transferred.
- The participant must be informed that his/her personal study-related data will be used by the sponsor in accordance with local data protection law. The level of disclosure must also be explained to the participant.

For peer review only

For peer review only - http://bmjopen.bmj.com/site/about/guidelines.xhtml

- The participant must be informed that his/her medical records may be examined by Clinical Quality Assurance auditors or other authorized personnel appointed by the sponsor, by appropriate IEC members, and by inspectors from regulatory authorities.
- Data may also be sent out to non- European countries.

Protocol Compliance and Breaches of GCP:

Prospective, planned deviations or waivers to the protocol are not allowed and must not be used. All participating sites must ensure that any substantial amendment is approved before implementation by an accredited EC.

However, deviations from the protocol should be avoided. If deviations do occur, the investigator must inform the monitor and the implications of the deviation must be reviewed and discussed. Protocol deviations must be adequately documented on the relevant forms and reported to the Chief Investigator and sponsor immediately.

Deviations must be documented and explained in a protocol deviation by stating the reason, date, and the action(s) taken. Some deviations, for which corrections are not possible, can be acknowledged and confirmed via edit checks in the eCRF or via listings from the protocol deviation forms.

Deviations from the protocol which are found to occur repeatedly will not be accepted and will require immediate action and could potentially be classified as a serious breach. Any potential/suspected serious breaches of GCP must be reported immediately to the sponsor without any delay.

Monitoring, trial documentation, archiving, audit & inspection:

The Trial Master File (TMF) will be kept up to date by the coordinating centre and each participating site will be responsible for maintaining their Investigator Site Files (ISF). These files need to be complete at the end of the trial and archived for 25 years. No records may be destroyed or transferred to another location or party without written notification of the sponsor during the retention period.

The sponsor will be responsible for archiving the TMF. Other participating sites will be responsible for archiving their ISF. Records and documents including source data will be stored at each participating site. The investigator must be able to access his/ her trial documents without involving the sponsor in any way. If applicable, electronic CRF and other subject data will be provided in an electronic readable format to the investigator before access is revoked to the systems supplied by the sponsor.

All essential and trial documentation will be securely archived after the last analysis of the study data has been completed and the final study report has been submitted to the relevant bodies.

The investigator must make all trial documentation and related records available should an MHRA or EMA inspection or any regulatory authority inspection occur. Should a monitoring visit or audit be requested, the investigator must make the trial documentation and source data available to the sponsor's representative. All participant data must be handled and treated confidentially.

The sponsor's monitoring frequency will be determined by an initial risk assessment performed prior to the start of the trial. A detailed monitoring plan will be generated detailing the frequency and scope of the monitoring for the trial. Throughout the course of the trial, the risk assessment will be reviewed and the monitoring frequency adjusted as necessary. The scope and frequency of the monitoring will be determined by the risk assessment and detailed in the Monitoring Plan for the study.

ETHICS AND DISSEMINATION:

Ethical committee review:

For peer review only - http://bmjopen.bmj.com/site/about/guidelines.xhtml

Before the start of the trial and upon ~~or~~ implementation of any amendment ~~we will obtain~~ approvals of the trial protocol, protocol amendments, informed consent forms and other relevant documents e.g., advertisements and general practitioner (GP) information letters if applicable were obtained from the research ethics committee (REC). Ethics approval was sought from the following ethics committees: Medical University of Graz Ethics Committee (ID: 32-664 ex 19/20), Commissie voor Medische Ethiek ZNA, p/a ZNA Koningin Paola Kinderziekenhuis Antwerpen (ID: 5494), Comité de Protection des Personnes Est-II, CHRU – Hôpital Saint Jacques (ID: 21.01.26.73506), Comitato Etico dell' IRCCS Ospedale S.Raffaele di Milano (ID: 9/05/22), Comitato Etico Regione Toscana – Area Vasta Sud Est (ID: 19709), Medizinische Hochschule Hannover Ethikkommission (Nr. 9465_AMG_mono_2020), Medizinische Hochschule Hannover Ethikkommission und Ethikkommission der Landesärztekammer Baden-Württemberg (Nr. 9465_AMG_M_2020) and NHS Health Research Authority, London – City & East Research Ethics Committee (REC reference: 20/LO/1295). Thus, all procedures were conducted in compliance with the ethical standards established by the institutional ethics and research committees. All participants provided written informed consent prior to enrolment in the study.

All correspondence with the REC ~~will be~~is retained in the Trial Master File/Investigator Site File and ~~.~~

a~~A~~nnual reports ~~will be~~are submitted to the REC in accordance with national requirements. It is the Chief Investigator's responsibility to produce the annual reports as required.

Regulatory Compliance:

The trial will not commence until a Clinical Trial Authorisation (CTA) is obtained from the applicable regulatory authorities. The protocol and trial conduct will comply with the Medicines for Human Use (Clinical Trials) Regulations 2004 and any relevant amendments. Regulatory authorities will receive the clinical trial application, protocol amendments, reports on SAEs, and the clinical trial report according to national requirements.

Development Safety Update Reports (DSURs) will be submitted to the regulatory authorities in accordance with national requirements. It is the Chief Investigators responsibility to produce the annual reports as required.

Protocol Amendments:

Protocol amendments must be reviewed and agreement received from the sponsor for all proposed amendments prior to submission to the HRA, REC and/or MHRA.

The only circumstance in which an amendment may be initiated prior to HRA, REC and/or MHRA approval is where the change is necessary to eliminate apparent, immediate risks to the participants (Urgent Safety Measures). In this case, accrual of new participants will be halted until the HRA, REC and/or MHRA approval has been obtained.

In the event of an important safety measure, the Principal Investigator or suitable qualified delegate at the participating site will be informed within 48 hours by the Chief Investigator or suitable qualified member of the study team.

Peer Review:

This study protocol has been peer reviewed by the sponsor, trial management group and Principal Statistician.

Declaration of Helsinki and Good Clinical Practice (GCP):

The trial will be performed in accordance with the spirit and the letter of the declaration of Helsinki, the conditions and principles of Good Clinical Practice, the protocol and applicable local regulatory requirements and laws.

GCP Training:

For peer review only - http://bmjopen.bmj.com/site/about/guidelines.xhtml

All trial staff must hold evidence of appropriate GCP training or undergo GCP training prior to undertaking any responsibilities on this trial. This training should be updated every 2 years or in accordance with your Trust's policy.

Authorisation of Participating Sites:

Prior to initiating a participating site, the following documentation will be in place: 1) Investigator Site File, 2) Ethics approval from each country in addition and following home country approval, 3) Competent Authority approval, 4) All relevant local institutional approvals (e.g. local hospital institution), 5) Signed participating site agreement when required, 6) Insurance statement, 7) Protocol signed and dated by PI, 8) Confirmation of receipt of investigator's brochure by PI, 9) Patient Information leaflets including informed consent form and any other study material for participants to be provided in English and translated to home country language, 10) Delegation of Responsibility and Signature Log, 11) PI signed and dated CV, 12) Signed and dated CVs from everyone listed on the delegation of responsibility log, 13) GCP certificate from PI and everyone listed on the delegation of responsibility log, 14) Final eCRF, 15) Study Manual and SOPs, 16) Signed Source Data Verification Agreement Form (SDVAF) and 17) Local laboratory accreditation (or equivalent) and reference ranges for the protocol-specified parameters.

Procedure for initiating/opening a new site:

The study manager and/or monitor will organize the initiation meeting on behalf of the CI and invite all the participating site study members. The CI or delegate, study manager and/or monitor and PI will present throughout the meeting. The PI's legal responsibilities will be listed in the Participating Site Agreement, if applicable, but each recruiting site will have a nominated PI who will be expected to:

- Read the protocol and agree to follow it and future amended protocols in accordance with ICH Good Clinical Practice guidelines, legal and regulatory requirements.
- Providing oversight of the conduct of the trial at the site and adherence to requirements of ICH guidelines, the IRB/IEC, and all other applicable local regulations
- Provide written summaries of the status of the trial in accordance with the requirements, policies, and procedures established by the IRB/IEC and/or regulatory authorities
- Notify the IRB/IEC of SAEs or other significant safety findings as required by IRB/IEC procedures
- Ensuring submission of the clinical trial report (CTR) synopsis to the IRB/IEC
- Attend initiation meeting and subsequent study meetings or delegate to suitable qualified team member
- Adhere to safety reporting timelines
- Have overall responsibility of data collection and responsibility of maintaining ISF
- Be thoroughly familiar with the appropriate use of the investigational product(s), as described in the protocol, in the current Investigator's Brochure, in the product information and in other information sources provided by the sponsor.
- Permit monitoring and auditing by the sponsor, and inspection by the appropriate regulatory authority(ies).
- Maintain a list of appropriately qualified persons to whom the investigator has delegated significant trial-related duties.

Sponsorship, Financial & Insurance:

The trial is sponsored by Medical University of Graz.

The trial will be funded by JDRF International and the Innovative Medicines Initiative 2 Joint Undertaking under grant agreement No 115797 (INNODIA) and No 945268 (INNODIA HARVEST). This

For peer review only - http://bmjopen.bmj.com/site/about/guidelines.xhtml

Joint Undertaking receives support from the Union's Horizon 2020 research and innovation programme, "EFPIA", "JDRF" and "The Leona M. and Harry B. Helmsley Charitable Trust".

The CE-marked CGM devices are provided by DexCom Inc. (USA) and supported by IMI2-JU under grant No 945268 (INNODIA HARVEST).

~~The trial will be funded by JDRF International and the Innovative Medicines Initiative.~~

~~The CGM will be provided by Dexcom.~~

Medical University of Graz will accept full financial liability for harm caused to participants in the clinical trial caused through the negligence of its employees and honorary contract holders. There are no specific arrangements for compensation should a participant be harmed through participation in the trial, but no-one has acted negligently.

Medical University of Graz will arrange insurance for negligent harm caused as a result of protocol design and for non-negligent harm arising through participation in the clinical trial.

Participants or their legal representatives of this study will not receive any payment for participating in this study, however, all reasonable travel costs incurred whilst travelling to the recruiting centre for each study visit will be reimbursed to the participant or legal representative by the coordinating centre.

Publications policy:

Ownership of the data arising from this study are owned by the beneficiary/ beneficiaries of the INNODIA Harvest consortium who generated them. On completion of the study the data will be analysed and tabulated and a Final Study Report prepared. Participating local investigators will have no rights to publish any of the study data without the permission of the Chief Investigator.

As outlined in the Consortium agreement each INNODIA partner (participant) has a maximum of 30 days to approve a publication or submit an objection after they have received the draft version in writing to the Coordination Team (publication@innodia.eu). If no response is gathered by day 30, then approval is assumed to be granted.

Nevertheless, the Beneficiaries acknowledge that some kind of publications may require shorter approval times due to given submission timelines:

Type of communication	Period for approval	Reminder sent out after	Approval required from
Full research paper	30 days	20 days	All INNODIA and ITC partners
Abstracts/ Posters	7 days	5 days	
Press releases*	5 days	--	
Public communication	5 days	--	

*Where national media releases are made, key messages and INNODIA researchers mentioned in the release should be circulated in English for approval.

In case of exceptional urgency, the Coordination team can grant permission to submit an abstract or a manuscript sub condition, meaning that the manuscript or abstract will have to be withdrawn from the review and publication process in case an INNODIA beneficiary objects.

Participants and legal representatives will be notified of the outcome of this study by a specifically designated newsletter, after the study has been published.

TRIAL STATUS:

For peer review only - http://bmjopen.bmj.com/site/about/guidelines.xhtml

Ver-A-T1D closed to recruitment on , 3 May 2024. Date of first enrolment was 8th February, 2021 in MUG. Ver-A-T1D received regulatory and ethics approval in Graz from the Ethics Committee of the Medical University of Graz on 24th August, 2020. Regulatory approval has also been granted by the Austrian competent authority in 11th February, 2021. Planned last patient last visit (LPLV) is 20 May 2025 and final reporting due May 2026.

DATA STATEMENT:

Data access:

No data are associated with this article. Data will be available in accordance with the data sharing plan and can be found in the online supplemental information (Ver-A-T1D_Data Sharing Plan_18.09.2024).

Extended data:

This project contains the following extended data:

1) Ver-A-T1D Informed Consent Version 5.0 11-Mar-2022.pdf (UK PIS, ICF and consent forms)
2) Ver-A-T1D Pharmacy Manual_Version 4.0.doc

REPORTING GUIDELINES:

SPIRIT checklist for ` A randomised, double-blind, placebo controlled, parallel group, multi-centre trial in adult subjects with newly diagnosed type 1 diabetes mellitus investigating the effect of Verapamil on preservation of beta-cell function (Ver-A-T1D)'[21].

AUTHOR CONTRIBUTIONS:

Writing – Original Draft Preparation: Wych J

Conceptualisation –: Pieber TR; Dayan C; Mander AP; Mathieu C

Funding Acquisition –: Pieber TR; Dayan C; Mander AP; Mathieu C

Methodology –: Mander AP; Pieber TR; Dayan, C

Writing, Review & Editing – Pieber TR; Dayan C; Mander AP; Mathieu C ; Brunner, M; Stenson, R; Chmura PJ; Danne, T; *Wych J.*

~~*Writing – Review & Editing: Pieber TR; Dayan C; Mander AP; Mathieu C ; Brunner, M; Stenson, R, Wych J.*~~

Project Administration –: Brunner M.

Pieber TR acted as guarantor.

COMPETING INTERESTS STATEMENT:

JW, MB, PJC, RS, TD, AM, CD, CM and TRP have no competing interests.

FUNDING STATEMENT:

This project has received funding from the Innovative Medicines Initiative 2 Joint Undertaking under grant agreement No 115797 (INNODIA) and No 945268 (INNODIA HARVEST). This Joint Undertaking receives support from the Union's Horizon 2020 research and innovation programme, "EFPIA", "JDRF" and "The Leona M. and Harry B. Helmsley Charitable Trust". The IMP is supplied by Medical University of Graz. The CE-marked CGM devices are provided by DexCom Inc. (USA) and supported by IMI2-JU under grant No 945268 (INNODIA HARVEST). Any dissemination of results must indicate that it reflects only the author's view and that the JU is not responsible for any use that may be made of the information it contains.

For peer review only - http://bmjopen.bmj.com/site/about/guidelines.xhtml

Any dissemination of results must indicate that it reflects only the author's view and that the JU is not responsible for any use that may be made of the information it contains.

REFERENCES:

1. DiMeglio LA, Evans-Molina C, Oram RA. Type 1 diabetes. Lancet. 2018;391(10138):2449-62.
2. Atkinson MA, Eisenbarth GS, Michels AW. Type 1 diabetes. Lancet. 2014;383(9911):69-82.
3. Sørensen JS, Johannesen J, Pociot F, Kristensen K, Thomsen J, Hertel NT, et al. Residual β-Cell function 3-6 years after onset of type 1 diabetes reduces risk of severe hypoglycemia in children and adolescents. Diabetes Care. 2013;36(11):3454-9.
4. Nathan DM, Genuth S, Lachin J, Cleary P, Crofford O, Davis M, et al. The effect of intensive treatment of diabetes on the development and progression of long-term complications in insulin-dependent diabetes mellitus. N Engl J Med. 1993;329(14):977-86.
5. Lachin JM, McGee P, Palmer JP. Impact of C-peptide preservation on metabolic and clinical outcomes in the Diabetes Control and Complications Trial. Diabetes. 2014;63(2):739-48.
6. Allen LA, Dayan CM. Immunotherapy for type 1 diabetes. Br Med Bull. 2021;140(1):76-90.
7. Zhou R, Tardivel A, Thorens B, Choi I, Tschopp J. Thioredoxin-interacting protein links oxidative stress to inflammasome activation. Nat Immunol. 2010;11(2):136-40.
8. Eissa LD, Ghobashy WA, El-Azab MF. Inhibition of thioredoxin-interacting protein and inflammasome assembly using verapamil mitigates diabetic retinopathy and pancreatic injury. Eur J Pharmacol. 2021;901:174061.
9. Domingues A, Jolibois J, Marquet de Rougé P, Nivet-Antoine V. The Emerging Role of TXNIP in Ischemic and Cardiovascular Diseases; A Novel Marker and Therapeutic Target. Int J Mol Sci. 2021;22(4).
10. Chen J, Saxena G, Mungrue IN, Lusis AJ, Shalev A. Thioredoxin-interacting protein: a critical link between glucose toxicity and beta-cell apoptosis. Diabetes. 2008;57(4):938-44.
11. Chen J, Hui ST, Couto FM, Mungrue IN, Davis DB, Attie AD, et al. Thioredoxin-interacting protein deficiency induces Akt/Bcl-xL signaling and pancreatic beta-cell mass and protects against diabetes. Faseb j. 2008;22(10):3581-94.
12. Chen J, Cha-Molstad H, Szabo A, Shalev A. Diabetes induces and calcium channel blockers prevent cardiac expression of proapoptotic thioredoxin-interacting protein. Am J Physiol Endocrinol Metab. 2009;296(5):E1133-9.
13. Cao X, He W, Pang Y, Cao Y, Qin A. Redox-dependent and independent effects of thioredoxin interacting protein. Biol Chem. 2020;401(11):1215-31.
14. Ovalle F, Grimes T, Xu G, Patel AJ, Grayson TB, Thielen LA, et al. Verapamil and beta cell function in adults with recent-onset type 1 diabetes. Nat Med. 2018;24(8):1108-12.
15. Xu G, Grimes TD, Grayson TB, Chen J, Thielen LA, Tse HM, et al. Exploratory study reveals far reaching systemic and cellular effects of verapamil treatment in subjects with type 1 diabetes. Nat Commun [Internet]. 2022 2022/03//; 13(1):[1159 p.].
16. Forlenza GP, McVean J, Beck RW, Bauza C, Bailey R, Buckingham B, et al. Effect of Verapamil on Pancreatic Beta Cell Function in Newly Diagnosed Pediatric Type 1 Diabetes: A Randomized Clinical Trial. JAMA. 2023;329(12):990-9.
17. Yin T, Kuo SC, Chang YY, Chen YT, Wang KK. Verapamil Use Is Associated With Reduction of Newly Diagnosed Diabetes Mellitus. J Clin Endocrinol Metab. 2017;102(7):2604-10.
18. Cooper-Dehoff R, Cohen JD, Bakris GL, Messerli FH, Erdine S, Hewkin AC, et al. Predictors of development of diabetes mellitus in patients with coronary artery disease taking antihypertensive medications (findings from the INternational VErapamil SR-Trandolapril STudy [INVEST]). Am J Cardiol. 2006;98(7):890-4.
19. Xu G, Chen J, Jing G, Shalev A. Preventing β-cell loss and diabetes with calcium channel blockers. Diabetes. 2012;61(4):848-56.

For peer review only - http://bmjopen.bmj.com/site/about/guidelines.xhtml

20. Dunger DB, Bruggraber SFA, Mander AP, Marcovecchio ML, Tree T, Chmura PJ, et al. INNODIA Master Protocol for the evaluation of investigational medicinal products in children, adolescents and adults with newly diagnosed type 1 diabetes. Trials. 2022;23(1):414.
21. Chan A-W TJ, Gøtzsche PC, Altman DG, Mann H, Berlin J, Dickersin K, Hróbjartsson A, Schulz KF, Parulekar WR, Krleža-Jerić K, Laupacis A, Moher D. SPIRIT 2013 Explanation and Elaboration: Guidance for protocols of clinical trials. BMJ. 2013;346:e7586.
22. Kostapanos MS, Milionis HJ, Elisaf MS. Rosuvastatin-associated adverse effects and drug-drug interactions in the clinical setting of dyslipidemia. Am J Cardiovasc Drugs. 2010;10(1):11-28.
23. Rowan CG, Brunelli SM, Munson J, Flory J, Reese PP, Hennessy S, et al. Clinical importance of the drug interaction between statins and CYP3A4 inhibitors: a retrospective cohort study in The Health Improvement Network. Pharmacoepidemiol Drug Saf. 2012;21(5):494-506.
24. Agency EM. Guideline on the exposure to medicinal products during pregnancy: Need for postauthorisation data 2005.

Figure 1 Ver-A-T1D Trial Design

Figure 2 Ver-A_T1D Trial Flow Chart

Figure 3 Ver-A-T1D AV-Block Management

For peer review only

For peer review only - http://bmjopen.bmj.com/site/about/guidelines.xhtml

Editor(s)' Comments to the Authors & Response from the Authors (in red):

1. Please update the article title to state that the manuscript is a protocol. Please also use sentence case rather than capitalising each word, and consider revising the format. Eg, 'Investigating the effect of verapamil on preservation of beta-cell function in adults with newly diagnosed type 1 diabetes mellitus (Ver-A-T1D): protocol for a randomised, double-blind, placebo-controlled, parallel-group, multi-centre trial' (or similar).

Recommendation accepted.

2. Please ensure that your protocol reports all outcome measures for your trial and ensure that the primary and secondary outcome measures are consistent between your protocol article and the trial registry records. Any discrepancies should be explained and corrected.

Completed, all outcomes aligned with https://www.clinicaltrialsregister.eu/ctr-search/trial/2020-000435-45/BE & Protocol V 8.0 (08-NOV-2021), see changes p7 & 8.

There are discrepancies between the outcome measures on clinicaltraials.gov and https://www.clinicaltrialsregister.eu/ctr-search/trial/2020-000435-45/BE): clinicaltraials.gov still shows Proinsulin, Insulin, Pro-IAPP and Proglucagon secretion as outcome measures. Each relevant authority is required to make the changes and we have contacted them but have not receive responses by the deadline for revisions to be submitted. However we are currently preparing to transfer the trial to CTIS, once this transfer is complete the discrepancies will be corrected automatically for all countries.

3. Please update the 'Ethics and dissemination' section in the abstract and main text to include the full name(s) and reference number(s) for the ethics committee(s) that approved the study and to include brief mention of participant informed consent requirements.

Completed, the following text has been included:

Abstract:

Ethics approval was sought from the research ethics committee (REC) of all participating countries. All participants provided written informed consent before joining the study.

Main text:

Ethics approval was sought from the following ethics committees: Medical University of Graz Ethics Committee (ID: 32-664 ex 19/20), Commissie voor Medische Ethiek ZNA, p/a ZNA Koningin Paola Kinderziekenhuis Antwerpen (ID: 5494), Comité de Protection des Personnes Est-II, CHRU – Hôpital Saint Jacques (ID:

For peer review only

21.01.26.73506), Comitato Etico dell' IRCCS Ospedale S.Raffaele di Milano (ID: 9/05/22), Comitato Etico Regione Toscana – Area Vasta Sud Est (ID: 19709), Medizinische Hochschule Hannover Ethikkommission (Nr. 9465_AMG_mono_2020), Medizinische Hochschule Hannover Ethikkommission und Ethikkommission der Landesärztekammer Baden-Württemberg (Nr. 9465_AMG_M_2020) and NHS Health Research Authority, London – City & East Research Ethics Committee (REC reference: 20/LO/1295). Thus, all procedures were conducted in compliance with the ethical standards established by the institutional ethics and research committees. All participants provided written informed consent prior to enrolment in the study.

4. Please move the trial registration details from the title page to the end of the abstract (after the 'Ethics and dissemination' section), in a section entitled 'Trial registration'.

Completed

5. Please revise the 'Strengths and limitations of this study' section of your manuscript after the abstract to ensure that key limitations of the study are included among the maximum of five bullet points. It may be clearer to use full sentences for each bullet point.

We have added the following bullet points:

- The investigational agent is a repurposed product with a well-established safety profile from over 50 years of use in different indications and if effective could be available at low cost.
- In contrast to previous treatments developed to alter the disease course in this autoimmune condition, the agent targets the beta cell rather than the immune system directly and hence has the potential to be used in the future in combination with immune modulatory interventions.
- The trial is based on a master protocol with standard efficacy and mechanistic outcomes which has been designed to form the basis of a future platform trial of combined interventions.
- A limitations of the study is that it does not include children, which comprise around 40% of the newly diagnosed type 1 diabetes population.
- The study will not establish the durability of the intervention since it only spans one year of treatment.

6. You have indicated in the abstract that ethics approval has been granted. However, in the 'Ethical committee review' section of the main text, you only indicate that ethics approval will be obtained (as if it had not already been). Please revise to clarify and please include full details of the ethics approval(s), including the name(s) of the approvers and any reference numbers.

Complete and changed to:

Ethical committee review:

Before the start of the trial and upon implementation of any amendment approvals of the trial protocol, protocol amendments, informed consent forms and other relevant

For peer review only

documents e.g., advertisements and general practitioner (GP) information letters if applicable were obtained from the research ethics committee (REC). Ethics approval was sought from the following ethics committees: Medical University of Graz Ethics Committee (ID: 32-664 ex 19/20), Commissie voor Medische Ethiek ZNA, p/a ZNA Koningin Paola Kinderziekenhuis Antwerpen (ID: 5494), Comité de Protection des Personnes Est-II, CHRU – Hôpital Saint Jacques (ID: 21.01.26.73506), Comitato Etico dell' IRCCS Ospedale S.Raffaele di Milano (ID: 9/05/22), Comitato Etico Regione Toscana – Area Vasta Sud Est (ID: 19709), Medizinische Hochschule Hannover Ethikkommission (Nr. 9465_AMG_mono_2020), Medizinische Hochschule Hannover Ethikkommission und Ethikkommission der Landesärztekammer Baden-Württemberg (Nr. 9465_AMG_M_2020) and NHS Health Research Authority, London – City & East Research Ethics Committee (REC reference: 20/LO/1295). Thus, all procedures were conducted in compliance with the ethical standards established by the institutional ethics and research committees. All participants provided written informed consent prior to enrolment in the study.

All correspondence with the REC is retained in the Trial Master File/Investigator Site File and annual reports are submitted to the REC in accordance with national requirements. It is the Chief Investigator's responsibility to produce the annual reports as required.

7. Please update the 'ETHICS AND DISSEMINATION' section of the main text to include summary information in participant informed consent requirements.

Complete, please see number 3 and 6 above.

8. Please update the 'TRIAL STATUS' section to include the planned or expected timeline for completion of the study.

Added 'Planned last patient last visit (LPLV) is 20 May 2026 and final reporting due May 2027.'

9.Thank you for including a copy of the consent form as a supplemental file. Please ensure that this (and any other supplemental files for publication) are cited in an appropriate place in the main text.

Checked and have added reference to the supplementary file on p.14 Informed consent section.

10. BMJ Open adheres to BMJ's Tier 2 data policy. We strongly encourage that data generated by your research that supports your article be made available as soon as possible, wherever legally and ethically possible. We also require data from clinical trials to be made available upon reasonable request. To adhere to ICMJE guidelines, we require that a data sharing plan must be included with trial registration for clinical trials that begin enrolling participants on or after 1st January 2019. We would therefore ask that you update the trial registry record with your data sharing plan in order to comply

For peer review only

with the BMJ Open data sharing policy.

The data sharing plan has been uploaded to the trial registry, included as a supplementary file (Ver-A-T1D_Data Sharing Plan_18.09.2024)and referred to under the section Data access.

Reviewer: 1
Dr. Kyu Yong Cho, Hokkaido University
Comments to the Author:

Dear Authors,
I was pleased to review your submitted protocol for an RCT to investigate whether verapamil can counteract the decline in endogenous insulin secretion in adult patients with newly diagnosed T1DM. This is clinically intriguing and, given its relative affordability, could potentially contribute to future therapeutic approaches.
The protocol is well designed and incorporates relevant considerations for preventing or suppressing the progression of T1DM in recently published papers. The administration of verapamil itself is not inappropriate, given its use in studies of pediatric T1DM and reports in adults.
I have no specific questions or comments at this time. It is interesting to consider why verapamil has not been shown off to have this effect in daily use, given its widespread use in cardiovascular disease. However, this is simply my observation and does not require an answer.
We thank Dr Kyu Yong Cho for his time to review our manuscript and positive comments.

Reviewer: 2
Dr. Giacomo Gastaldi, Geneva University Hospitals, Geneva, Switzerland., Hirslanden Clinique des Grangettes

Comments to the Author:
A Randomised, Double-blind, Placebo Controlled, Parallel Group, Multi-centre Trial in Adult Subjects with Newly Diagnosed Type 1 Diabetes Mellitus Investigating the Effect of Verapamil on Preservation of Beta-cell Function (Ver-A- T1D).
Ver-A-T1D is a randomized, double-blind, placebo-controlled, multi-center Trial that addresses a key question about early T1D management. Shall we consider Verapamil as an adjunct treatment to insulin at the diagnostic phase ?
Verapamil is an old calcium blocker that lowers TXNIP expression on beta-cell wall. It has shown enthusiastic results on beta cell preservation in case of mouse models of diabetes and human auto-immune diabetes. The postulated mechanism is the capacity to prevent beta-cell destruction. Few side effects have been observed in

For peer review only

human studies and verapamil can be easily taken (once a day at 24h intervals). It is therefore of uttermost importance to determine if Verapamil as an adjunct treatment of insulin can improve early T1D management.

The protocol is concise, clear, well-structured and with high standards of written English.
The methodology is clear. The research protocol components are described with the utmost care.
I have only minor suggestions for the authors:
- To extend the age for inclusion (45 years old is quite young)
- To extend to 8 weeks of the date of first insulin injection. It was 3 months in the Ovalle et al study.
- To quantify “tobacco consumption” and “alcohol intake” in the list of visit items due to their impact on insulin needs and to add them in table 3 (assessments at study visits).

We thank Dr Giacomo Gastaldi for his time to review our manuscript and insightful comments. Given the trial has now closed to recruitment it is not possible to make the three changes suggested, but these points will be taken forward in any future trials and we appreciate your careful consideration of the trial design.

Editors comments from 23-Sept-2024

1) You have indicated that your trial was not prospectively registered. Please provide an explanation for this in your cover letter. Please see our clincial trial registration policy for further details at https://authors.bmj.com/policies/trial-registration/

The trial was prospectively registered, and this has now been updated with the response ‘Yes’

2) Please provide a detailed point-by-point response to the Editor's and reviewer's comments as both an uploaded DOCX file (with file designation 'Response to Reviewer Comments') and an attached file in the 'Your Response' area of the online submission form.

The document Ver-A-T1D Study Protocol Paper v1.1 04 Oct 2024-RESPONSE TO COMMENTS has been uploaded to the Files section as Response to reviewers comments & as a file upload in Your Response.

3) Please include figure legends at the end of your main document file.

The following figure legends have been added to Ver-A-T1D Study Protocol Paper v1.1 04 Sept 2024-MAIN DOCUMENT and Ver-A-T1D Study Protocol Paper v1.1 04 Sept 2024-MAIN DOCUMENT - marked copy.

For peer review only

Figure 1 Ver-A-T1D Trial Design

Figure 2 Ver-A_T1D Trial Flow Chart

4) Your tables are too large to be included in the manuscript, specifically table 3. Please either reduce their size (maximum 2 pages / 8 columns) or upload them as supplemental material.

Table 1 is 3 columns and 2 pages and remains in the main body of the paper.

Table 2 is 1 column and 1 page and remains in the main body of the paper.

Table 3 has been moved to supplementary material file Ver_A-T1D Table 3 SUPPLEMENTARY MATERIAL.docx and referred to in the text as online supplemental information (see Ver-A_T1D Table 3 SUPPLEMENTARY MATERIAL).

5) We see that your study involved human participants but your ethics statement is incorrect. Please update the free text box in the online submission system to also include:
- confirmation of informed consent.

The Research Ethics free text statement has been updated to:

Confirmation of informed consent was obtained directly from patients and was approved by the following committees:

Austria: Medical University of Graz Ethics Committee (ID: 32-664 ex 19/20)

Belgium: Commissie voor Medische Ethiek ZNA, p/a ZNA Koningin Paola Kinderziekenhuis (ID: 5494)

France: Comité de Protection des Personnes Est-II, CHRU – Hôpital Saint Jacques (ID: 21.01.26.73506)

Italy:

- *Milan: Comitato Etico dell' IRCCS Ospedale S.Raffaele di Milano (ID: 9/05/22)*
- *Siena: Comitato Etico Regione Toscana – Area Vasta Sud Est (ID: 19709)*

Germany:

- *Hannover: Medizinische Hochschule Hannover Ethikkommission (Nr. 9465_AMG_mono_2020)*
- *Ulm: Medizinische Hochschule Hannover Ethikkommission and Ethikkommission der Landesärztekammer Baden-Württemberg (Nr. 9465_AMG_M_2020)*

UK: NHS Health Research Authority, London – City & East Research Ethics Committee (REC reference: 20/LO/1295)

For peer review only

6) Please ensure that all authors are included in your author contributor statement. Please ensure the contributor statement in your manuscript is the same as the statement included in the online submission system. For further information please see https://authors.bmj.com/policies/bmj-policy-on-authorship/

The statement has been updated to:

Writing, Review & Editing – Pieber TR; Dayan C; Mander AP; Mathieu C ; Brunner, M; Stenson, R; Chmura PJ; Danne, T; *Wych J.*

7) We note the guarantor name in your Contributorship statement missing: BMJ's Contributorship statement policy indicates that each statement must make clear who is responsible for the overall content as guarantor (https://authors.bmj.com/policies/bmj-policy-on-authorship/#contributorship%20statement). Please ensure the guarantor has been named in the contributorship statement accordingly. Examples include:
- Author name / Author initials are the guarantor
- Author name / Author initials acted as guarantor
- Guarantor is author name
- Author name / Author initials are responsible for the overall content [as guarantor].
- Author name accepts full responsibility for the finished work and/or the conduct of the study, had access to the data, and controlled the decision to publish.

The following statement has been added to the Author contributions section : *Pieber TR acted as guarantor.*

For peer review only