FULL TITLE OF THE TRIAL

Phase II multi-centre, double-blind, randomised trial of Ustekinumab in adolescents with new-onset Type 1 Diabetes

SHORT TRIAL TITLE / ACRONYM

USTEKID

Version 4.0 dated 4th May 2020

This protocol has regard for the HRA guidance and order of content

KEY INFORMATION

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Trial document repository	Log into trial website and use the password provided by the Trial Office	
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MACRO website	https://macro.swan.ac.uk/macro/	
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Safety reporting (SAEs, SARs & SUSARs)	• Complete an SAE form (ISF Section 7) • Contact the Chief Investigator see SAE form) • Email the form to : USTEKID@swansea.ac.uk • Or fax the form to: 01792 606298 • Report SAEs within **24 hours** of the trial team's awareness of the event.	
Urgent Safety Measures	• Complete a USM reporting form (ISF Section 7) • Email the form to : USTEKID@swansea.ac.uk • Or fax the form to: 01792 606298	

RESEARCH REFERENCE NUMBERS

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PROTOCOL HISTORY

Draft protocol versions were managed by electronic revision control.

Version control of all approved trial documents will be maintained using a version control log which will be held separately.

Amendment No.	Protocol version	Protocol date	Author(s) of changes	Details of changes made
NA	1.0	16 Feb 2018	NA	NA
01	2.0	16 Jul 2018	Kym Thorne	Additional procedural details, clarification of TB testing requirements
02	3.0	10 Jun 2019	Kym Thorne	Clarification of eligibility criteria, amendment of error in IMP stability time, reduction of treatment window to 1 week, updates to Table 1 following input from the DSMB, changes to blood sampling requirements and other minor amendments
03	4.0	04 May 2020	Kym Thorne	Addition of details regarding remote follow up process Addition of exocrine enzyme testing

SIGNATURE PAGE

The undersigned confirm that the following protocol has been agreed and accepted and that the Chief Investigator agrees to conduct the trial in compliance with the approved protocol and will adhere to the principles outlined in the Medicines for Human Use (Clinical Trials) Regulations 2004 (SI 2004/1031), amended regulations (SI 2006/1928) and any subsequent amendments of the clinical trial regulations, GCP guidelines, the Sponsor's (and any other relevant) 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

I also confirm that I will make the findings of the trial publically available through publication or other dissemination tools without any unnecessary delay and that an honest accurate and transparent account of the trial will be given; and that any discrepancies and serious breaches of GCP from the trial as planned in this protocol will be explained.

For and on behalf of the Trial Sponsor: Signature: Date: ...../...../..... ..... Name (please print): ..... Position: .....
Chief Investigator: Signature: Date: ...../...../..... ..... Name: (please print): ..... Position: .....
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LIST OF ABBREVIATIONS

AE	Adverse Event
AR	Adverse Reaction
AUC	Area under the curve
CI	Chief Investigator
CRF	Case Report Form
CTA	Clinical Trial Authorisation
CTIMP	Clinical Trial of Investigational Medicinal Product
CTU	Clinical Trials Unit
DPC	Drug Product Complaint
DSMB	Data Safety & Monitoring Board
DRUC	Diabetes Research Unit Cymru
DSUR	Development Safety Update Report
DTSQ	Diabetes Treatment Satisfaction Questionnaire
EC	European Commission
EMEA	European Medicines Agency
EU	European Union
EUCTD	European Clinical Trials Directive
EudraCT	European Clinical Trials Database
EudraVIGILANCE	European database for Pharmacovigilance
GCP	Good Clinical Practice
GMP	Good Manufacturing Practice
IB	Investigator Brochure
IAF	Informed Assent Form
ICF	Informed Consent Form
ICH	International Conference on Harmonisation of technical requirements for registration of pharmaceuticals for human use
IGRA	Interferon gamma release assay
IMP	Investigational Medicinal Product
IMPD	Investigational Medicinal Product Dossier
ISF	Investigator Site File (This forms part of the TMF)
ISRCTN	International Standard Randomised Controlled Trials Number
MA	Marketing Authorisation
MHRA	Medicines and Healthcare products Regulatory Agency
MMTT	Mixed Meal Tolerance Tests
NHS R&D	National Health Service Research & Development
PBMC	Peripheral Blood Mononuclear Cells
PedsQL	Paediatric Quality of Life questionnaire
PI	Principal Investigator
PIS	Participant Information Sheet
PK	Pharmacokinetics
PROMs	Patient / participant reported outcome measures
QA	Quality Assurance
QC	Quality Control
QP	Qualified Person
RCT	Randomised Control Trial
REC	Research Ethics Committee
SAE	Serious Adverse Event
SAP	Statistical Analysis Plan
SAR	Serious Adverse Reaction
SC	Subcutaneous
SDV	Source Data Verification
SOP	Standard Operating Procedure
SmPC	Summary of Product Characteristics
SMPU	St Mary's Pharmaceutical Unit
STU	Swansea Trials Unit
SUSAR	Suspected Unexpected Serious Adverse Reaction
T1D	Type 1 Diabetes
TMF	Trial Master File
TMG	Trial Management Group
TSC	Trial Steering Committee
UCPCR	Urine c-peptide/creatinine ratio
vPIS	Video Participant Information Sheet

TRIAL SUMMARY

Trial Title	Phase II multi-centre, double-blind, randomised trial of Ustekinumab in adolescents with new-onset Type 1 Diabetes	
Short title	USTEKID	
Clinical Phase	Phase II	
Trial Design	This is a double-blind Phase II study to assess the safety and efficacy of Ustekinumab (STELARA®) in children and adolescents aged 12-18 with new-onset Type 1 Diabetes (T1D). Participants will be given Ustekinumab subcutaneously at weeks 0, 4 and 12 in a dose depending on the body weight and subsequently every 8 weeks to week 44 (7 doses in total). Participants will be followed for 12 months after receiving the first dose of IMP. There will be 8 study visits over 52 weeks, three of which may be conducted at home. Mixed meal tolerance tests (MMTTs) will be performed at screening, weeks 28 and 52. All participants will be offered glucose monitoring using the Freestyle Libre system. An information video will be available at www.type1diabetesresearch.org.uk/current-trials	
Trial Participants	Children and adolescents aged 12-18 years with new-onset T1D (within 100 days of diagnosis). Participants should have evidence of residual functioning beta-cells (serum C-peptide level > 0.2nmol/L in the MMTT test) and be positive for at least one islet autoantibody (GAD, IA-2, ZnT8).	
Sample Size	72	
Treatment duration	44 weeks	
Follow up duration	52 weeks (remote follow-up to 104 weeks)	
Planned Trial Period	4 years and 6 months (not including remote follow-up to 104 weeks)	
	Objectives	**Outcome Measures**
Primary	To determine the efficacy of Ustekinumab (dose: 2mg/kg if ≤40kg) or 90mg if >40kg)) for preserving MMTT stimulated 2-hour C-peptide area under the curve (AUC) at Week 52 as compared to placebo in children and adolescents with new-onset T1D.	MMTT C-peptide AUC values at week 52
Secondary	To determine the efficacy of the Ustekinumab dosing to elicit response to treatment.	Number of responders (defined as participant who has HbA1c ≤ 48mmol/mol and mean daily insulin use <0.5 IU/kg/day) measured over 7 consecutive days during the 2 weeks preceding the visit in treatment and placebo group
	To investigate additional efficacy (metabolic) endpoints including MMTT C-peptide AUC at Week 28, HbA1C and insulin use measurements at Week 52.	- MMTT C-peptide AUC values at Week 28 - Hb1Ac - Exogenous insulin requirement as reflected in mean daily insulin usage over 7 consecutive days (IU units/kg body weight/day) as recorded in diaries prior to study visits - Insulin dose adjusted HbA1c (IDAAC)
	To compare alternative metabolic endpoint assays to MMTT: including glycaemic variability in glucose monitoring systems (Freestyle Libre) and hypoglycaemia rates.	- Glycaemic variability parameters downloaded from glucose monitoring. - Clinical hypoglycaemic events determined by patient diary reports and AE reports

	To determine safety of Ustekinumab dose in adolescents with new-onset T1D.	- Frequency and severity of all adverse events of the following categories:
		  - Injection reactions
		  - Hypersensitivity reactions
		  - Hypoglycaemic episodes
		  - Evidence of infection
		  - Evidence of posterior leukoencephalopathy syndrome
		  - All other AEs and SAEs

	To compare between treatment arms and across the course of treatment the age-appropriate PROMs scores completed by participants and parents / carers.	- HYPOFEAR, DTSQ, and PedsQL questionnaires completed by participants - HYPOFEAR, DTSQ, and PedsQL questionnaires completed by parents/carers
Tertiary	To investigate alternative ways of measuring insulin production other than MMTT C-peptide.	- Proinsulin - Glucagon, somatostatin levels - Dried blood spot (DBS) C-peptide - DBS C-peptide vs MMTT C-peptide
	To investigate changes in relevant immune mechanistic parameters include flow cytometry immune phenotyping of all IL-17 and IFN-gamma secreting T cell subsets, fluorospot analysis for IL-17 and IFN-gamma secretion in response to antigens for CD4+ T cells.	- Changes in immune phenotype of all IL-17, IFN-g secreting immune subsets - Changes in T cell responses to antigens or peptides derived from islet antigens (including proinsulin, GAD and IA-2) measured by cytokine FLOUROSPOT (IFN-g and IL-17) - Changes in T cell responses to antigens or peptides derived from islet antigens (including proinsulin, GAD, IA-2) measured by the level of IFNg, IL-17, IL-12 and IL-23 production in supernatants (Luminex) - Changes in additional immunological biomarkers (e.g. flow cytometry profiles, T cell responsiveness measured by activation profiles, T reg assays, autoantibodies)
	To investigate Ustekinumab pharmacokinetics and compliance with therapy	Ustekinumab drug levels in serum
	To explore association C-peptide changes with age appropriate PROMs	- C-peptide AUC - HYPOFEAR, DTSQ, and PedsQL questionnaires
	To compare participant and parent/carer proxy completed PROMs	- HYPOFEAR, DTSQ, and PedsQL questionnaires completed by participants - HYPOFEAR, DTSQ, and PedsQL questionnaires completed by parent/carer
	To investigate longer term effect of Ustekinumab on glycaemic control	- Insulin use - Severe hypoglycaemic events - HbA1c - C-peptide (using DBS samples) - CGM data
Investigational Medicinal Product(s)	Ustekinumab	
Formulation, Dose, Route of Administration	Ustekinumab is supplied as a sterile, preservative-free aqueous solution in a vial containing 45mg/0.5mL of Ustekinumab. It will be administered subcutaneously (SC) via prepared syringes as a single dose. For participants weighing ≤ 40kg, the dose will be 2mg/kg; for participants > 40kg, the dose will be fixed at 90mg at 0, 4, 12, 20, 28, 36, 44 weeks. On three occasions, dosing can be done at home by study nurses.	

FUNDING AND SUPPORT IN KIND

FUNDER(S)	FINANCIAL AND NON FINANCIAL SUPPORT GIVEN
• National Institute of Health Research Efficacy and Mechanism Evaluation Programme (NIHR-EME) • JDRF International	Financial support
Janssen-Cilag Ltd, 50 - 100 Holmers Farm Way, High Wycombe, Bucks, HP12 4EG.	Provision of Ustekinumab (STELARA®)
Abbott Diabetes Care, Vanwell Business Park, Maidenhead, Berkshire, SL6 4XE Contact: Dee Percival Tel 0800 0721020 Senior Order Entry Clerk Email: abbott.freestylelibre@nhs.uk or Dee.Percival@abbott.com Customer helpline: 0800 1701020 (for product related issues)	Provision of Freestyle Libre glucose monitoring devices and some of the sensors

ROLE OF TRIAL SPONSOR, FUNDER AND CLINICAL TRIALS UNIT

The Trial Sponsor will be Cardiff University, who are the employers of the Chief Investigator.

The study will be conducted in collaboration with Swansea Trials Unit (STU), a registered Clinical Trials Unit (UKCRN registration number 58) funded by Health and Care Research Wales with a specialist interest in diabetes trials.

The study will also be supported by the Diabetes Research Unit Cymru (DRUC) who are co-located with STU at Swansea University and also funded by Health and Care Research Wales.

STU will provide trial services including trial, data and pharmacovigilance management, site setup and close-down and overseeing trial monitoring, ensuring that all procedures are MHRA compliant.

The study is primarily funded by a grant from NIHR-EME (NIHR-EME 16/36/01) who require regular update reports to confirm progress of the study and expenditure. KCL laboratories are in receipt of funding from JDRF for enhanced testing of blood samples investigated for USTEKID.

ROLES AND RESPONSIBILITIES OF TRIAL MANAGEMENT COMMITEES/GROUPS & INDIVIDUALS

Trial Steering Committee (TSC)

The trial will be overseen by a TSC chaired by a senior, independent UK paediatric clinical investigator with experience of T1D studies in children. The TSC will also comprise, as a minimum, an independent statistician with appropriate experience in the design and conduct of CTIMP studies, a clinical investigator with experience of the use of immunotherapeutic biologic agents and at least one service user (parent/carer or patients with T1D), all based in the UK.

The TSC will meet every 6 months or more frequently as required, receiving information from the Trial Management Group (TMG) and the Data Safety & Monitoring Board (DSMB) (see below) and will advise the Sponsor and the TMG. Observers from the funder will be invited to all TSC meetings. The TSC will operate with agreed terms of reference.

Role of the TSC:

- To monitor and supervise trial progress towards interim and end objectives.
- To monitor and advise on scientific credibility.
- To consider and act upon the recommendations of the DSMB.

Data Safety & Monitoring Board (DSMB)

An independent DSMB will be convened for the duration of the trial chaired by a consultant paediatrician with trials experience and knowledge of the use of biologic agents, and will have as a minimum two consultant paediatricians with specialist expertise in diabetes and endocrinology, an experienced methodologist/statistician and at least one service user (parent/carer or patient with T1D).

The DSMB will meet at agreed intervals throughout the trial and receive reports of all adverse events from the Chief Investigator and/or other members of the trial team, as well as assessing progress in recruitment. The chair of the DSMB may also call additional meetings as necessary. The DSMB will have responsibility for advising the TSC and Sponsor on whether to continue the trial, or suspend or terminate treatment of one or a group of participants if participant safety is considered at risk.

Role of the DSMB:

- To assess the progress of the trial, safety data and critical efficacy endpoints.
- To recommend whether the trial should be continued, modified or stopped.

Trial Management Group (TMG)

The project will be run by a TMG comprising the lead investigators, trial manager, data manager, statistician (STU-hosted DRU Cymru staff), recruitment leads, laboratory leads, patient/parent representatives, STU representatives and Sponsor representative. The TMG will oversee the day to day trial management and should meet in person or by teleconference monthly or quarterly (as required) for the duration of the study. The TMG will overview and provide guidance on all aspects of regulatory approval, set-up, recruitment, protocol deviations, adverse events, data management, data analysis and dissemination. The TMG will report at agreed intervals to the TSC, DSMB and to the study sponsor.

Role of the TMG:

- To monitor all aspects of the trial conduct and progress.
- To ensure adherence to the approved protocol.
- To take appropriate action to safeguard participants and the quality of the data.

Operational meetings

Key members of the TMG will meet by teleconference on a weekly basis to discuss operational issues and safety reporting with sites.

Other operational meetings will be held on an *ad hoc* basis as required.

Site meetings

Key members of the Trial Office will be available at regular intervals for sites to call in to discuss their progress and any safety issues.

PROTOCOL CONTRIBUTORS

Professor Colin Dayan, Chief Investigator, Cardiff University – overall protocol design

Professor John Gregory, Paediatric Chief Investigator, Cardiff University – paediatric clinical aspects

Dr Danijela Tatovic, Adult (age 16-18) lead co-investigator, Cardiff University - young adolescent's clinical aspects

Professor Stephen Luzio, Diabetes Research Unit Cymru, Swansea University – sample analysis

Dr Wai-Yee "Ivy" Cheung - Diabetes Research Unit Cymru, Swansea University – statistical aspects

Swansea Trials Unit – trial management, research governance, data collection and analysis

St Mary's Pharmaceutical Unit – IMP handling

Rachel Stenson, Jane Bowen-Morris, T1D UK Consortium – study visits, screening and amendments

Dr Ash Marwaha, Toronto Children's Hospital, Canada – rationale and use of Ustekinumab, mechanistic studies

Diabetes Research Unit Cymru patient panel – patient relevant aspects of protocol

Dr Tim Tree, King's College London (T1D UK Consortium, mechanistic core) – mechanistic studies

TRIAL FLOW CHART

A flowchart illustrating the trial can be found in Appendix 1.

KEYWORDS

Type 1 diabetes, adolescents, Ustekinumab

1. BACKGROUND

Nearly 100 years after the discovery of insulin, over 70% of patients with Type 1 diabetes (T1D) continue to have unsatisfactory glycaemic control putting them at risk of long-term complications [1]. Tragically, death rates amongst adolescents have not improved in two decades [2]. Despite major advances in closed loop insulin pump therapy, much of the morbidity arises from young people failing to engage with complex therapies.

Several experimental approaches have been suggested as potential cures for established T1D, including islet cell transplantation, production of insulin producing beta cells from stem cells, and activation of endogenous beta cell regeneration, coupled with sufficient protection from immune destruction. Islet transplantation, using the Edmonton Protocol, holds promise as an effective treatment for long-term T1D patients. However, to date, transplanted islets do not maintain long-term function [3-6] and therapy is limited by the lack of donor tissue and a lifelong need for potentially toxic immunosuppressive therapy.

Most individuals have 10-20% of beta-cell function remaining at the time of diagnosis of T1D. Preservation of even 5% of beta-cell function has been shown to lower HbA1c by 1%, permit over 50% of people to reach target glycaemic levels, reduce hypoglycaemic risk by >50% and reduce long-term complications by 50% [7, 8]. Immunotherapy has the potential to preserve endogenous beta-cell function and thereby improve metabolic control even in poorly compliant individuals [9-11].

Novel low-risk targeted biologic therapies are widely used in other autoimmune diseases such as rheumatoid arthritis, psoriasis, inflammatory bowel disease and multiple sclerosis, but no treatment is yet licensed for use in T1D. There is an urgent need to identify which agents will work in T1D and bring these into clinical practice.

We propose to test a targeted and well-tolerated therapy that may halt T cell and cytokine-mediated destruction of beta cells in the pancreas at the time of diagnosis. Among the many molecular candidates for inhibition in this complex disease, we have chosen to simultaneously target two major autoimmune cytokine pathways, IL-12/IFN-γ and IL- 23/IL-17, for which extensive evidence exists to implicate their role in beta cell destruction. The drug to be tested, Ustekinumab (STELARA®), binds and inhibits the p40 molecular subunits of both IL-12 and IL-23 thus blocking their action in inducing pathogenic CD4 Th1 and Th17 T cell subsets [12].

Ustekinumab is licenced in the UK for the treatment of psoriasis in children and adults, psoriatic arthritis in adults and Crohn's disease in adults. In a 1-year study of 110 adolescent patients, Ustekinumab at the standard dose improved plaque psoriasis with no unexpected adverse effects [13], which led to its licencing for the use in adolescents (>12 years of age) with psoriasis. Another pilot study indicated its potential efficacy in inflammatory bowel disease in the paediatric population [14].

2. RATIONALE

We propose that for T1D, permanent or long-term interruption of T cell-mediated, autoimmune beta cell destruction at the time of clinical presentation will preserve sufficient beta cells so that physiological insulin secretion may be maintained. This concept is based on preliminary data generated from a model of autoimmune diabetes, the non-obese diabetic (NOD) mouse, and from human participants with recent-onset T1D. The approach is feasible because functional beta cells remain present within islets at the time of disease presentation. The surviving beta cells account for the numerous observations of endogenous insulin production during the so-called “honeymoon period”, which occurs shortly after metabolic stabilization of newly diagnosed patients. We predict that simultaneous inhibition of two pro -inflammatory pathways, which are mediated by T cells that secrete IL-17 and IFN-γ, will halt or reverse disease in participants with recent-onset T1D. Agents to facilitate this approach are currently in clinical use: for example, Ustekinumab a humanized monoclonal antibody that targets these two pathways, has been approved for the treatment of psoriasis in North America and UK (NICE) since 2009 [15]. Ustekinumab is highly effective and safe in the treatment of psoriasis, a disease whose pathogenesis depends upon both IFN-γ and IL-17 [16, 17].

Animal studies have implicated the IL-17 and IFN-γ pathways in the pathogenesis of autoimmune diabetes. In diabetes-prone BioBreeding (DP-BB) rats, the potentially pathogenic Th17 cell population increases in the first months of age but the proportion and function of T regulatory cells does not change. In NOD mice, inhibition of IL- 17, through the use of blocking antibodies, delays disease onset. However, when beta cell specific CD4+ T cells from TCR-transgenic BDC2.5 NOD mice are polarized to a Th17 phenotype, and then transferred to non-diabetic NOD-SCID recipients, the cells accelerate diabetes *only after* differentiating to a Th1-like phenotype [18, 19]. This complementary pathogenic role of IFN-γ has also been suggested by experiments in which antigen-specific Tc17 cells that targeted hemagglutinin on pancreatic β cells were able to induce diabetes *only when* co-transferred with diabetogenic CD4+ T cells that secrete IL-12 (presumably allowing Tc17 conversion to an IFN-γ secreting phenotype). A very recent and definitive study in NOD mice has shown that genetic ablation (knock out) of both the IFN-γ receptor and IL-17 is required to prevent the onset of T1D [20]. These data are consistent with a synergistic pathogenic effect between IL-17 and IFN-γ, as the effect of disabling of both pathways is much stronger than knocking out either pathway alone. Finally, treatment of NOD mice with neutralizing antibody to the p40 subunit of IL-12/IL-23 (C17.8, a murine equivalent to Ustekinumab) suppresses insulitis and prevents disease [21].

It has been shown that peripheral lymphocytes from children with recent-onset diabetes, in contrast to age-matched healthy controls, have an increased proportion of a subset of FOXP3+ T cells that secretes a substantial amount of IL-17. It was also observed that children with T1D have an increased number of CD8+ T cells that secrete IL-17 (Tc17 cells). These data are supported by a Finnish study showing an increase in IL-17 mRNA transcription in cells from children with T1D, and by reports showing that in addition to peripheral T cells, T1D participants have an increased proportion of monocytes that secrete Th17 polarizing cytokines [22] and islet-antigen specific Th17 cells. There is also evidence that (i) pancreatic lymph nodes from T1D patients have an expansion in Th17 cells [23] and (ii) that islets from recent-onset T1D patients express IL-17A, RORC (the human, lineage-defining IL-17 transcription factor) and IL-22 [24].

Together, these observations suggest that IL-17 and IL-12/IFN-γ driven responses together have an enhanced pathogenic role in T1D. Our ***overarching hypothesis*** is that interrupting the IL-17 and IFN-γ axes in individuals with recent-onset T1D will halt or slow the autoimmune destruction of beta cells sufficient to permit beta cell preservation and maintain residual physiological insulin secretion. Given the therapeutic success of biologics that target immune molecules in other autoimmune and inflammatory diseases, and the evidence that IL-17 and IFN-γ producing cells are pathogenic to beta cells, we propose that drugs already approved for use in humans (e.g. Ustekinumab) may be beneficial for the treatment of T1D.

2.1 Assessment and management of risk

Participants will be given Ustekinumab subcutaneously (SC) in an enhanced dose depending on the body weight: 2mg/kg (if they weigh ≤40kg) or 90mg (if they weigh >40kg) at weeks 0, 4 and 12 weeks and subsequently every 8 weeks up to week 44. Participants allocated to the placebo will receive it at the same intervals.

This dosing frequency and route of administration has already been proven safe in adolescents with psoriasis [13] and the proposed higher dose has been approved for use in a study of Ustekinumab in adolescents with Crohn’s disease (ClinicalTrials.gov identifier: NCT02968108). In addition, preliminary unpublished data from the

Canadian UST1D trial of Ustekinumab in young adults (20 participants) with new onset diabetes (within 100 days from diagnosis) are available to us via Dr Ash Marwaha (ClinicalTrials.gov identifier: NCT02117765). No serious adverse events related to the Investigational Medical Product (IMP) were noted. The most stable C-peptide levels were seen in the 90mg group that received 5 doses throughout the study (loading dose at 0 and 4 weeks followed by additional 3 doses every 12 weeks).

The IMP will initially be administered at a clinical research facility at each site and drug recipients will remain in the unit for at least 1 hour after the first injection to ensure no immediate adverse effects (local or systemic allergic reactions). If no serious adverse effects are detected after the first dose, participants will be suitable for home administration as per the dosing schedule (doses 4, 6 and 7).

The Sponsor (Cardiff University) has assessed that the study is viable given the current state of knowledge about the risks and benefits of Ustekinumab. Ustekinumab has undergone extensive Phase I-IV testing in adults with psoriasis vulgaris. In the 1-year CADMUS study of 110 adolescent patients, Ustekinumab at the standard dose improved plaque psoriasis with no unexpected adverse effects [13], which led to its licencing for the use in adolescents (>12 years of age) with psoriasis.

The IMP/placebo will be delivered via the standard subcutaneous route. Protocol training will be provided by the Chief Investigator or their representative.

This trial is categorised as: **Type B – Somewhat higher than the risk of standard medical care**.

3. OBJECTIVES AND OUTCOME MEASURES/ENDPOINTS

Our overarching hypothesis is that interrupting the IL-17 and IFN-γ axes in individuals with recent-onset T1D will halt or slow the autoimmune destruction of beta cells sufficient to permit beta cell preservation and maintain residual physiological insulin secretion. Given the therapeutic success of biologics that target immune molecules in other autoimmune and inflammatory diseases, and the evidence that IL-17 and IFN-γ producing cells are pathogenic to beta cells, we propose that drugs already approved for use in humans (e.g. Ustekinumab) may be beneficial for the treatment of T1D.

3.1 Primary objective

To determine the efficacy of Ustekinumab for preserving Mixed Meal Tolerance Test (MMTT) stimulated 2-hour C-peptide area under the curve (AUC) at week 52 as compared to placebo in children and adolescents with new-onset T1D.

3.2 Secondary objectives

1. To determine the efficacy of Ustekinumab (dose: 2mg/kg (≤40kg); 90mg (>40kg)) in eliciting a metabolic response to treatment defined as HbA1c ≤ 48mmol/mol and mean daily insulin use < 0.5 IU/kg/day.
2. To investigate additional efficacy (metabolic) endpoints including MMTT C-peptide AUC at week 28, HbA1c and insulin use measurements at week 12, 28 and 52.
3. To compare alternative metabolic endpoint assays to MMTT: including glycaemic variability in glucose monitoring and hypoglycaemia rates.
4. To determine safety of Ustekinumab (dose: 2mg/kg (≤40kg); 90mg (>40kg)) in this patient group including rate, frequency and severity of all adverse events.
5. To compare between treatment arms and across the course of treatment the age appropriate patient-reported outcome measures (PROMs) scores completed by participants and parents/carers.

3.3 Tertiary objectives

1. To investigate alternative ways of measuring islet activity other than MMTT C-peptide including MMTT urine C-peptide/creatinine ratio (UCPCR), dried blood spot (DBS) measurements for C-peptide and fasting, post-meal proinsulin/C-peptide ratio, glucagon and somatostatin levels and fasting and post-meal plasma PI/C-peptide ratio.
2. To determine changes in relevant immune mechanistic parameters including flow cytometry immune phenotyping of all IL-17 and IFN-gamma secreting T cell subsets, fluorospot analysis for IL-17 and IFN-gamma secretion in response to antigens for CD4+ T cells and islet derived serum cell free DNA.
3. To measure Ustekinumab serum levels to assess pharmacokinetics and compliance.
4. To explore the association of C-peptide changes with age appropriate PROMs including the HYPOFEAR, DTSQ, and PedsQL questionnaires.
5. To compare participant and parent/carer proxy completed PROMs.
6. To investigate longer term effects of Ustekinumab on glycaemic control including insulin usage, severe hypoglycaemic events,HbA1c, C-peptide and CGM data (remote data collection to week 104).

3.4 Outcome Measures/Endpoints

The primary outcome to measure is the efficacy of Ustekinumab in preserving insulin production by the beta cells. As insulin is metabolised quickly as soon as it is released to the bloodstream, other markers of beta cell function are required. C-peptide is released at the same time as insulin. For each molecule of insulin produced

there is a molecule of C-peptide but C-peptide tends to remain in the blood longer than insulin. The current study will therefore use C-peptide as the primary outcome as is standard in new onset T1D immunointervention studies.

Other potentially useful efficacy parameters e.g. glycaemic control and exogenous insulin use will also be used as secondary outcome outcomes. Safety, quality of life and participants' satisfaction with treatments received (measured by PROMs) will also be assessed as secondary outcome measures.

Exploratory (tertiary) outcomes will include:

i. Alternative ways of measuring islet activity.

ii. Mechanistic assessment of immune biomarkers to explore potentially favourable changes in the immune response to self-antigens.

iii. Correlation of PROMs scores with C-peptide level and parent/carer proxy reports.

Table 1 overleaf details the endpoints, outcome measures and time points of evaluation for the trial, as well as the method of evaluation.

Objectives	Outcome Measures	Time point(s) of evaluation	Analysis method
Primary Objective			
To determine the efficacy of Ustekinumab (dose: 2mg/kg (≤40kg); 90mg (>40kg)) for preserving MMTT stimulated 2-hour C-peptide area under the curve (AUC) at Week 52 as compared to placebo in children and adolescents with new-onset T1D.	MMTT C-peptide AUC values at week 52	Week 52	Analysis of covariance adjusted for baseline MMTT C-peptide [1] (measured at week -2), gender and age, baseline insulin use and HbA1c at screening (week -2).
Secondary Objectives			
1. To determine the efficacy of the Ustekinumab dosing to elicit response to treatment	Number of responders (defined as participant who has HbA1c ≤ 48mmol/mol and mean daily insulin use <0.5 IU/kg/day) measured over 7 consecutive days during the 2 weeks preceding the visit in treatment and placebo group	Week 52	Generalised linear modelling based on appropriate count models with adjustment by important covariates eg gender and age, baseline insulin use and HbA1c at week -2.
2. To investigate additional efficacy (metabolic) endpoints including MMTT C-peptide AUC at Week 28, HbA1c and insulin use measurements at Week 52	MMTT C-peptide AUC values at Week 28	Week 28	Analysis of Covariance adjusted for age, gender baseline MMTT C-peptide [1] baseline insulin use and HbA1c (measured at week -2).
	HbA1c	Weeks 0, 12, 28 and 52	Analysis of Covariance adjusted for age, gender, baseline HbA1c (measured at week -2).
	Exogenous insulin requirement as reflected in mean daily insulin usage over 7 consecutive days (IU units/kg body weight/day) as recorded in diaries prior to study visits	Weeks 12, 28 and 52	Multiple regression based on appropriate transformation (eg log) if required with adjustment by important covariates eg gender and age, baseline insulin use and HbA1c at week -2.
	Insulin dose adjusted HbA1c (IDAAC)	Week 52	Multiple regression based on appropriate transformation (eg log) if required with adjustment by important covariates eg gender and age and baseline IDAAC.

[1] Transformed by log (1+x)

Objectives	Outcome Measures	Time point(s) of evaluation	Analysis method
3. To compare alternative metabolic endpoint assays to MMTT: including glycaemic variability in glucose monitoring systems –Freestyle Libre) and hypoglycaemia rates.	Glycaemic variability parameters downloaded from glucose monitoring, e.g. • Blood glucose level at 1,2,3 hours before and after each meal • Number of episodes and length of time within the following glucose level: below 4.0 mmol/L, >10 mmol/L and >15 mmol/L • % Time hypoglycaemic (<3.0 mmol/ and <4.0 mmol)	Weeks 0, 4, 12, 20, 28, 36, 44 and 52	Data will be described by summary (mean, median) and dispersion statistics (SD, IQR,CV, see below) of glycaemic variability parameters; % time and frequency < 3 mmol/L, < 4.0 mmol/L, > 10 mmol/L and >15 mmol/L. Two-tailed non parametric tests (e.g. Mann Whitney U test) will be used to compare differences. Coefficient of variation will be calculated over 24 hours and 2 hours post each meal.
	Clinical hypoglycaemic events determined by patient diary reports and AE reports	Week 52	Generalised linear modelling based on appropriate count models adjusted for baseline MMTT C-peptide [2] (measured at week -2), gender and age, baseline insulin use and HbA1c at week -2
4. To determine safety of Ustekinumab dose in adolescents with new-onset T1D.	Frequency and severity of all adverse events of the following categories: • Injection reactions • Hypersensitivity reactions • Hypoglycaemic episodes • Evidence of infection • Evidence of posterior leukoencephalopathy syndrome • All other AEs and SAEs	Week 52	Summary of cumulative incidence classified by pre-defined categories i.e. AEs, ARs, SAEs, SARs and SUSARs. Analysis of cumulative incidence of events classified by pre-identified categories with the appropriate count models.
5. To compare between treatment arms and across the course of treatment the age appropriate PROMs scores completed by participants and parents/carers.	• HYPOFEAR, DTSQ, and PedsQL questionnaires completed by participants and their parent/carer	Weeks -2, 28 and 52	Analysis of Covariance adjusted for baseline (week -2) values.

[2] Transformed by log (1+x)

Tertiary Objectives			
1. To investigate alternative ways of measuring insulin production other than MMTT C-peptide	Proinsulin	Weeks 28 and 52	Proinsulin/C-peptide ratio will be calculated. Analysis of Covariance, adjusted for covariates including gender, age, baseline (week -2) value of Proinsulin/C-peptide ratio.
	Glucagon, somatostatin levels	Weeks 28 and 52	Analysis of Covariance, adjusted for covariates including gender, age, baseline (week -2) values of the relevant tests.
	Dried blood spot (DBS) C-peptide	Weeks 28 and 52	Analysis of Covariance, adjusted for covariates including gender, age, baseline (week 0) values of the relevant tests.
	DBS C-peptide vs MMTT C-peptide	Week -2, 28 and 52	Intraclass correlation, Bland and Altman plot, measures of responsiveness to change in β-cell function.
2. To investigate changes in relevant immune mechanistic parameters include flow cytometry immune phenotyping of all IL-17 and IFN-gamma secreting T cell subsets, fluorospot analysis for IL-17 and IFN-gamma secretion in response to antigens for CD4+ T cells.	Changes in immune phenotype of all, IL-17, IFN-g secreting immune subsets	Weeks 12, 28 and 52	Assessed by flow cytometry in comparison to baseline (week 0). Where the outcome measures of the laboratory tests are: • Counts: Non parametric rank analysis of covariance (e.g. Quade test). • Percentages: Analysis of Covariance after appropriate transformation (e.g. Arcsine transformation) to stabilise variance and normalise residuals.
	Changes in T cell responses to antigens or peptides derived from islet antigens (including proinsulin, GAD and IA-2) measured by cytokine FLOUROSPOT (IFN-g and IL-17)	Weeks 12, 28 and 52	Where the outcome measures of the laboratory tests are: • Counts: Non parametric rank analysis of covariance (e.g. Quade test). • Percentages: Analysis of Covariance after appropriate transformation (e.g. Arcsine transformation) to stabilise variance and normalise residuals.
	Changes in T cell responses to antigens or peptides derived from islet antigens (including proinsulin, GAD, IA-2) measured by the level of IFNg, IL-17, IL-12 and IL-23 production in supernatants (Luminex)	Weeks 12, 28 and 52	Where the outcome measures of the laboratory tests are: • Counts: Non parametric rank analysis of covariance (e.g. Quade test). • Percentages: Analysis of Covariance after appropriate transformation (e.g. Arcsine transformation) to stabilise variance and normalise residuals.

	Changes in additional immunological biomarkers (e.g. flow cytometry profiles, T cell responsiveness measured by activation profiles, T reg assays, autoantibodies)	Weeks 12, 28 and 52	Where the outcome measures of the laboratory tests are: • Counts: Non parametric rank analysis of covariance (e.g. Quade test). • Percentages: Analysis of Covariance after appropriate transformation (e.g. Arcsine transformation) to stabilise variance and normalise residuals.
3. To investigate Ustekinumab pharmacokinetics (PK) and compliance with therapy	Ustekinumab drug levels in serum	Weeks 4, 12, 28 and 52	To be performed by an approved laboratory, informed by their initial PK work with adults. Outputs of the PK work with the study samples will be fed back to the trial team for consideration and review.
4. To explore association of C-peptide changes with age appropriate PROMs	• C-peptide AUC • HYPOFEAR, DTSQ, and PedsQL questionnaires	Weeks -2, 28 and 52	Rank order correlation coefficients between PROMs scores and C-peptide values at the same time points (Weeks -2, 28 and 52)
5. To compare participant and parent/carer proxy completed PROMs	• HYPOFEAR, DTSQ, and PedsQL questionnaires completed by participants and their parent/carer	Weeks -2, 28 and 52	Paired t-tests or Wilcoxon signed rank tests depending on distribution of underlying data
6. To investigate longer term effect of Ustekinumab on glycaemic control	Severe hypoglycaemic events	Weeks 78 and 104	Generalised linear modelling based on appropriate count models adjusted for baseline MMTT C-peptide [3] (measured at week -2), gender and age, baseline insulin use and HbA1c at week -2
	Insulin use	Weeks 78 and 104	Multiple regression based on appropriate transformation (eg log) if required with adjustment by important covariates eg gender and age, baseline insulin use and HbA1c at week -2
	HbA1c	Weeks 78 and 104	Analysis of Covariance adjusted for age, gender, baseline (week 0) HbA1c
	C-peptide using DBS samples	Weeks 78 and 104	IC to complete
	CGM data	Weeks 78 and 104	IC to complete

Table 1: Endpoints and outcome measures for the trial.

[3] Transformed by log (1+x)

4. TRIAL DESIGN

This is a double-blind Phase II study to assess the safety and efficacy of Ustekinumab in children and adolescents aged 12-18 with new-onset T1D. Participants will be given Ustekinumab subcutaneously at weeks 0, 4 and 12 in a dose depending on their body weight: 2mg/kg (if ≤40kg) or 90mg (>40kg) and subsequently every 8 weeks to week 44 (7 doses) with a window of +/- 1 week. The total dosage of Ustekinumab administered depends on the body weight but will not be higher than 630mg for any participant.

Participants will be followed up for 12 months after receiving the first dose of IMP. During the first 12 months, there will be visits at each dose (home or clinic as per study dosing schedule). Unscheduled visits will occur as medically necessary. The primary endpoint will be assessed at week 52 at clinic. Safety data will be reviewed by the DSMB. The final safety data analysis will occur at the end of the trial (week 52) once all participants have received the full IMP course.

Participants will also be invited to consent to remote follow-up via access to their health records and telephone contact. This will include extracting data on insulin usage, severe hypoglycaemic events and HbA1c (routine measurements) from outpatient appointments closest to weeks 78 and 104. In cases where such information is not available from health records, participants will be contacted via telephone to obtain information on hypoglycaemic events and insulin usage. Patients will also be asked to provide a dried blood spot sample and Continuous Glucose Monitoring data wherever possible at time points coinciding with weeks 78 and 104.

The study will be conducted according to the timeline shown in Table 2 below, with Month 0 defined as the beginning of recruitment i.e. first study site open.

Stage 1 Piloting. This stage will provide extensive information for the main study. Identification and selection of participants will be as described in Section 6. Participants recruited across sites in the first 6 months, and all aspects of effective recruitment, retention and complete data collection will be formally reviewed. This will include information materials, time burden, reasons for non-engagement, balance of recruitment between paediatric (age 12-15) and young adult (age 16-18) groups, retention incentives, completion of outcome assessments, SOPs, sample logistics and database performance. The DSMB will also review the data from this piloting stage. Following a review, any amendments to the protocol and patient-facing material will be prepared for regulatory submission and taken through to approval at all existing and new sites by month 12. Recruitment will continue throughout this period.

Stage 2: Main study. This stage will combine with the data from participants randomised in Stage 1 for use in determining the efficacy of Ustekinumab.

The complete study analysis dataset will be the combination of the piloting and stage 2 data.

Table 2: Trial stages

	Months																			
	-3	0	3	6	9	12	15	18	21	24	27	30	33	36	39	42	45	48	51	54
Regulatory approvals (6m)																				
Recruitment (2y)																				
Treatment & Follow up (2y)																				
Analysis (6m)																				
Report (3m)																				

5. TRIAL SETTING

Recruitment for this study will be performed in paediatric and adult diabetes research centres across the UK, primarily through the Type 1 Diabetes UK Immunotherapy Consortium (T1DUK) (www.type1diabetesresearch.org.uk).

We anticipate that enrolment and screening will require 24 months with the aim to recruit 2-3 patients per month on average.

6. PARTICIPANT ELIGIBILITY CRITERIA

72 participants aged 12 to 18 years, within 100 days of the confirmed diagnosis of (defined as date of first insulin dose) and with residual endogenous insulin production (serum C-peptide > 0.2nmol/l during MMTT) will be included in the study. Autoimmune diabetes will be confirmed by measurement of islet cell autoantibodies.

6.1 Inclusion criteria

- Clinical diagnosis of immune-mediated Type 1 diabetes mellitus as defined by American Diabetes Association (ADA) [25, 26].
- Commenced on insulin within 1 month of **clinical** diagnosis (defined as confirmed raised blood sugar (ADA criteria), not symptoms alone).
- An interval of ≤100 days between the **confirmed** diagnosis (defined as date of first insulin dose) and the first planned dose of the IMP.
- Written and witnessed informed consent/assent to participate.
- Male or female, aged 12-18 years inclusive at the time of randomisation.
- Evidence of residual functioning beta-cells (peak serum C-peptide level > 0.2nmol/L in the MMTT test).
- Positive for at least one islet autoantibody (GAD, IA-2, ZnT8).
- Body weight < 100kg.
- Willing to record all insulin doses and blood glucose levels required for monitoring during the study, including reporting any hypoglycaemic events.
- Willing to provide dried blood spot (DBS) samples.
- Willing to wear the FreeStyle Libre Flash Glucose Monitor (FGM) device at least two weeks prior to a study visit.
- Willing to complete a diary and quality of life questionnaires.
- Willing to consent to remote follow up via health records and telephone contact.
- Female participants have a negative urine test for pregnancy; all participants must agree to use adequate contraception if they become / are sexually active (hormonal based contraception, double barrier contraception, abstinence) until 4 months following the date of their final treatment of IMP.

6.2 Exclusion criteria

- Breastfeeding, pregnancy or unwillingness to comply with contraceptive advice and regular pregnancy testing throughout the trial.
- Prior exposure to Ustekinumab within 3 months of the first dose of IMP.
- Use of more than 10 mg prednisolone daily (or equivalent) for >5 days within 3 months of the first dose of IMP. *Note: intranasal, inhaled and topical corticosteroid medications are permitted at recommended doses. Use of systemic corticosteroids during the trial should be avoided unless such treatment is medically necessary and alternative treatments are not considered safe or effective*
- Prior exposure to any anti-lymphocyte monoclonal antibody, such as anti-CD20, anti-thymocyte globulin (ATG), Rituximab (Rituxan®), or Alemtuzumab (Campath®).
- Use of immunosuppressive or immunomodulatory therapies, including systemic steroids (e.g., methotrexate, cyclosporine, or anti-TNF agents) within 30 days prior to receiving the first dose and/or intent on using any monoclonal antibody therapy given for any indication for the duration (including follow up) of the trial
- Use of any hypoglycaemia agents other than insulin, for more than 6 weeks, at any time prior to trial entry, including SGLT2 inhibitors.
- Use of inhaled insulin.

- Known alcohol abuse, drug abuse.
- Evidence of active Hepatitis B, Hepatitis C, HIV or considered by the investigator to be at high risk for HIV infection.
- Significant systemic infection during the 6 weeks before the first dose of the IMP (e.g. infection requiring hospitalisation, major surgery, requiring IV antibiotic treatment). Other infections e.g. glandular fever, bronchitis, sinusitis, cellulitis, or urinary tract infections must be assessed on a case by case basis by the investigator to assess whether they are serious enough to warrant exclusion or delay to inclusion.
- History of current or past active tuberculosis (TB) infection and no latent tuberculosis according to the British Thoracic Society recommendations [27]. Active TB will be assessed using a **mandatory** chest x-ray and one of the following :

  a) a blood test e.g. T-spot (preferred), interferon gamma release assay (IGRA), quantiferon test

  b) the Mantoux skin test.

  A positive result from any TB test will exclude the subject from the study and the subject and their medical care team will be informed. An intermediate result from blood sample testing will not exclude the participant from randomisation if the chest x-ray is negative. The blood test for TB only needs to be repeated if there is a change in the perceived clinical risk of TB.
- Participants should not have had live immunisations[4] for 1 month prior to trial entry. *Note that most injected (as opposed to nasal) influenza vaccines are not live vaccines and are permitted.* Planned live immunisations are also not permitted during the study period.
- Previous use of any other investigational drug within the 3 months prior to the first dose and/or intent on using any investigational drug for the duration (including follow up) of the trial.
- Recent (within 3 months) participant's involvement in other research studies which, in the opinion of investigators, may adversely affect the safety of the participants or the results of the study.
- Significantly abnormal laboratory results during the screening period, other than those due to T1D.
- Prior allergic reaction, including anaphylaxis, to any component of the IMP product.
- Prior allergic reaction, including anaphylaxis, to any human, humanised, chimeric or rodent antibody treatment.
- Any major planned surgery scheduled within the 30 day period prior to the first drug dose or anticipating requiring major surgery during the study period.
- Any other medical condition or treatment which, in the opinion of investigators, could affect the safety of the participant's participation or outcomes of the study, including malignancy, immunocompromised states and autoimmune conditions.
- Participants or parents/carers who lack the capacity to comply with trial requirements.

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[4] Live attenuated vaccines contain whole bacteria or viruses which have been "weakened" so that they create a protective immune response but do not cause disease in healthy people. Live vaccines are not suitable for people whose immune system is compromised either due to underlying illness or drug treatment.

***Live attenuated vaccines used in the UK** include Rotavirus vaccine, MMR vaccine, Nasal spray flu vaccine, Shingles vaccine, Chickenpox vaccine (special groups only), BCG vaccine against TB (special groups only).*

***Note: Nasal spray flu vaccine** (live attenuated influenza vaccine) is a live vaccine and may be recommended for children with T1D in age range for trial. In the autumn/winter of 2018/19, nasal spray live flu vaccine recommended for: children aged 2 - primary school year 5; children aged 2 -17 with long-term health conditions including children with diabetes (previously given annual flu jab). Programme for 2-17 year olds to be phased in over several years. It is an annual vaccine.*

***Live vaccines for exotic travel** include Yellow Fever vaccine and oral typhoid vaccine.*

***Vaccines that may be recommended for our age group and OK to have** include HPV cervical cancer vaccine, Dip/Tet/polio 3 in 1 teenage booster and Men ACWY.*

7. TRIAL PROCEDURES

The flowchart in Appendix 1 illustrates how the trial will be conducted at sites.

7.1 Recruitment

Potential participants will be identified from health records, clinical contacts, patient registry and self-referrals. 72 participants aged 12 to 18 years with a confirmed diagnosis of T1D within 100 days (defined from first insulin dose) and residual endogenous insulin production (peak serum C-peptide >0.2nmol/L during MMTT) will be asked to consent to screening for possible inclusion in the trial.

7.1.1 Participant identification

Eligible participants will be approached to consider participation into the study using one of the following steps:

- Patients with T1D will be identified by their local diabetes teams (hospital doctors or diabetes nurses), from clinic records, during clinic visits or inpatient admissions. For potential participants identified by health records or clinical contacts, the study will be discussed with the young person and their parents/carers by a member of their clinical care team and, with the young person's and parent's agreement, details will be passed to the local coordinator of the study.
- Some patients may self-refer and contact the T1DUK Consortium directly, from seeing internet information regarding participating in diabetes research on the T1DUK website. We will be hosting an ethically approved Participant Information video (vPIS) at (www.type1diabetesresearch.org.uk/current-trials) for anyone to view. The Consortium will facilitate contact between the patient and the relevant trial site.
- Information about the USTEKID trial will be posted on the T1DUK website and the ADDRESS-2 website (www.address2.org) along with contact forms so that patients visiting these websites can register an interest in hearing more about the study. The T1DUK / ADDRESS-2 teams will refer these patients to the local trial team at an appropriate research site.

The local coordinator of the study or research nurse/doctor will contact the young person and/or their parents/carers initially by phone, email or in person to discuss the trial, explain the aims of the study and provide copies of the Participant Information Sheet (PIS) which includes a link to the vPIS mentioned above.

Full information on the study procedures and the benefits and risks will be provided to parents/carers and on age-appropriate information for young people aged 12-15 and aged 16-18.

Approval for all age-specific participant information and the video, the trial protocol, additional documents and any subsequent amendments will be obtained from the stated NHS Research Ethics Committee (REC). We have obtained guidance on the design and content of the protocol and participant material from service users. Potential participants will have a minimum of 24 hours to consider this information and usually at least 5-7 days. They will be encouraged to discuss the trial with family and friends before making a decision. Participants will be invited to call the site's research nurse or Principal Investigator for any queries about the PIS and to indicate if they wish to take part.

If the child (and parent/carer if aged <16y) wants to take part, the local coordinator should agree a date for the first screening visit where the consent (and assent if participant is aged 12-15y) forms will be signed. Whilst arranging this, the local coordinator should also ascertain if the child and parent/carer wish to combine both screening visits as they will need to arrive fasted if they do.

Parents of adolescents aged 16-18y should also be asked to participate in the trial to complete the parent quality of life questionnaires. This may need to be done remotely if they do not attend study visits with the participant. They may decline without affecting the ability of the 16-18y old to participate.

The local coordinator should also be mindful of the timeframes within which screening activities have to be done to adhere to the requirements of the first planned treatment dose - within 100 days of confirmed diagnosis (first insulin dose) and 37 days of the MMTT.

An enrolment log should be completed to record all potential participant contacts about the trial, who consented and for those who decline, the reasons for their decision. Please also record any reasons for not approaching a potentially eligible patient e.g. 100d timeframe due to expire, resource issues, known ineligibility prior to screening.

7.1.2 Consent

Written informed consent will be obtained for all participants at the beginning of their first screening visit. For participants under 16, written assent for participants aged under 16 will be obtained in addition to written consent from a parent/carer (ideally the person most likely to attend all appointments with the participant to ensure consistent data collection for PROMs).

Consent and assent will be taken by paediatrically trained local investigators. The investigator taking consent must be trained to take consent for trials and also have been trained on the trial protocol. The potential participant and their parents/carers will have adequate time to review the information sheet and have all questions answered before giving consent/assent.

A nominated parent/carer will be asked to consent to their child taking part if the child is of an age where they are only able to provide assent for the trial. The parent/carer will also be asked to consider consenting to participate in the completion of the adult version of the PROMS to allow a comparison between parent/carer and child responses to address one of the trial objectives. We recommend that the parent most likely to attend screening and trial visits with the child is the one asked to provide consent and complete the PROMs.

Routinely, a parent/carer for participants aged 16-18y will be asked to consent to take part in the trial to allow us to collect their quality of life questionnaire data. If a parent does not wish to attend the consent/screening visit to do this, the site can contact the parent by telephone, discuss the trial and their involvement and ask them to sign a consent form and post it to the site. Quality of Life questionnaires can be sent and returned by post if the parent does not attend the visit in person or answer the questions over the phone. Should there be instances where participants aged 16-18y indicate that they do not wish their parent/carer to be aware of the trial, they should be encouraged to include them but if they still chose not to, this will be respected and will not prevent participant inclusion in the trial. Please inform the Trial Office if the parent/carer has not been approached for this reason.

Consent will be sought to allow the transport of samples within and outside the UK (e.g. Europe, USA, Canada) for analysis in designated research laboratories as part of the study. Consent will also be sought to store samples for 5 years beyond the last study visit and subsequently transfer them to a Human Tissue Authority (HTA) approved repository for indefinite storage. Any analyses outside the study protocol will be subject to REC permission. Samples from patients who do not consent to this will be flagged for destruction by laboratories in accordance with HTA requirements.

When a 12-15y old participant who provided assent reaches 16y, they should be given the 16-18y information sheet and asked to reconsent at the next study visit using an ICF. The parent should be advised that their ongoing consent for the participant is no longer required but that they should still reconsent to complete the PROMs questionnaires using the parent 16-18y ICF.

Consent to the remote follow up period (weeks 78 and 104) will be requested at visit 8. Participants will be given a new information sheet and asked to sign a new consent form specifically for the remote follow up process. Participants do not have to agree and can allow their active participation in the trial to end naturally once visit 8 has been completed.

7.1.3 Payment

Reimbursement of travel expenses for the child and their parent/carer to bring children to clinics for screening, treatment and follow up visits will be provided.

Small value vouchers (£10 per treatment visit (visits 1 to 7) and £30 for the final visit at week 52) will be given to participants to encourage continued participation at the treatment and follow up visits.

7.2 Screening

Screening evaluations should be performed during the 100 days between confirmed diagnosis and the first planned dose of IMP with the exception of MMTT which must be within 37 days of the first planned dose.

Screening will involve the following tests and checks being done at screening visits 1 and 2 (if appropriate, screening visits 1 and 2 can be combined):

	Screening visit 1	**Screening visit 2** *Must occur within 37 days of first planned treatment*
Medical history	✓	
Concomitant medication	✓	✓

Height and weight	✓	✓ (weight only)
Physical examination	✓	
Vital signs	✓	✓
Safety / eligibility bloods	✓	
Islet autoantibody testing	✓	
HIV, Hep B and C	✓	
TB testing *(chest x-ray and either blood test/Mantoux test)*	✓	
MMTT (see section 7.5.3 for details)		✓*
Adverse events		✓

It is routine to exclude active TB before use of biologic immunomodulatory agents. This will be done at the **first** screening visit and will be done in accordance with local practice which should follow the British Thoracic Society recommendations [27] which recommends a chest x-ray and any one of the following tests:

a) **A blood test** e.g. T-spot (preferred due to faster results), interferon gamma release assay (IGRA), Quantiferon test or other equivalent blood test. Sites should adhere to their local blood collection protocol for this test.
OR
b) **A Mantoux test** will require an additional visit 48-72h later to assess the injection site for any skin reactions by a trained healthcare professional. This may be done at home.

If the participant is still eligible after first screening visit then the local research team will continue with the appointment for the second screening visit (approximately 2 weeks later) which will include the MMTT and must be no more than 37 days from the planned first treatment date. This requires the child to be fasted on arrival.

Please try to avoid booking the second screening visit with the MMTT blood samples on Fridays as the KCL laboratory will not be able to process samples over the weekend. The only exception to this is if the trial site is able to send the sample using same day delivery e.g. London sites. Please contact the Trial Office to check whether this is feasible for your site prior to booking it. MMTT samples to the DRUC laboratory are frozen and can be stored locally for shipment when convenient (e.g. Friday samples can be couriered Monday so long as they are frozen over the weekend).

During the second screening visit, participants will be asked to do the following tasks to provide a baseline measure in the event that they are subsequently confirmed as eligible and randomised into the trial:

1) Begin completing a diary with any illnesses, concomitant medications, symptomatic hypoglycaemic events and insulin doses within the timeframes specified in the diary.
2) Begin dried blood spot (DBS) testing at home (kits will be provided) - see Section 7.5.8.
3) Start wearing their glucose monitor - see Section 7.5.5. They should go home with the first sensor attached wherever possible.

Results for auto-antibody testing and peak (highest) screened C-peptide results will be sent from DRUC to the Trial Office where it will be forwarded to the relevant site staff as soon as possible.

A qualified medical person at site will review all screening test results and make a decision as to whether the patient can be randomised into the trial. Potential participants who fulfil all inclusion and no exclusion criteria, and have been approved by a qualified delegated medic, will be informed of their screening results by the local research staff, and randomisation will be done **as soon as possible** by a delegated person to allow Pharmacy to make arrangements for the relevant treatment to be ordered (up to 5 working days if ordering Ustekinumab depending on the location of the site). The first study treatment visit must be agreed with the participant so that it falls within the required timeframe for the participant to remain eligible (no more than 100d from diagnosis and 37 days from MMTT).

Permission will be sought to inform the participant's GP about their enrolment in the trial. This will only be sent if the participant passes screening and is randomised for the trial.

If a participant in the trial receives their normal diabetes clinical care at a site other than the research site they attend for the trial, the participant's clinical care team will be contacted by the research site PI and informed of their patient's involvement in the trial. They should send a letter (REC-approved template provided by the trial) outlining the trial and how to contact the site PI and Trial Office if there are any questions or concerns.

The participant can be provided with a school letter (REC-approved template provided by the trial) to explain the reason for absences during term time due to trial visits.

7.3 The randomisation scheme

Minimisation by age (12-15 versus 16-18), and screened peak C-peptide levels (0.2 - 0.7 vs > 0.7 nmol/L) will be used to ensure balance between treatment groups. The treatment:placebo ratio will be 2:1 to provide additional data on drug safety (n=48:24). The minimisation algorithm and randomisation list will be provided by Sealed Envelope Ltd (https://sealedenvelope.com) working in consultation with statisticians in STU.

A STU statistician will liaise with Sealed Envelope Ltd to monitor allocation of study groups across the minimisation criteria which will be continuously monitored to inform adjustment of allocation algorithm if and when required according to pre-specified criteria.

As randomisation is not time-sensitive, we do not anticipate sites being significantly affected if the web-based system ever failed. However, a backup randomisation service will be provided in exceptional situations by STU by emailing USTEKID@swansea.ac.uk.

7.3.1 Method of implementing the randomisation/allocation sequence

After confirmation of participant eligibility and consent, the site PI or their delegate will enter relevant participant data via the secure web-based randomisation system https://www.sealedenvelope.com/redpill/ustekid available 24 hours a day run by Sealed Envelope Ltd. When the data have been entered, a unique participant randomisation code will be generated and the system will provide an immediate confirmatory email to nominated site staff and the Trial Office. The treatment allocation will not appear on the email, only the randomisation code.

7.3.2 Notification of treatment allocation

Only trial pharmacy staff at sites will be aware of the treatment allocation as all site staff and research nurses will be blinded. Delegated pharmacists will have access to a code break list which they will use to cross reference the randomisation code in the email with the corresponding treatment allocation on the code break list.

Trial pharmacists or other delegated, trained unblinded staff will make up the appropriate syringe (active drug or placebo) on the morning of the planned study visit (as advised by the research nurse) making sure that they are identical in appearance (see section 8.5.2).

The research nurse will provide a prescription in advance and will usually collect the blinded syringe on the day of the study visit and ensure that it is kept at the appropriate temperature (see Section 8) prior to administration. Any unblinded trained research staff who prepare the syringe may administer the treatment themselves rather than hand over the blinded syringe to a blinded research nurse.

7.3.3 Blinding

Dosage and regimen of placebo and Ustekinumab will be matched. There is no visible difference in appearance between the active drug and placebo. Randomisation emails will be blinded. Only pharmacy staff will be provided with a code break list to unblind themselves to the treatment allocated.

Participants and site health care professionals (other than the trial pharmacists) and site research staff will be blinded to the treatment allocation, as will the Trial Manager, Data Manager and Trial Statistician. Key members of STU will be aware of the allocation to perform back up randomisations, authorise Ustekinumab release from the distributor and conduct unblinded monitoring. An independent STU statistician will review the randomisation allocations at intervals to ensure that they follow the specification in the protocol.

To ensure blinding at sites, the study treatment will be drawn out of vials by pharmacy staff or other delegated persons and relabelled when dispensed into syringes. The blinded syringe will be provided to blinded research staff for administration. If unblinded research staff are to prepare and administer the blinded syringe, they will collect the relevant supplies and documents from pharmacy and may also be delegated to administer the treatment. Research staff will inform pharmacy staff when the participant's future dose is required and provide a prescription in advance.

Assessment of immune responses will be conducted blinded from metabolic parameters in the first instance.

All blood and urine samples will be labelled with the participant trial ID, visit ID and sample date (and time - relevant to the MMTT), so that laboratory staff will know whether samples are from the same participant and which visit they refer to but not the identity of the participants.

All adverse events (AEs) will be reported blinded to the TMG. Unblinded Serious Adverse Events (SAEs) and Suspected Unexpected Serious Adverse Events (SUSARs) will only be reported to independent members of the DSMB. The Trial Statistician should not take part in any DSMB discussion of unblinded SAEs and SUSARs.

Final unblinding of all participants will take place after the creation of a locked analysis dataset and the finalisation of the statistical analysis plan.

7.3.4 Emergency unblinding

Emergency unblinding (24/7) will be managed by Sealed Envelope Ltd.

The randomisation allocation should only be broken for valid medical or safety reasons e.g. in the case of an SAE. All emergency unblinding of SUSARs will be at the discretion of the local investigators when clinically indicated for participant safety. Researchers with access to the randomisation system can initiate an unblind with permission from the PI or delegate but are not unblinded themselves during the process. An unblinding action will be notified by email to one nominated individual at the site for action. STU will notify the REC, site R&D offices, MHRA, specific members of the TMG and co-investigators who are designated as not required to be blinded.

Details of the request must be documented using an Unblinding form and stored in the Investigator Site File (ISF). A copy of the form should sent to the Trial Office for the Trial Master File (TMF). Any unblinded documentation e.g. the unblinding email, should be filed in a confidential section of the ISF by an unblinded person.

In the event that the web-based unblinding system is not available, sites should inform the Trial Office at USTEKID@swansea.ac.uk to seek advice.

If emergency unblinding is delayed, the treating clinician should treat the patient as if the active drug has been given.

7.4 Baseline data

Baseline variables (characteristics) used to determine efficacy of treatments will be measured. These will include the following:

7.4.1 Primary efficacy outcome baseline value at screening visit 2

Residual insulin production at baseline will be assessed by measurement of stimulated C-peptide production during the MMTT. Blood samples will be taken from fasting participants at time 0 immediately before the participant starts drinking the liquid meal and then at 15, 30, 60, 90 and 120 minutes after the meal.

7.4.2 Patient reported outcomes during MMTT C-peptide at screening visit 2

Patients' quality of life will be assessed by age-appropriate PROMs: the HYPOFEAR, DTSQ, and PedsQL questionnaires (see section 7.5.11). They will be given to each participant and a nominated, consented parent/carer while the MMTT is being performed. Baseline PROMs scores will be used as covariates to adjust comparisons between treatment arms for secondary analyses.

7.4.3 Immunological outcomes at screening visit 2

A panel of immunological outcomes to assess immune phenotype, T cell responses to antigens and islet derived cell free DNA will be collected at screening visit 2 and treatment visit 1 (week 0). These will be used as covariates to adjust comparisons between treatment arms for the secondary analyses.

7.4.4 Secondary efficacy parameters at treatment visit 1 (Week 0)

Glycated haemoglobin (HbA1c levels expressed in mmol/mol) values measured at Week 0 will be used as the baseline blood glucose level to adjust for comparison between treatment arms in glycaemic control.

Mean daily insulin use will be calculated over 7 consecutive days during the 2 weeks prior to Visit 1 (Week 0). 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.

7.4.5 Tertiary efficacy outcome baseline value at screening visit 2

Other indicators of residual insulin production e.g. proinsulin, glucagon and somatostatin levels, UCPCR and DBS will also be measured at this time point to provide a baseline measure.

7.5 Trial Assessments

An overview of the trial assessments can be found in Appendix 2 (Schedule of events) with a breakdown of blood draw and urine collection requirements in Appendices 3 and 4 respectively.

7.5.1 Overview of Assessments

The trial will involve the following general procedures:

- Medical History.
- Vital signs.
- Physical examination (including height and weight).
- Record of concomitant medication.
- Insulin dose usage.
- Metabolic review.
- Adverse events assessment.
- Blood sampling for the assessment of safety, metabolic and immunological outcomes. *Blood volumes required for the study within an 8-week period (Appendix 3) align with guidelines from the National Institute of Health and those used by the T1D Clinical Trial Consortium (www.diabetestrialnet.org)*
  - *no more than 5ml/kg in a single day (250ml for individual with 50kg of weight).*
  - *no more than 9.5ml/kg in any 8 week period (475ml for individual with 50kg of weight)).*
- Urine sampling for the assessment of pregnancy, safety and metabolic outcomes.
- Glucose monitoring subcutaneously using a glucose monitor to assess safety (hypoglycaemia) and metabolic outcomes.
- DBS testing.
- Participant diary.
- Questionnaires to assess patient- and parent/carer-related secondary outcome measures.
- Remote follow-up at weeks 78 and 104.

7.5.2 Blood sampling priorities

In the event that the required blood samples are not fully available for any reason (e.g. patient unwell, persistent vein collapse), **blood samples should be prioritised** according to the list below:

1) Screening visit 1
   a. Safety / eligibility bloods to local laboratory [5]
   b. HIV and Hepatitis B and C to local laboratory

[5] Local eligibility/safety blood sample testing should include: Full blood count; urea, electrolytes and creatinine; liver function tests (total bilirubin, total protein, albumin, AST (SGOT), SGPT (ALT), alkaline phosphatase; thyroid stimulating hormone; immunoglobulins (G, A, M); calcium; magnesium, phosphate, lipid profile (total cholesterol, LDL, HDL, triglyceride).

Results of these tests do not need to be normal but they should not have clinically significant abnormal results to be eligible. If they do, an (S)AE must be reported.

c. TB testing (if using a blood sample, not the Mantoux test) e.g. T-spot, IGRA, Quantiferon, as per local procedures (local/offsite lab)
d. Islet autoantibodies to the Diabetes Research Unit Cymru (DRUC)

2) Screening visit 2
   a. MMTT [6] to DRUC
   b. Mechanistic blood draw to King's College London (KCL) laboratories

3) Study visits (1, 2, 3, 5 and 8)
   a. Safety bloods to local laboratory (visits 1, 2, 3, 5 and 8)[5]
   b. MMTT to DRUC (visits 5 and 8)
   c. HbA1c to DRUC (visits 1, 3, 5 and 8)
   d. Mechanistic blood draw to KCL (visits 1, 2, 3, 5 and 8)
   e. Islet autoantibodies to DRUC (visits 5 and 8)
   f. Sample for cell free DNA to KCL (visits 1, 2, 3, 5 and 8)
   g. Sample for pharmacokinetics analysis to external contractor (visits 2, 3, 5 and 8)

Where possible, please avoid booking study visits 1, 2, 3 and 5 and 8 on Fridays as the KCL laboratory cannot process fresh samples at weekends. Only trial sites who can arrange a same day delivery to KCL should consider booking Friday appointments e.g. London sites. Please check with the Trial Office whether a same day delivery is feasible.

DBS tests are done at home by the participant and posted to the DRUC laboratory using pre-paid, addressed envelopes.

At dosing visits, the blood draw will take place prior to administration of the IMP.

7.5.3 Guidance on glycaemic control during the study

Glycaemic control will be maintained according to clinical guidelines and conducted in collaboration with the participant's diabetes clinical care team.

HbA1c will be measured as per study schedule based on the local laboratory results with a target value set according to 2015 NICE guidelines [28] in agreement with the participant and their clinical care team. Where this target is not met, advice will be given as clinically required.

Glycaemic control will be reviewed at every study visit.

Should insulin requirements fall to less than a total of 8 IU per day, continuation of insulin therapy will be with the agreement of the participant and their clinical care team. Discontinuation of insulin should be discussed with the Chief Investigator. Continuation of a low dose of insulin where possible is considered preferable.

7.5.4 Mixed meal tolerance test (MMTT) (laboratory test)

Secretion of C-peptide will be tested using a MMTT at screening, weeks 28 and 52. The MMTT is part of the screening test and cannot be done more than 37 days before their first treatment dose.

The MMTT should be started between 7AM and 11AM. Participants will be asked to test their blood glucose at home 2 hours before attending for their MMTT and contact the research team via the telephone number provided with the result. The MMTT should be conducted only if the fasting value by capillary blood glucose meter is between 4.0 and 11.1mmol/L (inclusive).

Other criteria should also be checked before confirming that the participant can attend the MMTT:

- Must have had no food or drink (with the exception of water) since midnight.
- Must not smoke from 12 (midnight) or 8 hours prior to the start of the test.
- Must withhold taking long acting insulin on the morning of the test. They can take very short acting insulin (e.g. Humalog, Apidra, Novorapid, Fiasp) up to 2 hours before the test. They can also take long-acting insulin (Lantus, Levemir, Tresiba, Insulatard, Humulin I) up to 6 hours before the test if necessary.

[6] *MMTT is the primary outcome measure for the trial*

- If using an insulin pump, the participant should be advised to continue their basal regime but not have a bolus [29].

Participants will be advised that their blood glucose level may rise during the MMTT, but insulin will be given if necessary following the test to correct this.

When the participant phones with their blood glucose result:

- If the fasting value is in the hypoglycaemic range (< 4mmol/L) the test should be postponed to a different day and hypoglycaemia treated appropriately.
- If the value is > 11.1 mmol/L the participant should be advised to take an appropriate correction bolus of very short acting insulin and be prepared for the possibility that the test may need to be postponed if the glucose is not in the target range after 2 hours.

The MMTT procedure should be carried out as follows:

a) Measure BG value prior to beginning MMTT to ensure patient is still eligible for the MMTT.

b) Ask participant to void their bladder – discard this urine sample.

c) Insert IV line.

d) Obtain baseline MMTT blood sample at 0 minutes (prior to the ingestion of the liquid meal), and all other blood samples required at that visit (see Appendix 3). The **Sample Preparation Manual** provides guidance on samples to be taken.

e) The patient is given the standardised liquid meal: Ensure Plus 6 ml/kg (Maximum 360ml) to be ingested within 5 minutes. If this is not possible, please complete a protocol deviation form and send it to the Trial Office.

f) Blood samples are drawn at times: 15, 30, 60, 90 and 120 minutes, after the start of ingestion of Ensure Plus.

g) At 120 minutes, measure capillary blood glucose and ketones.

h) At 120 minutes, ask the participant for a urine sample. This will be collected in a boric acid container.

i) After the test is completed, the participant eats and receives insulin as appropriate and prescribed by the local investigator.

Participants will be asked if possible not pass urine between time point 0 and 120 minutes; if this is not possible the intermediary urine sample will be collected and combined with the 120 minutes sample for testing.

Proinsulin, glucagon and somatostatin levels will also be measured on stored samples from the MMTT. Glucagon and somatostatin levels will be measured at screening and weeks 28 and 52 by the Royal Devon and Exeter Hospital Clinical Chemistry Department. All other laboratory measurements listed in this section will be performed in the DRUC laboratories, Swansea University.

7.5.5 Urine C-peptide/creatinine ratio (UCPCR)

Used as an alternative marker of insulin production. This will be measured from the 120min urine sample taken during the MMTT at screening, weeks 28 and 52 (see section 7.5.3).

7.5.6 Glucose monitoring

Blood glucose variability will be studied through subcutaneous glucose variation, using data derived from glucose monitor for the 2 weeks prior to each dosing visit (Weeks 0, 4, 12, 20, 28, 36, 44) and week 52. Mean, median, standard deviation and interquartile range of glucose variability will be calculated for frequency of and number of episodes of hypoglycaemia (< 4.0mmol/L), and also instances of elevated values i.e. > 10mmol/L and > 15 mmol/L.

All participants will be provided with sensors and a reader for the Abbott Freestyle glucose monitoring system (Freestyle Libre) during their second screening visit and trained in using this system by qualified staff. Only the FreeStyle Libre can be used for the trial assessments. Participants with other devices must agree to use the FreeStyle Libre device for the two weeks prior to each visit to be eligible. Participants who already have a FreeStyle Libre may continue to use it. Sites can order the device and sensors by following the instructions in the Sample Preparation Manual.

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 (see Appendix 2). Participants are encouraged to use the sensors continuously outside of these 2 week periods to guide insulin adjustment and provide additional information. Sensors can be used for two weeks before a new one is needed. Sufficient sensors will be given to participants at each study visit to cover until the next visit. All glucose data will be saved and the percentage of time for which the device is used recorded.

Any patients found to be subsequently ineligible after the screening visit will not be asked to return the monitor if it was supplied by the trial as they cannot be reused. Only 10% of screened patients are likely to be ineligible at this point.

Data from the device should be downloaded as a .CSV file (raw data, not summary data) and will be transferred anonymously from the site to the Trial Office at USTEKID@swansea.ac.uk. Training materials are available to describe how to do this using LibreView and Diasend. The export must be amended so that it only has the participant's trial ID and device ID to link it to the data in the database. All identifiers must be removed prior to sending to the Trial Office.

7.5.7 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 PI or delegate should review the diary during the participant visit wherever possible to discuss any hypoglycaemic events documented to allow them to categorise them on the Hypoglycaemic Events Assessment Form.

Clinical hypoglycaemic events rates will be calculated from records downloaded from the FreeStyle Libre device, symptoms records in the diary and self-recorded blood tests and assessed and categorised in two ways for analysis according to American Diabetes Association (ADA) Guidelines [30, 31]:

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 hypoglycemia

Level 3 - Severe hypoglycemia, as defined by the ADA [31] denotes severe cognitive impairment requiring external assistance for recovery (see clinical characterisation below)

2) Clinical characterisation

a) **Severe hypoglycemia**. Severe hypoglycemia 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 hypoglycemia**. Documented symptomatic hypoglycemia is an event during which typical symptoms of hypoglycemia are accompanied by a measured plasma glucose concentration ≤ 3.9 mmol/L.

c) **Asymptomatic hypoglycemia**. Asymptomatic hypoglycemia is an event not accompanied by typical symptoms of hypoglycemia but with a measured plasma glucose concentration ≤ 3.9 mmol/L.

d) **Probable symptomatic hypoglycemia**. Probable symptomatic hypoglycemia is an event during which symptoms typical of hypoglycemia 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.

The categorisation of hypoglycaemia according to these criteria will be made initially by the local PI. Severe hypoglycaemic events will be further adjudicated in blinded fashion by the DSMB.

The number of severe hypoglycaemic events will be recorded at weeks 78 and 104 to cover the period since the previous data collection time point. Severe will be defined as:

a) Admission to hospital
b) An ambulance being called but no transfer to hospital was needed
c) Being given glucagon but no ambulance was called and no admission to hospital was needed
d) Convulsions (fits) or loss of consciousness

The data will be requested from medical records and from the participant (or parent) using a questionnaire.

7.5.8 HbA1c level (external laboratory test)

HbA1c will be tested in the local laboratories of the study sites to guide clinical care. A blood sample will also be taken for centralised measurement of all HbA1c at weeks 0, 12, 28 and 52 by DRUC, Swansea University.

7.5.9 Dried blood spot (DBS) measurements

An instruction sheet will be given to participants and their parents/carers at the second screening visit about collection of DBS samples via finger prick at home between visits and what to do with those samples. Testing should begin as soon as possible after the kits have been given to participants. Weekends are likely to be the most convenient testing days. Research staff will pre-complete the trial ID on the information sheets and sample cards provided at each visit to allow the lab to track the participant's samples and data without the participant's name being used.

DBS sampling will be taken once a week (+/- 2 days), one before the first meal of the day, and one 60 minutes afterwards from baseline until week 28 and then monthly up to 12 months for the measurement of C-peptide and CRP. If a study visit day is chosen for the DBS sample, then the sample *must* be taken before treatment is given.

The DBS samples should be collected only if the fasting value by capillary blood glucose meter is between 4.0 and 11.1mmol/L (inclusive). DBS samples and blood glucose measurements will be taken immediately before a standardised meal (the first meal of the day) and at 60 minutes from the start of the meal, by finger prick in the home setting applying the blood to filter paper strips. Patients will be asked to withhold their pre-meal insulin until after the post-prandial DBS samples have been taken so as not to interfere with the C-peptide/CRP result. Following the 60 minute DBS sample, the participant will give a correction dose either via injection or pump, according to the patient's own insulin sensitivity factor.

DBS samples will be posted by participants to the DRUC laboratories in the pre-paid envelope provided as soon as they are completed and dried (24h after testing).

Reminders to patients to do the DBS should be provided by the research nurses. The Trial Office will be notified of samples received by DRUC on a weekly basis and can alert sites if participants are not providing samples correctly or on time. Sites will be asked to query any non-compliance with the participant.

Remote data collection at weeks 78 and 104 will also include a request for participants to complete one DBS sample per time point.

7.5.10 Insulin dose (clinical care measurement)

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.

7.5.11 Body weight and BMI (clinical care measurement)

Body weight and height will be recorded at some visits (see Appendix 2) and the most recent weight recorded in the CRFs will be used to calculate IMP dosages for forthcoming treatment visits. Body mass index will be calculated as: weight (kg)/ [height (m)]^2.

7.5.12 Patient and Parent Reported Outcome Measures (PROMS)

Patients' quality of life will be assessed by age-appropriate participant-reported and parent-reported outcome measures (PROMs) compiled into a questionnaire booklet:

- the Hypoglycaemia Fear Scale - HYPOFEAR
- Diabetes Treatment Satisfaction Questionnaire for inpatients - DTSQ
- Paediatric Quality of Life inventory - PedsQL (generic core scale and diabetes-specific modules)

Questionnaires will be administered to participants and their nominated (consented) parent/carer at screening and weeks 28 and 52. The same parent/carer must complete the questionnaire at each time point. If the parent does not consent to complete these, please let the Trial Office know. If necessary, the questionnaires can be sent prior to the appointment and returned at the visit if it is more convenient.

7.5.13 Exocrine enzymes

Serum samples will also be analysed for the exocrine enzymes, trypsinogen, amylase and lipase at visits -2, 5 and 8.

7.6 Long term follow-up assessments

There will be assessments made of insulin dose, severe hypoglycaemia and HbA1c levels recorded at routine outpatient visits closest to weeks 78 and 104. We will ask both the participant (using a questionnaire) and the patient's clinical care team/research team to provide the data from the corresponding routine diabetes outpatient visit.

Whilst consent is sought for remote data follow up at the start of the trial, explicit consent will be sought from participants to send them the questionnaire, DBS sample cards and sensors for a CGM device (if they don't have them routinely provided by the NHS). We will also seek consent to request relevant data from their medical records where possible.

7.7 Qualitative assessments

No additional qualitative assessments will be performed.

7.8 Withdrawal criteria

A participant or their parent/carer may terminate their participation in the trial at any time without giving a reason and with no personal disadvantage.

Withdrawal can occur:

- **At any time**: Participant (or parent/carer) withdrawal of consent; Withdrawal of participant by the Chief Investigator, Principal Investigator or delegate; Early termination of the trial at the request of the TSC / Sponsor.
- **After receipt of first dose**: To be considered by DSMB in case of potential SAE attributable to the IMP.

Where possible, participants will be withdrawn from treatment only and invited to attend trial follow up visits to obtain outcome data in accordance with the planned analysis, but have the option to decline this.

Should a participant become pregnant they will not be withdrawn from the trial, but will be withdrawn from further treatment doses. The participant will be invited to attend trial follow up visits to obtain outcome data in accordance with the planned analysis. The pregnancy will (with consent) be recorded on a pregnancy reporting form and the participant will be followed up until pregnancy outcome. As a precautionary measure all resulting children will be surveyed for their first 12 months if consent is given (see section 9.8.2 for further details).

The Sponsor has the right to terminate this study at any time. In terminating the study, the Sponsor and the Chief Investigator will ensure that adequate consideration is given to the protection of the participants' interests. If the study is terminated, participants who are already enrolled will be encouraged to attend all subsequent visits so that safety information may be collected. If it is not possible for a participant to attend all subsequent visits, the participant will be asked at least to undergo safety assessments until the Week 52 visit.

If the study is suspended or terminated for safety reasons, the Sponsor will promptly inform the Chief Investigator. The Sponsor will also promptly inform the relevant regulatory authorities of the suspension/termination and of the reasons for this action.

Participants will usually be withdrawn from treatment if they exceed the treatment dosing window stated in the protocol for any reason. The site PI should discuss the treatment window deviation with the Chief Investigator as soon as possible, providing reasons why the deviation has or will occur. Participants should be alerted to this possibility when they are informed about the trial and trial visits should all be planned in advance to foresee any potential issues with holidays, exams, etc which will allow preceding visits to be planned to avoid them.

7.9 Storage and analysis of clinical samples

Appendix 5 describes the flow of blood and urine samples from sites to research laboratories and from research laboratories to secondary laboratories.

A study-specific sample management process will be provided to sites in the form of a Sample Preparation Manual. Laboratories will adhere to their internal Standard Operating Procedures for sample testing and storage.

Samples for local laboratory assessment may be taken at a time convenient for same day processing by the local laboratory. Research samples for immunologic or metabolic studies or autoantibodies should be drawn before 12PM wherever possible and sent by approved courier to the appropriate laboratory or, in some instances, stored locally for later analysis following batched transport. The Sample Preparation Manual will provide further details on this.

7.9.1 General laboratory assessments at local sites

The following general laboratory assessments will be performed at sites for the study:

- Full blood count; urea, electrolytes and creatinine; liver function tests (total bilirubin, total protein, albumin, AST (SGOT), SGPT (ALT), alkaline phosphatase; thyroid stimulating hormone; immunoglobulins (G, A, M); calcium; magnesium, phosphate, lipid profile (total cholesterol, LDL, HDL, triglyceride). – Screening, treatment and follow up visits (as per Appendix 3)
- Urine pregnancy test (all female participants). This test should be performed at the visit with a urine pregnancy testing kit for an immediate result – Screening, treatment and follow up visits (as per Appendix 4)
- Urinalysis for pH, blood and protein by dipstick urinalysis and laboratory analysis for albumin/creatinine ratio. – Screening, treatment and follow up visits (as per Appendix 4)
- HbA1c testing.– Screening, treatment and follow up visits (as per Appendix 3)
- HIV and hepatitis B and C tests and TB tests at screening visit only and are a trial-specific test – first screening visit only

7.9.2 Specialist testing at laboratories

Samples will be collected from sites and transported to the corresponding laboratory for analysis as shown in Table 3.

Test	Laboratory
1. Autoimmune antibody assessments - GAD-65, IA-2 and ZnT8	Diabetes Research Unit Cymru, Swansea
2. HbA1c testing (centralised laboratory trial specific measurement of HbA1c – separate from routine care)	
3. MMTT (including, proinsulin, glucose and C-peptide)	
4. UCPCR	
5. Dried blood spot samples	
6. Storage of serum for transport to Exeter (test 13 below)	
7. Exocrine enzymes	
8. T cell assays to include cytokine FLUOROSPOT to measure T cell responses to islet cell autoantigens	Kings College London

9. Flow-cytometry profiles of leucocyte populations including T and B cell lymphocytes and detailed phenotyping of T cell subsets as described elsewhere [32-34].	
10. Storage of samples (serum and plasma) for transport to: a) Bristol (test 11 below) b) an external contractor (tests 14 and 15 below)	
11. Cytokine production by CD4 and CD8 T cells will be assessed by intracellular cytokine staining (ICS) following stimulation of whole blood or PBMC with polyclonal activators.	
12. Blood samples will be taken and the PBMCs cryopreserved as well as samples stored for later DNA extraction and analysis (to be done elsewhere).	
13. Cell free DNA assays (for beta cell and T cell apoptosis)	University of Bristol
14. Glucagon and somatostatin	Royal Devon & Exeter Hospital
15. Anti-drug (Ustekinumab) antibodies	External contractor
16. Ustekinumab serum levels	

Table 3: List of tests being done by each laboratory

7.10 End of trial

The end of trial data collection is defined as the last follow up data collection point (i.e. last patient, last routine follow up visit at approx. week 104) for the last patient recruited and retained in the trial. The end of the trial itself will be defined as one year after the database has been locked to allow adequate time for analysis.

The authorising REC, R&D offices and the MHRA will be notified of end of study within 90 days of from completion of the trial or within 15 days if an early termination.

8. TRIAL TREATMENTS

8.1 Name and description of investigational medicinal product(s)

USTEKINUMAB (STELARA®)

Ustekinumab is a fully human IgG1k monoclonal antibody (mAb) and will be manufactured, QP released and shipped to St Mary's Pharmaceutical Unit (SMPU) by the marketing authorisation holder Janssen-Cilag Ltd to Good Manufacturing Practice (GMP).

Ustekinumab is supplied as a sterile single use 2 ml glass vial closed with a coated butyl rubber stopper contained in an outer carton. Each vial comprises 0.5 ml of solution with 45 mg of Ustekinumab for injection.

PLACEBO

Saline in the form of Sodium Chloride 0.9% w/v solution for injection will be used as the placebo.

Any brand of saline with a marketing authorisation in the UK can be used for this trial. It is likely to be available as 5 ml and 10 ml hermetically sealed translucent plastic ampoules, polypropylene Ph. Eur., packed in cardboard cartons to contain 10, 20, 50 and 100 ampoules.

Site pharmacies will maintain the blind by provided blinded site staff with a syringe containing the appropriate amount of IMP or placebo according to the received trial prescription and randomisation number.

8.2 Regulatory status of the IMP

The CI, site trial pharmacist, or other personnel authorised to store and dispense IMP are responsible for ensuring that the IMP used in the clinical trial is securely maintained as specified by the Sponsor and in accordance with the applicable regulatory requirements.

Ustekinumab is licensed and marketed in the UK for the treatment of psoriasis in adults and children, psoriatric arthritis and for Crohn's disease in adults. The manufacturer Janssen-Cilag Ltd will provide vials for injection as per the marketing authorisation number EU/1/08/494/002.

Placebo will be generic sterile 0.9% w/v saline solution for injection as available at sites. A representative Summary of Product Characteristics (SmPC) will be used to represent all saline (marketing authorisation number PL 02848/0157).

SMPU will be responsible for receiving Ustekinumab from Janssen, storing the vials and dispatching Ustekinumab to site pharmacies for trial purposes.

Any Drug Product Complaints (DPCs) and temperature excursions relating to Ustekinumab by sites or SMPU should be reported to the Trial Office for onward reporting to the Quality Department of Janssen: QAJCUK@its.jnj.com, as well as Janssen Trial Manager immediately, but in any event within 1 business day, after becoming aware of the event.

The IMP will be delivered by SMPU to clinical trial pharmacies at sites.

8.3 Product Characteristics

No Investigator Brochure (IB) will be available for this trial. The SmPC available for (STELARA®), and the SmPC for the saline solution will form the simplified Investigational Medicinal Product Dossier (IMPD).

Section 4.8 of the SmPC will be used as the Reference Safety Information (RSI) for pharmacovigilance purposes. Should a new version of the SmPC be issued during the Development Safety Update Report (DSUR) period, a documented risk assessment will determine whether the RSI requires updating. Any update will consider the impact on the DSUR. An amendment will be submitted and authorised before any new RSI is implemented.

IMP is a clear to slightly opalescent, colourless to light yellow solution and may contain a few small translucent or white particles of protein. Saline is a clear and colourless solution. Both solutions should be visually inspected for particulate matter or discolouration prior to administration. Neither solution should not be used if discoloured or cloudy, or if foreign particulate matter is present.

The risk of unblinding due to colour change has been assessed. Due to the small volumes of solutions used IMP and placebo will be indistinguishable when used in a standard single use injection syringe fitted with a hypodermic needle.

8.4 Drug storage and supply

8.4.1 Supply

Janssen-Cilag Ltd will supply Ustekinumab in the quantities required by the trial at no cost to the Sponsor. Sponsor or their delegate will inform Janssen-Cilag Ltd in writing of the need for any additional Ustekinumab in accordance with the period of notice stated in the sponsor agreement. IMP will be sent via courier.

SMPU are the appointed contractor for the receipt and storage for the IMP prior to distribution to trial sites. IMP will be sent to SMPU or distributed to sites via courier (or other signed for delivery service) with a signature required on receipt by the relevant party. A nominated trial pharmacist at sites will be responsible for the receipt and storage of the IMP.

Placebo (saline 0.9%) will be taken from local pharmacies stock in accordance with a signed sponsor agreement.

8.4.2 Storage

Ustekinumab does not contain an antimicrobial agent and has a shelf life of two years. Ustekinumab vials must be kept in their outer carton and stored in a refrigerator (2°C – 8°C) in a secure area with restricted access. Ustekinumab must not be frozen. Prior to dispensing into the syringe, Ustekinumab should be allowed to reach room temperature (approximately 30 minutes).

The placebo (saline 0.9%) does not contain an antimicrobial agent has a shelf life of three years. Saline ampoules must be stored below 25^{o}C in a secure area with restricted access.

Unused portions of either IMP or placebo must never be reused and should be disposed of in accordance with local requirements. Detailed instructions for use of Ustekinumab or placebo are provided in the package leaflet.

8.5 Preparation and labelling of Investigational Medicinal Product

8.5.1 At St Mary's Pharmaceutical Unit (SMPU) as distributor

On receipt of Ustekinumab from Janssen, SMPU will assess for temperature excursions and any deficiencies in, condition, packaging, appearance, associated documentation, expiry date etc. Any issue with temperature deviations or quality will be directed to Janssen-Cilag promptly.

SMPU will store the Ustekinumab vials for trial use until they distribute to sites according to the requirements of Annex 13.

8.5.2 At sites

Site pharmacists will order sets of vials (up to 14 vials per full participant treatment) from SMPU if a participant has been randomised to receive IMP. This should be done as soon as possible to allow for courier time from SMPU to the site.

On receipt of Ustekinumab, trial pharmacies will assess for temperature excursions and any deficiencies in condition, packaging, appearance, associated documentation, expiry date, etc. Any issue with quality will be directed to the trial office promptly.

Following randomisation, a trial specific prescription issued by a delegated site investigator will be received by the site pharmacy. Providing this quickly will allow the pharmacists to order the correct number of vials as the dose is weight-dependent. If no weight is on the prescription, pharmacies can order 7 vials and submit an additional request for another 7 if the participant's weight requires 2 vials per treatment.

The site trial pharmacist or other delegated person will be responsible for preparing and labelling the syringe according to trial requirements to ensure that the blind is maintained for participants and researchers.

The trial pharmacist or other delegated person will ensure that vials of IMP are kept in the outer carton to protect from light, are not shaken and at the correct temperature prior to withdrawing the required amount in millilitres into a standard syringe as per the randomisation and prescription provided. The syringe will be prepared on the day of

the dosing visit and labelled with the participant trial ID, date and time of dispensing and the expiry time of the syringe. The labelled syringe will be collected by the blinded research nurse for administration on that day either at the research facility or the participants' home. Chemical and physical in-use stability has been demonstrated for 4 hours at 15-25°C, hence all syringes must be used **within 4 hours of preparation** (defined as the time the vial was removed from the refrigerator) or returned unused to Pharmacy.

If unblinded research staff are responsible for IMP preparation and administration, they will work closely with Pharmacy to ensure the syringes are prepared correctly and the relevant documentation is completed.

Pharmacy staff will inform the Trial Office of any issues with local stock such as breakages, unused stock, incorrect use of stock, etc so that the Trial Office can accurately track vial allocation and use. All contact between Pharmacies and the Trial Office must use the IMP@swansea.ac.uk email address to maintain the blind for the Trial Manager and Data Manager.

The Trial Office (at IMP@swansea.ac.uk) will advise sites on which batches of vials should be used for each participant. Whilst the vials can be used for any participant, "borrowing" should only be applied in exceptional circumstances whereby a shipment is delayed and a treatment visit is due for a different participant.

8.6 Dosage schedules

The schedule of dosing is shown in Appendix 2 and will be determined by the participant's body weight recorded at a prior visit.

Ustekinumab or matched placebo will be administered subcutaneously (SC) via prepared syringes as a single dose. For participants weighing ≤ 40kg, the dose will be 2mg/kg; for participants > 40kg, the dose will be fixed at 90mg. The maximum total amount of Ustekinumab that will be administered to any participant for the trial is 630 mg.

Injections will occur at week 0 and 4 and then every 8 weeks for a duration of up to 44 weeks.

For all participants, the first dose of Ustekinumab will be administered in a hospital setting and the participant observed for 1hr. No significant local or systemic reactions are expected, however, any observed reactions will be documented. If no unexpected or serious events are observed after the injection, further dosing, including home administration, will continue as per protocol.

8.7 Dosage modifications

Each dose will be aligned to the participants' most recent weight measurement. Participant attendance and compliance, together with reasons for deviations from the dosing plan (missed injections, wrong dose administered, etc.) will be recorded.

With the exception of loading doses 1 and 2 (at weeks 0 and 4), participants will be allowed 8 weeks (+/- 1 week) between treatment. It should be noted, however, that every effort should be made to administer all doses at exactly the correct time interval to ensure optimal efficacy. Trial visits should all be planned in advance to allow the prediction of issues with future dates and preceding visits can be booked to fall outside problematic dates whilst still adhering to the treatment window stated.

Where a visit is outside the 1 week window it must be reported as a protocol deviation to the Trial Office immediately at USTEKID@swansea.ac.uk. The Trial Office will liaise with the CI who will provide advice on how the site should proceed.

Every effort should be made to dose exactly 4 weeks apart during the loading period (doses 1 and 2). The second loading dose should not be given sooner than 3 weeks after the first dose and no later than 1 week after the week 4 requirement. If the second loading dose is >1 week late, it will be considered that appropriate loading did not happen and the event must be reported as a protocol deviation and may be withdrawn from further treatments as described in section 7.8.

Any required insulin dose modifications will be undertaken in accordance with standard care and clinical advice.

8.8 Known drug reactions and interaction with other therapies

The available SmPC for Ustekinumab describes all essential information for the use of the medicine including benefits and risks for plaque psoriasis (including paediatric), psoriatric arthritis and Cohn's disease. Known interactions with medicinal products and other forms of interaction for Ustekinumab are described in the SmPC and summarised below along with additional risk mitigation strategies as they relate to this trial.

- **Severe hypersensitivity or acute anaphylaxis** is known to occur with monoclonal antibody therapies. It has not been observed to date in clinical trials with Ustekinumab, but has been reported in post-marketing surveillance. The risk is considered to be < 1%, but the exact risk is not known. Individuals with previous hypersensitivity to monoclonal antibodies will be excluded and the use of a CRF for the first dose is required.
- **Vaccinations**: Live viral or bacterial vaccines are prohibited from 30 days before the first dose of IMP and any requirement for a live vaccine during the trial (e.g. for travel reasons) will result in the IMP being withheld for 15 weeks prior to the vaccination and resumed 2 weeks after the vaccination in accordance with the manufacturer's advice. ***Note****: most injected (as opposed to nasal) influenza vaccines are not live vaccines and are permitted.* If a participant has a vaccination of any kind, it should be reported in the Concomitant Medication Log.
- **Anti-lymphocyte monoclonal antibodies**: Any prior use of such antibodies is prohibited e.g. anti-CD20, anti-thymocyte globulin (ATG), Rituximab (Rituxan®), or Alemtuzumab (Campath®).
- **Immunosuppressive agents** (e.g., methotrexate, cyclosporine, or anti-TNF agents) are prohibited from 30 days before the first dose of IMP through the duration of the study (including follow-up).
- **Allergic Immunotherapy**: should be avoided unless such treatment is medically necessary and alternative treatments are not considered safe or effective.
- **Corticosteroids**: Use of systemic corticosteroids should be avoided unless such treatment is medically necessary and alternative treatments are not considered safe or effective. Use of more than 10mg prednisolone daily (or equivalent) for more than 5 days is prohibited within 4 months prior to the first dose of the IMP; *Note: intranasal, inhaled and topical corticosteroid medications are permitted if used at recommended dosages. The Chief Investigator must be notified of any systemic corticosteroid treatment; if systemic corticosteroid use is considered in a non-emergency situation, study staff should document that an alternative treatment was ineffective or was not considered safe.*
- **Surgery** – If a participant requires surgery, then Ustekinumab should be stopped 12 weeks prior to the planned surgery and resumed once the wound has healed to avoid possible complications around infection. The participant may be withdrawn from the trial, depending on the time in the trial when surgery is needed.

Previous use of Ustekinumab or any other investigational drug within the 3 months prior to the first dose and/or intent on using any investigational drug for the duration of the trial until 4 months after visit 8 is prohibited.

No interaction studies have been performed in humans, however, as described in the SmPC the effect of the most frequently used concomitant medicinal products in patients with psoriasis (including paracetamol, ibuprofen, acetylsalicylic acid, metformin, atorvastatin, levothyroxine) on the pharmacokinetics of Ustekinumab was explored with no indication of an interaction for at least 100 patients.

The pharmacokinetics of Ustekinumab was not impacted by concomitant use of methotrexate, NSAIDs, 6-mercaptopurine, azathioprine and oral corticosteroids, or prior exposure to anti-TNFα agents, in patients with psoriatic arthritis or Crohn's disease.

The results of an *in vitro* study do not suggest the need for dose adjustments in patients who are receiving concomitant CYP450 substrates.

8.9 Concomitant medication

All medications/supplements that the participant has taken from 3 months before the first dose of IMP will be recorded and assessed against the eligibility criteria in section 6.

At subsequent visits all changes to concomitant medications will be recorded and assessed against the eligibility criteria.

8.10 Trial restrictions

IMP should not be administered if a participant has had a febrile illness within the last 3 days as this may activate T cells non-specifically. Under these circumstances, the missed study visit should be delayed to the earliest next feasible date (but no longer than 1 week) and the study continued.

All females will have a urine pregnancy test at screening and all study visits. All participants will be advised that if sexually active they must use adequate contraception (hormonal based contraception, double barrier contraception, abstinence) until 4 months following the date of their final treatment of IMP.

8.11 Assessment of compliance with treatment

At all clinic/home visits the research nurse will administer the IMP assigned to that participant based on their weight at the previous visit where weight was recorded. Amounts and dosages given to each participant group will be in accordance with the protocol.

If the participant or their parent/carer feel that their weight has changed significantly which would potentially change their treatment dose, the next dosing visit should take place in the hospital setting where they can be weighed beforehand to provide a more accurate measure for the prescription if pharmacy are able to accommodate this. Other means of reweighing the participant prior to the visit should be considered to ensure an accurate dose is provided. Any increases in weight when the participant is already on the maximum dose need not result in reweighing the participant urgently.

The research nurse will record the details of the IMP administration, along with any issues arising.

8.12 Non-Investigational Medicinal Product (NIMP)

Insulin: daily insulin use over 7 consecutive days during the 2 weeks preceding all visits will need to be recorded by participants. Participants may use long-acting, intermediate-acting, regular, and/or very short-acting insulin. Use of an insulin pump is permitted but not required. Insulin dosage may be changed and insulin therapy may be stopped or re-started whenever necessary to help the participant achieve and maintain optimum glycaemic control. The use of inhaled insulin is not permitted for the duration of the trial.

For detail on dose modification, please see section 8.7.

9. PHARMACOVIGILANCE

9.1 Definitions

Term	Definition
Adverse Event (AE)	Any untoward medical occurrence in a participant to whom a medicinal product has been administered, including occurrences which are not necessarily caused by or related to that product.
Adverse Reaction (AR)	An untoward and unintended response or reaction in a participant to whom any dose of IMP has been administered in the trial and is considered as having a reasonable causal relationship to the IMP. ARs may be classified as: **Expected**: AR is consistent with the AR profile of the medicinal product as listed in the trial protocol, Investigator Brochure (IB), or Summary of Product Characteristics (SmPC). **Unexpected**: AR is not consistent with the AR profile expected in the trial protocol, IB or SmPC **OR** the documented AR has occurred at a frequency or severity greater than expected.
Serious Adverse Event (SAE) or Serious Adverse Reaction (SAR)	Defined criteria for seriousness is any AE or AR in a trial participant at any dose which: • results in death • is life-threatening *(participant was at risk of death at time of event)* • requires hospitalisation or prolongation of existing hospitalisation *(any inpatient admission regardless of length of stay)* • results in persistent or significant disability or incapacity • consists of a congenital anomaly or birth defect • Any other important medical event not immediately life threatening, result in hospitalisation or death, but may jeopardise the participant or require intervention to prevent one of the other outcomes listed above Medical judgement by the PI/CI or medical delegate should be exercised in deciding whether an AE or AR is serious. **NOTE**: The term "life-threatening" in the definition of "serious"* refers to an event in which the participant was at risk of death at the time of the 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)	Any AR classed as serious and possibly, probably or definitely caused by the IMP, but not consistent with the known profile of the IMP as detailed in the SmPC and set out in the reference safety information: For this trial of Ustekinumab section 4.8 of the SmPC is used as the reference safety information.

***NB:** to avoid confusion or misunderstanding of the difference between the terms "serious" and "severe", the following note of clarification is provided: "Severe" is often used to describe intensity of a specific event, which may be of relatively minor medical significance. "Seriousness" is the regulatory definition supplied above.*

Product Quality Complaint (PQC): Any written, electronic, or oral communication that alleges deficiencies related to the identity, quality, durability, reliability, safety, effectiveness, or performance of a product after it is released for distribution. A complaint is any indication of the failure of the product to meet consumer or user expectations for quality or to meet performance specifications. It may allege an adverse reaction, injury, or malfunction associated with the use of the product. It may also involve the design, literature, packaging, advertising, availability, physical appearance, or promotion of a product.

Special Reporting Situations which must be reported are:

- drug exposure during pregnancy (paternal, maternal)
- suspected transmission of any infectious agent via administration of a Janssen medicinal product
- exposure to a Janssen medicinal product from breastfeeding
- overdose of a Janssen medicinal product, medication error involving a Janssen medicinal product (with or without patient exposure to the Janssen medicinal product, e.g., name confusion)
- suspected abuse/misuse of a Janssen medicinal product,
- unexpected therapeutic benefit,
- inadvertent or accidental exposure to a Janssen medicinal product

9.2 Operational definitions for (S)AEs

The risk of major adverse unexpected events is anticipated to be low, as Ustekinumab has a marketing authorisation in the age group being studied for another indication (psoriasis). There is therefore wide experience with drug exposure and it has been found to be well tolerated. The available SmPC describes all essential information for the use of the medicine, and the qualitative and quantitative information on benefits and risks.

However, it is noted that participants being exposed to Ustekinumab are a different disease population from those described in the SmPC (new onset T1D rather than psoriasis, psoriatic arthritis or Crohn's disease). In addition, the dose used in this trial is higher than that currently licensed for psoriasis in adolescents, although it (and higher doses) have been used in adults with both psoriasis and Crohn's disease.

Expected AEs – the expected AEs from the IMP are listed in section 9.4. Hypoglycaemic events are frequent in this disease population and may not necessarily be IMP related. Hypoglycaemia rates are an important secondary outcome, as it is anticipated that these should be reduced by the intervention if effective.

Anticipated SAEs will be recorded for the duration of the trial but will not be considered as SUSARs unless the severity and/or frequency of the event is considered unexpected.

9.2.1 Reporting procedures

All AEs will be recorded on an AE log and added to the database.

All SAEs must be reported on an SAE form to the CI and the Trial Office by the PI or delegate no later than 24 hours of awareness of the event (see Appendix 6 for details). Initial reports should be submitted as soon as any of the following minimum criteria are met:

- A suspected SAE is identified;
- A participant is identified (trial ID);
- An AE has occurred that is assessed by a qualified delegated person as serious and unexpected, and for which there is a reasonable suspected causal relationship (a potential SUSAR);
- A recognised reporting source is identified (e.g. clinical research fellow).

Following the initial report, all SAEs should be followed to resolution with follow up SAE forms submitted. The PI may be requested to provide further information. The PI is also responsible for reporting AEs to their NHS Trust as per their local NHS Trust procedures.

9.2.2 Sponsor and Chief Investigator Responsibilities

The Sponsor (or delegate) is responsible for ensuring all SAEs, SARs and SUSARs (except those specified in this protocol as not requiring reporting) will be reported in the appropriate timescale to the MHRA and REC (see Appendix 7 for details).

Once an SAE is sent by the PI or delegate, the CI (or appropriate delegate) will complete a clinical review (assessment of causality and expectedness) within 24 hours of receipt. The assessment will be notified to the site and the Trial Office in accordance with the Clinical Review Form.

Only SUSARs should be expedited to MHRA and REC. They will be reported according to the following timelines:

- Fatal and life threatening SUSARs not later than 7 days after receipt;
- Non-fatal or non-life-threatening SUSARs not later than 15 days after receipt.
- Follow up information should be reported within 8 days of receipt of the follow up information.

A copy of the SUSAR report should be provided to the Sponsor.

In addition to reporting to the REC and MHRA, SUSARs will also be reported to all members of the TMG and the DSMB and to Janssen as part of IMP supply contract requirements. The CI shall ensure that all co-investigators receive regular safety updates of SAE's and SUSARs that occur in relation to the IMP in the trial.

Dose interrupting and suspension of dosing will be managed as per the risk mitigation, see section 7.

9.3 Serious Adverse Events

SAEs will be recorded from the time the participant consents to join the trial until visit 8. It is the responsibility of the PI or delegate to review all documentation (e.g. medical notes, laboratory and diagnostic reports) related to the event. The Investigator should record all relevant information on a trial SAE form.

9.3.1 Specification, timing and recording of safety parameters

The major associated eligibility and safety parameters are evidence of induction of unexpected adverse events and/or accelerated beta cell loss. To address general safety concerns at screening and selected visits, a physical examination will be conducted.

A review of AEs will be performed at all visits and eligibility/safety bloods will be drawn at screening and 0, 12, 28 and 52 weeks to examine the full blood count; urea, electrolytes and creatinine; liver function tests; (total bilirubin, total protein, albumin, AST (SGOT), SGPT (ALT), alkaline phosphatase; thyroid stimulating hormone; immunoglobulins (G, A, M); calcium; magnesium, phosphate, lipid profile (total cholesterol, LDL, HDL, triglyceride). Urinalysis for pH, protein and albumin/creatinine ratio will be done at screening and 0, 12, 28 and 52 weeks. A urine pregnancy test will be completed on all females at all trial visits. PIs will be expected to assess any values outside the laboratory reference range for clinical significance.

9.3.2 Disease exacerbation

Clinical assessment for disease exacerbation will be increases in insulin use and insulin dose adjusted HbA1c (IDAAC – defined as A1C (%) x [4 x insulin dose (units per kilogram per 24 h)] [35]. Data on these parameters will reviewed by the DSMB.

Laboratory tests for exacerbation of beta cell specific autoimmunity are:

- Measurement of islet cell autoantibodies (against insulin, GAD-65, IA-2 and ZnT8) at weeks 0, 28 and 52.
- Measurement of pro-inflammatory β-cell specific T cell responses weeks 0, 12, 28 and 52.
- Measurement of secreted C-peptide AUC after MMTT will be done at weeks 0, 28 and 52.

However, these assessments will not be measured by the laboratories in "real time", hence the data will not be available for review by the DSMB.

9.4 Assessing AEs

All participants will be asked by the research nurse about new or unexpected symptoms at each follow-up visit. The patient diary will also be checked for any illnesses or diagnoses since the last study visit.

Details of AEs will be recorded from screening visit 2 until visit 8, evidencing 8 weeks post the final dose.

Below are listed AEs that are considered expected for newly diagnosed T1D patients. If the events lead to death, that would be considered unexpected. These events may be classified and recorded as serious events but will not require immediate reporting to the REC:

- Hypoglycaemia

- Diabetic Ketoacidosis

All other AEs will be assessed for seriousness and causality in relation to the IMP (see Appendix 6). The PI should exercise medical judgement in deciding whether an Adverse Event/Reaction is serious.

The PI will grade all AEs in relationship to the study treatment according to their clinical judgement as follows:

a) Causality

- **Unrelated**: where the AE is not considered to be related to the investigational medicinal product.
- **Possibly**: although a relationship to investigational medicinal product cannot be completely ruled out, the nature of the event, the underlying disease, concomitant medication or temporal relationship make other explanations possible.
- **Probably**: the temporal relationship and absence of a more likely explanation suggest the event could be related to the investigational medicinal product.
- **Definitely**: the known effects of the investigational medicinal product or its therapeutic class, or based on challenge testing, suggest that the investigational medicinal product is the most likely cause.

***Note**: that neither CI nor Sponsor can downgrade a PI causality assessment, however, upgrading of an event is possible. In the event of differing opinions during assessment, BOTH must be provided on reports.*

b) Expectedness

If an event is judged to be an AR/SAR, the evaluation of expectedness will be made using the reference safety information below as based on knowledge of the reaction and the relevant product information documented in section 4.8 of the SmPC.

In summary, the expected side effects of Ustekinumab are:

• Infections and infestations	○ Upper respiratory tract infection, nasopharyngitis
• Nervous system disorders	○ Dizziness, headache
• Respiratory, thoracic and mediastinal disorders	○ Oropharyngeal pain
• Gastrointestinal disorders	○ Diarrhoea, nausea, vomiting
• Skin and subcutaneous tissue disorders	○ Pruritus
• Musculoskeletal and connective tissue disorders	○ Back pain, myalgia, arthralgia
• General disorders and administration site conditions	○ Fatigue, injection site erythema, injection site pain

Adverse event reporting, including SUSARs will be carried out in accordance with the applicable regulations.

All sites involved in the trial will inform the trial office of any SAEs within 24 hours to ensure that appropriate safety reporting procedures are followed by the Sponsor.

Safety data will be continuously monitored throughout the study via Adverse Event logs and Case Report Forms. Specific data items will include adverse events observed at each dosing visit (Weeks 0, 4, 12, 20, 28, 36, 44) and follow-up visit (week 52) e.g. hypoglycaemic episodes; injection reactions (fever, chills, headache, nausea, vomiting and injection site pain); hypersensitivity reactions (signs and symptoms of anaphylaxis, angioedema, wheezing, dyspnoea, urticaria, and hypotension). Other adverse events to be collected will include evidence of infection (EBV, CMV, TB or opportunistic bacteria); and evidence of posterior leukoencephalopathy syndrome.

9.5 Recording and reporting of SAEs, SARs AND SUSARs

All **SAEs** occurring from the time of consent until eight weeks post cessation of trial treatment (visit 8) must be recorded on the trial SAE form as appropriate and faxed or emailed to the CI and the Trial Office within 24 hours of the research staff becoming aware of the event (see Appendix 6). The CI should be contacted using the number

on the SAE Form to alert him to the SAE Form as quickly as possible. The Trial Office will acknowledge receipt of the forms within 2 working days. Once all resulting queries have been resolved, the Trial Office will request the original form and a copy to be retained on site. Posting of SAE forms to the Trial Office will be completed periodically.

Any change of condition or other follow-up information should be sent to the Trial Office as soon as it is available, but no later than 24 hours of the information becoming available. Events will be followed up until the event has resolved or a final outcome has been reached.

All SAEs will be forwarded to Janssen by the Trial Office in accordance with contract requirements. The Trial Office will submit the following safety information:

- all Serious Adverse Events
- special reporting situations including pregnancy reports (including reports unblinded as to treatment for blinded studies)
- product quality complaints (PQCs) in clinical trials involving the Study Products (Ustekinumab) regardless of whether causality with the administration of the Study Products is suspected by the investigator.

The Sponsor or delegate (STU) will transmit SAE reports by facsimile to +44 1494 567799 in English within 24 hours of becoming aware of the event(s). Follow-up information will be transmitted within the same timelines.

All SAEs assigned by the CI or delegate (or following central review) as both suspected to be related to IMP treatment and unexpected will be classified as SUSARs and will be subject to expedited reporting (see Appendix 7) to the MHRA. The Sponsor will inform the MHRA, the REC and Janssen of SUSARs within the required expedited reporting timescales.

9.6 Responsibilities

9.6.1 Principal Investigator (PI):

- Checking for AEs and ARs when participants attend for treatment / follow-up.
- Using medical judgement in assigning seriousness, causality and whether the event/reaction was anticipated using the RSI approved for the trial.
- Ensuring that all SAEs are recorded and reported to the Trial Office within 24 hours of becoming aware of the event and provide further follow-up information as soon as available.
- Ensuring that SAEs are chased with the Trial Office if a record of receipt is not received within 2 working days of initial reporting.
- Ensuring that AEs and ARs are recorded and reported to the Trial Office in line with the requirements of the protocol.

Appendix 9 summarises the role of a trial site.

9.6.2 Chief Investigator (CI) / delegate or independent clinical reviewer:

- Clinical oversight of the safety of patients participating in the trial, including an ongoing review of the risk / benefit.
- Using medical judgement in assigning the SAEs seriousness, causality and whether the event was anticipated (in line with the RSI) where it has not been possible to obtain local medical assessment.
- Using medical judgement in assigning whether an event/reaction was anticipated or expectedness in line with the RSI.
- Immediate review of all SUSARs.
- Review of specific SAEs and SARs in accordance with the trial risk assessment and protocol as detailed in the Trial Monitoring Plan.
- Reviewing Medical Dictionary for Regulatory Activities (MedDRA) coding to all SAEs and SARs proposed by STU.
- Preparing the clinical sections and final sign off of the Development Safety Update Report (DSUR).

9.6.3 Sponsor: (NB where relevant these can be delegated to CI and Trials Unit)

The sponsor retains responsibility for the oversight of the trial but will delegate tasks to the CI and STU.

9.6.4 Trial Steering Committee (TSC):

In accordance with the Trial Terms of Reference for the TSC, periodically reviewing safety data and liaising with the DSMB regarding safety issues.

9.6.5 Data Safety & Monitoring Board (DSMB):

In accordance with the Terms of Reference for the DSMB, periodically reviewing overall safety data to determine patterns and trends of events, or to identify safety issues, which would not be apparent on an individual case basis.

The PI will be required to report all SAEs which occur during the Trial on an SAE Form and keep a record of AEs in the case report form (CRF). AEs will be collected from the time the participant receives their first dose of IMP until the last visit (visit 8, week 52). The AEs will be reported at agreed intervals to the DSMB and if there is any concern a DSMB meeting will be convened.

9.6.6 Trial Management Group (TMG):

The TMG will ensure all aspects of regulatory approval are in place. The TMG will report at agreed intervals to the TSC, DSMB and to the study Sponsor. The CI, as the chair of the TMG, will ensure DSUR and APRs are completed and SUSARs reported within required regulatory timelines.

Appendix 10 summarises the role of the TMG in trial management.

9.7 Notification of deaths

All deaths that occur during the trial between screening and visit 8 will be recorded.

Deaths that are assessed to be caused by the IMP will be reported to the MHRA and REC within 7 days of notification.

Deaths that do not constitute a SAR or SUSAR will be recorded and reported in the DSUR and Annual Progress Report (APR).

The CI will ensure that required APRs and sent to the REC and the MHRA within the timelines defined in the Regulations.

9.8 Pregnancy reporting

9.8.1 Pregnancy Exposure in Patients Receiving Ustekinumab

Data from Janssen-Cilag Ltd indicated that there have been 417 maternal exposures to Ustekinumab during pregnancy. 109 resulted in live births with no defects or AEs, 8 had live births with AEs or congenital defects, 28 were elective terminations, 45 spontaneous abortions, 7 premature births, 1 unspecified abortion, 1 ectopic pregnancy and 218 with unknown outcome.

Of the 180 paternal exposures to Ustekinumab during pregnancy, 95 resulted in live births without AEs, congenital anomaly or birth defect, 11 live births with congenital anomaly, birth defect or AEs, 2 elective termination, 11 spontaneous abortions, 2 neonatal deaths, 2 premature births and 57 with an unknown outcome.

In the Psoriasis Clinical Development program, in the 26 pregnancies with known outcomes, the rate of live births, elective and spontaneous abortions were comparable to rates reported in the US general population.

The effects of Ustekinumab on human fertility have not been evaluated.

9.8.2 Pregnancy Precautions

The SmPC for Ustekinumab does not have adequate data for the use of Ustekinumab in pregnant women or the female partners of male participants.

All female participants will be tested for pregnancy at each visit. Sexually active participants will be advised to use effective methods of contraception during treatment and for 4 months after the last dose.

It is unknown whether Ustekinumab is excreted in breast milk or if it would be absorbed systemically after ingestion. Because of the potential for ARs in nursing infants breast feeding is an exclusion criteria.

Following a live birth, the 'normality' of the new born can be assessed at the time of birth. The 'normality' of an aborted foetus can be visually assessed, unless pre-abortion test findings are suggestive of a congenital anomaly.

As a precautionary measure due to the participant population being aged 12-18 and the associated risks where the mother is not fully mature all children born will be surveyed for their first 12 months [36] with the permission of the participant (or their parent/carer if they are aged <16y when the pregnancy is confirmed). Further follow up of birth outcomes will be assessed on a case-by-case basis. It is advised that babies exposed to biologics like Ustekinumab *in utero* should not receive live vaccines before the age of 1 year.

All neonatal deaths that occur within 30 days of birth shall be assessed for potential relatedness to exposure *in utero* to the IMP.

9.8.3 Pregnancy Reporting Procedure

Pregnancy in either a participant or the partner of a participant taking IMP must be recorded on a pregnancy reporting form and reported to the Trial Office and CI within 24 hours of awareness.

Pregnant participants will be withdrawn from IMP dosing and encouraged to attend trial visits to collect trial data to pregnancy completion.

Pregnant participants and pregnant partners of male participants will be given an information sheet and consent form to request permission to follow up the pregnancy until completion and the child for 12 months. Should the participant or pregnant partner not wish for the pregnancy outcome to be followed this should be noted in the CRF and medical notes as appropriate.

Pregnancy is not considered an AE unless a negative or consequential outcome is recorded for the mother/foetus. If the outcome meets criteria for classification as a SAE, the procedures for reporting SAEs should be followed.

Pregnancy in participants (female or the female partner of a male participant) who are under 16y old will be automatically referred to the safeguarding team at their local hospital as per local NHS procedures. The trial will not be responsible for any safeguarding activities themselves.

9.9 Overdose

Ustekinumab dose will be calculated by healthcare professionals and confirmed by pharmacists according to relevant standard operating procedures. IMP will be administered by a qualified healthcare provider in either a clinical or home setting thus overdose will be unlikely to occur.

9.10 Reporting urgent safety measures

The CI and PIs may take immediate safety measures to protect research participants against any hazard to their health or safety without prior authorisation form the REC or sponsor. The Sponsor, CI and Trial Office must be alerted to an urgent safety measure as soon as possible.

The CI shall be responsible for discussing any urgent safety measures with the MHRA safety scientist by telephone ideally within 24 hours of implementation. The CI will notify the MHRA, REC and local R&D department in writing within 3 days of the urgent measure describing the reasons for the measure and plan for further action (see Appendix 8).

9.11 The type and duration of the follow-up of participants after adverse reactions.

Any SUSAR will require reporting to the Sponsor irrespective of how long after IMP administration the reaction occurred.

The drug being used is approved for use in the proposed age group – 12-18 year olds – for a different indication (psoriasis) and reported risks are low. In this trial, the drug will be used at higher dose, which is not licensed in this age group, but has been used in adults and trialled in children with inflammatory bowel disease, In addition, it is being used for a new indication (type 1 diabetes).

9.12 Development safety update reports

An annual Development Safety Update Report (DSUR) will be submitted to the MHRA and REC listing all SARs and SUSARs. The CI (or delegate) is responsible for submitting this report on the anniversary of the Clinical Trial Authorisation approval.

10. STATISTICS AND DATA ANALYSIS

Data cleaning and preparation processes will be carried out prior to final analysis. A statistical analysis plan (SAP) with be produced separately, see 10.3 for more details.

All participants enrolled will be followed up and included unless they withdraw from the study before the administration of the first dose. An intention to treat analysis will be carried out. Per protocol analysis of the primary outcome may also be carried out alongside the intention to treat analysis if deemed necessary by the TSC.

The primary data analysis will be the application of analysis of covariance to the 12 month recorded AUC mean values of C-peptide taking into account the baseline values of these measures and using transformations as suggested by Lachin et al [37]. The analysis will be by intention to treat and adjusted by important covariates such as gender, age at recruitment, baseline insulin use and glycaemic control.

For the secondary outcomes including the mechanistic and PROM studies we will evaluate the various outcomes using the most appropriate statistical approach i.e. binomial or logistic regression for binary outcomes, Poisson or related count outcome models for number of events/objects and linear models for continuous outcomes. Where necessary mixed or multilevel models will be used to account for correlation within observations. No interim analysis is planned.

10.1 Sample size calculation

The power calculation follows Lachin [37] based on data for children or adolescents aged 13-17.

A sample size of 66 apportioned in a 2:1 ratio has > 85% power to detect a 0.2pmol/ml difference between MMTT AUC C-peptide values of the intervention and control arms which are assumed to be 0.5 and 0.3 (pmol/ml) respectively at twelve months. Seventy- two participants (48 active: 24 placebo) will be recruited to allow for an approximate 10% loss to follow-up.

10.2 Planned recruitment rate

Recruitment for the trial will be conducted by the UK Type 1 diabetes immunotherapy Consortium (www.type1diabetesresearch.org.uk), a network for trial sites including paediatric (recruiting age 12-16) and adult (recruiting age 16-18) research teams. Recruitment will be assisted by the ADDRESS-2 network (www.address2.org) which currently identifies new onset T1D cases from > 140 hospitals in the UK.

The planned approach to recruitment is derived from data from the following sources:

- The Brecon registry of new onset T1D in children in Wales;
- ADDRESS-2 recruitment data; recruitment to the SCIPI study of insulin pump therapy in new onset T1D in children (courtesy of the SCIPI investigators);
- the DECIDE study in new onset children (CI- Prof Gregory);
- recruitment to the Monopeptide study peptide immunotherapy of new-onset adults with T1D (CI – Prof Dayan);
- published data on recruitment to the Diabetes TrialNet immunotherapy study of MMF and Daclizumab in T1D [38].

Identification of newly-diagnosed T1D participants aged 12-18 years identified by the ADDRESS-2 network each month for 2016-7 was an average 21/month = 252 per year; this is estimated to represent around 1/3 of all new cases in the UK. Using the other data sources, we estimated that around 40% of the ADDRESS-2 cases are adjacent to one of our study centres. We propose to recruit for screening 35% of identified cases, amounting to 3-4 cases per month across all sites or 1 every 3-4 months per study centre (3-4 per year per study centre). This is higher than in some studies but equivalent to that seen with adults in the Monopeptide study [39] and we believe is achievable because:

a) Our sites are active in this area.
b) Some individuals from ADDRESS-2 may be willing to travel greater distances.
c) Additional participants will be recruited directly through the Consortium website and the generic study video as well as the trial specific video (both aimed at the adolescent age group) which will be promoted through social media.
d) Glucose monitoring will be offered free of charge to all participants.

e) The protocol has been designed with PPI input to be of low burden – all visits are scheduled either at home or to coincide with the expected time of a clinic visit.
f) We have the support of the BSPED Children's clinical study group and the recently formed Diabetes UK T1D clinical study group (Prof Dayan, Chair) to promote recruitment.

Using these estimates, we anticipate screening 88-105 subjects over 24 months. From the previous studies we expect a dropout rate of 20% prior to randomisation due to absence of autoantibodies, inadequate c-peptide levels and other reasons, providing 72 patients in an average of 24 months. In the event that recruitment is too slow, the study is of low enough risk to be conducted in DGH departments and additional study centres will be added. Drop out after screening and after randomisation was low in all the studies referred to above (< 10%).

10.3 Statistical Analysis Plan

A version-controlled SAP will be produced and agreed to prior to the completion of recruitment to address the research question and to generate a CONSORT compliant report.

All analysis will be by intention-to treat and detailed in the SAP. Participants will be analysed "as randomised" i.e. according to the group they were originally allocated. Outcome data obtained from all participants will be included in the data analysis, regardless of protocol adherence.

The finalised SAP is a detailed description of the planned analyses and will contain as a minimum the following items:

- Short synopsis of the trial background, research question and study objective
- Study methods
- Presentation of data for analysis
- Statistical principles
- Study population
- Analysis strategy for primary outcome, secondary efficacy and safety outcomes and mechanistic analyses
- Amendments made and reasons
- Statistical software to be used
- References

Any changes between the methods in the protocol and SAP will be explained in the SAP and an assessment made of the need for a protocol amendment.

10.3.1 Summary of baseline data and flow of patients

Baseline comparability of the randomised group will be assessed in terms of gender, age and the baseline values of all parameters described in section 7.6. Baseline values will be used as covariates to adjust for comparisons between treatment arms.

10.3.2 Primary outcome analysis

MMTT C-peptide AUC values will be assessed at 52 weeks using analysis of covariance, adjusted for covariates including baseline MMTT C-peptide values, baseline insulin use and glycaemic control HbA1c at screening, gender and age.

10.3.3 Secondary and tertiary outcome analyses

Secondary and tertiary outcome analyses will be detailed in the SAP and are summarised in Table 1 in section 6.

10.4 Subgroup analyses

No subgroup analysis is planned. Should there be substantial non-fidelity to allocated treatment, a per-protocol analysis for the primary outcome will be considered after approval by the Trial Steering Committee.

10.5 Adjusted analysis

Efficacy analyses will be adjusted by gender, age and baseline test values. Safety analysis will not be adjusted.

10.6 Interim analysis and criteria for the premature termination of the trial

No interim analysis on primary and secondary outcomes is planned. Interim analysis on safety will be conducted if requested by TSC/DSMB. Decision criteria based on safety as part of a guideline for early stopping or other adaptations will be set by TSC with input from DSMB.

10.7 Participant population

All randomised participants will be included in trial analyses and analysed according to treatment allocated. Participants randomised who do not complete the study will, as far as possible, be included in trial analyses.

10.8 Procedure(s) to account for missing or spurious data

Every attempt should be made to minimise missing data, encouraging subjects to provide week 52 data even if they are no longer taking the interventional medication. Patterns and level of missing data will be examined. Multiple imputation will be considered if required, if there are more than 5% [13] and less than 10% [14] (>3 and <7 participant) missing.

10.9 Other statistical considerations.

Assessment of pharmacokinetics and anti-drug antibodies

Serum samples will be taken at the time of mechanistic blood draws at times 4, 12, 28 and 52 weeks for measurement of Ustekinumab drug levels and anti-drug antibodies by an external contractor.

10.10 Economic evaluation

No health economic evaluation is planned.

11. DATA MANAGEMENT

11.1 Data collection tools and source document identification

Source documents produced for this trial will be filed with the participant's medical records. Source data will be entered into trial-specific database of electronic Case Report Forms (eCRFs) at the end of each trial visit within a site agreed timespan. These eCRFs will be coded with the participants study number and will not include patients' names and addresses. This database will be hosted on a Swansea University server with back up and restoration procedures in place.

The Investigator Site File (ISF) containing original signed informed consent forms will be kept in secure premises. Access to the ISF will be restricted to researchers working on the trial, Sponsor representatives and representatives of regulatory authorities required to audit the conduct of the research study.

Participant data will be anonymised by the use of study numbers. A copy of the study number code identifying participants will be kept securely within the ISF. Minimal identifiable data to link participants' names, their study number and to send them relevant trial information will be stored separately from the ISF. Electronic data containing personalised information will be saved on Swansea University computers in password protected files with access restricted to those who can be unblinded.

11.2 Data handling and record keeping

The trial electronic database will be managed and operated as required by GCP. The site investigator or delegate will record all study data using the trial specific electronic database provided by STU. This also applies to data for those patients who consented but were not included in the study. Patients who were approached but not consented are to be added to the screening log. The PI is responsible for keeping a list of all consented patients. In addition the investigator will prepare a list of patients who were screened for participation of the trial but were not randomised and the reason for non-eligibility. The investigator will ensure accuracy, completeness, and timeliness of the data entered on to the eCRFs. All data will be handled and stored in accordance with the Data Protection Act or applicable legislation.

Data will be checked according to the trial Data Management Plan and queries will be generated and sent to the site investigator for response using the electronic database. Corrections resulting from these queries will be confirmed and sent back to STU. The queries and their responses will be stored in the audit trail of the electronic database.

Data from laboratories and the anonymised glucose monitoring and diary data from patients will be securely transferred to STU for mapping with the trial database (see Appendix 5).

Data will be transferred to KCL for specialist analysis at the end of the trial once the database has been locked and an exploratory data analysis plan has been approved by the TSC and TMG.

11.3 Access to Data

The Investigator(s) will permit trial-related monitoring, audits, REC review, and regulatory inspections by providing direct access to source data and other documents (i.e. patients' case sheets, blood test reports, X-ray reports, histology reports, etc).

11.4 Archiving

CI, will act as custodian of the trial data, however this role will be delegated to STU. Personal data will be stored for a minimum of 15 years. Access will be controlled by the CI who will continue to act as custodian for all data held by the Sponsor and will permit trial related monitoring, audits, REC review, and regulatory inspections.

The TMF will be archived for 25 years. Sites will be expected to archive their ISF locally. Trial samples and material will be stored in accordance with HRA guidance during the trial. Samples will be transferred to a biobank if consent has been obtained for storage for continued use/further analysis after the trial end according to HTA guidance.

Destruction of the TMF and individual ISF's will require authorisation from the Sponsor.

12. MONITORING, AUDIT & INSPECTION

Monitoring of this trial to ensure compliance with Good Clinical Practice (GCP) and scientific integrity will be conducted by STU via central and on-site monitoring as per the data and trial monitoring plans.

This will include 100% central monitoring of all primary outcome data, with site initiation and closedown visits for all sites, and a minimum of one monitoring visit during the recruitment period to complete 100% SDV on primary outcome data in accordance with the trial monitoring plan. In addition, the trial office will facilitate monitoring by local R&D departments at any of the trial sites, should this be requested.

Principal Investigators and sites involved in the trial will permit trial monitoring, audits and regulatory inspection(s). In the event of an inspection, the site will enable direct access to representatives of the Sponsor and regulatory authorities as detailed in the site agreement.

13. ETHICAL AND REGULATORY CONSIDERATIONS

13.1 Research Ethics Committee (REC) review & reports

The trial will be conducted in accordance with the principles of GCP.

For all nations, a favourable ethical opinion will be obtained from an appropriate REC and local NHS R&D approval will be obtained at each site. Before the start of the trial all participant facing documents and the trial protocol will be submitted to the HRA for approval at all sites within England (and the equivalent organisations for Wales and Scotland).

A Clinical Trial Authorisation (CTA) will be sought from the UK regulatory authority (MHRA).

No substantial amendment will be implemented until they have received a favourable opinion from the HRA, REC or MHRA as appropriate. Non substantial amendments will be sent to the HRA using the appropriate template. Sites will be notified of the outcome of the amendment via the trial office prior to implementation.

An Annual Progress Report (APR) and Development Safety Update Report (DSUR will be sent by the CI to the REC and MHRA respectively within 30 days of the anniversary of the favourable opinion or CTA as appropriate until trial end. The CI will notify the REC and MHRA within 30 days of the end of the trial (or 15 days if the trial terminates early).

Within 12 months of trial end the CI will submit to the REC a final report, using the appropriate template indicating the results of the trial, including copies of any publication or abstracts.

All correspondence and submission details will be filed in the TMF.

13.2 Peer review

The Detailed Descrpiton of the Project which summarises the principles of the trial has received an independent and expert peer review by NIHR-EME as the funders of the trial (Reference 16/36/01).

The sponsor will also conduct a proportionate governance and risk assessment of the protocol prior to accepting the role.

13.3 Public and Patient Involvement (PPI)

Young people and their families were involved in the design of the trial. Open meetings involving 15-20 families were held at the initial stage to define key design points in the protocol that would influence trial involvement. Three families with children with T1D aged 14-16 then took part in a focus group to discuss the protocol design in more detail, using an interactive format and “turning point” private voting technology. The patient information sheet and video patient information were each also subsequently reviewed by 2-3 young people with T1D and their families from the Diabetes Research Unit Cymru (DRUC) Public Reference Panel. Their comments were included in formulating the final documents.

Parents and young people have already been involved in the design of the research. As recent trials in new-onset T1D have been slow to recruit, and following our PPI work so far on recruitment issues, we have prepared a generic information video and website targeted to young people. (type1diabetesresearch.org) in partnership with eHealth Digital Media Ltd (http://ehealthdigital.co.uk) and the PPI panel. A study-specific video will also be available to potential participants.

Patient representative(s) will be recruited from Involving People Network, Involve and the DRUC Public Reference Panel and will be involved in either the TMG meetings or the TSC meetings and will be asked to:

1. Comment on patient facing materials
2. Trouble shooting to support recruitment and retention of participants;
3. Reporting the final results to the trial participants;
4. Preparing information for web site inclusion.
5. Disseminate findings to a wider audience
6. Help set the agenda for future research in this field

Training and support for our patient representatives will be flexible and tailored to their individual needs. It will include training on the study background, methods and outcomes and where indicated IT training will be provided. Patients will be reimbursed in line with HCRW's AcoRD guidance (Attributing the costs of Health and Social Care Research & Development). PPI representatives will be supported by the DRUC Public Reference Panel.

As this is a study of adolescents (age 12-18), patient involvement will focus on young people in or near the target age range and their parents/carers. Separate groups of young people and carers will be consulted to ensure that the young people can contribute freely.

At the key analysis points e.g. end of one year follow up and final analysis, we will present to a convened panel of parents, children and others with T1D for advice on improvements and troubleshooting.

Our partners, Juvenile Diabetes Research Foundation, Diabetes UK, The Type1 Diabetes Consortium and DRUC will be involved to identify key messages and use social media for dissemination of findings.

13.4 Regulatory Compliance

The trial will be conducted according to the protocol and in compliance with the principles of the Declaration of Helsinki (2013), the principles of Good Clinical Practice (GCP) and in accordance with Medicines for Human Use (Clinical Trials) Regulations 2004, and all subsequent amendments, the UK policy framework for health and social care research (2017), and other regulatory requirements as appropriate. The Protocol will be submitted for approval by an NHS Research Ethics Committee (REC) and to the Medicines and Healthcare products Regulatory Agency (MHRA) for a Clinical Trial Authorisation prior to the trial commencing. R&D permission will be gained from each site prior to any site being initiated.

13.5 Protocol compliance

The site PI is responsible for the overall conduct of the trial at the site and compliance with the protocol and any subsequent amendments.

In accordance with the principles of GCP, prospective, planned deviations or waivers to the protocol are not allowed under the UK Clinical Trial regulations and will not be used.

Accidental protocol deviations can happen at any time. In the event that a PI or delegate has deviated from the protocol, the nature of and reasons for the deviation will be adequately documented on a trial specific deviation forms and reported to the CI (via the trial office) and Sponsor within 24 hours of awareness.

Deviations from the protocol which are found to frequently recur are not acceptable, will require immediate action and could potentially be classified as a serious breach. All such instances will be investigated. Protocol amendments and reporting of the events will occur as required.

13.6 Notification of Serious Breaches to GCP and/or the protocol

A "serious breach" is a breach which is likely to effect to a significant degree –

- the safety or physical or mental integrity of the participants of the trial; or
- the scientific value of the trial

The CI (via the trial office) and the sponsor will be notified immediately of any case where the above definition applies during the trial conduct phase.

The sponsor of a clinical trial will notify the licensing authority in writing of any serious breach of the conditions and principles of GCP in connection with that trial, or the protocol relating to that trial, as amended from time to time, within 7 days of becoming aware of the serious breach

13.7 Data protection and patient confidentiality

At sites

Paper records will be kept in a locked cabinet in secure premises at all times when the record is not in use for a study visit. Access to the records will be restricted to researchers working on the study, Sponsor representatives and representatives of regulatory authorities required to audit the conduct of the research study.

Identifiable data including the link between the patients' names and the study number will be stored separately from other data in a secure cabinet at sites.

At Swansea Trials Unit

The electronic database will be stored and regularly backed up on a Swansea University server. All data files held at STU will be password protected.

Participant data will be anonymised on the database by the use of study numbers. Analysis will be conducted by the study team on anonymised data.

13.8 Financial and other competing interests for the chief investigator, PIs at each site and committee members for the overall trial management

At the time of writing the protocol no financial conflict or any other relevant connection or shared interest was declared for the CI, known site PIs, committee members or anyone involved in the trial management. Declarations confirming the absence of any conflict of interest will be signed for key personnel.

Janssen-Cilag supply IMP for the trial, while Abbott supply glucose monitoring devices. Neither have been granted, nor sought to obtain any financial or in kind advantage or reward for supplying the products. However, glucose sensors will be purchased from Abbott at cost price for the duration of the trial. Both parties will be contracted by the sponsor.

13.9 Indemnity

The sponsor, Cardiff University, has arranged appropriate insurance and indemnity to meet the potential legal liability for harm to the participants arising from the design or management of the trial for negligent harm. In addition, the trial health professionals hold substantive or honorary NHS contracts, giving them the protection of the appropriate NHS clinical negligence arrangements.

13.10 Amendments

Throughout the trial the TMG will decide whether any amendments to the trial are required.

The Trial Manager (TM) will complete an Amendment Assessment form which will include the following categories and this will be submitted to and reviewed, agreed and signed off by the CI and Sponsor:

a) Description of the amendment

b) Amendment Classification

c) Substantial Amendment category

d) Type of notification required

e) List of any updated documents e.g. protocol, PIS, ICF

f) Any additional action required e.g. update to other trial documents - Risk assessment form, Monitoring plan, CRF, Database)

Once the amendment assessment form is signed off, the TM will prepare and submit a valid notice of amendment to the relevant governing bodies for consideration.

For substantial amendments to the CTA, a valid notice of amendment to the licencing authority (MHRA) will be submitted for review.

For substantial amendments to the REC application or the supporting documents, a valid notice of amendment to the REC will be submitted for review.

Substantial Amendments will also be submitted to the HRA (England) and the relevant organisations in Wales and Scotland. Details of the amendment will be made available to participating R&D offices in the UK for impact review and contract revision as required (agreement of which should not delay implementation).

Once all relevant approvals are obtained, the amendment can be implemented.

Non-substantial amendments will be emailed to the HRA (England) and the relevant organisations in Wales and Scotland and may also be sent to REC and MHRA for information.

The Sponsor/CI is responsible for providing details of amendments and approvals including copies of revised documents, to all participating Investigators and study teams. This role will be completed by the TM.

The TM will maintain records of all amendments and version control of all trial documents.

The TM will communicate changes to relevant collaborators and update trial registries e.g. clinitrials.gov, ISRCTN, Clinical Research Portfolio.

13.11 Post trial care

Following completion of their trial participation, participants will be kept informed by newsletter of ongoing trial developments including final outcomes following statistical analyses. Should participants be concerned about implications arising from their trial participation, they will be asked to discuss these with their local clinicians. Senior members of the trial team (Profs Colin Dayan and John Gregory) will be available for further advice should the local clinician require.

Once the trial is complete, following unblinding, individual participants and their local clinicians will be informed by letter on request as to which arm of the trial they were randomised to and whether they received active Ustekinumab or placebo.

After completing the trial, clinical care and follow-up will be provided by the participant's local diabetes care team. Ustekinumab will not be available for ongoing therapy.

13.12 Access to the final trial dataset

The CI and trial statistician will have access to the final dataset. Should PIs or others require access to the final dataset this will require approval by the TMG, TSC and Sponsor.

14. DISSEMINATION POLICY

14.1 Dissemination policy

It is intended that the results of the study will be reported and disseminated at international conferences and in peer-reviewed scientific journals. Written feedback will also be provided to the study participants as described in section 13.

14.2 Authorship eligibility guidelines and any intended use of professional writers

Authorship will be agreed upon by the CI, PIs, and members of the TMG and will follow the guidance provided by the International Committee of Medical Journal Editors.

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16. APPENDICIES

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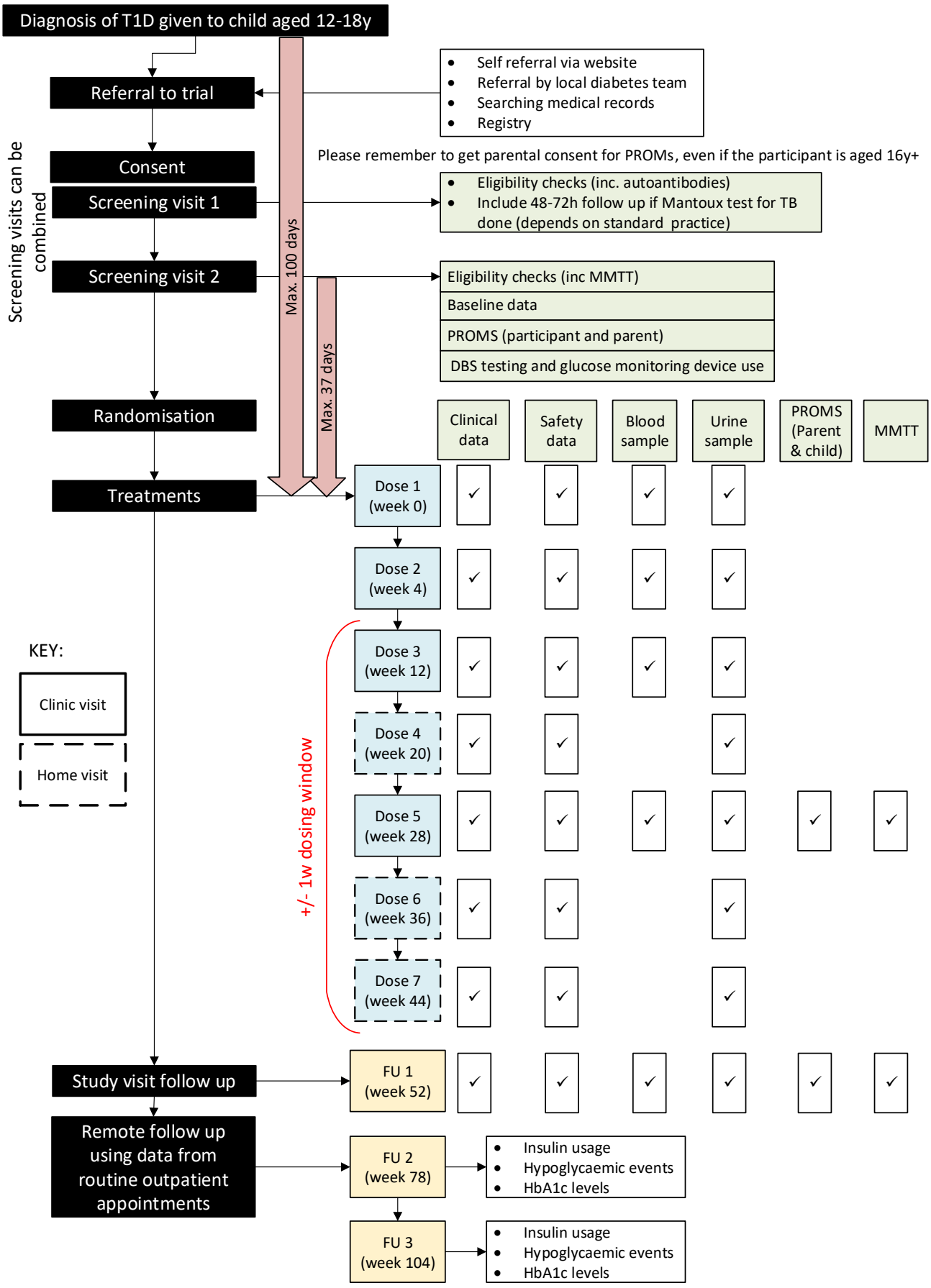
Appendix 1: Trial flowchart



Appendix 2: Schedule of events at sites

	Screening (visits may be combined)		**Dosing**							**Follow-up**		
	Within 37* to 100 days before Dose 1		Dose 1	Dose 2	Dose 3	Dose 4	Dose 5	Dose 6	Dose 7	F/U	Remote	Remote
Visit	SC1	SC2	1	2	3	4	5	6	7	8	R1	R2
Week		≤ 37 days to dose 1	0	4	12	20	28	36	44	52	78	104
Window allowed	NA	NA	Within 100d diagnosis and 37d of MMTT	+/-1w	+/-1w	+/-1w	+/-1w	+/-1w	+/-1w	+/-1w from week 52		
Location	Clinic	Clinic	Clinic	Clinic	Clinic	Home / clinic	Clinic	Home / clinic	Home / clinic	Clinic	Remote	Remote
Consent	X											
Medical History	X											
Physical exam	X		X		X		X			X		
Concomitant medication	X	X	X	X	X	X	X	X	X	X		
Weight	X	X	X		X		X			X	X	X
Height	X		X		X		X			X	X	X
Vital signs	X	X	X		X		X			X		
TB tests †	X											
Adverse events		X	X	X	X	X	X	X	X	X		
Blood draw (see appendix 3)	X	X	X	X	X		X			X		
Urine collection (see appendix 4)	X	X	X	X	X	X	X	X	X	X		
Dried blood spot review ‡		X	X	X	X	X	X	X	X	X	X	X
Glucose monitoring ǂ		X	Readings done 2 weeks prior to each visit									
Download of glucose monitoring data			(X)	X	X	(X)	X	(X)	X	X	X	X
Insulin dose usage		X	X	X	X	X	X	X	X	X	X	X
Metabolic review		X	X	X	X	X	X	X	X	X		
PROMs (adolescent & parent)		X					X			X		

* MMTT to be done no more than 37 days of 1st planned dose.

† TB tests must include a chest x-ray **and** one of the following: blood sample (see Appendix 3) or Mantoux test. The Mantoux test will require the participant to be assessed within 48-72h to determine whether there has been a reaction.

‡ Samples taken at home once a week (+/-2d) until visit 5, then monthly. Review involves asking if testing has been completed and posted back to the lab, not a review of the results.

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

(X) = Optional data download. Please collect this data as a .CSV file.

Appendix 3: Blood draw schedule

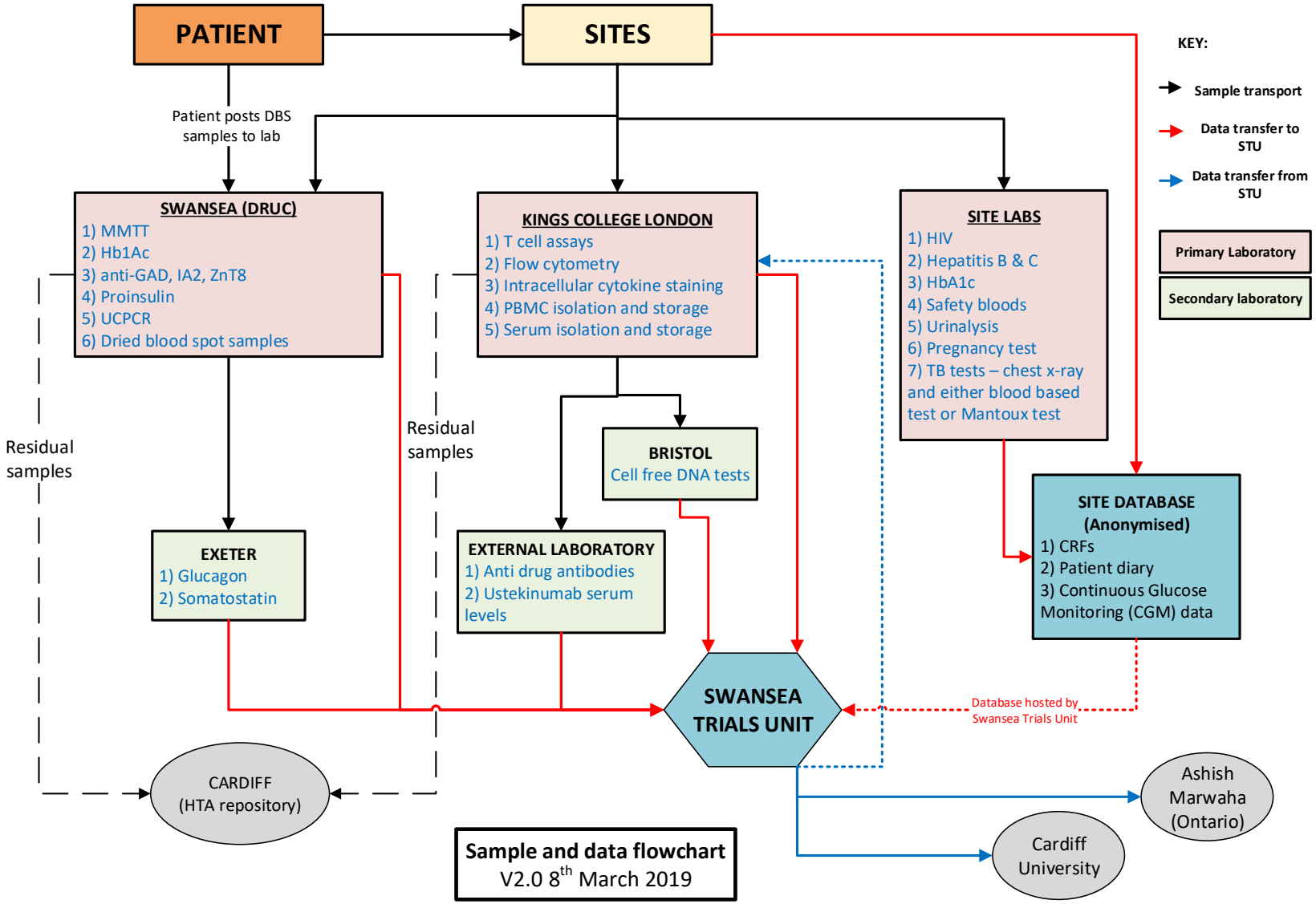
	Location of analysis	Screening (visits may be combined)		Dose							Follow-up		
		Within 37* to 100 days before Dose 1		1	2	3	4	5	6	7	F/U	Remote	
Visit		SC1	SC2	1	2	3	4	5	6	7	8	R1	R2
Week			≤ 37 days to dose 1	0	4	12	20	28	36	44	52	78	104
Location (C = clinic; H = home; R = remote)		C	C	C	C	C	C / H	C	C / H	C / H	C	R	R
Blood draw (ranges are provided to reflect local variation at sites. Volumes may exceed those stated for tests by site laboratories)		X	X	X	X	X		X			X		
Islet autoantibodies (GAD, IA-2 and ZnT8) (ml)	Swansea	2						2			2		
HIV, Hep B and C (ml)	Site ◆	3-20											
Blood-based TB test (as per local procedures) (ml) ‡	Site ◆	4-8											
Biochem – (Paediatric if possible - 1.2ml) Haem - (Paediatric if possible - 1.2ml) Glucose – (finger prick if possible) HbA1c - (finger prick if possible)	Site ◆	2-10		2-10		2-10		2-10			2-10		
HbA1c (ml)	Swansea			1		1		1			1		
MMTT (ml) †	Swansea		10*					10			10		
Glucagon and somatostatin (from MMTT)	Exeter (via Swansea)		A					A			A		
Mechanistic blood draw (ml) ╫	KCL		40	40	40	40		40			40		
Cell free DNA (from mechanistic draw) (ml)	Bristol (via KCL)			8.5	8.5	8.5		8.5			8.5		
Drug level & Anti-drug antibodies (ml) ┼	External contractor (via KCL)				2	2		2			2		
Total maximum ◆blood volume range (ml)		**7-38‡**	**50**	**51.5 - 57.5**	**50.5**	**53.5 – 59.5**		**65.5 – 71.5**			**65.5 – 71.5**		

◆ *Site volumes will vary according to local requirements. Approximate ranges are shown in the table. Volumes may exceed those stated at some sites according to standard practice.*
** MMTT to be done no more than 37 days before 1st planned dose*
‡ Blood sample will only be taken if this form of TB testing is standard practice at the site
† MMTT samples taken over 2 hours through a cannula
A = Sample tested taken from an aliquot already listed in the table (i.e. no additional blood drawn)
╫ Samples can be as low as 25ml as a minimum requirement
┼ Samples taken for all participants to avoid unblinding

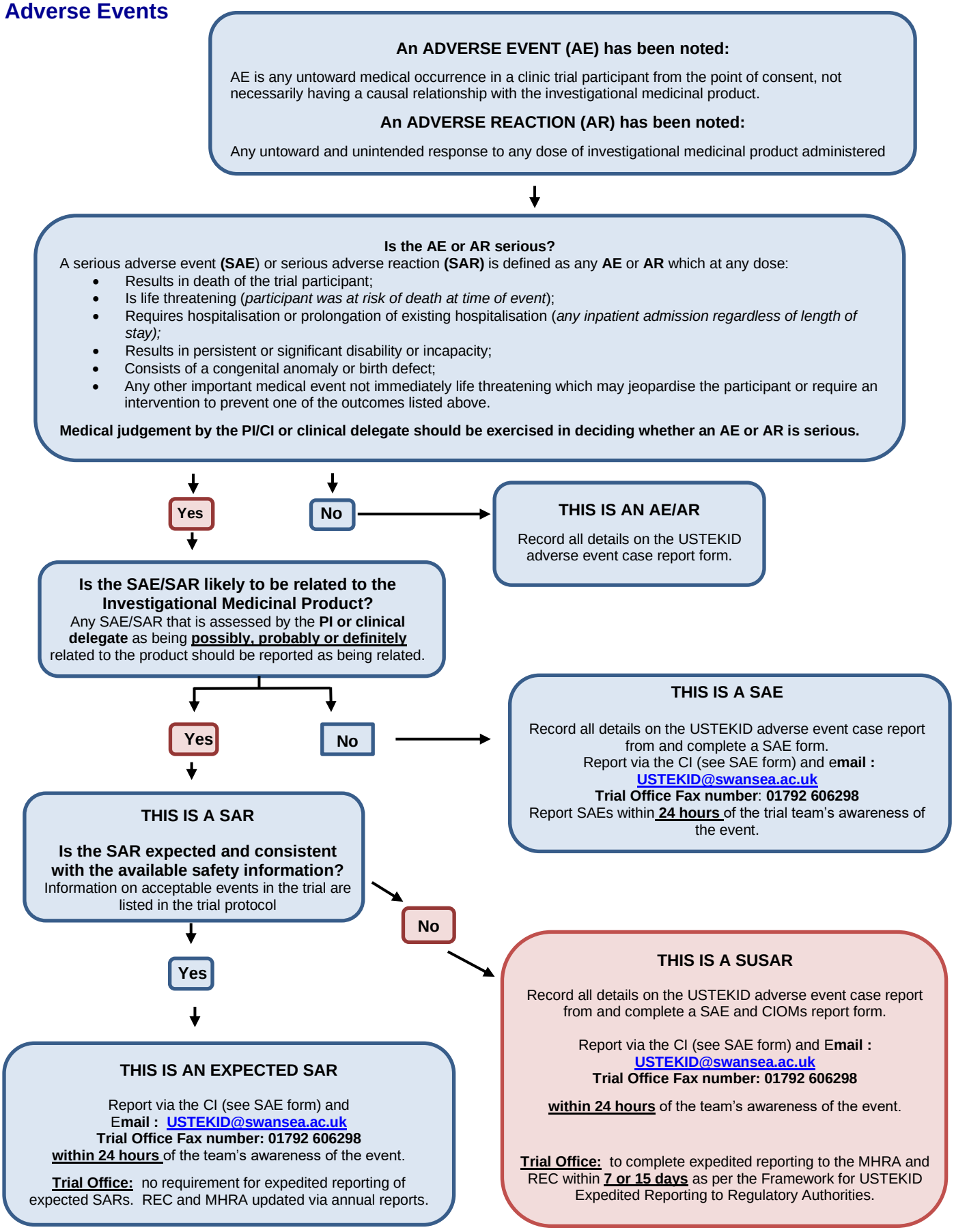
Appendix 4: Urine collection schedule

	Location of analysis	Screen		Dosing							Follow-up		
		Up to 100 days before Dose 1		Dose 1	Dose 2	Dose 3	Dose 4	Dose 5	Dose 6	Dose 7	F/U	Remote	Remote
Visit		SC1	SC2	1	2	3	4	5	6	7	8	R1	R2
Week				0	4	12	20	28	36	44	52	78	104
Location (C = clinic; H = home; R = remote)		C	C	C	C	C	C / H	C	C / H	C / H	C	R	R
Urine collection		X	X	X	X	X	X	X	X	X	X		
Urinalysis	Site	X		X		X		X			X		
Pregnancy test	Site	X	X	X	X	X	X	X	X	X	X		
MMTT (UCPCR)	Swansea		X*					X			X		
	** MMTT are to be done no more than37 days before 1st dose*												

Appendix 5: Sample and data flow from sites to laboratories



Appendix 6: Safety Reporting - Decision Framework to be used for Assessment of Adverse Events



AVAILABLE SAFETY INFORMATION

Reference Safety Information: STELARA® SmPC section 4.8

Note: only SmPC version provided by the trial office should be used for RSI for the trial

The SmPC should be used as the reference for all expectedness assessments.

Safety data will be continuously monitored throughout the study via Adverse Event and Case Report Forms. Specific data items will include adverse events observed at each dosing visit (Weeks 0, 4, 12, 20, 28, 36, 44) and follow-up visit (week 52) e.g. hypoglycaemic episodes; injection reactions (fever, chills, headache, nausea, vomiting and injection site pain); hypersensitivity reactions (signs and symptoms of anaphylaxis, angioedema, wheezing, dyspnoea, urticaria, and hypotension). Other adverse events to be collected will include evidence of infection (EBV, CMV, TB or opportunistic bacteria); and evidence of posterior leukoencephalopathy syndrome.

Appendix 7: Safety Reporting - Decision Framework for Expedited Reporting to Regulatory Authorities

A related SAR, SUSAR or USM has been reported to the trial office:

Sites have reported an event as per the:

- Decision Framework to be used for the Assessment of Adverse Events in the USTEKID trial.
- Framework for Reporting Urgent Safety Measures in the USTEKID trial

All **SUSARs** require expedited reporting as do **all USMs**.

Trial sites will report all events to the trial office email **USTEKID@swansea.ac.uk** or fax number 01792 6062980

On receipt of an event, the trial office will notify the CI or independent reviewer within 24 hours of STU awareness of an event indicating a response is required within 24 hours. Should the event indicate a possible SUSAR this will be highlighted within 24 hours of awareness.

Expedited reporting to the regulatory authorities, REC and Sponsor will occur via the trial office

↓

TRIAL SAFETY PROCESS
Alert from Site to indicate that an event has occurred.

Trial Manager (or delegate) has responsibility to**:**

- Ensure that the CI or independent reviewer is aware of the need for an assessment indicating time frame for reporting;
- *****Complete all expedited reporting to the MHRA within **7 days** (fatal or life threatening) or **15 days** (all others) of awareness of the event;
- Liaise with site(s) for missing information and complete the CIOMS form as required ;
- Forward updated information to the CI or Independent Reviewer;
- Remain vigilant of the timeframe for reporting of an event;
- File reports and relevant communication in the TMF.

***USM reporting**
Must be reported immediately to the Sponsor (by email) and to the MHRA (by telephone, details below) to a safety scientist.

A written report, usually in the form of a substantial amendment should follow to the MHRA (usually be email unless an alternative given) and REC (by email) as soon as possible and in all cases **within 3 days of the incident.**

The MHRA website should always be checked for the current information:
https://www.gov.uk/guidance/clinical-trials-for-medicines-manage-your-authorisation-report-safety-issues

When contacting the **MHRA Clinical Trial Unit:**
Tel: + 44 20 3080 6456 Office hours, within 24h of event knowledge.

The MHRA will advise of the email contact address

Appendix 8: Safety Reporting - Decision Framework for Urgent Safety Measure Reporting

An immediate hazard to the health and safety of a research participant(s) has been identified.
An USM is an action taken in order to protect a clinical trial participant against any immediate hazard to their health or safety where changes in trial conduct need to be implemented before approval from an ethics committee or regulatory body can be sought.

Examples of when USMs may be required:

- A single report of an expected adverse reaction with an unexpected outcome e.g. fatality;
- An increase in the intensity or frequency of expected events and reactions, judged to be clinically important;
- Unexpected reactions that occur during or following trial completion;
- A serious event associated with trial procedures resulting in a protocol modification;
- A major safety finding from newly completed animal studies;
- Serious Breach of the protocol or Good Clinical Practice (GCP) procedures.

↓

Following the identification of a USM any action required must be taken to secure the health and safety of the research participant(s).
Where possible the CI should be contacted for advice on the immediate action to be taken via:

Email: USTEKID@swansea.ac.uk
Trial Office Fax number: 01792 606298

USMs might include:

- An urgent change to a trial procedure(s);
- A temporary halt to the trial at one site or trial-wide;
- A permanent halt to the trial;
- The addition of new trial procedures yet to be reviewed by the ethics committee or regulatory body.

↓

Subsequently to implementing a USM the site should notify of action taken immediately via:

Email: USTEKID@swansea.ac.uk

Trial Office Fax number: 01792 606298

Appendix 9: Trial site responsibilities

- National approvals will be sought for all NHS sites in England, Wales and Scotland.
- NHS R&D permission will be obtained at each site prior to site initiation.
- A list of all documentation required by sites in accordance with GCP will be held as a separate document.

Procedure for initiating/opening a new site

The CI will authorise the initiation of the trial and IMP release to individual sites. The Trial Manager will coordinate the authorisations required for individual sites and liaise with the sponsor to document a regulatory green light prior to the initiation of any site. The Trial Manager will liaise with SMPU to ensure that IMP is shipped to sites under quarantine if necessary.

Principal Investigator responsibilities

The PIs responsibilities are detailed and agreed in the signed site agreement. A summary of the PIs responsibilities are:

- Ensure all local approvals are in place
- Protect the rights, safety, dignity and welfare of potential participants
- Supervision of site staff conduct
- Obtain participant consent / delegate to appropriate individuals
- Complete eligibility assessments
- Contribute to participant visits
- Review of completed SAE forms
- Document review of safety information provided by the CI in a timely manner
- Document correspondence e.g. emails
- Maintain accurate, complete and current records of site activities
- Availability at monitoring visits
- Document review of participant visit data in a timely manner
- Review of completed CRFs and respond to medical queries in a timely manner

Appendix 10: Trial Management responsibilities

- **Trial management** - Sponsor ensures completion of a delegation of responsibilities / agreements for all parties. These are held as separate documents.
- **Randomisation procedure** – Sealed Envelope Ltd will provide a customised randomisation system for the trial. Details of the randomisation procedure will be written in the Randomisation handbook which will be held as a separate document.
- **Data management -** The trial will involve data collection in a custom designed and validated trial database as authorised by the Sponsor and CI. General data management will be delegated to STU who will oversee the process of sites data entry, cleaning and query management through central and onsite monitoring. A data management plan outlining how data will be handled during all stages of the trial is held as a separate document.
- **Preparation and submission of amendments -** The Sponsor will assess all amendments to be submitted during to the trial. The CI will be responsible for obtaining the required authorisations and disseminating to sites before implementation. All amendments will be coordinated by the Trial Manager.
- **Preparation and submission of Annual Safety Report/Annual Progress Report –** The APR and DSUR will be sent by the CI to the REC and MHRA respectively annually, within 30 days of the anniversary of the favourable opinion or CTA as appropriate until trial end. Additionally, progress reports to the funder will be generated as required. All reports will be coordinated by the Trial Manager.
- **Data protection/confidentiality –** STU will be responsible for holding trial data in a secure database which will have restricted access and be password protected. Data from sites and laboratories will be transferred in using secure methods agreed by sponsor. All data held by STU will be regularly backed up on Swansea University servers.
- **Trial documentation and archiving -** The CI will be responsible for overseeing the archiving of the electronic database and the TMF. Source data and the ISF for participating sites will be archived locally as detailed in local site agreements. Archiving will be coordinated by the Trial Manager.