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The efficacy and safety of ustekinumab in adolescents newly diagnosed with type 1 diabetes: the USTEK1D RCT

Kymberley Carter, Wai-Yee Cheung, Hayley A Hutchings, Greg Fegan, Gail Holland, Steve Luzio, Gareth Dunseath, Stephen Hiles, Susie Marques-Jones, John W Gregory, Danijela Tatovic, Peter Taylor, Jane Bowen-Morris, Rachel Stenson, Stephanie Hanna, Zainab Mahmood, Jennie Yang, Evangelia Williams, Timothy Tree, Ashish Marwaha and Colin M Dayan

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Extended Research Article

The efficacy and safety of ustekinumab in adolescents newly diagnosed with type 1 diabetes: the USTEK1D RCT

Kymberley Carter,[1] Wai-Yee Cheung,[2] Hayley A Hutchings,[1] Greg Fegan,[1] Gail Holland,[1] Steve Luzio,[2] Gareth Dunseath,[2] Stephen Hiles,[1] Susie Marques-Jones,[3] John W Gregory,[4] Danijela Tatovic,[5] Peter Taylor,[5] Jane Bowen-Morris,[5] Rachel Stenson,[5] Stephanie Hanna,[5] Zainab Mahmood,[5] Jennie Yang,[6] Evangelia Williams,[6] Timothy Tree,[6] Ashish Marwaha[7] and Colin M Dayan[5*]

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Abstract

Background: Type 1 diabetes is an autoimmune disease affecting over 400,000 children and adults in the United Kingdom for which currently the only available therapy is insulin.

Objective(s): To determine the efficacy and safety of the monoclonal antibody ustekinumab targeting the interleukin 12/interleukin 23 immune pathway that generates T helper 1/T helper 17 T cells to slow down the autoimmune process and preserve beta cell production in type 1 diabetes.

Design: Randomised, double-blind, placebo-controlled, parallel-group phase II trial.

Setting: Paediatric and young adult diabetes clinics across 16 sites in the United Kingdom.

Participants: Newly diagnosed with type 1 diabetes and aged 12–18 years.

Eligibility criteria: Type 1 diabetes confirmed by islet autoantibody testing, within 100 days of first insulin injection, and with residual beta cell function (stimulated C-peptide level > 0.2 nmol/l).

Interventions: Ustekinumab at the highest approved doses or control (saline) subcutaneously at weeks 0, 4 and 12 and subsequently every 8 weeks to week 44 (seven doses).

Main outcome measures: Preservation of Mixed Meal Tolerance Test stimulated 2-hour insulin C-peptide area under the curve at week 52 as compared to control (saline) treatment by analysis of covariance adjusted for baseline parameters.

Randomisation: 2 : 1 Remote computerised randomisation with minimisation by age and baseline C-peptide groups.

Blinding: Blinding of participants, investigators, laboratory and trial staff.

Numbers randomised: Seventy-two participants were randomised, 60% male, 18% aged 16–18 years.

Recruitment: Two hundred and eight potentially eligible patients were approached, and 88 patients were screened. Four participants were lost to follow-up (6%). Four participants withdrew from the treatment but attended the primary end-point assessment.

Numbers analysed: Six participants were missing baseline data for the primary analysis. The final analysable sample was $n = 62$.

Outcome: Ustekinumab was associated with a 49% higher endogenous stimulated insulin production than control at week 52 after adjustments for baseline factors [geometric ratio of ustekinumab to control was 1.49 (95% confidence interval 1.08 to 2.06; $p = 0.02$)].

Secondary analyses showed no difference in C-peptide at week 28 suggesting that the effect was 'late' or 'delayed'. Ancillary analysis showed a significant reduction in activated T helper 17.1 T cells ($p < 0.001$) in the treatment group which was associated with C-peptide preservation from week 28 to week 52.

Harms: No severe adverse events were reported and there were no differences between ustekinumab and control groups in the proportion of participants overall experiencing mild (87% vs. 88%) or moderate (32% vs. 32%) events.

Limitations: Sensitivity analysis showed the primary end point to be robust to exclusion of small numbers of participants with some protocol deviations and extreme values in key covariates, but not to imputation of all missing data.

Conclusions: Ustekinumab appears to slow down the autoimmune process providing the first clinical trial evidence that interleukin 17-secreting T cells play a pathogenic role in type 1 diabetes. Alone, it is insufficient to halt the autoimmune process.

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Future work: Replication of this result is ongoing in a trial with a similar design in Canada. If confirmed, consideration may be given to testing other drugs targeting the interleukin 17 pathway, using ustekinumab in combination with other agents or using it earlier in the disease pathway (preclinical disease) since it is so well tolerated and simple to use.

Study registration: Current Controlled Trials ISRCTN14274380.

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Supplementary material can be found on the NIHR Journals Library report page (https://doi.org/10.3310/FQLN7416).

Supplementary material has been provided by the authors to support the report and any files provided at submission will have been seen by peer reviewers, but not extensively reviewed. Any supplementary material provided at a later stage in the process may not have been peer-reviewed.

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List of abbreviations

ADA	American Diabetes Association
AE	adverse event
ANCOVA	analysis of covariance
anti-TNF	anti-tumour necrosis factor
AR	adverse reaction
AUC	area under the curve
BMI	body mass index
CGM	continuous glucose monitoring
CONSORT	Consolidated Standards of Reporting Trials
DBS	dried blood spot
DRUC	Diabetes Research Unit Cymru
DSMB	Data and Safety Monitoring Board
DTSQ	Diabetes Treatment Satisfaction Questionnaire
DTSQc	Diabetes Treatment Satisfaction Questionnaire Change
GM-CSF	granulocyte-macrophage colony-stimulating factor
HbA1c	glycated haemoglobin
HRQoL	health-related quality of life
ICF	informed consent form
IDAAC	insulin dose-adjusted glycated haemoglobin
IFN-γ	interferon-gamma
IL	interleukin
IMP	investigational medicinal product
IRR	incidence rate ratio
ITT	intention to treat
KCL	King's College London
MD	medication deviation(s)
MHRA	Medicines and Healthcare products Regulatory Agency
MMTT	Mixed Meal Tolerance Test
NIHR	National Institute for Health and Care Research
NOD	non-obese diabetic
NPDA	National Paediatric Diabetes Audit
PD	protocol deviation(s)
PedsQL	Paediatric Quality of Life Inventory
PI	principal investigator
PIS	participant/parent information sheet
PPI	patient and public involvement
PROM	participant-reported outcome measure
RCT	randomised controlled trial
REC	Research Ethics Committee
RSI	Reference Safety Information
SAE	serious adverse event
SAP	statistical analysis plan
SAR	serious adverse reaction
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
TB	tuberculosis
TMG	Trial Management Group
TSC	Trial Steering Committee
UCPCR	urine C-peptide/creatinine ratio

Plain language summary

USTEK1D was a clinical trial of the immune therapy ustekinumab in teenagers (aged 12–18) who had been diagnosed in the previous 3 months with type 1 diabetes. The aim was to stop the loss of the body's insulin-making cells. Ustekinumab was given subcutaneously (into the skin) at the start of the trial, 4 weeks later, and then every 8 weeks until week 44 (i.e. seven doses in total) and then patients were followed up at week 52. Forty-seven teenagers received ustekinumab and 25 received saltwater injections that looked the same as the medicine (the 'control' treatment).

The study showed that after 12 months, teenagers given ustekinumab produced 49% more insulin in their own bodies than those given the control. The treatment was very safe with no serious side effects. Laboratory studies confirmed that the ustekinumab treatment reduced the number of immune cells making the interleukin 17 protein. Interleukin 17-making immune cells are known to damage other cells. Teenagers with the greatest reduction in interleukin 17-making cells had the best protection in their insulin-making capacity. However, the treatment appeared to take up to 6 months to have an effect, and by that stage, over 40% of the insulin-making capacity had been lost. There were no differences in average blood glucose levels or low blood glucose episodes (which can lead to loss of consciousness) between the treatments.

We conclude that ustekinumab appears to slow down the autoimmune disease process in type 1 diabetes. The study also provides evidence that interleukin 17-making immune cells are important in causing type 1 diabetes. Ustekinumab had very few side effects. However, on its own, ustekinumab does not seem able to stop the autoimmune process altogether and a lot of insulin-making capacity is lost before it takes effect. For greater effect, future studies could combine ustekinumab with other treatments to protect insulin-making cells in type 1 diabetes.

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Scientific summary

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. Despite major advances in closed-loop insulin pump therapy, much of the morbidity arises from young people failing to engage with complex therapies.

T1D is an autoimmune disease. Immunotherapy has the potential to preserve endogenous beta cell function (insulin-making capacity) and thereby improve metabolic control even in poorly compliant individuals. 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 new-onset T1D.

Data from preclinical and observational studies suggest a role for interferon-gamma [IFN-γ; T helper 1 (Th1)] and interleukin 17 (IL-17)-secreting (Th17) T cells in T1D. Ustekinumab (STELARA®, Janssen-Cilag Ltd International NV, Beerse, Belgium) 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. Ustekinumab is licensed in the UK for the treatment of psoriasis in children and adults, psoriatic arthritis in adults and Crohn's disease in adults and is very well tolerated.

Objectives

The primary objective was to determine the efficacy of ustekinumab for preserving Mixed Meal Tolerance Test (MMTT) stimulated 2-hour insulin C-peptide area under the curve (AUC) at week 52 as compared to control in children and adolescents with new-onset T1D. Secondary objectives included changes in clinical metabolic parameters including glycated haemoglobin (HbA1c), insulin usage, hypoglycaemia and treatment-related harms.

Methods

We conducted a double-blind phase II randomised controlled trial of subcutaneous (SC) ustekinumab in 72 young people aged 12–18 with recent-onset T1D (within 100 days of the first insulin injection) with residual endogenous insulin production (serum C-peptide > 0.2 nmol/l during MMTT) and autoimmune diabetes confirmed by measurement of islet cell autoantibodies. Participants were given ustekinumab or control (saline) SC at weeks 0, 4 and 12 and subsequently every 8 weeks to week 44 (seven doses) with the dose depending on their body weight: 2 mg/kg (if ≤ 40 kg) or 90 mg (if > 40 kg). These equate to the highest doses used previously in trials in other conditions. Participants were followed up 52 weeks after receiving the first dose of ustekinumab/control. The primary end point was assessed at week 52. The final safety data analysis also occurred at week 52. Minimisation by age (12–15 years vs. 16–18 years) and screened peak C-peptide levels (0.2–0.7 vs. > 0.7 nmol/l) was used to ensure balance between treatment groups. The ustekinumab-to-control ratio was 2 : 1 to provide additional data on drug safety (n = 48 : 24).

Results

1. **The recruited sample** was reflective of the national population of teens with T1D in National Paediatric Diabetes Audit (NPDA) 2019–20 (82% vs. 80% Caucasian) with a slightly higher male-to-female ratio (60% vs. 54%). The sample of 16- to 18-year-olds was lower than planned (18% vs. 40%), and lower than the percentage of 16- to 17-year-olds in the 12- to 17-year-old age group of newly diagnosed individuals in the NPDA (30%). This was possibly due to loss of some potential participants to adult care teams but did not appear to be due to a lower consent rate of eligible participants.

2. **Retention of participants and final analysable sample:** Retention of participants over 52 weeks to the primary end point was generally good, especially considering overlap with the COVID-19 pandemic, with four participants (6%) lost to follow-up. However, an additional six participants could not be included in the planned primary outcome intention-to-treat analysis due to missing baseline data, so the final analysed sample was *n* = 62 (86%). The planned sample size in the power calculation was *n* = 66. Missing participants were balanced across the treatment arms considering the 2 : 1 ratio of recruitment (six ustekinumab, four control). Four participants withdrew from treatment (three ustekinumab, one control) but attended for primary end-point collection. Minimisation by age (12–15 years vs. 16–18 years) and initial C-peptide level (< 0.7 vs. > 0.7 nmol/l) ensured balance of these parameters between the groups. Body mass index *z*-score was somewhat higher in the control group, while insulin use per kilogram was higher in the treatment group. Age and entry C-peptide were lower in the treatment group and HbA1c was higher, all of which are factors associated with more rapid C-peptide loss post diagnosis. Adjustment for these baseline factors was pre-planned in the analysis.
3. **Primary end-point analysis:** For the pre-specified primary end-point analysis, ustekinumab was associated with a 49% higher endogenous stimulated insulin production (AUC C-peptide in 2-hour MMTT) than control after adjustments for baseline factors at 52 weeks {geometric ratio of ustekinumab to control was 1.49 [95% confidence interval (CI) 1.08 to 2.06; $p = 0.02$]}.
4. **Additional C-peptide end-point analyses:** Despite treatment, there was still substantial loss of C-peptide in both arms over the 52-week period. At this time point, the mean stimulated AUC C-peptide levels was 65% of baseline in the ustekinumab group (0.45 vs. 0.84 nmol/l) and 45% of baseline in the control group (0.3 vs. 0.87 mmol/l). Secondary analysis of C-peptide levels at week 28 was conducted. However, it should be noted that there was more missing data at this time point (*n* = 55 vs. *n* = 62 at primary end point). At this time point, the geometric mean ratio of ustekinumab to control was not significantly different (1.15, 95% CI 0.81 to 1.63; $p = 0.45$). Hence, it appeared that the benefit of ustekinumab predominantly developed 'late', in the second 6 months of the study, although the missing data at week 28 resulted in a less precise estimated effect value at this time point. 'Late' or 'delayed' effects have not previously been seen in immunotherapy studies.
5. **Secondary end-point analyses – HbA1c:** HbA1c levels rose across both groups from 50 mmol/mol at baseline to around 56 mmol/mol at week 52. No significant difference was seen in HbA1c between the groups, although with insulin use as a covariate (not pre-specified, but found to be relevant), point estimates at weeks 28 and 52 were 2–3 mmol/mol lower in the ustekinumab group. It is noted that sample sizes around two- to threefold larger than in this study would have been required for adequate power to study HbA1c differences.
6. **Secondary end-point analyses – other metabolic parameters:** Exogenous insulin use increased from baseline to week 52 in both groups (0.42–0.63 U/kg in the control group; 0.51–0.63 U/kg in the ustekinumab) with no significant difference after adjustment for baseline factors. Insulin dose-adjusted HbA1c also increased in both groups (8.23–9.46% in the control group and 8.90–9.69% in the ustekinumab group) with no significant difference between the groups.
7. Data from continuous glucose monitoring (CGM) showed decreasing median percentage of time in range of > 70 mg/dl (3.9 mmol/l) to < 180 mg/dl (10 mmol/l) over 52 weeks in both groups (82.40– 61.32% in the control group and 77.30–60.33% in the ustekinumab group). There was no significant difference between the groups in any of the time points of assessment (82.40% in control group vis-à-vis 77.30% in ustekinumab group $p = 0.61$ at baseline; 67.46% vis-à-vis 66.18%, $p = 0.98$ at week 28 and 61.32% vis-à-vis 60.33% at week 52).
8. **Secondary end-point analyses – hypoglycaemic events:** Data from participant diaries identified 68 participants reporting 2946 hypoglycaemic events reviewed and verified by clinicians as either having a blood glucose level that reached the alert value (≤ 3.9 mmol/l) or being a probable symptomatic hypoglycaemic event. Two thousand two hundred and twenty-eight (around 32/person/year) were classed as level 1 (a glucose alert value of > 3.0 but ≤ 3.9 mmol/l) and 615 (around 9/person/year) were classed as level 2 (a glucose level of ≤ 3.0 mmol/l – clinically important hypoglycaemia). Only one person (in the control group) had an event classed as level 3 (severe cognitive impairment requiring external assistance). Participants in the ustekinumab group reported a lower overall incidence per person-year of all types of hypoglycaemia (39.38) than those in the control group (43.80) but the difference did not reach statistical significance [incidence rate ratio (IRR) 1.11, 95% CI 0.69 to 1.79; $p = 0.66$]. Data from CGM showed a lower incidence rate of level 2 hypoglycaemic events in the control group than the ustekinumab group (week 28 IRR 0.49, 95% CI 0.21 to 1.15; $p = 0.1$; week 52 IRR 0.40, 95% CI 0.12 to 1.30; $p = 0.12$), but the difference did not reach statistical significance.

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9. **Secondary end-point analyses –participant-reported outcome measures (PROMs):** Participant-reported outcomes were collected using the Paediatric Quality of Life Inventory (PedsQL), PedsQL™ (MAPI Research Trust PROVIDE™, Lyon, France) Diabetes Module (PedsQL Diabetes), Diabetes Treatment Satisfaction Questionnaire (DTSQ), Hypoglycaemia Fear Survey-Behaviour (HypoFear-Behaviour, Hypoglycaemia Fear Survey-Worry (HypoFear-Worry) and Hypoglycaemia Fear Survey-Total (HypoFear-Total) at baseline, week 28 and week 52. The DTSQ Change version was used at week 52 to identify changes in level of satisfaction with diabetes treatment. Completion of questionnaires was > 90% at baseline and > 80% during follow-up for almost all questionnaires. There was no significant change in any of the participant PROM scores from baseline to week 52 in either group and no significant differences between the groups.
10. **Secondary end-point analyses – parent/ proxy PROMs:** There were no significant differences in parent/proxy PROMs between the groups.
11. **Secondary end-point analyses – comparison of participant and parent/proxy PROM score:** In ancillary analysis, there was a strong correlation between participant and parent PROM scores for all PROMs with a rho of 0.23–0.68 which was significant at all time points. An exception was the HypoFear (behaviour) scores at week 52. Parents had significantly higher HypoFear (particularly 'Worry') than participants at all time points and lower PedsQL diabetes quality-of-life scores than participants at baseline and week 28.
12. **Sensitivity analyses:** Sensitivity analyses were performed to confirm robustness of the conclusions about the analysis of the primary outcome to protocol deviations. Excluding one participant who accidentally became unblinded, one participant whose primary outcome visit was delayed by 6 months and one participant with a hereditary red cell disorder affecting HbA1c separately had no effect on the primary outcome. Hence the model for analysing the primary outcome was robust to small numbers of people with some protocol deviations and extreme values in key covariates.
13. **Missing data imputation:** According to the pre-specified statistical analysis plan, multiple imputation would be considered if there were > 5% and < 10% (> 3 and < 7 participants) missing. Data were missing for 10 participants (4 withdrawals; 4 with no baseline exogenous insulin use and 2 with missing HbA1c at baseline), affecting > 10% of the participants. A decision was made to perform multiple imputation, purely as a sensitivity check for the primary analysis. Multiple imputation showed that the conclusion about treatment group difference might be sensitive to missing values as the geometric ratio of ustekinumab to control changed to 1.36 (95% CI 0.81 to 1.63; $p = 0.27$) and did not reach statistical significance. The model may therefore be sensitive to missing data.
14. **Ancillary end-point analyses – harms:** Ustekinumab was very well tolerated. No severe adverse events (AEs) were reported and there were no differences between ustekinumab and control in the proportion of participants overall experiencing mild (87% vs. 88%) or moderate (32% vs. 32%) events. When evaluating the AEs deemed by investigators likely to be attributable to study drug, a higher proportion of participants in the ustekinumab group had one AE deemed likely to be related to the study drug in each level of attributability (mild = 32% of participants in ustekinumab group vs. 20% in control; moderate = 11% in ustekinumab group vs. 8% in control). The bulk of the events were mild ($n = 124$) with only 12 events of moderate severity. These moderate AEs attributable to the study drug were experienced by seven participants (control: 2; ustekinumab: 5). In evaluating the evidence of infection, we found 37/117 AEs categorised in the Infection and Infestation class deemed to be possibly related to the study drug. These 37 events were experienced by 17 participants. A higher proportion of participants in the ustekinumab group (30%, $n = 14$) than those in the control group (12%, $n = 3$) experienced one AE deemed to be possibly related to the study drug. Thirty-four of these events were mild. Two moderate AEs were experienced by one ustekinumab participant. They were fever and upper respiratory tract infection. There were six events of injection reaction experienced by five participants (ustekinumab: 9%, $n = 4$, control: 4%, $n = 1$). All six events were mild and resolved with no sequelae. There were no hypersensitivity reactions.
15. **Ancillary end-point analyses – immunology:** We observed significant differences between the ustekinumab and control groups in relevant T-cell populations targeted by the drug. A significant decline in the CD4+ Th17 and Th17.1 populations but not the Th1 population was seen after 6 months of treatment in the ustekinumab group, which became more pronounced by week 52. The most pronounced effect was seen in cells that expressed all four cytokines [IFN-γ, IL-17, granulocyte-macrophage colony-stimulating factor (GM-CSF+), IL-2+], representing around 0.1% of the CD4 T-cell population, which showed a reduction as early as 3 months after beginning therapy. This was unlikely to be an artefact of multiple testing, as the highly significant changes in T-cell populations ($p \leq 0.001$) all clustered around the Th17 positive subpopulations. We additionally analysed the antigen-specific response by using a cytokine FluoroSpot assay. Overall, 28/64 participants had a positive response after in vitro stimulation

with proinsulin at baseline. A highly significant fall in beta cell targeted (proinsulin specific) IL-17A-secreting T cells was also seen (p = 0.0003) in comparison to baseline from 3 months in ustekinumab group only. There was no significant change in the IFN-γ FluoroSpot response. Preservation of C-peptide from 28 to 52 weeks after baseline correlated with the reduction in T cells co-secreting IL-17 and IFN-γ (Th17.1 cells, p = 0.04), and in particular with the change in a subset also co-expressing IL-2 and GM-CSF (p = 0.04) representing < 0.1% of circulating CD4 cells.

Conclusions

1. Ustekinumab was very well tolerated with no treatment-related withdrawals.
2. Participants treated with ustekinumab had 49% higher levels of MMTT stimulated C-peptide at week 52 (primary end point) than those treated with the control.
3. Stabilisation of C-peptide loss appeared to occur late (between weeks 28 and 52).
4. C-peptide preservation from week 28 to week 52 was correlated with reduction in a highly specific subset of T cells expressing the cytokines IL-17, IFN-γ, IL-2 and GM-CSF, representing as few as 0.1% of circulating CD4 T cells.
5. No significant differences in metabolic end points or PROMs were seen between the groups, although the study was not powered for these end points.
6. Ustekinumab appears to slow down the autoimmune process providing the first clinical trial evidence that IL-17-secreting T cells play a pathogenic role in T1D. Alone, it is insufficient to halt the autoimmune process. Consideration may be given to testing other drugs targeting the IL-17 pathway, using ustekinumab in combination with other agents or using it earlier in the disease pathway (preclinical disease) since it is so well tolerated and simple to use.

Study registration

Current Controlled Trials ISRCTN14274380.

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Chapter 1 Introduction

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 glycated haemoglobin (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 new-onset T1D. There is an urgent need to identify which agents will work in T1D and bring these into clinical practice.

We tested 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 chose to simultaneously target two major autoimmune cytokine pathways, interleukin (IL)-12/interferon-gamma (IFN-γ) and IL-23/IL-17, for which extensive evidence exists to implicate their role in beta cell destruction. The drug 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 T helper 1 (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]

Scientific background and rationale

We proposed 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 stabilisation of newly diagnosed patients. We predicted 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 were in clinical use: for example, ustekinumab, a humanised monoclonal antibody that targets these two pathways, has been approved for the treatment of psoriasis in North America and the UK 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]

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Animal studies have implicated the IL-17 and IFN-γ pathways in the pathogenesis of autoimmune diabetes. In diabetes-prone BioBreeding rats, the potentially pathogenic Th17 cell population increases in the first months of age, but the proportion and function of T regulatory cells do 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 T-cell receptor-transgenic BDC2.5 NOD mice are polarised to a Th17 phenotype, and then transferred to non-diabetic NOD-severe combined immunodeficiency 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 haemagglutinin on pancreatic beta 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 neutralising antibodies 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 forkhead box P3+ 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 messenger ribonucleic acid 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 polarising cytokines[22] and islet-antigen-specific Th17 cells. There is also evidence that (1) pancreatic lymph nodes from T1D patients have an expansion in Th17 cells[23] and (2) islets from recent-onset T1D patients express IL-17A, retinoid-related orphan receptor C (the human, lineage-defining IL-17 transcription factor) and IL-22.[24]

These observations suggest that IL-17 and IL-12/IFN-γ-driven responses together have an enhanced pathogenic role in T1D. Our overarching hypothesis was that interrupting the IL-17 and IFN-γ axes in individuals with recent-onset T1D would halt or slow down 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 proposed that drugs already approved for use in humans (e.g. ustekinumab) may be beneficial for the treatment of T1D.

Potential risks and benefits of the trial

Trial participants were given ustekinumab or the control treatment (saline) subcutaneously (SC) in an enhanced dose (compared to the standard psoriasis dosing regimen) depending on the body weight: 2 mg/kg (if they weigh ≤ 40 kg) or 90 mg (if they weigh > 40 kg) at weeks 0, 4 and 12 weeks and subsequently every 8 weeks up to week 44.

This dosing frequency and route of administration have 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 data are available from the Canadian UST1D trial of ustekinumab in young adults (20 participants) with new-onset T1D (within 100 days from diagnosis).[25] No serious adverse events (SAEs) related to the investigational medicinal product (IMP) were noted. The most stable C-peptide levels were seen in the 90-mg group that received five doses throughout the study (loading dose at 0 and 4 weeks followed by additional three doses every 12 weeks).

The trial 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 serious adverse effects (local or systemic allergic reactions). If none are detected after the first dose, participants will be suitable for home administration as per the dosing schedule (doses 4, 6 and 7).

Ustekinumab has undergone extensive Phase I–IV testing in adults with psoriasis vulgaris. In the 1-year Cancer Detection by Multiparametric Ultrasound of the prostate 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 use in adolescents (> 12 years of age) with psoriasis.

In alignment with UK categories, this trial was categorised as: Type B – somewhat higher than the risk of standard medical care.

Objectives

Our overarching hypothesis was that interrupting the IL-17 and IFN-γ axes in individuals with recent-onset T1D will halt or slow down the autoimmune destruction of beta cells sufficient to permit beta cell preservation and maintain residual physiological insulin secretion.

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 the control treatment in children and adolescents aged 12–18 years with new-onset T1D.

Secondary objectives

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

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-γ-secreting T-cell subsets, FluoroSpot analysis for IL-17 and IFN-γ 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 Hypoglycaemia Fear Survey (HypoFear), Diabetes Treatment Satisfaction Questionnaire (DTSQ) and Paediatric Quality of Life Inventory (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 continuous glucose monitoring (CGM) data (remote data collection to week 104).*
7. To determine whether any participants had COVID-19 during their time in the trial and to ascertain whether it had any effects.

Note: The objectives listed in italics were supported by funders other than National Institute for Health and Care Research (NIHR) as part of separate projects and not all data from these are listed in this report.

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Chapter 2 Methods

Our trial methodology was published by *BMJ Open*[26], but key information is described within this report.

Design

This was a double-blind phase II study to assess the safety and efficacy of ustekinumab in children and adolescents aged 12–18 years with new-onset T1D. Participants were given ustekinumab or control treatment (saline) in a 2 : 1 ratio SC at weeks 0, 4 and 12 in a dose depending on their body weight: 2 mg/kg (if ≤ 40 kg) or 90 mg (> 40 kg) and subsequently every 8 weeks to week 44 (seven doses) with a window of ± 1 week (*Figure 1*). The total dosage of ustekinumab administered depended on the body weight but was not higher than 630 mg for any participant.

Participants were followed up for 52 weeks after receiving the first dose of IMP. Unscheduled visits occurred as medically necessary. The primary end point was assessed at week 52. The final safety data analysis also occurred at week 52.

Changes to protocol after trial commencement

The following changes were made to the original protocol dated 16 February 2018 during the trial:

- 16 July 2018 – Additional procedural details, clarification of tuberculosis (TB) testing requirements
- 10 June 2019 – 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 Data and Safety Monitoring Board, changes to blood sampling requirements and other minor amendments
- 4 May 2020 – Addition of details regarding remote follow-up process and exocrine enzyme testing
- 16 October 2020 – Addition of antibody testing for COVID-19 at the end of the trial and a survey for participants to ask their opinion about the recruitment video.

Eligibility criteria

Seventy-two participants aged 12–18 years, within 100 days of the confirmed diagnosis of T1D (defined as date of first insulin dose) and with residual endogenous insulin production (serum C-peptide > 0.2 nmol/l during MMTT) were included in the study. Autoimmune diabetes was confirmed by measurement of islet cell autoantibodies.

Inclusion criteria

- Clinical diagnosis of immune-mediated T1D mellitus as defined by the American Diabetes Association (ADA)[27,28]
- 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 > 0.2 nmol/l in the MMTT test)
- Positive for at least one islet autoantibody (glutamic acid decarboxylase, islet antigen type 2, zinc transporter 8)
- Body weight < 100 kg
- Willing to record all insulin doses and blood glucose levels required for monitoring during the study, including reporting any hypoglycaemic events
- Willing to provide DBS samples

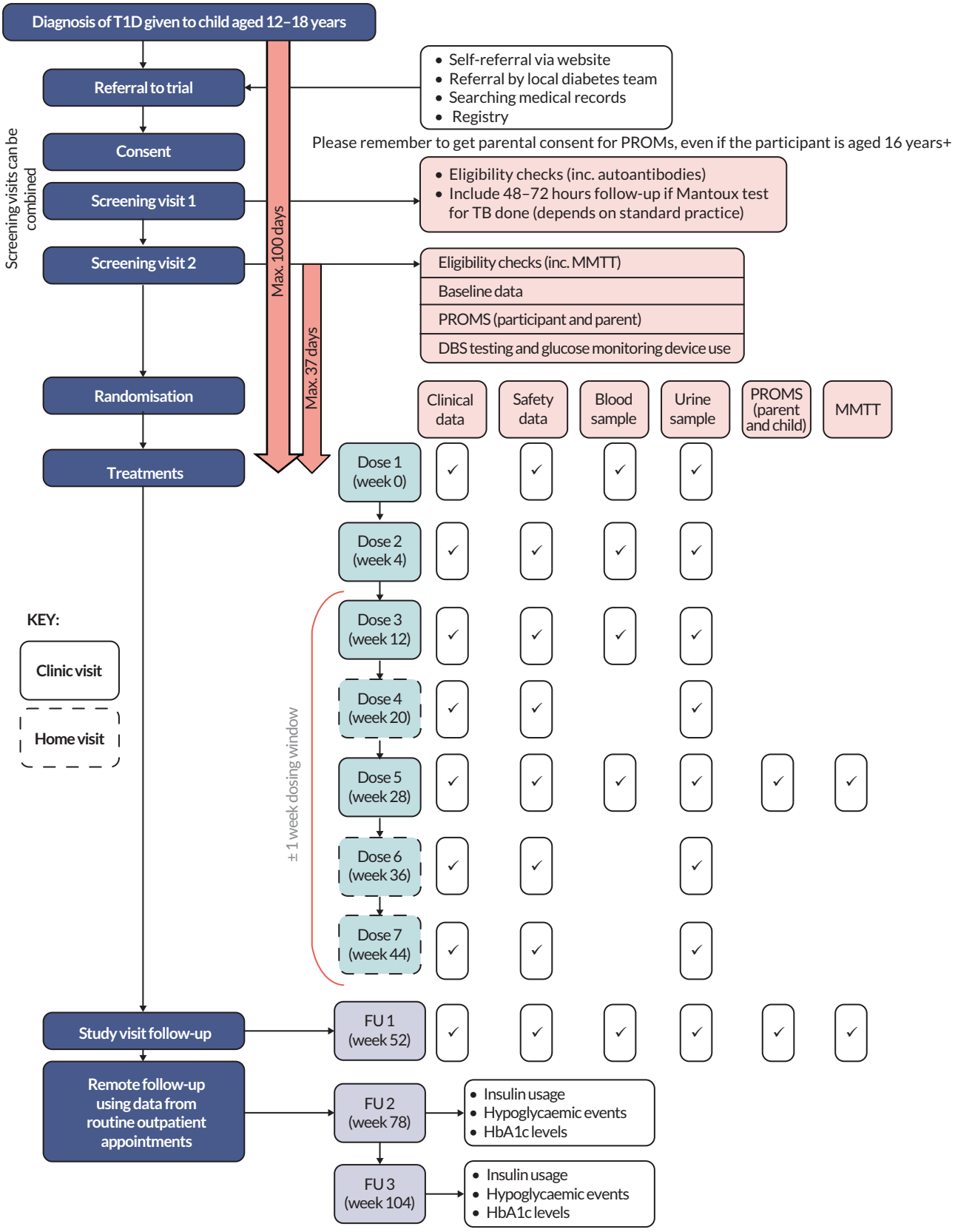


FIGURE 1 Flow chart of trial recruitment and follow-up visits. FU, follow-up.

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TABLE 1 Screening tests completed by participants

	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, hepatitis B and C	✓	
TB testing – chest X-ray	✓	
TB testing – blood test/Mantoux test	✓	
MMTT		✓
AEs		✓

- Willing to wear the FreeStyle Libre glucose monitor device at least 2 weeks prior to a trial 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 had a negative urine test for pregnancy; all participants agreed to use adequate contraception if they become/are sexually active (hormone-based contraception, double barrier contraception, abstinence) until 4 months following the date of their final treatment of IMP

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 more than 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, rituximab (Rituxan®, Biogen and Genentech, USA) or alemtuzumab (Lemtrada®, Sanofi, UK)
- Use of immunosuppressive or immunomodulatory therapies, including systemic steroids [e.g. methotrexate, cyclosporine or anti-tumour necrosis factor (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 sodium-glucose cotransporter-2 inhibitors
- Use of inhaled insulin
- Known alcohol abuse, drug abuse
- Evidence of active hepatitis B, hepatitis C, human immunodeficiency virus (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 intravenous (IV) antibiotic treatment]. Other infections, for example, 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 TB infection and no latent TB according to the British Thoracic Society recommendations.[29] Active TB was assessed using a *mandatory* chest X-ray and one of the following:

  a. a blood test, for example T-spot (preferred), IFN-γ release assay, quantiferon test
  b. the Mantoux skin test

  A positive result from any TB test excluded the subject from the study and the subject and their medical care team would be informed. An intermediate result from blood sample testing did not exclude the participant from randomisation if the chest X-ray was negative. The blood test for TB only needed to be repeated if there was a change in the perceived clinical risk of TB.
- Participants should not have had live immunisations[1] 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 reactions, 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

Setting

Recruitment for this study was performed in 16 paediatric and adult diabetes research centres across the UK which are named in *Report Supplementary Material 1*.

Recruitment procedure

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

Participant identification and recruitment

Potentially eligible participants were approached to consider participation into the study by their local diabetes teams from clinic records, during clinic visits or inpatient admissions. Some patients self-referred via the T1DUK Consortium website (https://type1diabetesresearch.org.uk/).

The local co-ordinator of the trial contacted the young person and/or their parents initially by phone, e-mail or in person to discuss the trial, explain the aims of the study and provide copies of the NHS Research Ethics Committee (REC) approved, age-appropriate participant and parent information sheets (PISs). They were also signposted to a short REC-approved video explaining the trial aimed at a young audience (www.youtube.com/watch?v=8kuCefuBSW4&t=105s).

For the purposes of this report, carers and guardians were also grouped under the 'parent' term as having responsibility for the decision to consent. Parents were provided with an information sheet but for parents of 16- to 18-year-olds,

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this only reflected the need to complete PROMs questionnaires as no parental consent for the trial was required for the older age group. Potential participants (and parents of participants who were aged 12–15 years) had a minimum of 24 hours to consider this information and usually at least 5–7 days.

If the child (and the parent the child was aged < 16 years) wanted to take part, the local co-ordinator agreed a date for the first screening visit where the informed consent forms (ICFs) (and informed assent forms if the child was aged 12–15 years) were signed. While arranging this, the local co-ordinator offered to combine both screening visits wherever possible.

Consent

Written informed consent was obtained from all participants at the beginning of their first screening visit. For participants under 16, written assent was obtained in addition to written consent from a parent. The parents of participants aged 16 years or more were asked to consent to completing PROMs only.

When a 12- to 15-year-old participant who provided assent reached 16 years, they were given the 16–18 years PIS and asked to reconsent at the next study visit using an age-appropriate ICF. The parent was advised that their ongoing consent for the participant was no longer required but that they should still reconsent to complete the PROMs questionnaires using the parent 16–18 years ICF.

Payment

Reimbursement of travel expenses for the participant and their parent to attend clinics for screening, treatment and follow-up visits was provided. We offered £10 Love2Shop vouchers per treatment visit (visits 1–7) and £30 in vouchers for the final visit at week 52 to participants to compensate for their inconvenience and to encourage continued participation.

Screening

Screening evaluations were performed during the 100 days between confirmed diagnosis and the first planned dose of IMP with the exception of the MMTT which had to be within 37 days of the first planned dose. Screening involved the tests described in *Table 1*.

During the second screening visit, participants were asked to provide baseline data for the following in the event that they were subsequently confirmed as eligible and randomised into the trial:

1. Starting a diary to record any illnesses, concomitant medications, symptomatic hypoglycaemic events and insulin doses within the time frames specified in the diary.
2. DBS testing at home.
3. Wear their glucose monitor. They went home with the first sensor already attached wherever possible.

The first IMP treatment visit was agreed in advance with the participant so that it fell within the required time frame for the participant to remain eligible (no more than 100 days from diagnosis and 37 days from MMTT).

Interventions

Ustekinumab (STELARA)

Ustekinumab is a fully human IgG1k monoclonal antibody and was manufactured, QP released and shipped to a distributor by Janssen-Cilag Ltd (Beerse, Belgium) to good manufacturing practice.

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

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

Ustekinumab does not contain an antimicrobial agent and has a shelf life of 2 years. Ustekinumab vials must be kept in their outer carton and stored in a refrigerator (2–8 °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). Chemical and physical in-use stability has been demonstrated for 4 hours at 15–25 °C; hence all syringes were used within 4 hours of preparation (defined as the time the vial was removed from the refrigerator) or returned unused to Pharmacy.

Placebo (control)

Saline in the form of sodium chloride 0.9% w/v solution for injection was used as the control treatment and was taken from local pharmacies' stock in accordance with a signed sponsor agreement.

A representative summary of product characteristics (SmPC) was used to represent all saline (marketing authorisation number PL 02848/0157).

It does not contain an antimicrobial agent and has a shelf life of 3 years. Saline ampoules must be stored below 25 °C in a secure area with restricted access.

Site pharmacies maintained the blind by providing blinded site staff with a syringe containing the appropriate amount of IMP or control according to the received trial prescription and randomisation number.

No investigator brochure was available for this trial. The SmPC required for STELARA and the SmPC for the saline solution formed the simplified Investigational Medicinal Product Dossier. Section 4.8 of the SmPC was used as the Reference Safety Information (RSI) for pharmacovigilance purposes.

Ustekinumab 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 were visually inspected for particulate matter or discolouration prior to administration. Neither solution was used if discoloured or cloudy, or if foreign particulate matter was present. The risk of unblinding due to colour change was assessed. Due to the small volumes of solutions used, ustekinumab and the saline control were indistinguishable when used in a standard single-use injection syringe fitted with a hypodermic needle.

The schedule of dosing is shown in *Report Supplementary Material 2* and was determined by the participant's body weight recorded at a prior visit.

Injections of ustekinumab or control treatment were administered SC via prepared syringes as a single dose. For participants weighing ≤ 40 kg, the dose was 2 mg/kg; for participants > 40 kg, the dose was fixed at 90 mg. The maximum total amount of ustekinumab administered to any participant for the trial was 630 mg. Injections occurred at weeks 0 and 4 and then every 8 weeks for a duration of up to 44 weeks. The participant's weight was checked at visits and the dose adjusted if required.

For all participants, the first dose was administered in a hospital setting and the participant observed for 1 hour. No significant local or systemic reactions were reported for ustekinumab or control.

During the COVID-19 lockdown, the trial was adapted to allow home dosing of blinded IMP for participants not permitted to come to a hospital visit for the trial. Wherever possible, the site provided a blinded pre-prepared syringe for delivery to the participant's home via an approved courier within the required time frame (4 hours). Where this was not possible, blinded vials and a kit for preparing the syringe were delivered to the participant's home and an unblinded research nurse video-called the participant to talk them through drawing up the IMP into the syringe. As participants were already used to regular SC injections with insulin, the additional IMP administration would be very similar and was deemed acceptable to allow participants to continue in the trial if they so wished.

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Outcome measures

The primary outcome was 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 has a longer half-life and is not metabolised by the liver. This trial used C-peptide as the primary outcome as is standard in new-onset T1D immune-ustekinumab studies.

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

Exploratory (tertiary) outcomes included:

1. Alternative ways of measuring islet activity
2. Mechanistic assessment of immune biomarkers to explore potentially favourable changes in the immune response to self-antigens
3. Correlation of PROMs scores with C-peptide level and parent reports.

Appendix 1 details the end points, outcome measures and time points of evaluation for the trial, as well as the method of evaluation.

Changes to outcome measures during the trial

We added one outcome measure concerning participants who may have contracted COVID-19 during their time in the trial and to explore its potential impact. This was the only change to the original outcomes planned.

Participant timelines

Potential participants were approached about the trial within 100 days of their diagnosis. They were consented and screened and eligibility checks were completed prior to randomisation. Both screening visits could be combined if needed. Dose 1 was given no more than 37 days after the screening MMTT if the participant was randomised.

Dosing occurred at weeks 0, 4, 12, 20, 28, 36 and 44 and the follow-up visit was 52 weeks after dose 1 (see *Report Supplementary Material 2*). The treatment window permitted was originally 2 weeks, but 10 months after the first site opened (October 2019) it was reduced to 1 week.

At the 52-week visit, participants were asked if they wanted to continue to provide a reduced data set at 78 and 104 weeks after dose 1. This was optional and did not affect their return to standard clinical care after the 52-week follow-up visit. Data collection from this visit was not funded by NIHR and is not included in this report.

Sample size

The power calculation followed Lachin *et al.*[30] 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 0.2 nmol/l difference between MMTT AUC C-peptide values of the ustekinumab and control arms which are assumed to be 0.5 and 0.3 (nmol/l), respectively at week 52. Seventy-two participants (48 treatment; 24 control) were required to allow for an approximate 10% loss to follow-up.

No interim analysis was planned for the trial.

Randomisation and blinding

Minimisation by age (12–15 years vs. 16–18 years) and screened peak C-peptide levels (0.2–0.7 vs. > 0.7 nmol/l) were used to ensure balance between treatment groups. The treatment-to-control ratio was 2 : 1 to provide additional data on drug safety (n = 48 : 24). The minimisation algorithm and randomisation list were provided by Sealed Envelope Ltd (London, UK) (https://sealedenvelope.com) working in consultation with statisticians in Swansea Trials Unit (STU).

After confirmation of participant eligibility and consent, the site principal investigator (PI) or their delegate entered relevant participant data via the secure web-based randomisation system (www.sealedenvelope.com/redpill/ustekid) available 24 hours a day run by Sealed Envelope Ltd.

A unique participant randomisation code was generated and an immediate confirmatory e-mail was sent to the nominated site staff and the Trial Office. The treatment allocation did not appear on the e-mail, only the randomisation code. Pharmacy staff were able to break the code and provide the appropriate treatment allocated to each participant. Blinded syringes were prepared by delegated staff in pharmacy or unblinded research nurses in accordance with local requirements.

Blinding

Dosage and regimen of control treatment and ustekinumab were matched and there was no visible difference in appearance between the two. Randomisation e-mails were blinded. Only pharmacy staff and key independent STU personnel were in possession of the code break list.

To ensure blinding at sites, the IMP was drawn out of vials by pharmacy staff or other delegated persons and relabelled when dispensed into syringes. The blinded syringe was provided to blinded research staff for administration. If unblinded research staff prepared and administered the blinded syringe, they collected the relevant supplies and documents from pharmacy to administer the treatment.

Final unblinding of all participants took place after the creation of a locked analysis data set and the finalisation of the statistical analysis plan (SAP).

Emergency unblinding (24/7) was managed by Sealed Envelope Ltd. The randomisation allocation would only be broken for valid medical or safety reasons, for example in the case of a SAE. All emergency unblinding of suspected unexpected serious adverse reactions (SUSARs) was at the discretion of the local investigators when clinically indicated for participant safety. If emergency unblinding was delayed, the treating clinician was instructed to treat the patient as if the active drug had been given.

Trial assessments

An overview of the trial assessments can be found in *Report Supplementary Material 2* with a breakdown of blood and urine sample collection requirements in *Report Supplementary Material 3* and *Report Supplementary Material 4*, respectively. The trial involved the following general procedures:

- medical history
- vital signs
- physical examination (including height and weight)
- record of concomitant medication
- insulin dose usage
- metabolic review
- AE assessment
- blood sampling for the assessment of safety, metabolic and immunological outcomes

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- urine sampling for the assessment of pregnancy, safety and metabolic outcomes
- glucose monitoring SC using a glucose monitor to assess safety (hypoglycaemia) and metabolic outcomes
- DBS testing
- participant diary
- questionnaires to assess patient- and parent-related secondary outcome measures
- exocrine enzymes
- COVID-19 antibody testing
- remote follow-up at weeks 78 and 104.

At dosing visits, the blood draw always took place prior to administration of the IMP.

Guidance on glycaemic control during the study

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

Glycated haemoglobin was measured as per study schedule based on the local laboratory results with a target value set according to 2015 National Institute for Health and Care Excellence guidelines[31] in agreement with the participant and their clinical care team. Where this target was not met, advice was given as clinically required.

Glycaemic control was reviewed at every study visit.

Mixed Meal Tolerance Test (laboratory test)

Secretion of C-peptide was tested using a MMTT at baseline, week 28 and week 52. The MMTT was part of the screening test and could not be done more than 37 days before their first treatment dose.

Participants were asked to test their blood glucose at home 2 hours before attending for their MMTT that morning. The MMTT was conducted only if the fasting value was between 4.0 and 11.1 mmol/l (inclusive). Other checks relating to their fasting status, smoking and insulin administration that morning were also carried out to ensure eligibility for the MMTT.

The MMTT procedure was carried out as follows:

1. Ask participant to void their bladder – discard this urine sample.
2. Insert IV line.
3. 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 *Report Supplementary Material 3*).
4. The participant drinks the standardised liquid meal: Ensure Plus 6 ml/kg (maximum 360 ml) to be ingested within 5 minutes.
5. Blood samples drawn at 15, 30, 60, 90 and 120 minutes, after the start of ingestion of Ensure Plus.
6. At 120 minutes, measure capillary blood glucose and ketones.
7. At 120 minutes, ask the participant for a urine sample to be collected in a boric acid container. Any urine passed prior to this point was also collected and combined with the 120-minute sample.

Once the MMTT was completed, the participant was allowed to eat and receive insulin as appropriate.

Urine C-peptide/creatinine ratio

This was used as an alternative marker of insulin production and was measured from the 120-minute urine sample taken during the MMTT at screening and at weeks 28 and 52.

Glucose monitoring

Blood glucose variability was studied through SC glucose variation, using data derived from glucose monitor for the 2 weeks prior to each dosing visit and at 52 weeks. Mean, median, standard deviation (SD) and interquartile range (IQR)

of glucose variability were calculated for frequency of and number of episodes of hypoglycaemia (< 4.0 mmol/l), and also instances of elevated values, that is > 10 mmol/l and > 15 mmol/l.

All participants were provided with sensors and a reader for the Abbott Freestyle glucose monitoring system (FreeStyle Libre) at screening visit 2. Participants were asked to wear a sensor for 2 weeks prior to each study visit and were advised to read their measurements at least four to seven times a day to guide insulin dose adjustment. The sensor data were downloaded by research staff or at home by participants at study visits. Participants were encouraged to use the sensors continuously outside of these 2-week periods to guide insulin adjustment and provide additional information. Data from other sensors were collected when the FreeStyle Libre device was not used and an algorithm applied to adjust for the difference in data.

Record/categorisation of hypoglycaemia

Participants were advised to record in a trial diary any symptoms possibly related to hypoglycaemia and their timing to allow us to compare to glucose readings with the glucose monitor data. A finger-prick blood glucose recording was completed and the result recorded in the diary any time hypoglycaemic symptoms occurred, even if the glucose monitor sensor was also being worn.

The PI or delegate reviewed the diary during the participant visit wherever possible to discuss any hypoglycaemic events documented. Clinical hypoglycaemic events rates were calculated from records downloaded from the FreeStyle Libre device, symptoms recorded in the diary and self-recorded blood tests and were assessed and categorised in two ways for analysis according to ADA guidelines.[32,33]

1. Level of hypoglycaemia

Level 1 – A glucose alert value of > 3.0 but ≤ 3.9 mmol/l (or less)

Level 2 – A glucose level of ≤ 3.0 mmol/l – clinically important hypoglycaemia

Level 3 – Severe hypoglycaemia, as defined by the ADA,[33] denotes severe cognitive impairment requiring external assistance for recovery (see clinical characterisation below)

2. Clinical characterisation

Severe hypoglycaemia. Severe hypoglycaemia is an event requiring assistance of another person to actively administer carbohydrates, glucagon, or take other corrective actions. Plasma glucose concentrations may not be available during an event, but neurological recovery following the return of plasma glucose to normal is considered sufficient evidence that the event was induced by a low plasma glucose concentration.

Documented symptomatic hypoglycaemia. Documented symptomatic hypoglycaemia is an event during which typical symptoms of hypoglycaemia are accompanied by a measured plasma glucose concentration ≤ 3.9 mmol/l.

Asymptomatic hypoglycaemia. Asymptomatic hypoglycaemia is an event not accompanied by typical symptoms of hypoglycaemia but with a measured plasma glucose concentration ≤ 3.9 mmol/l.

Probable symptomatic hypoglycaemia. Probable symptomatic hypoglycaemia is an event during which symptoms typical of hypoglycaemia are not accompanied by a plasma glucose determination but that was presumably caused by a plasma glucose concentration ≤ 3.9 mmol/l.

Hypoglycaemic events were treated according to local clinical guidelines.

Glycated haemoglobin level (external laboratory test)

Glycated haemoglobin was tested in the local laboratories of the study sites to guide clinical care. A blood sample was also taken for centralised measurement of all HbA1c at baseline, then weeks 12, 28 and 52 by the good clinical laboratory practice (GCLP)-accredited Diabetes Research Unit Cymru (DRUC) laboratory, Swansea University.

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Dried blood spot measurements

An instruction sheet was given to participants at screening visit 2 about collection of DBS samples via finger prick at home between visits and what to do with those samples. DBS sampling was performed once a week, preferably at weekends, one before the first meal of the day, and one 60 minutes afterwards from baseline until 28 weeks after dose 1, and then monthly up to week 52 for the measurement of C-peptide.

The DBS samples were collected only if the fasting value by capillary blood glucose meter was between 4.0 and 11.1 mmol/l (inclusive). DBS samples were posted by participants to the DRUC laboratories in the pre-paid envelope provided as soon as they were completed and dry.

Insulin dose (clinical care measurement)

Mean daily insulin use was calculated over 7 consecutive days during the 2 weeks preceding all visits and participants were asked to record all insulin usage in their diary during those 2 weeks. This value was calculated in units of IU/kg/day and combined doses of all different types of insulin administered over this study period. Where data from consecutive days were not available, the 3 days closest together were used.

Body weight and body mass index (clinical care measurement)

Body weight and height were recorded at some visits and the most recent weight recorded were used to calculate IMP dosages for forthcoming treatment visits. Body mass index (BMI) was calculated as: weight (kg)/[height (m)]^2.

Participant- and parent-reported outcome measures

Participant quality of life was assessed by age-appropriate PROMs compiled into a questionnaire booklet:

- The Hypoglycaemia Fear Scale – HypoFear[34]
- DTSQ for inpatients – DTSQ (which also included a 'change' score for the 12 month visit – the DTSQc)[35]
- PedsQL (generic core scale and diabetes-specific modules)[36]

Questionnaires were administered to participants and their nominated (consented) parent at screening and weeks 28 and 52. The same parent completed the questionnaire at each time point.

Statistical methods

Trial design

This was a randomised, double-blind, placebo-controlled Phase II parallel-group trial. The treatment-to-control ratio was 2 : 1 to provide additional data on drug safety.

Participants allocated to receive the active treatment were given ustekinumab (STELARA) SC in a dose depending on the body weight at weeks 0, 4, 12, 20, 28, 36 and 44 weeks. For participants weighing ≤ 40 kg, the dose was 2 mg/kg; for participants > 40 kg, the dose was fixed at 90 mg. Those allocated to the control group were given saline (0.9% sodium chloride).

Framework

The overall objective of the trial was to test the effect of ustekinumab versus a control treatment.

Statistical interim analyses and stopping guidance

No interim analysis on primary and secondary outcomes was planned or carried out. Safety data were provided to both the Trial Steering Committee (TSC) and the DSMB on a regular basis, who did not request any additional analysis on safety. Similarly, no early stopping or other adaptations were requested by TSC and DSMB. *Report Supplementary Material 5* lists the members of the TSC and DSMB for the trial.

Confidence intervals and p-values
Outcomes were analysed with two-sided tests at the 5% significance level. Appropriate confidence intervals (CIs) were calculated for all estimates of effect.

Analysis populations
All randomised participants who had not withdrawn from the trial before the first day of treatment were included in trial analyses and analysed according to treatment allocated.

Recruitment
We conducted an intention-to-treat (ITT) analysis using participants receiving at least one treatment dose. Details of the loss of participants and reasons why were recorded throughout the trial post screening.

Withdrawal/follow-up
Participants could withdraw from the trial at any time point. Data on timing of withdrawal or loss to follow up data were incorporated into a Consolidated Standards of Reporting Trials (CONSORT) diagram.

There was a potential 4-day gap between randomisation and the ordering of the IMP. In the event of a withdrawal prior to treatment, the Sealed Envelope Ltd procedure of 'randomisation in error' was followed in managing subsequent allocation to maintain the integrity of the minimisation. The event was recorded as 'withdrawal prior to treatment' in the CONSORT diagram. These participants were not included in the primary ITT analysis.

Method of analysis
Analysis methods, time points of evaluation, covariates adjusted for each outcome are specified in *Appendix 1*.

Checking assumptions for statistical methods
For continuous measures, distribution of residuals was examined to check for departures from the normality and homoscedasticity assumptions. Shapiro–Wilk's (normality) and White's (homoscedasticity) tests were also performed. Appropriate data transformation was performed if required.

For count measures, distributional assumptions were investigated graphically in line with recommendations by Wilson.[37]

Subgroup analysis
No subgroup analysis was planned.

Additional analysis
Assessment of pharmacokinetics and anti-drug antibodies was performed by an external contractor, and not covered in this report.

Statistical software
The analysis was carried out using SPSS version 28 (SPSS Inc., Chicago, IL, USA) and STATA 17 (StataCorp LP, College Station, TX, USA).

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Chapter 3 Trial management, procedures and timelines

Trial timelines

Funding timelines and milestones for the trial are described in *Table 2*.

Trial set-up

The Trial Sponsor was Cardiff University, who were the employers of the Chief Investigator.

The study was conducted in collaboration with STU, a registered Clinical Trials Unit (UKCRN registration number 58) partly funded at that time by Health and Care Research Wales as part of their research infrastructure funding and with a specialist interest in diabetes trials. STU provided trial services including trial, data and pharmacovigilance management, site setup and close down and overseeing trial monitoring, ensuring that all procedures were Medicines and Healthcare products Regulatory Agency (MHRA) compliant.

TABLE 2 Trial timelines

Milestone	Date
Outline submission to National Institute for Health and Care Research Efficacy and Mechanism Evaluation (NIHR EME)	24 July 2016
Full submission	5 January 2017
Responses to feedback	31 May 2017
Final revision	6 July 2017
Funding letter issued	18 September 2017
Project start	1 November 2017
Collaboration Agreement signed	19 July 2018
Initial REC approval	14 June 2018
Initial MHRA approval	26 June 2018
Sponsor green light	7 November 2018
First site opened	10 December 2018
First participant consented	11 December 2018
First participant randomised	14 December 2018
Recruitment halted due to COVID-19 pandemic	16 March 2020
Recruitment restarted after COVID-19 lockdown eased	3 July 2020
Last participant consented	5 August 2021
Last participant randomised	19 August 2021
Last participant completing 12 month follow-up visit	31 August 2022
Last participant completing the optional 24 month follow-up visit	31 August 2023

The study was also supported by the DRUC laboratory who are co-located with STU at Swansea University and King's College London (KCL).

The study was primarily funded by a grant from NIHR-EME (Ref: 16/36/01). KCL laboratories were also in receipt of funding from the Juvenile Diabetes Research Foundation for enhanced testing of blood samples investigated for USTEK1D. Funding was provided by Janssen-Cilag for pharmacokinetics and anti-drug antibody analysis.

Ethical approval was granted by Wales REC 3 reference 18/WA/0092 (IRAS ID 230113) on 14 June 2018 and the MHRA on 26 June 2018.

The trial had two oversight committees: a TSC and a DSMB. Independent members for both committees are listed in *Report Supplementary Material 5*. Both met twice a year as a standard requirement and ad hoc meetings were held when the need arose. All independent members were pre-approved by the NIHR EME before reviewing and agreeing to a committee charter.

The Trial Management Group (TMG) met quarterly and a smaller trial team meeting occurred weekly. During recruitment and follow-up the trial team held open forums for sites to dial in twice a week with any questions or concerns.

Accountability for trial medication

Ustekinumab

Janssen-Cilag Ltd supplied ustekinumab in the quantities required by the trial at no cost to the sponsor.

St Mary's Pharmaceutical Unit (SMPU) was the appointed contractor for the receipt and storage of ustekinumab prior to distribution to trial sites. Storage was compliant with Annex 13 requirements. Ustekinumab was sent from SMPU to sites via their approved courier with a signature required on receipt by the relevant party. A nominated trial pharmacist at sites was responsible for the receipt and storage of the ustekinumab vials.

Ustekinumab does not contain an antimicrobial agent and has a shelf life of 2 years. Ustekinumab vials must be kept in their outer carton and stored in a refrigerator (2–8 °C) in a secure area with restricted access. Ustekinumab must not be frozen.

At sites, ustekinumab vials were checked for temperature violations and damage prior to accepting them for the trial.

Ustekinumab was administered within 4 hours of it being taken from the fridge. If this time was exceeded, the syringe was returned unused to pharmacy for disposal. The same time frame was applied to saline, even though it was stored at room temperature.

Placebo (control)

The control treatment (saline 0.9%) was taken from local pharmacies stock in accordance with a signed sponsor agreement.

The saline did not contain an antimicrobial agent and had a shelf life of 3 years. Saline ampoules were stored below 25 °C in a secure area with restricted access.

Dispensing at sites

Some sites were unable to dispense a blinded syringe within pharmacy and unblinded research nurses had to be trained to prepare the blinded syringe with local approval. Where home dosing was required during COVID-19 lockdown,

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pharmacies prepared either a blinded syringe or blinded vials with the necessary kit to allow home dosing, with an unblinded research nurse on video call to advise on preparation and administration and to observe the compliance of dosing.

Unused portions of IMP were never reused and were disposed of in accordance with local requirements. Detailed instructions for use of ustekinumab or control were available in the package leaflet.

Safety

A review of AEs was performed at all visits and eligibility/safety blood samples were drawn at screening and baseline, and at weeks 12, 28 and 52 to examine the full blood count; urea, electrolytes and creatinine; liver function tests; (total bilirubin, total protein, albumin, aspartate aminotransferase (serum glutamic oxaloacetic transaminase), serum glutamate pyruvate transaminase (alanine aminotransferase), alkaline phosphatase); thyroid-stimulating hormone; immunoglobulins (G, A, M); calcium; magnesium, phosphate, lipid profile (total cholesterol, low-density lipoprotein, high-density lipoprotein, triglyceride). Urinalysis for pH, protein and albumin-to-creatinine ratio was carried out at screening and baseline, and at weeks 12, 28 and 52. A urine pregnancy test was completed on all females at all trial visits. PIs and other delegated medical staff at sites were expected to assess any values outside the laboratory reference range for clinical significance.

Participants were asked about new or unexpected symptoms at each visit. The diary was checked for any illnesses or diagnoses recorded since the last study visit.

Details of AEs were recorded from screening visit 2 until visit 8 at week 52, evidencing 8 weeks after the final dose.

Below are listed AEs that were considered expected for newly diagnosed T1D patients. If the events led to death, that was considered unexpected. These events could be classified and recorded as serious events but did not require immediate reporting to the REC:

- hypoglycaemia
- diabetic ketoacidosis.

All other AEs were assessed for seriousness, causality and expectedness in relation to the IMP.

Adverse reactions (ARs) and serious ARs (SARs) were evaluated for expectedness using the RSI 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 were:

- 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 SC 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.

Safety data were continuously monitored throughout the study via AE logs and case report forms. Specific data items included AEs observed at each dosing visit and the week 52 follow-up visit, for example 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 AEs to be reported included evidence of infection (Epstein–Barr virus, cytomegalovirus, TB or opportunistic bacteria) and evidence of posterior leucoencephalopathy syndrome.

Chapter 4 Results

Participant flow

The CONSORT diagram in *Figure 2* illustrates the number of patients who were approached, consented, screened, randomised, received the intended treatment and were analysed for the primary outcome.

Approximately 46.6% of participants consenting to be screened for the trial (41 of 88) received their diabetes clinical care from a different Trust/Health Board to the trial site where they were recruited at. This was partly due to participant or parent actively seeking out research opportunities and approaching the UKT1D Research Consortium website (https://type1diabetesresearch.org.uk/) which advertised the trial, and the willingness of trial sites to take on out-of-area patients for trial visits and, in some cases, their short-term clinical care. Additionally, trial sites already open were happy to take on participants for screening and early dosing visits while a closer trial site was being set up with the intention of transferring the patient back after dose 2. Six patients were transferred back to their local hospital once they opened to recruitment.

Two hundred and six patients were approached. Eighty-eight (42%) consented to become participants and to be screened. Thirteen of these participants were found not to be eligible after screening (15%). The balance between males and females and those ≥ 16 and < 16 years of age was similar between those approached and those screened (*Table 3*). The approached to consented ratio was better than predicted (predicted number to be approached = 260, 35% agree to screening) and the ineligibility rate through screening was lower than predicted (predicted 20%). No individuals were found ineligible due to insufficient C-peptide (predicted 5%), but five were not randomised due to inability to cannulate for the MMTT (predicted 0%). Four were excluded due to lack of islet autoantibodies (predicted 10%). Other reasons for ineligibility included: TB positive test (n = 1), patient withdrawal (n = 2) and site withdrawal due to COVID restrictions (n = 1).

We randomised 75 participants, of which 72 received a first dose and were included in the ITT analysis. The other three were not dosed because either the participant withdrew (n = 1) or the site withdrew them (n = 2).

Four participants withdrew from the trial altogether (two ustekinumab, two control – 6%); four others withdrew from treatment but attended the final primary outcome assessment (three ustekinumab, one control – 6%). However, six individuals did not have sufficient baseline data recorded for the planned primary analysis adjustment (four ustekinumab, two control) – two lacked baseline HbA1c values and four lacked baseline insulin use. The final cohort for primary outcome assessment was therefore 62 (86% – 72 minus 4 complete withdrawals and 6 inadequate baseline data). Thus, overall retention was good (especially considering that the trial was conducted over the COVID-19 pandemic period 2020–2), although missing baseline data reduced the sample size to less than that in the original power calculation (n = 66). Withdrawals were generally well balanced across the treatment arms (five ustekinumab: three control) given the 2 : 1 ustekinumab:control treatment allocation.

Recruitment

Recruitment started on the 10th of December 2018 and the last patient was recruited on the 5th of August 2021. On the 16th of March 2020, recruitment to the trial was temporarily halted due to the impact of the COVID-19 pandemic in the UK. Dosing of participants already in the trial continued in the majority of cases as one of two methods of administration were offered:

1. Site remained open for research visits.
2. Site pharmacy provided blinded medication to be couriered to the participant's home for home administration. An unblinded member of the trial team observed administration via videocall and provided advice where required.

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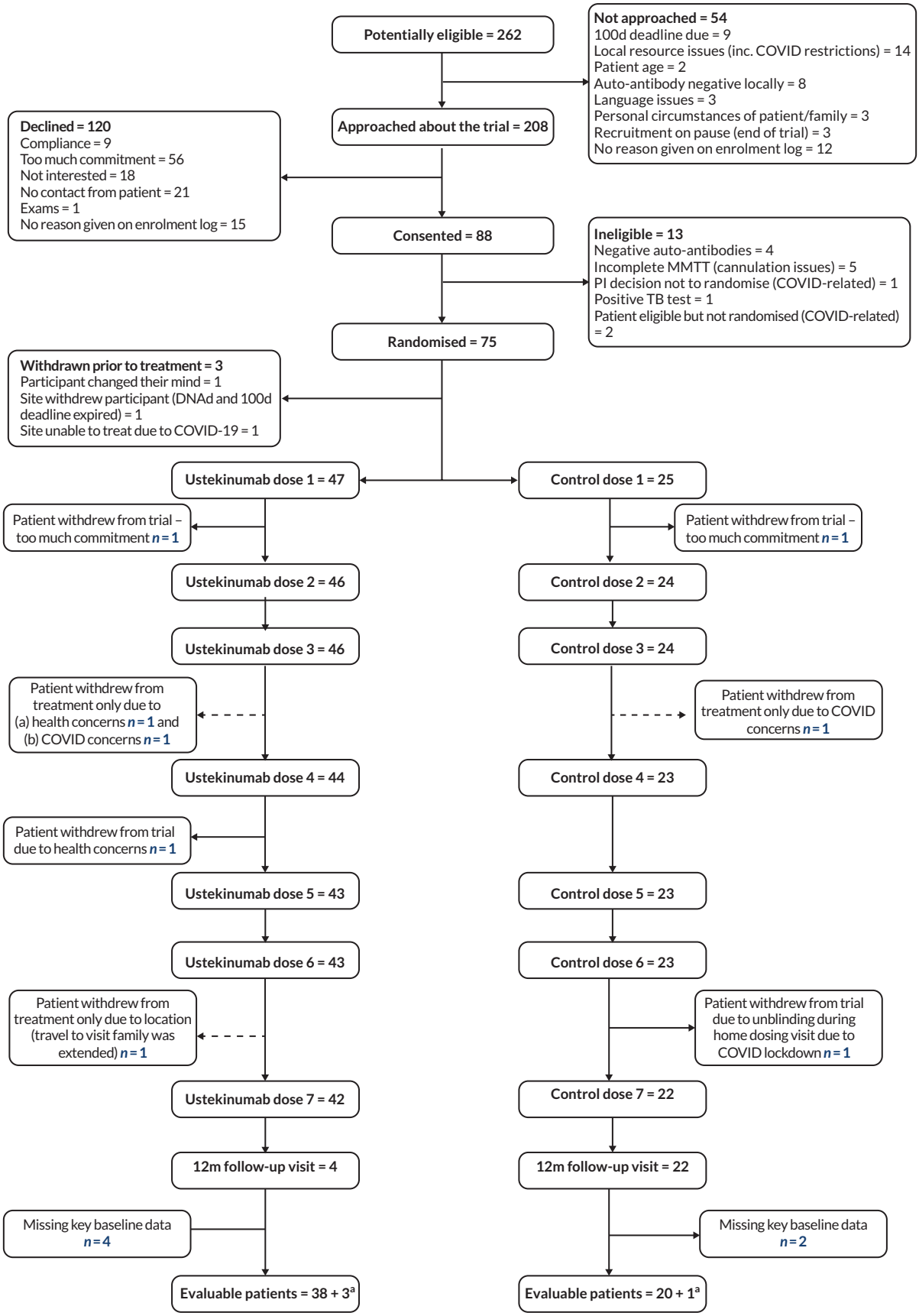


FIGURE 2 Unblinded CONSORT diagram. a, Including individuals who withdrew from treatment but returned for the primary outcome visit Note: Dashed lines indicate participants who withdrew from dosing but stayed in the trial and were included in the final analysis. 12m = 12 months; 100d = 100 days; DNAd = did not attend.

TABLE 3 Gender and age group balance

Gender	Age group		Total
	12–15 years	16–18 years	
Male	36	7	43
Female	23	6	29
Total	59	13	72

Sites were asked to reopen to recruitment subject to local approvals from the 16th of June 2020 (i.e. recruitment paused for 3 months). Recruitment recovered well after this time (*Figure 3*). Hence, overall, the recruitment period was 27 months which was slightly longer than the predicted recruitment period (24 months), but acceptable given the exceptional pandemic restrictions which caused the termination of a large number of trials.

As we were in COVID-19 lockdown from March to July 2020, no new randomisations were possible as we asked sites to pause recruitment. However, existing participants were able to continue self-medicating for the trial using blinded pre-prepared syringes or blinded vials with the support of an unblinded research nurse on video call advising on syringe preparation and administration of the medication at home for sites unable to accept research-related hospital visits.

Eligibility violations

No patients were recruited who were in violation of the eligibility criteria for the trial.

Baseline characteristics

Seventy-two participants were recruited, with control treatment allocated to 25 participants and ustekinumab allocated to 47 participants. The demographic characteristics of both treatment groups were well balanced. Most participants were younger teens (12–15 years), white, with higher standardised BMI and had peak C-peptide concentration > 0.7 nmol/l at screening (*Table 4*). BMI *z*-score was somewhat higher in the control group, while insulin use per kilogram was higher in the treatment group. Age and entry C-peptide were slightly lower in the treatment group and HbA1c was slightly higher, all of which are factors associated with more rapid C-peptide loss post diagnosis.

In the whole cohort, the percentage of older teens was less than predicted (18% vs. 40% predicted) which appeared to be due to fewer older teens being available to be approached rather than failing to consent for screening. This may relate to some loss of over 16 patients to adult diabetes treatment teams in centres where the main recruiting team was paediatric. The percentage with lower baseline C-peptide (< 0.7 mmol/l) was less than predicted (18% vs. 50%).

The ethnicity balance (82% white) is reflective of the national balance and increased frequency of T1D in people of White European ancestry [80% white in National Paediatric Diabetes Audit for England and Wales (NPDA) 2019–20] and the male-to-female ratio (60% male) was slightly more skewed towards males than in the NPDA report (NPDA: 54% male age 12–17). The percentage of 16- to 17-year-olds newly diagnosed with T1D in 2019–20 (vs. 12- to 17-year-olds) in the NPDA was 31%. Hence, overall, the randomised cohort was reasonably well reflective of the national cohort of newly diagnosed 12- to 17-years-olds with T1D.

Numbers analysed

We randomised 75 patients, of which 72 received a first dose and were included in the ITT analysis. Four participants withdrew from the trial altogether (two ustekinumab, two control – 6%); others withdrew from treatment but attended the final primary outcome assessment (three ustekinumab, one control – 6%).

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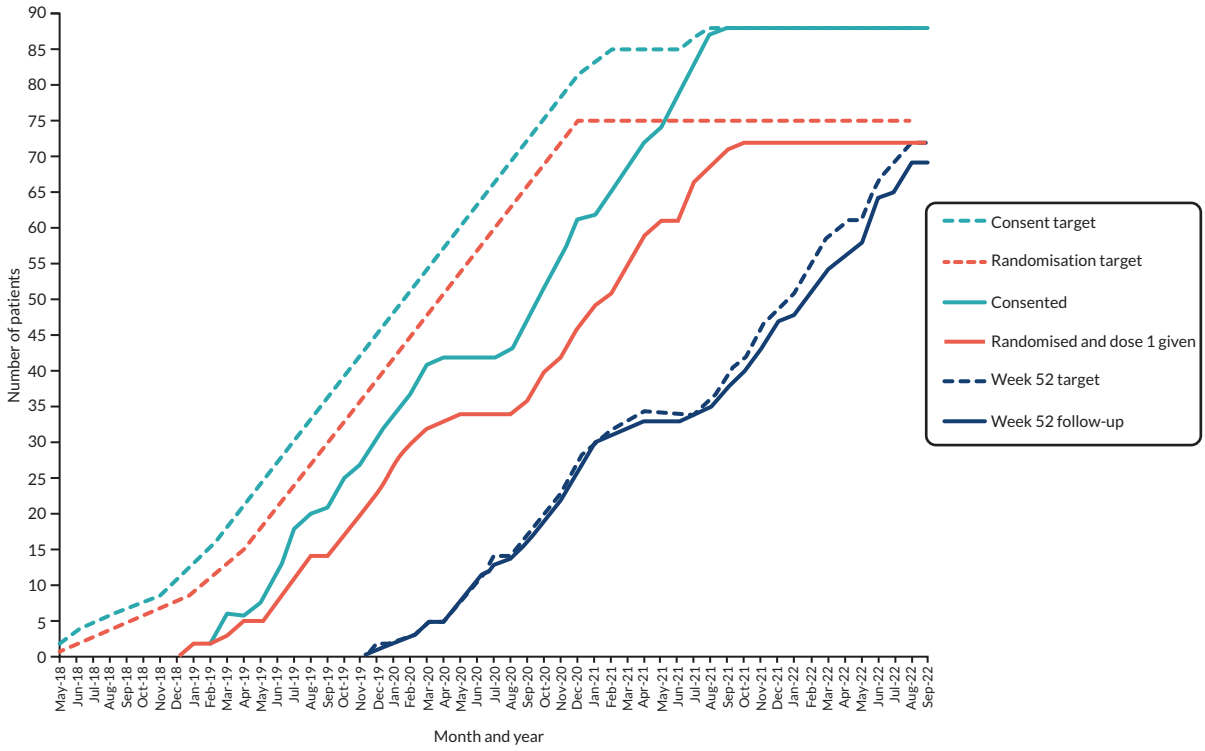


FIGURE 3 Recruitment and retention graph.

TABLE 4 Baseline characteristics

	Control (*n* = 25)	Ustekinumab (*n* = 47)
Sex N (%)		
Male	16 (64%)	27 (57%)
Female	9 (36%)	20 (43%)
Age of diagnosis in years mean (SD)	14.28 (1.65)	13.83 (1.74)
(Minimum, maximum)	(12, 18)	(11, 18)
Age (categorical) N (%)		
12–15 years	20 (80%)	39 (83%)
16–18 years	5 (20%)	8 (17%)
Age at screening in years mean (SD)	15.0 (1.63)	14.49 (1.78)
(Minimum, maximum)	(12.46, 18.77)	(12.18, 18.53)
Peak C-peptide level at screening (nmol/l) N (%)		
0.2–0.7	5 (20%)	8 (17%)
> 0.7	20 (80%)	39 (83%)
Ethnicity N (%)		
White	20 (80%)	39 (83%)
Mixed race	1 (4%)	4 (9%)
Black or Black British	1 (4%)	2 (4%)
Asian or Asian British	1 (4%)	1 (2%)

TABLE 4 Baseline characteristics (*continued*)

	Control (*n* = 25)	Ustekinumab (*n* = 47)
Other ethnicity	2 (8%)	1 (2%)
Height cm mean (SD)	167.7 (10.57)	165.2 (10.21)
(Minimum, maximum)	(147.8, 189.8)	(144.2, 184.0)
Weight kg mean (SD)	60.6 (13.70)	57.7 (13.85)
(Minimum, maximum)	(37.6, 96.6)	(31.0, 97.8)
BMI mean (SD)	21.3 (3.39)	21.0 (4.09)
(Minimum, maximum)	(15.5, 28.4)	(14.9, 32.7)
zBMI mean (SD)	0.51 (0.97)	0.40 (1.19)
(Minimum, maximum)	(−1.58, 2.47)	(−1.84, 3.02)
HbA1c mean (SD)	48.6 (13.25)	49.9 (10.15)
(Minimum, maximum)	(8[a], 74)	(33, 80)
Daily insulin dose (units/kg) mean (SD)	0.42 (0.19)	0.49 (0.32)
(Minimum, maximum)	(0.07, 0.80)	(0.04, 1.39)
Duration of follow-up months mean (SD)	12.78 (0.32)	12.78 (0.98)
(Minimum, maximum)	(11.86, 13.31)	(12.06, 18.16)
C-peptide AUC at screening (nmol/l/minute) mean (SD)	0.92 (0.48)	0.89 (0.50)
(Minimum, maximum)	(0.22, 1.87)	(0.17, 2.75)

a One patient had a hereditary blood disorder; the impact of this data point was checked in a sensitivity analysis.

Note
Continuous data displayed as arithmetic mean and standard deviation; categorical data displayed as number and percentage. $p > 0.5$ for all treatment comparisons.

However, six individuals did not have the sufficient baseline data recorded for the planned primary analysis adjustment (four ustekinumab, two control) – two lacked baseline HbA1c values and four lacked baseline insulin use. The final cohort for primary outcome assessment was therefore 62 (86% – 72 minus 4 complete withdrawals and 6 inadequate baseline data).

Numbers analysed in assessment of each secondary outcome are reported in the relevant tables in *Analysis of primary and secondary outcomes*. All analyses were conducted according to the treatment allocated.

Adherence to trial protocol and medication

Protocol deviations (PDs) and medication deviations (MDs) were reported to the Trial Office and were discussed at weekly meetings to determine clinical and statistical impact and seriousness. *Table 5* reports the number of PDs and MDs for the trial reported by sites. *Report Supplementary Material 6* details the individual PDs and MDs.

Analysis of primary and secondary outcomes

Mixed Meal Tolerance Test stimulated 2-hour C-peptide area under the curve at week 52

The primary outcome of the trial was MMTT-stimulated 2-hour C-peptide AUC measured at week 52. Data were transformed by the ln(x + 1) transformation before analysis. Mean 2-hour C-peptide AUC in both the ustekinumab and

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TABLE 5 Protocol and MDs reported for the trial

Category	Number of deviations	PD/MD IDs
PDs		
Missing primary outcome measure data	1	33
Missing secondary outcome measure data	8	2, 4, 6, 7, 8, 11, 15, 19
MMTT issue	11	9, 13, 20, 21, 27, 30, 38, 39, 41, 52, 64
Treatment window	14	25, 26, 42, 43, 45, 46, 51, 55- 61
Safety	9	1, 3, 10, 16, 17, 18, 28, 63, 65
Unblinding	1	31
Consent	2	22, 23
Blood sample integrity	4	5, 14, 54, 62
Vaccinations	6	32, 40, 44, 48, 49, 50
Staffing	1	35
Sample collection incorrect	1	24
Planned surgery	1	47
Hypo assessments	1	53
MDs		
IMP	5	12, 29, 34, 36, 37
Total	65	

the control group were lower by the end of the study than at baseline, both before transformation. The reduction in AUC C-peptide at week 52 was around 46% of baseline in the ustekinumab group and 66% in the control group.

After adjustment for gender, baseline C-peptide, age, HbA1c and exogenous insulin use with an analysis of covariance (ANCOVA) model, the ustekinumab group showed a larger geometric mean C-peptide AUC at week 52 than the control group (*Figure 4*).

After back transforming from the ln(x + 1) transformation, geometric mean of the week 52 C-peptide AUC_{0-120} in the control group was 0.3 nmol/l/minute and 0.45 nmol/l/minute for the ustekinumab group. Ratio of geometric mean of ustekinumab to control was 1.49 (95% CI 1.08 to 2.06; p = 0.02) at week 52 (*Table 6*).

Mixed Meal Tolerance Test stimulated 2-hour C-peptide area under the curve at 28 weeks

At 28 weeks, there was no significant difference in MMTT-stimulated 2-hour C-peptide AUC between the ustekinumab and the control group. After adjustment for baseline C-peptide, gender, HbA1c and exogenous insulin use with an ANCOVA model, ustekinumab group had a greater week 28 geometric mean C-peptide AUC (0.49 nmol/l/minute) than the control group (0.42 nmol/l/minute), but the difference was not statistically significant. The geometric mean ratio of ustekinumab to control was 1.15 (95% CI 0.81 to 1.63; p = 0.45) at 6 months (see *Table 6*).

Data were missing for 17 participants (23%) at this time point (4 withdrawals; 7 missed week 28 study visits, 4 with no baseline exogenous insulin use and 2 with missing HbA1c at baseline). The lack of significance could be a result of both a small effect size and reduced power due to a reduction in sample size at 28 weeks.

The control group had smaller C-peptide AUC than the ustekinumab group at 28 and 52 weeks, but the differences were only significant at 52 weeks. Hence, it appears that the benefit of the ustekinumab was ‘delayed’ with the

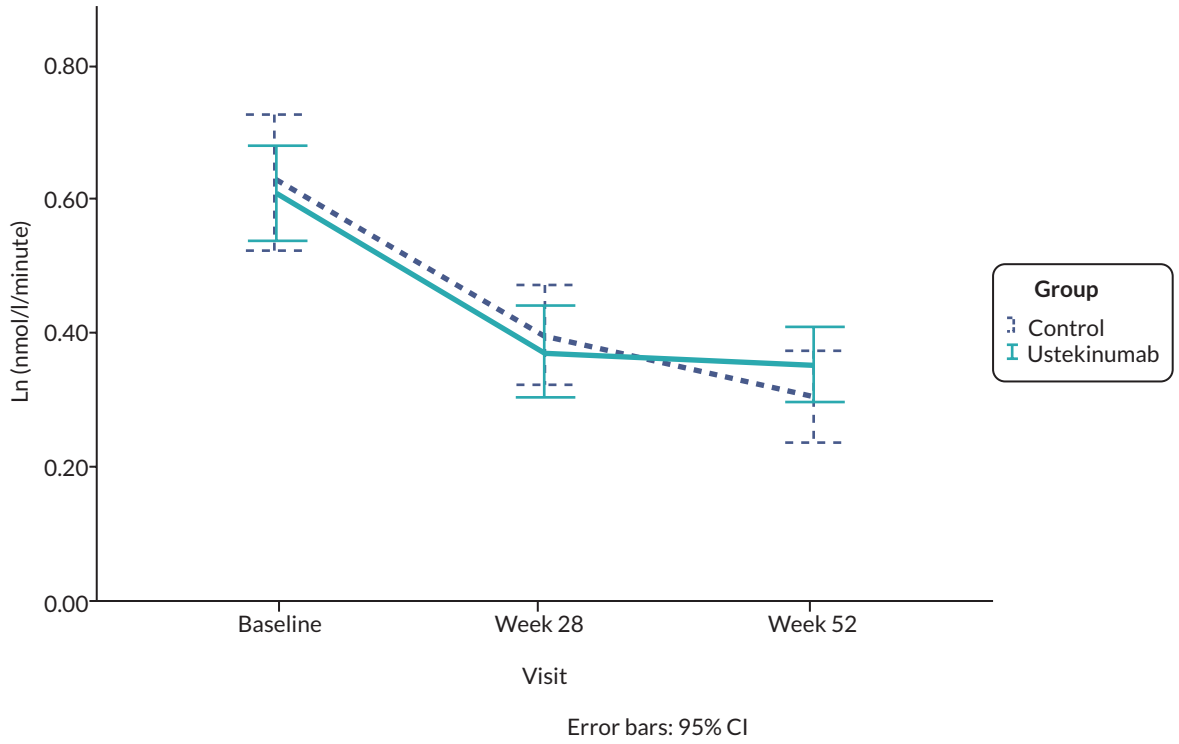


FIGURE 4 Geometric mean (95% CI) of C-peptide AUC by visit by group: transformed and after adjustment with covariates.

TABLE 6 Geometric mean ratio (95% CI) of C-peptide AUC (nmol/l/minute): ustekinumab/control

Visit	Ustekinumab (SD) *N*	Control (SD) *N*	Ustekinumab/ control (%)	95% CI Lower (%)	95% CI Upper (%)	*p*-value	Adjusted R^2
Week 2	0.84 (0.28) *n* = 47	0.87 (0.27) *n* = 25	97	74	127	0.82	NA
Week 28	0.49 (0.23) *n* = 36	0.42 (0.22) *n* = 19	115	81	163	0.45	0.42
Week 52[a]	0.45 (0.20) *n* = 41	0.3 (0.20) *n* = 21	149	108	206	0.02	0.44

a 95% CI does not include one (100%) and is statistically significant.

advantage being gained in the period 28–52 weeks, although the uncertainty around the week 28 estimates referred to in the previous paragraph needs to be borne in mind.

The models had modest explanatory power as shown by the adjusted R^2 for both 28 and 52 weeks' C-peptide AUC. Although there were some extraneous factors explaining variance in C-peptide AUC not accounted for by the models, the models worked reasonably well.

Glycated haemoglobin

Glycated haemoglobin was assessed at baseline, 12, 28 and 52 weeks. In general, participants' mean HbA1c values became higher by the end of the study (*Figure 5*). There was one participant (allocated to receive control treatment) with a hereditary blood disorder affecting their HbA1c values (8 mmol/mol at baseline, 9 mmol/mol at week 12, 22 mmol/mol at week 28 and 18 mmol/mol at week 52) which could distort assessment of the impact of the ustekinumab on participants' HbA1c as the average HbA1c values of the control would be reduced (*Figure 6*). HbA1c values of this

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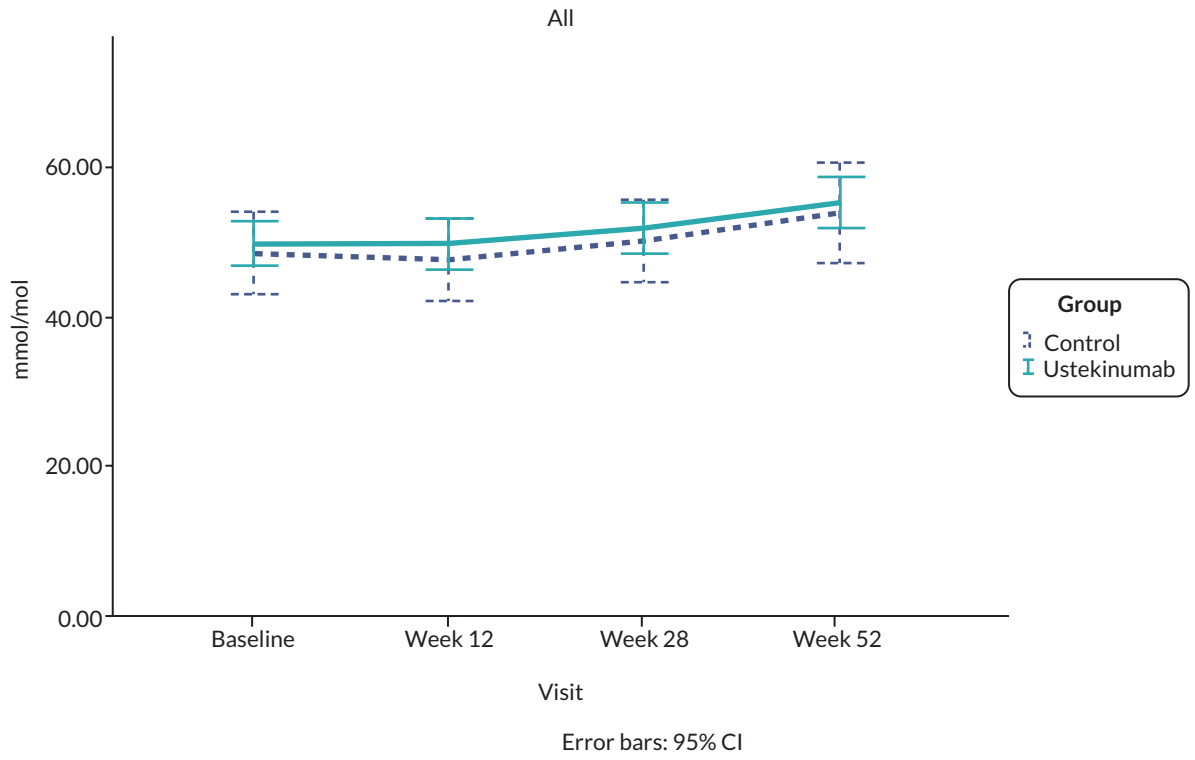


FIGURE 5 Glycated haemoglobin (95% CI) by visit by group – all participants.

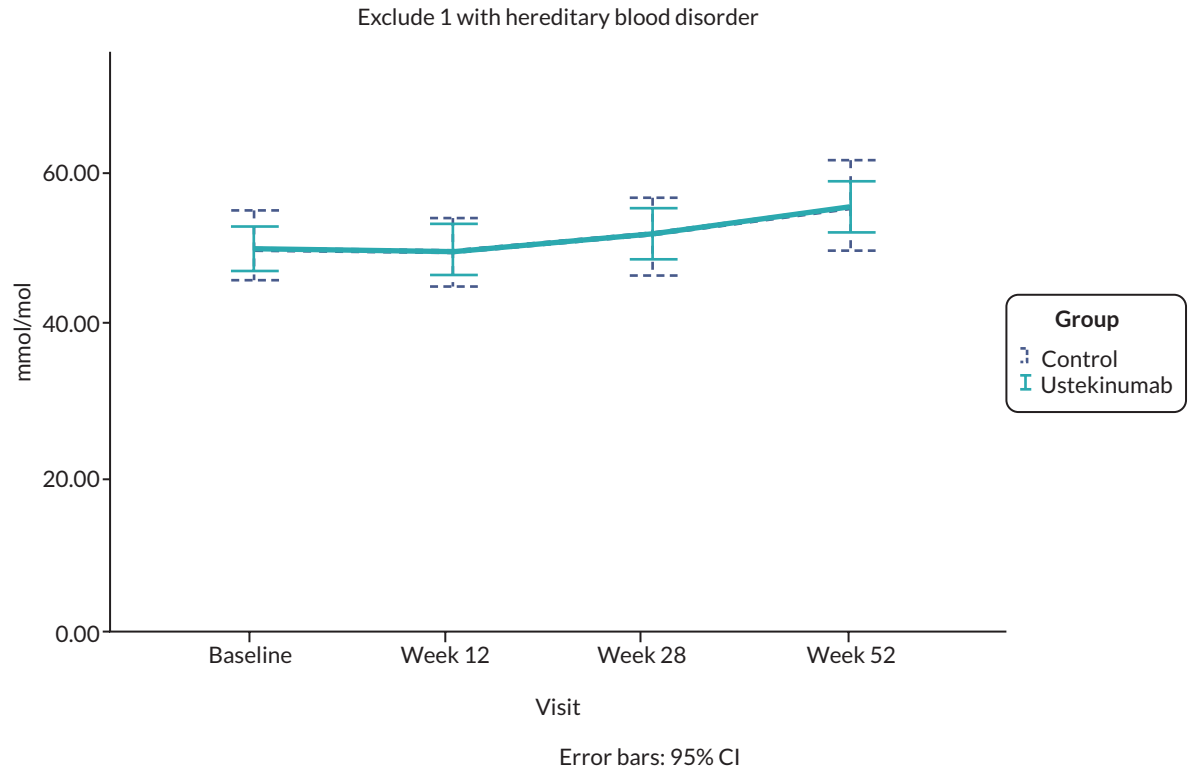


FIGURE 6 Glycated haemoglobin (95% CI) by visit by group – one excluded participant.

participant were excluded from estimation of effect size of the ustekinumab. The impact of this exclusion will be discussed in the section on sensitivity analysis (see *Sensitivity Analyses*).

Impact of the ustekinumab on HbA1c was initially assessed with an ANCOVA model with gender, baseline age and baseline HbA1c as the key covariates according to the SAP. After discussion at the TMG, baseline exogenous insulin use was also added to the model which improved the model fit. Findings of both the SAP-specified and the modified model were reported.

There were no statistically significant differences in HbA1c values between those allocated to receive the control and the ustekinumab at 12, 28 and 52 weeks in either set of analyses (*Tables 7* and *8*).

Differences in HbA1c between those who received the control and ustekinumab treatments were not significant in either of the models tested, although the point estimates were generally lower in the treated group. Note that the study was not powered to assess differences in HbA1c which typically requires two to three times larger sample sizes.[38] The exclusion of a control participant with a hereditary blood disorder might have increased the average HbA1c of the control group slightly, but the magnitude of the differences between the control and ustekinumab groups were so small that the conclusions of no significant difference at all the various time points would not be affected.

TABLE 7 Difference in arithmetic mean (95% CI) in HbA1c (mmol/mol): SAP-specified

Visits	Ustekinumab (SD) *n*	Control (SD) *n*	Ustekinumab – control	95% CI Lower	95% CI Upper	*p*-value	Adjusted R^2
Week 0	49.91 (10.15) *n* = 46	50.39 (10.25) *n* = 23	−0.48	−5.14	4.78	0.86	NA
Week 12	49.37 (8.94) *n* = 41	50.69 (9.11) *n* = 21	−1.33	−6.19	3.54	0.59	0.3
Week 28	52.07 (10.73) *n* = 40	52.56 (10.96) *n* = 20	−0.49	−6.33	5.34	0.87	0.16
Week 52	56.10 (11.28) *n* = 44	56.93 (12.14) *n* = 20	−0.83	−7.2	5.55	0.8	0.15

Note
One participant with hereditary blood disorder was excluded.
Week 12, 28 and 52 analyses adjusted by sex, baseline age and baseline HbA1c.

TABLE 8 Difference in arithmetic mean (95% CI) in HbA1c (mmol/mol): with exogenous insulin used as additional covariate

Visits	Ustekinumab (SD)	Control (SD)	Ustekinumab – control	95% CI Lower	95% CI Upper	*p*-value	Adjusted R^2
Week 0	49.91 (10.15) *n* = 46	50.39 (10.25) *n* = 23	−0.48	−5.14	4.78	0.86	NA
Week 12	48.90 (8.94) *n* = 38	51.47 (9.11) *n* = 20	−2.57	−7.63	2.49	0.31	0.41
Week 28	51.13 (9.49) *n* = 37	53.94 (9.59) *n* = 19	−2.81	−8.26	2.65	0.31	0.31
Week 52	55.05 (11.39) *n* = 41	58.28 (11.58) *n* = 19	−3.22	−9.7	3.26	0.32	0.19

Note
One participant with hereditary blood disorder was excluded.
Weeks 12, 28 and 52 analyses adjusted by sex, age, HbA1c and exogenous insulin use at baseline.

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Adjusted R^2 showed that models with baseline exogenous use explained variance in HbA1c better but values of the adjusted R^2 were small, indicating that there were extraneous factors explaining variance in HbA1c not accounted for by either model.

Glycated haemoglobin data are positively skewed, but the skewedness was not extreme, especially after exclusion of the participant with hereditary blood disorder. Models on log-transformed A1c were also performed for sensitivity checks, with similar results (see *Report Supplementary Material 7*). The simpler linear models were reported for ease of interpretation and parsimony.

Exogenous insulin use

Mean daily exogenous insulin use adjusted by bodyweight was assessed at baseline, 12, 28 and 52 weeks. In general, participants of both the ustekinumab and the control group used more exogenous insulin at the end of the study than at baseline (*Figure 7*).

Impact of the ustekinumab on exogenous insulin use was assessed with a regression model with gender, baseline age, baseline HbA1c and baseline exogenous insulin use as the key covariates.

After adjusting for gender, baseline age, baseline HbA1c and baseline exogenous insulin use, no significant differences in daily amount of exogenous insulin use were found between those allocated to receive the control and the ustekinumab. The control group used less insulin at 12 and 52 weeks and more insulin at 28 weeks, but none of these were significant (*Table 9*).

The models had low to modest explanatory power as shown by the adjusted R^2. There were extraneous factors explaining variance in daily exogenous insulin use not accounted for by the models.

Bodyweight-adjusted insulin dose data were positively skewed. Models on log-transformed insulin use were also performed for sensitivity checks and the results were similar (see *Report Supplementary Material 7*). The simpler linear models were reported for ease of interpretation and parsimony.

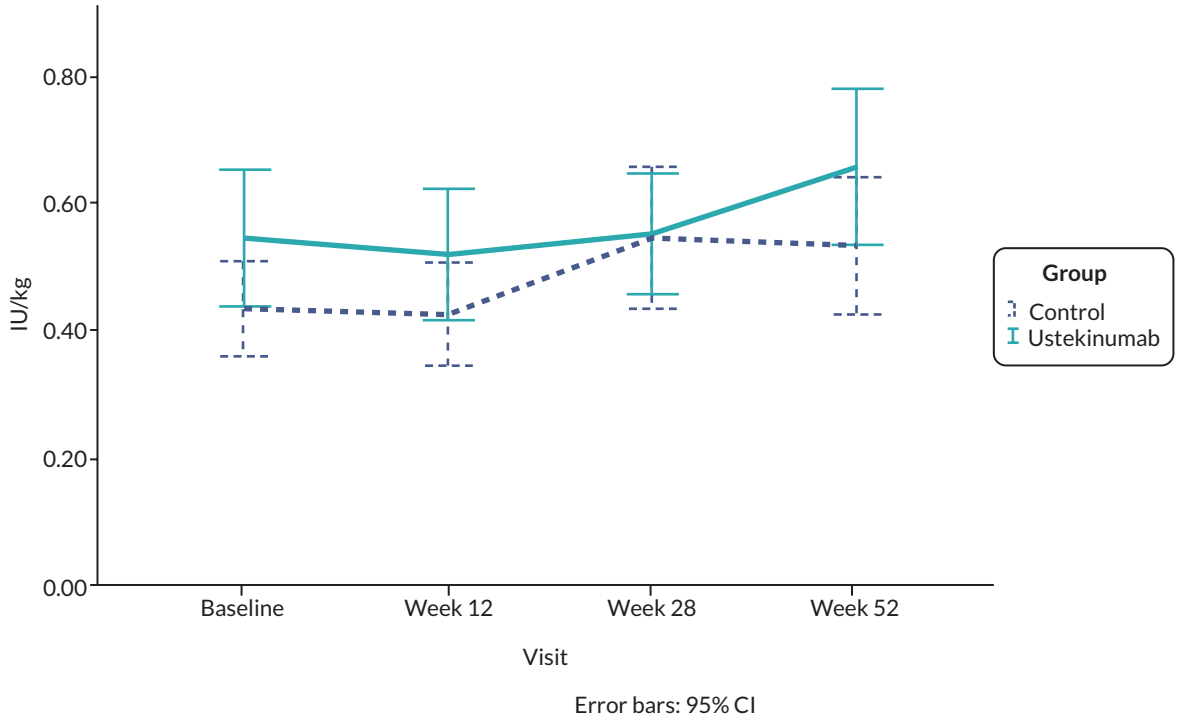


FIGURE 7 Mean daily exogenous insulin use adjusted by bodyweight by visit by group.

TABLE 9 Difference in arithmetic mean (95% CI) in bodyweight-adjusted insulin dose (IU/kg)

Visit	Ustekinumab (SD)	Control (SD)	Ustekinumab – control	95% CI		*p*-value	Adjusted R^2
				Lower	Upper		
Week 0	0.51 (0.37), *n* = 47	0.42 (0.18), *n* = 25	0.10	−0.03	0.23	0.14	NA
Week 12	0.49 (0.17), *n* = 38	0.48 (0.16), *n* = 20	0.01	−0.08	0.11	0.77	0.66
Week 28	0.53 (0.21), *n* = 33	0.58 (0.22), *n* = 18	−0.05	−0.18	0.08	0.42	0.4
Week 52	0.63 (0.30), *n* = 43	0.59 (0.31), *n* = 18	0.04	−0.13	0.21	0.64	0.38

Note
Weeks 12, 28 and 52 analyses adjusted by sex, age, HbA1c and exogenous insulin use at baseline.

Insulin dose-adjusted glycated haemoglobin

Insulin dose-adjusted HbA1c was assessed at baseline, 12, 28 and 52 weeks. In general, participants in both the ustekinumab and the control group had a higher insulin dose-adjusted glycated haemoglobin (IDAAC) at the end of the study than at baseline (*Figure 8*).

The impact of the ustekinumab on IDAAC was assessed with a regression model with gender, baseline age and baseline IDAAC as the key covariates. After adjusting for gender, baseline age and baseline IDAAC, no significant differences in IDAAC were found between those allocated to receive the control and the ustekinumab treatment (*Table 10*).

The models had modest explanatory power as shown by the adjusted R^2. Although there were some extraneous factors explaining variance in IDAAC not accounted for by the models, the models worked reasonably well. Models on log-transformed IDAAC were also performed for sensitivity checks and the results were similar (see *Report Supplementary Material 7*). The simpler linear models were reported for ease of interpretation and parsimony.

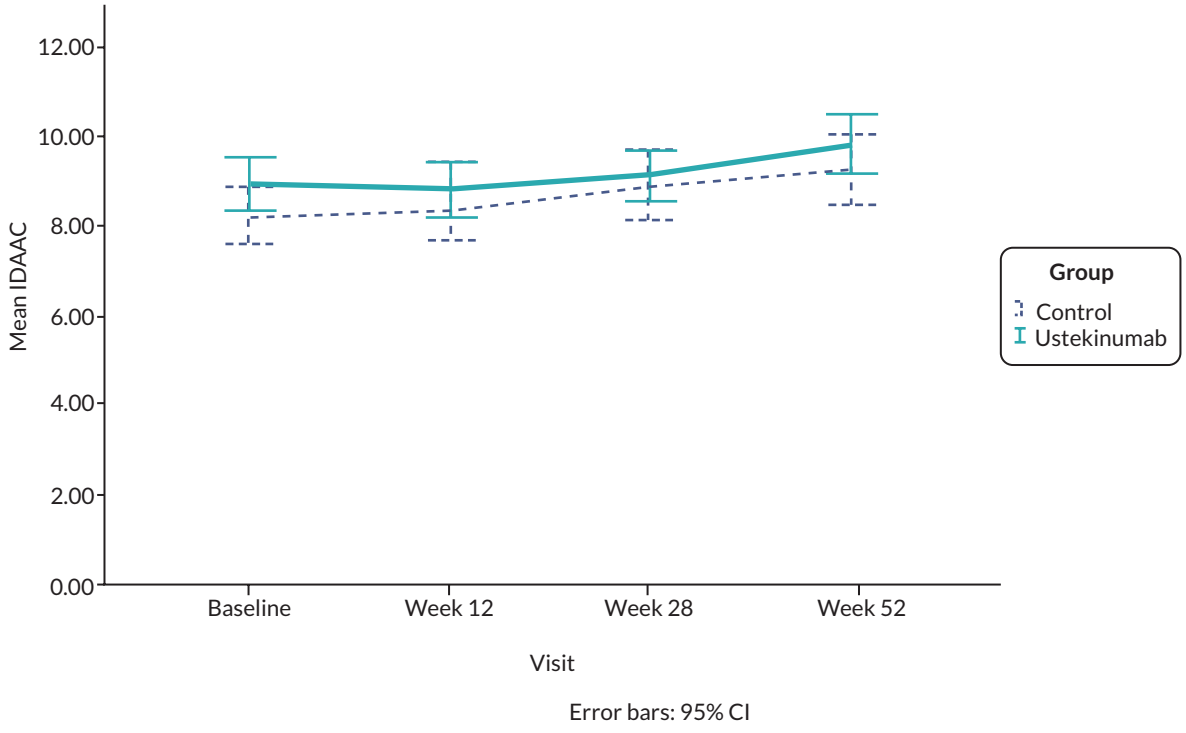


FIGURE 8 Mean IDAAC (95% CI) by visit by group.

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TABLE 10 Difference in arithmetic mean (95% CI) in IDAAC control vis-à-vis ustekinumab

Visit	Ustekinumab (SD)	Control (SD)	Ustekinumab – control	95% CI		*p*-value	Adjusted R^2
				Lower	Upper		
Week 0	8.90 (1.97), *n* = 45	8.23 (1.37), *n* = 21	0.67	−0.28	1.62	0.12	NA
Week 12	8.56 (1.14), *n* = 36	8.67 (1.15), *n* = 20	−0.1	−0.76	0.55	0.75	0.59
Week 28	8.92 (1.32), *n* = 33	9.15 (1.34), *n* = 18	−0.23	−1.02	0.56	0.56	0.4
Week 52	9.69 (1.77), *n* = 43	9.46 (1.79), *n* = 18	0.23	−0.79	1.24	0.65	0.31

Note
Weeks 12, 28 and 52 analyses adjusted by sex, age and IDAAC at baseline.

Glycaemic variability

Continuous glucose monitoring data were available for 58 participants at baseline and 28 weeks as well as 56 participants at week 52. The percentage of time participants spent in different thresholds of glucose levels are shown in the following subsections.

Percentage of time participants spent in range between 54 mg/dl and 70 mg/dl

Median percentage of time in range of > 54 mg/dl to < 70 mg/dl over 52 weeks in both groups was 82.40% to 61.32% in the control group and 77.30% to 60.33% in the ustekinumab group. There was no significant difference between the groups in any of the time points of assessment (82.40% in the control group vis-à-vis 77.30% in the ustekinumab group $p = 0.61$ at week 0; 67.46% vis-à-vis 66.18%, $p = 0.98$ at week 28 and 61.32% vis-à-vis 60.33% at week 52) (*Table 11*).

Percentage of time participants were hyperglycaemic

Median percentage of time when participants were hyperglycaemic increased over 52 weeks in either the control or the ustekinumab group at both the > 140 mg/dl and the > 180 mg/dl thresholds. There was no significant difference between the groups in any of the time points of assessment (*Table 12*).

Percentage of time participants were hypoglycaemic.

Median percentage of time when participants were hypoglycaemic at the < 70 mg/dl threshold increased over 52 weeks in both the control and the ustekinumab group, but there was no significant difference between the groups in any of the time points of assessment (*Table 13*). Median percentage of time when participants were hypoglycaemic at the < 54 mg/dl threshold decreased over 52 weeks in the control group and increased in the ustekinumab group, but there was no significant difference between the groups in any of the time points of assessment (see *Table 13*).

Clinical hypoglycaemic events

Hypoglycaemic events from patient diaries and adverse event forms

Sixty-eight participants reported 2946 hypoglycaemic events reviewed and verified by clinicians as either having a blood glucose level that reached the alert value (≤ 3.9 mmol/l) or being a probable symptomatic hypoglycaemic event

TABLE 11 Percentage of time in range of 54–70 mg/dl across assessment time points

Time points of assessment	Control median (IQR)	Ustekinumab median (IQR)	*p*-value[a]
Week 0	82.40 (69.77–88.29), *n* = 19	77.30 (62.94–85.95), *n* = 39	0.61
Week 28	67.46 (47.70–85.42), *n* = 19	66.18 (51.71–80.35), *n* = 39	0.98
Week 52	61.32 (42.44–77.04), *n* = 17	60.33 (49.35–81.37), *n* = 38	0.54

a Assessed by Mann–Whitney U-tests.

TABLE 12 Percentage of time hyperglycaemic at different thresholds across assessment time points

Time points of assessment	Control median (IQR), *n*	Ustekinumab median (IQR), *n*	*p*-value[a]
Percentage time > 140 mg/dl			
Week 0	31.64 (22.87–50.14), *n* = 19	35.95 (21.85–55.00), *n* = 39	0.6
Week 28	55.50 (33.09–68.17), *n* = 19	52.10 (33.81–71.41), *n* = 39	0.81
Week 52	61.50 (47.48–74.56), *n* = 17	55.62 (35.14–69.85), *n* = 38	0.33
Percentage time > 180 mg/dl			
Week 0	12.25 (5.57–22.56), *n* = 19	16.39 (5.00–30.42), *n* = 39	0.66
Week 28	29.06 (12.10–52.11), *n* = 19	26.77 (14.31–45.63), *n* = 39	0.65
Week 52	37.89 (21.64–54.95), *n* = 17	36.08 (15.85–47.06), *n* = 38	0.5
Percentage time > 250 mg/dl			
Week 0	1.22 (0.60–4.65), *n* = 19	2.36 (0.38–6.67), *n* = 39	0.55
Week 28	4.11 (1.90–25.58), *n* = 19	7.13 (0.98–16.36), *n* = 39	0.65
Week 52	12.11 (3.67–28.15), *n* = 17	8.69 (2.25–20.87), *n* = 38	0.39

a Assessed by Mann–Whitney U-tests.

TABLE 13 Percentage of time hypoglycaemic at different thresholds across assessment time points

Time points of assessment	Control median (IQR), *n*	Ustekinumab median (IQR), *n*	*p*-value[a]
Percentage time < 70 mg/dl			
Week 0	2.94 (1.22–10.16), *n* = 19	3.14 (0.79–6.39), *n* = 39	0.67
Week 28	2.64 (0.83–3.76), *n* = 19	2.05 (0.65–5.42), *n* = 39	0.88
Week 52	1.10 (0.52–3.14), *n* = 17	1.80 (0.44–5.53), *n* = 38	0.27
Percentage time < 54 mg/dl			
Week 0	0.18 (0.00–0.85), *n* = 19	0.12 (0.00–1.09), *n* = 39	0.99
Week 28	0.18 (0.00–0.44), *n* = 19	0.15 (0.00–0.99), *n* = 39	0.84
Week 52	0.03 (0.00–0.33), *n* = 17	0.17 (0.00–0.53), *n* = 38	0.66

a Assessed by Mann–Whitney U-tests.

(*Table 14*). Participants in the ustekinumab group reported lower incidence per person-year (39.38) than those in the control group (43.80), but the difference did not reach statistical significance [incidence rate ratio (IRR) 1.11, 95% CI 0.69 to 1.79; $p = 0.66$].

Except for shakiness, participants in the ustekinumab group reported lower incidence per year for all hypoglycaemic symptoms including hypoglycaemia at night, sweating, lost concentration, dizziness, headache, hunger, palpitations, weakness, nervousness, lost consciousness and other symptoms (*Table 15*).

Most of the hypoglycaemic events were treated with oral carbohydrates ($n = 2556$ events), followed by glucagon ($n = 51$ events), going to hospital ($n = 5$ events) and using IV glucose ($n = 1$). Participants in the ustekinumab group reported higher incidence of treating hypoglycaemia with oral carbohydrates per person-year (38.25) than those in the control group (36.38), but the difference did not reach statistical significance (IRR 0.95, 96% CI 0.60 to 1.51;

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TABLE 14 Distribution of hypoglycaemic events among participants by groups

	Number of participants			
	Control (*n* = 25)		Ustekinumab (*n* = 47)	
Number of hypos (*n* = 2946)	*n*	%	*n*	%
0	1	4	3	6
1–9	2	8	7	15
10–19	6	24	6	13
20–29	1	4	6	13
30–39	1	4	6	13
40–49	6	24	4	9
50–59	1	4	5	11
60–69	2	8	2	4
70–79	2	8	2	4
80–89	0	0	1	2
90–99	1	4	0	0
100 +	2	8	5	11

TABLE 15 Incidence of hypoglycaemic symptoms per person-year by groups

	Incidence per person-year		IRR		
Symptoms	Control[a]	Ustekinumab[b]	Control/ustekinumab	95% CI for IRR	*p*-value
Hypo at night (*n* = 281)	5.29	3.5	1.51	0.73 to 3.13	0.27
Sweating (*n* = 740)	17.67	7.18	2.46	0.98 to 6.20	0.06
Lost concentration (*n* = 593)	12.88	6.45	2	0.84 to 4.72	0.12
Dizziness (*n* = 630)	12.42	7.55	1.65	0.67 to 4.07	0.28
Headache (*n* = 335)	7.25	3.66	1.98	0.81 to 4.86	0.14
Hunger (*n* = 920)	15.21	12.61	1.21	0.51 to 2.86	0.67
Shakiness (*n* = 1859)	25.17	28.52	0.82	0.51 to 1.52	0.65
Palpitations (*n* = 159)	4.17	1.34	3.11	0.96 to 10.10	0.06
Weakness (*n* = 865)	14.54	14	1.04	0.53 to 2.05	0.91
Nervousness (*n* = 168)	3.08	2.14	1.44	0.43 to 4.86	0.55
Lost consciousness (*n* = 9)	0.17	0.11	1.47	0.36 to 5.98	0.59
Other symptoms (*n* = 221)	5.17	2.2	2.34	0.67 to 8.26	0.19

a One set of records missing.
b Three sets of records missing.

p = 0.83). They also reported higher incidence per person-year (0.84) of treating hypoglycaemia with glucagon than those in the control group (0.58), but the difference did not reach statistical significance (IRR 0.65, 95% CI 0.09 to 5.47; p = 0.73). Participants in the control group reported higher incidence per person-year (0.17) of going to hospital for hypoglycaemia than those in the ustekinumab group (0.02), but the difference was not significant (IRR 7.33, 95% CI 0.71 to 76.12; p = 0.10).

The only instance of treating hypoglycaemia with IV glucose was reported by a participant in the control group. There was no consistent difference between ustekinumab and the control group in the different levels of severity of hypoglycaemic events as assessed by clinicians, with no statistical significance between the two groups. Participants in the control group had more hypoglycaemic events (2.12 per person-year) not classified by clinicians than those in the ustekinumab group (0.32 per person-year) and this difference was statistically significant (IRR 6.68, 95% CI 1.21 to 36.82; p = 0.03) (*Table 16*).

There was no statistical difference between ustekinumab and control groups in incidence of hypoglycaemic events categorised as severe, documented symptomatic hypos or unlikely hypos as assessed by clinicians. Participants in the control group (4.95 per person-year) had more probable symptomatic hypoglycaemic events than those in the ustekinumab group (1.13 per person-year) as assessed by clinicians. The difference was statistically significant (IRR 4.36, 95% CI 1.39 to 3.69; p = 0.012). No hypoglycaemic events were reported as SAEs (*Table 17*).

TABLE 16 Levels of severity of hypoglycaemic events assessed by clinicians by groups

	Incidence per person-year		IRR		
Level of hypo	Control	Ustekinumab	Control/ ustekinumab	95% CI for IRR	*p*-value
Level 1 – A glucose alert value of > 3.0 but ≤ 3.9 mmol/l (*n* = 2228)	34.88	31.61	1.1	0.71 to 1.72	0.67
Level 2 – A glucose level of ≤ 3.0 mmol/l – clinically important hypoglycaemia (*n* = 615)	8.13	9.55	0.85	0.51 to 1.42	0.54
Level 3 – Severe hypoglycaemia, as defined by the ADA denotes severe cognitive impairment requiring external assistance for recovery (*n* = 1)	1 person (407) in the control group had 1 hypo assessed to be at level 3				
Not classified (*n* = 65)	2.12	0.32	6.68	1.21 to 36.82	0.03[a]

a Significant at 0.05.

TABLE 17 Clinical characterisation of hypoglycaemic events assessed by clinicians by groups

	Incidence per person-year		IRR		
Clinical characterisation of hypoglycaemic event	Control	Ustekinumab	Control/ ustekinumab	95% CI for IRR	*p*-value
Severe hypoglycaemia (*n* = 10)	0.13	0.16	0.79	0.19 to 3.32	0.74
Documented symptomatic hypoglycaemia (*n* = 2665)	39.54	39	1.01	0.66 to 1.57	0.95
Probable symptomatic hypoglycaemia (*n* = 169)	4.95	1.13	4.36	1.39 to 3.69	0.012[a]
Hypoglycaemia unlikely (*n* = 59)	0.33	1.16	0.29	0.04 to 2.09	0.29
Reported as SAE	0	0			

a Significant at 0.05 level.

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Continuous glucose monitoring measured level 2 hypoglycaemic events at week 52

Records of level 2 hypoglycaemic events were available for 58 participants (control: 19, ustekinumab: 39) at baseline. Forty-seven participants (control: 14, ustekinumab: 33) had records of level 2 events at both baseline and week 52.

Participants in the control group (0.93 per person-year) had fewer level 2 hypoglycaemic events than those in the ustekinumab group (2.32 per person-year). The difference did not reach statistical significance (IRR 0.40, 95% CI 0.12 to 1.30; $p = 0.12$) at week 52 after adjustment by sex, age, number of available data points and number of level 2 hypoglycaemic events.

Participant-reported outcome measures

Participant-reported outcomes were collected by the PedsQL, PedsQL™ Diabetes Module (PedsQL Diabetes), DTSQ, Hypoglycaemia Fear Survey-Behaviour [HypoFear-Behaviour, Hypoglycaemia Fear Survey-Worry (HypoFear-Worry) and Hypoglycaemia Fear Survey-Total (HypoFear-Total)] at baseline, 28 and 52 weeks. The DTSQ Change version (DTSQc) was used at week 52 to identify changes in the level of satisfaction with diabetes treatment.

Participants and their parents completed the questionnaires at baseline, 28 and 52 weeks. Seventy participants and 68 parents completed ≥ 1 of the PROMs questionnaires.

Participant-reported outcome measures participant reported

There were no significant differences in PedsQL, PedsQL-diabetes, DTSQ, HypoFear-Behaviour, HypoFear-Worry and HypoFear-Total as reported by participants at either 28 or 52 weeks (*Table 18*). Participants in both the ustekinumab (mean = 8.45, SD = 4.97) and the control group (mean = 7.05, SD = 5.49) showed more satisfaction with diabetes treatment at 52 weeks by the DTSQc, but the difference (1.45, 95% CI −1.58 to 4.38; $p = 0.35$) did not reach significance level by *t*-test. Non-parametric analysis by Mann–Whitney U-test showed a similar conclusion.

The control group had better generic health-related quality of life (HRQoL) than the ustekinumab group at baseline as measured by PedsQL. Differences between the study groups in PedsQL scores as reported by participants were not significantly different at either 28 or 52 weeks after adjustment by baseline differences. The models had modest explanatory power as shown by the adjusted R^2. Although the models worked reasonably well, factors other than baseline and treatment group differences were required to explain variations in 28-week as well as 52-week PedsQL scores.

There was no significant difference in participant-reported diabetes-specific HRQoL between the two groups at either 28 or 52 weeks, after adjustment by baseline. The models had modest explanatory power as shown by the adjusted R^2. Although the models worked reasonably well, factors other than baseline and study group differences were required to explain variations in 28- and 52-week diabetes-specific HRQoL.

There was no significant difference in participant-reported satisfaction with diabetes treatment between the groups at either 28 or 52 weeks, after adjustment by baseline. Adjusted R^2 for the 28-week model was < 0.1, indicating that the model explained < 10% of the variation in participant-reported satisfaction with diabetes treatment. Adjusted R^2 (0.14) for the week-52 model was slightly better but still indicated a poor model fit.

Alternative analysis with more complex models such as adding extra quadratic terms (square of baseline DTSQ scores) and extra covariates (sex, age, duration of diagnosis, baseline C-peptide, baseline HbA1c and baseline bodyweight adjusted insulin intake) were performed, with similar results. The simpler linear models using treatment group and baseline DTSQ scores to explain variations in 28- and 52-week DTSQ scores were reported.

There were no significant differences in participant-reported fear of hypoglycaemia (Behaviour, Worry and Total scores) between the two treatment groups at either 28 or 52 weeks, after adjustment by baseline. The models had modest explanatory power as shown by the adjusted R^2. Although the models worked reasonably well, factors other than baseline and treatment group differences were required to explain variations in 28- and 52-week fear of hypoglycaemia scores.

TABLE 18 Differences in mean participant-reported outcomes by groups at 28 and 52 weeks, adjusted by baseline

Participant-reported PROMs	Visit	Control (SD)	Ustekinumab (SD)	Ustekinumab – control	95% CI		p-value	Adjusted R^2
		n	*n*		Lower	Upper		
PedsQL (0–100)	Week 2 *N* = 67	84.87 (11.31) *n* = 24	76.52 (13.08) *n* = 43	−8.36	−14.47	−2.24	0.008*	NA
Higher score, better generic HRQoL	Week 28 *N* = 60	79.19 (10.51) *n* = 21	80.72 (10.30) *n* = 39	1.54	−4.29	7.36	0.6	0.3
	Week 52 *N* = 58	80.78 (8.89) *n* = 21	80.12 (8.72) *n* = 37	−0.662	−5.65	4.33	0.79	0.43
PedsQL diabetes (0–100)	Week 2 *N* = 70	76.81 (13.00) *n* = 25	75.61 (12.58) *n* = 45	−1.2	−7.64	5.24	0.71	NA
Higher score, better diabetes-specific HRQoL	Week 28 *N* = 63	75.48 (8.94) *n* = 22	73.87 (8.93) *n* = 41	−1.61	−6.35	3.12	0.5	0.48
	Week 52 *N* = 64	74.48 (10.87) *n* = 22	73.00 (10.87) *n* = 42	−1.48	−7.2	4.25	0.61	0.45
DTSQ (0–36)	Week 2 *N* = 66	24.61 (4.04) *n* = 23	24.81 (3.84) *n* = 43	0.25	−1.86	2.28	0.84	NA
The higher, the more satisfied	Week 28 *N* = 56	23.82 (4.61) *n* = 18	24.11 (4.60) *n* = 38	0.292	−2.35	2.94	0.83	0.05
	Week 52 *N* = 58	23.54 (4.24) *n* = 19	24.92 (4.24) *n* = 39	1.38	−1.00	3.76	0.25	0.14
HypoFear-Behaviour (0–4)	Week 2 *N* = 67	1.7 (0.80) *n* = 24	1.81 (0.80) *n* = 43	0.11	−0.3	0.52	0.59	NA
Higher score, greater tendency to avoid hypo or its negative consequences	Week 28 *N* = 60	1.73 (0.54) *n* = 21	1.77 (0.54) *n* = 39	0.04	−0.26	0.33	0.81	0.33
	Week 52 *N* = 61	1.81 (0.49) *n* = 21	1.82 (0.49) *n* = 40	0.01	−0.25	0.28	0.92	0.36
HypoFear-Worry (0–4)	Week 2 *N* = 69	0.77 (0.54) *n* = 25	0.91 (0.79) *n* = 44	0.14	−0.18	0.46	0.38	NA
Higher score, more worry concerning hypo and its consequences	Week 28 *N* = 62	0.88 (0.47) *n* = 22	0.94 (0.25) *n* = 40	0.06	−0.19	0.32	0.61	0.45
	Week 52 *N* = 63	0.86 (0.49) *n* = 22	0.96 (0.49) *n* = 41	0.1	−0.16	0.36	0.46	0.25
HypoFear-Total (0–4)	Week 2 *N* = 70	1.09 (0.47) *n* = 25	1.21 (0.64) *n* = 45	0.12	−0.17	0.42	0.36	NA
Higher score, greater fear of hypo	Week 28 *N* = 63	1.23 (0.39) *n* = 22	1.25 (0.40) *n* = 41	0.11	−0.19	0.23	0.84	0.45
	Week 52 *N* = 64	1.24 (0.42) *n* = 22	1.29 (0.42) *n* = 42	0.05	−0.17	0.27	0.65	0.32

* means that the difference is significant at 0.05 level.

Participant-reported outcome measures parent reported

There were no significant differences in PedsQL, PedsQL-diabetes, DTSQ, HypoFear-Behaviour, HypoFear-Worry and HypoFear-Total as reported by parents of the participants in the two groups at either 28 or 52 weeks (*Table 19*). Parents of the participants in both the ustekinumab (mean = 7.64, SD = 5.81) and the control group (mean = 4.67, SD = 5.69) showed more satisfaction with diabetes treatment at week 52 by the DTSQc, but the difference (2.97, 95% CI −0.39 to 6.33; $p = 0.08$) did not reach significance level by t-test. Non-parametric analysis by Mann–Whitney U-test showed a similar conclusion.

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TABLE 19 Differences in mean parent-reported outcomes by groups at 28 and 52 weeks, adjusted by baseline

Parent-reported PROMs	Visit	Control (SD) *n*	Ustekinumab (SD) *n*	Ustekinumab – control *n*	95% CI Lower	95% CI Upper	*p*-value	Adjusted R^2
PedsQL (0–100)	Week 2 *N* = 67	79.07 (16.08) *n* = 22	78.28 (16.95) *n* = 45	−0.79	−9.37	7.8	0.85	NA
Higher score, better generic HRQoL	Week 28 *N* = 59	76.44 (13.20) *n* = 21	80.86 (13.19) *n* = 38	4.42	−2.76	11.6	0.22	0.21
	Week 52 *N* = 59	80.62 (13.03) *n* = 19	79.58 (13.03) *n* = 40	−1.04	−8.33	6.25	0.78	0.26
PedsQL diabetes (0–100)	Week 2 *N* = 68	67.54 (15.63) *n* = 22	71.42 (15.48) *n* = 46	4.88	−4.28	12.04	0.34	NA
Higher score, better diabetes-specific HRQoL	Week 28 *N* = 59	77.75 (13.75) *n* = 21	80.13 (13.75) *n* = 38	2.38	−5.13	9.89	0.53	0.15
	Week 52 *N* = 59	82.37 (13.29) *n* = 19	78.74 (13.28) *n* = 40	−3.63	−11.07	3.81	0.33	0.23
DTSQ (0–36)	Week 2 *N* = 60	23.53 (5.90) *n* = 19	26.32 (4.50) *n* = 41	2.79	−0.33	5.92	0.08	NA
The higher, the more satisfied	Week 28 *N* = 49	22.83 (4.03) *n* = 18	25.00 (4.01) *n* = 31	2.17	−0.26	4.6	0.08	0.25
	Week 52 *N* = 49	23.70 (4.48) *n* = 16	24.82 (4.42) *n* = 33	1.12	−1.65	3.89	0.42	0.18
HypoFear-Behaviour (0–4)	Week 2 *N* = 67	1.92 (0.70) *n* = 22	1.74 (0.88) *n* = 45	−0.18	−0.58	0.22	0.38	NA
Higher score, greater tendency to avoid hypo or its negative consequences	Week 28 *N* = 60	1.53 (0.55) *n* = 21	1.53 (0.56) *n* = 39	0	−0.3	0.3	1	0.13
	Week 52 *N* = 59	1.65 (0.44) *n* = 19	1.59 (0.44) *n* = 40	0.06	−0.31	0.18	0.61	0.43
HypoFear-Worry (0–4)	Week 2 *N* = 67	1.54 (0.77) *n* = 22	1.38 (0.91) *n* = 45	−0.16	−0.59	0.27	0.45	NA
Higher score, more worry concerning hypo and its consequences	Week 28 *N* = 59	1.49 (0.82) *n* = 21	1.42 (0.81) *n* = 38	−0.07	−0.51	0.38	0.77	0.22
	Week 52 *N* = 59	1.11 (0.65) *n* = 19	1.37 (0.67) *n* = 40	0.26	−0.12	0.64	0.17	0.26
HypoFear-Total (0–4)	Week 2 *N* = 67	1.69 (0.67) *n* = 22	1.53 (0.78) *n* = 45	−0.17	−0.54	0.2	0.37	NA
Higher score, greater fear of hypo	Week 28 *N* = 60	1.50 (0.64) *n* = 21	1.47 (0.62) *n* = 39	−0.025	−0.37	0.32	0.88	0.22
	Week 52 *N* = 59	1.31 (0.53) *n* = 19	1.45 (0.53) *n* = 40	0.13	−0.16	0.43	0.37	0.36

There was no significant difference in parent-reported HRQoL between the two groups at either 28 or 52 weeks, after adjustment by baseline. The adjusted R^2 was small, indicating factors other than baseline and group differences were required to explain variations in 28- and 52-week HRQoL.

There was no significant difference in parent-reported diabetes-specific HRQoL between the two groups at either 28 or 52 weeks, after adjustment by baseline. The small adjusted R^2 showed that factors other than baseline and group differences were required to explain variations in 28- and 52-week diabetes-specific HRQoL.

There was no significant difference in participant-reported satisfaction with diabetes treatment between the treatment groups at either 28 or 52 weeks, after adjustment by baseline. The adjusted R^2 were small, indicating factors other than baseline and group differences were required to explain variations in 28- and 52-week satisfaction with diabetes treatment.

There were no significant differences in participant-reported fear of hypoglycaemia (Behaviour, Worry and Total scores) between parents of participants in the two treatment groups at either 28 or 52 weeks, after adjustment by baseline. The adjusted R^2 was small to modest, indicating factors other than baseline and group differences were required to explain variations in 28- and 52-week fear of hypoglycaemia scores.

Ancillary analyses

No subgroup analysis was planned. Planned ancillary analyses were listed as follows:

- To investigate changes in relevant immune mechanistic parameters including flow cytometry immune phenotyping of all IL-17 and IFN-γ-secreting T-cell subsets, FluoroSpot analysis for IL-17 and IFN-γ secretion in response to antigens for CD4+ T cells
- Exploration of the association of C-peptide changes with age-appropriate PROMs including the HypoFear, DTSQ and PedsQL questionnaires
- Comparison of participant- and parent proxy-completed PROMs
- To determine whether any participants had COVID-19 during their time in the trial and to explore its potential impact.

Changes in relevant immune mechanistic parameters

Immunological effects

We observed significant differences between the ustekinumab and control groups in relevant T-cell populations targeted by the drug (*Figures 9–16*). A significant decline in the CD4+ Th17 and Th17.1 populations but not the Th1

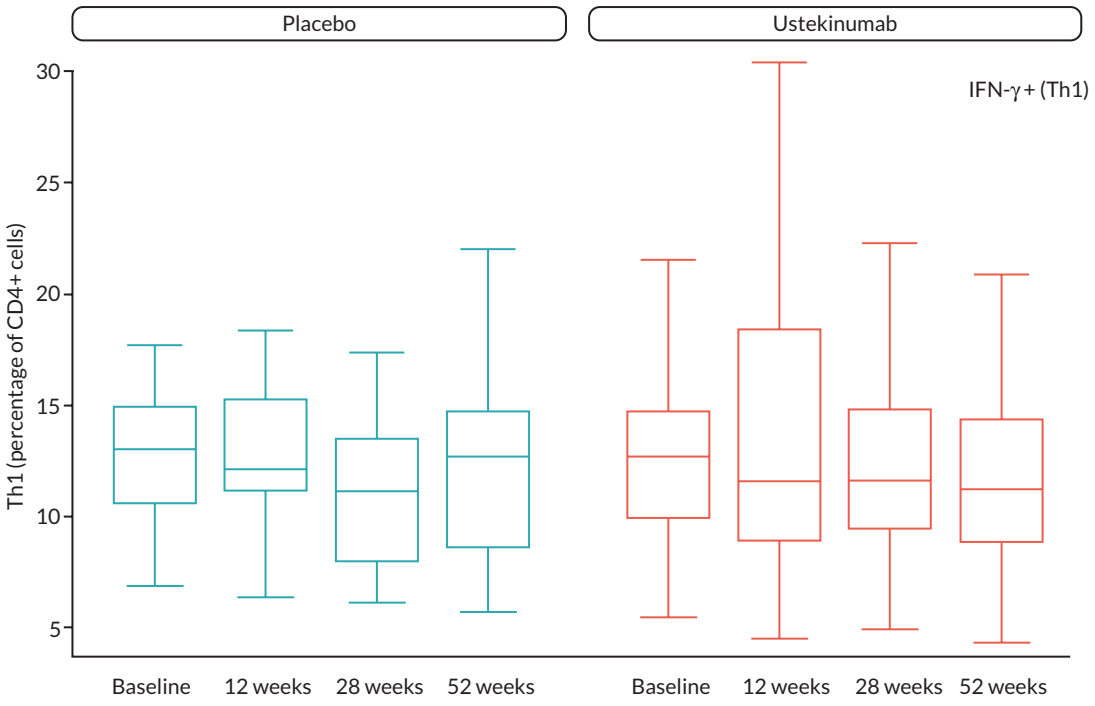


FIGURE 9 Analysis of the frequency of cytokine-producing CD4 T-cell subsets: boxplots of frequencies of CD4+ T cells producing IFN-γ (Th1). Note: line represents median, box represents IQR and whiskers 95% range. Ustekinumab (orange) and control (blue).

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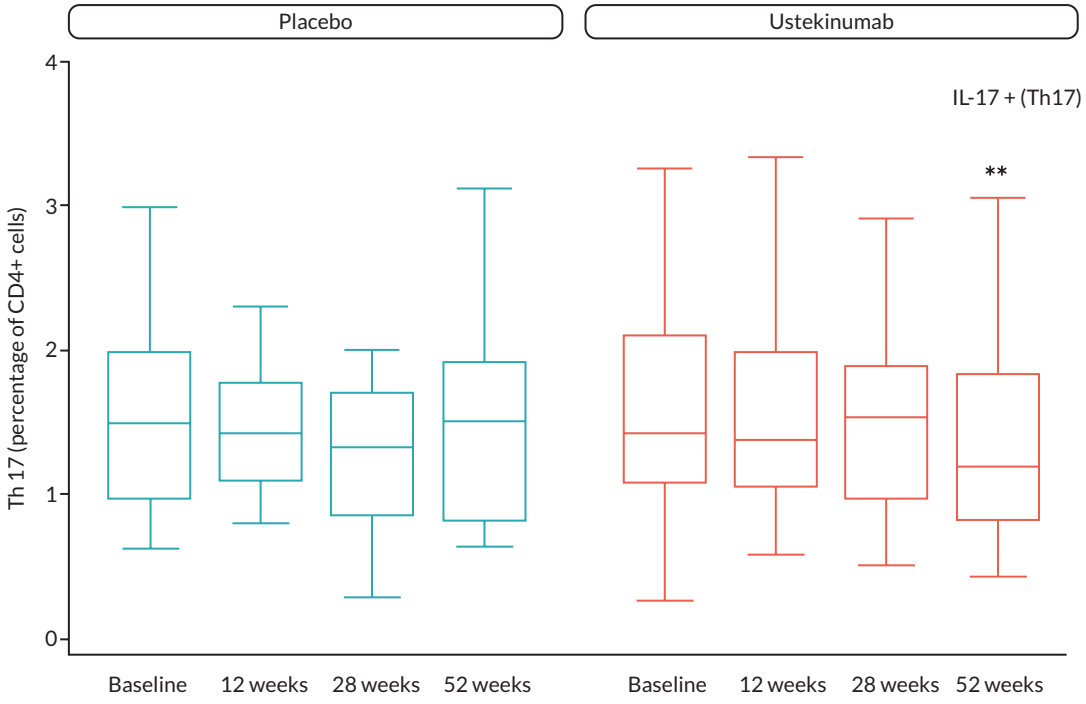


FIGURE 10 Analysis of the frequency of cytokine-producing CD4 T-cell subsets: boxplots of frequencies of CD4+ T cells producing IL-17A (Th1). Note: ** $p < 0.01$. Line represents median, box represents IQR and whiskers 95% range. Ustekinumab (orange) and control (blue).

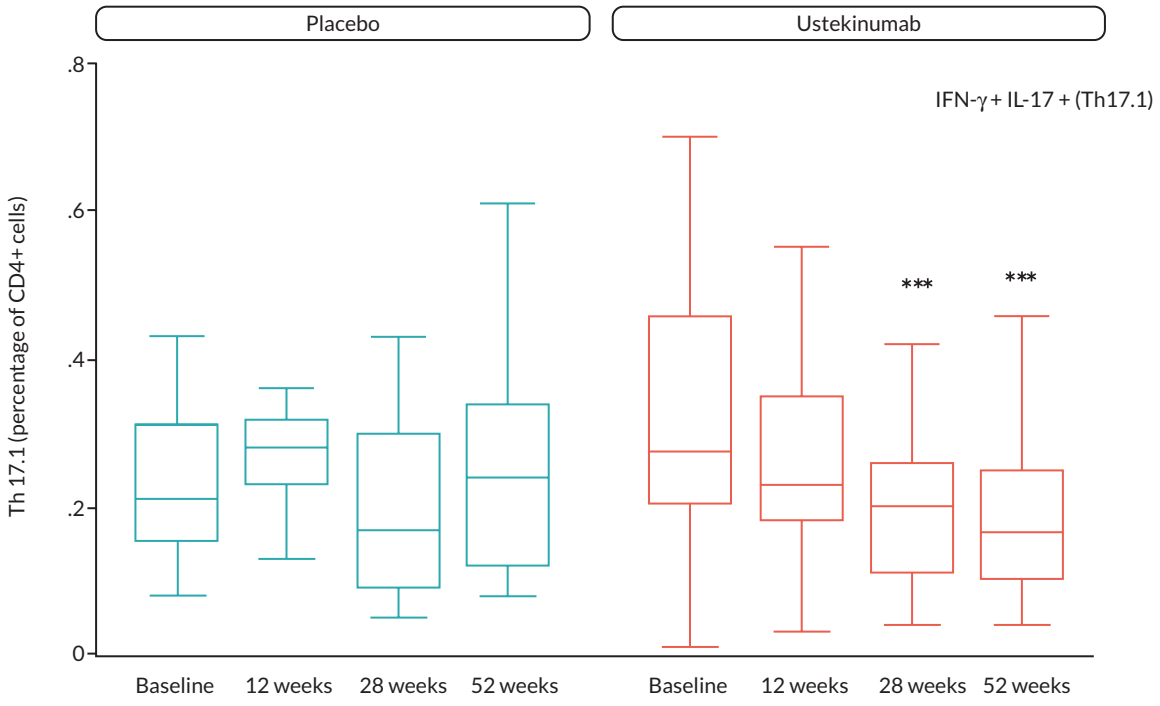


FIGURE 11 Analysis of the frequency of cytokine-producing CD4 T-cell subsets: boxplots of frequencies of CD4+ T cells producing IFN-γ and IL-17A (Th17.1). Note: ***$p < 0.001$. Line represents median, box represents IQR and whiskers 95% range. Ustekinumab (orange) and control (blue).

population was seen after 28 weeks of treatment in the ustekinumab group, which became more pronounced by week 52. To explore this further, Th17.1 subsets co-expressing the additional cytokines granulocyte-macrophage colony-stimulating factor (GM-CSF) and IL-2 were studied. The most pronounced effect was seen in cells that expressed all four cytokines (IFN-γ, IL-17, GM-CSF+, IL-2+), representing around 0.1% of the CD4 T-cell population, which showed a reduction as early as 12 weeks after beginning therapy.

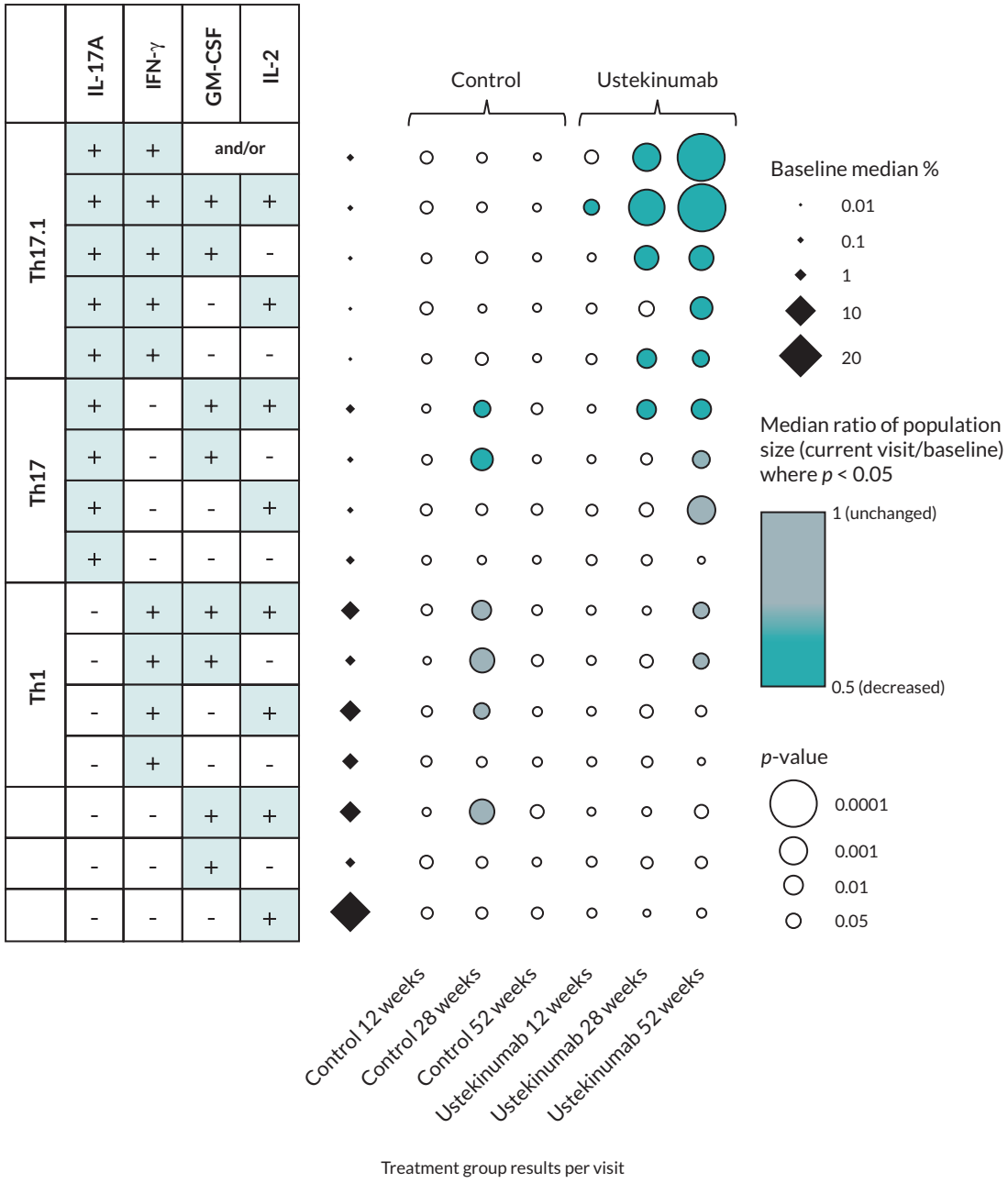


FIGURE 12 Dotplot of changes in cytokine-producing CD4 T-cell subsets during treatment. Note: The ratio of each population was calculated as the current visit/baseline for each participant for every time point for which they had data. Circle size is scaled by *p*-value, with more significant *p*-values represented by larger circles. Data points with $p < 0.05$ are coloured by the median ratio of population size [grey = 1 (unchanged) to purple = 0.5 (halved)]. Data points with $p > 0.05$ are coloured white. The baseline median percentage of each population is represented by scaled black diamonds.

This was unlikely to be an artefact of multiple testing, as the highly significant changes in T-cell populations ($p < 0.001$) all clustered around the Th17 positive subpopulations as shown in the heatmap in *Figure 12*.

We additionally analysed the antigen-specific response by using a cytokine FluoroSpot assay. Overall, 28/64 participants had a positive response after in vitro stimulation with proinsulin at baseline. Of these, IL-17A and IL-17F cytokine-producing cells were significantly reduced in comparison to baseline from 12 weeks in the ustekinumab group only (*Figures 17* and *18*). There was no significant change in the IFN-γ FluoroSpot response (data not shown).

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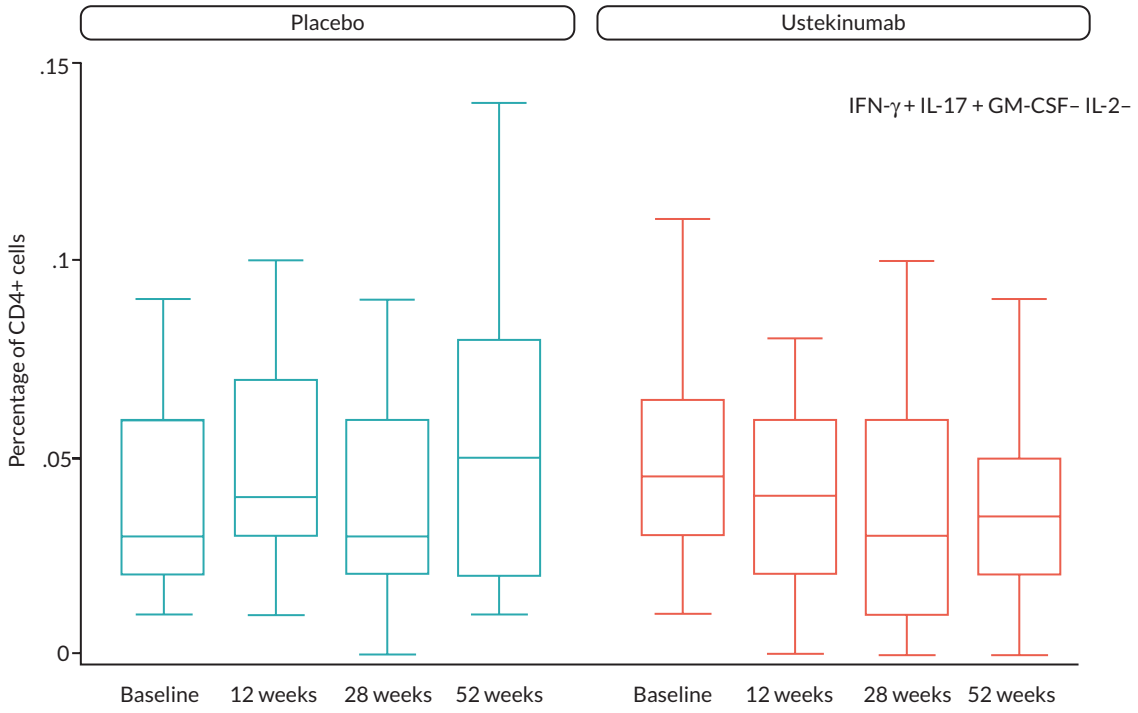


FIGURE 13 Boxplots of frequencies of CD4+ T cells: IL-17 + IFN-γ + GM-CSF−IL-2−. Note: Line represents median, box represents IQR and whiskers 95% range. Ustekinumab (orange) and control (blue).

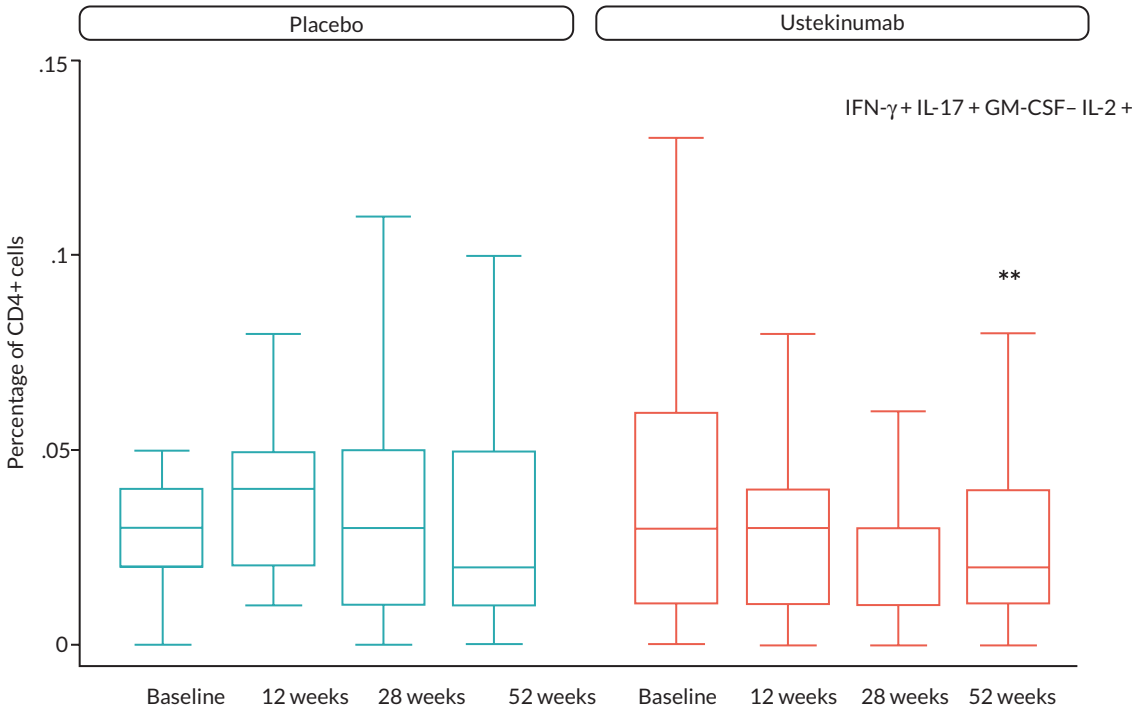


FIGURE 14 Boxplots of frequencies of CD4+ T cells: IL-17 + IFN-γ + GM-CSF−IL-2+. Note: $^{**}p < 0.01$. Line represents median, box represents IQR and whiskers 95% range. Ustekinumab (orange) and control (blue).

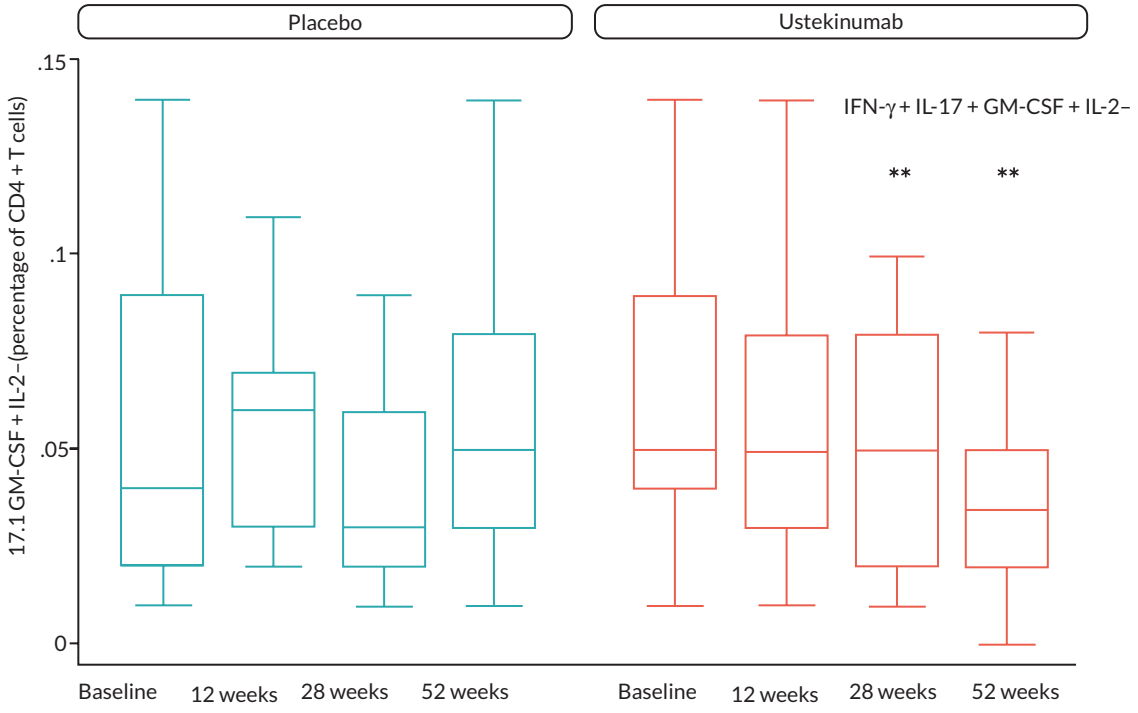


FIGURE 15 Boxplots of frequencies of CD4+ T cells: IL-17 + IFN-γ + GM-CSF + IL-2−. Note: $^{**}p < 0.01$. Line represents median, box represents IQR and whiskers 95% range. Ustekinumab (orange) and control (blue).

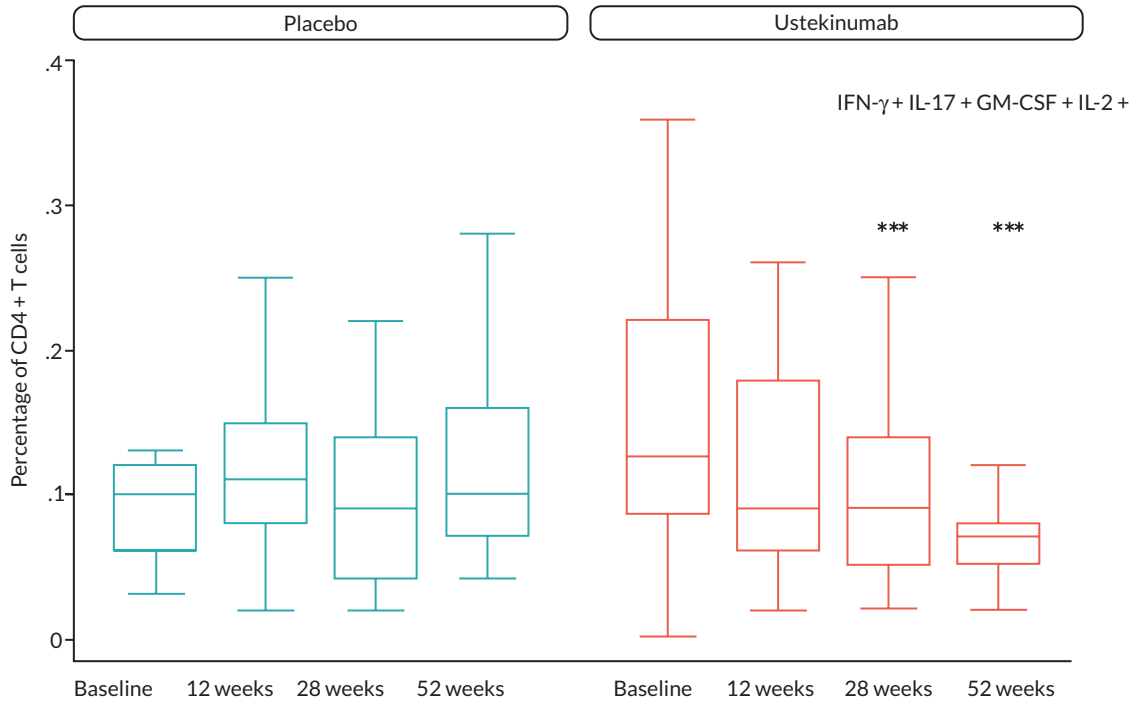


FIGURE 16 Boxplots of frequencies of CD4+ T cells: IL-17 + IFN-γ + GM-CSF + IL-2+. Note: $^{***}p < 0.001$. Line represents median, box represents IQR and whiskers 95% range. Ustekinumab (orange) and control (blue).

Relationship between C-peptide preservation and immune changes

To determine the likely pathological significance of the T-cell changes observed, we investigated if participants in the ustekinumab group who showed better immunological response also had better C-peptide preservation. We observed that preservation of the C-peptide response between weeks 28 and 52 of the trial was associated with the highest responders in terms of Th17.1 cell population changes and the subset Th17.1 GM-CSF + IL-2+ in response to ustekinumab but not the control (*Figure 19*).

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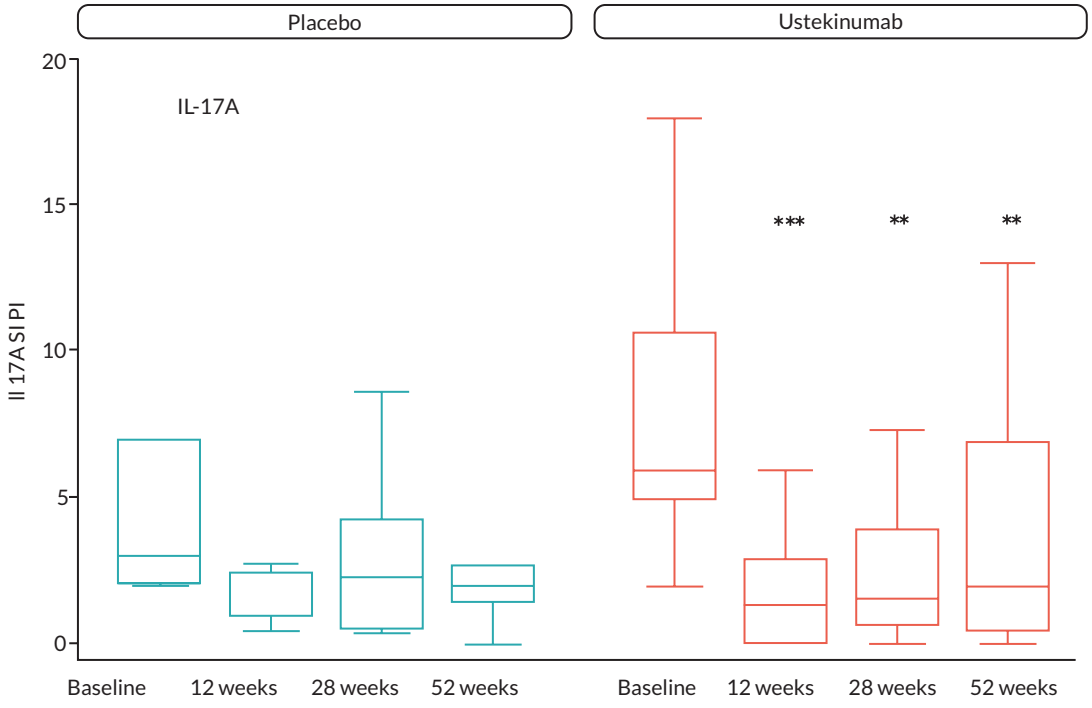


FIGURE 17 Box plot of cell producing IL-17 in response to stimulation with proinsulin in individuals treated with ustekinumab (orange) and control (blue) IL-17A response. Note: Stimulation Index (SI) = mean number of spots in proinsulin stimulated well/mean number of spots in unstimulated well. Individuals with a baseline SI of < 2 were removed. $^{**}p < 0.01$, $^{***}p < 0.001$. Line represents median, box represents IQR and whiskers 95% range.

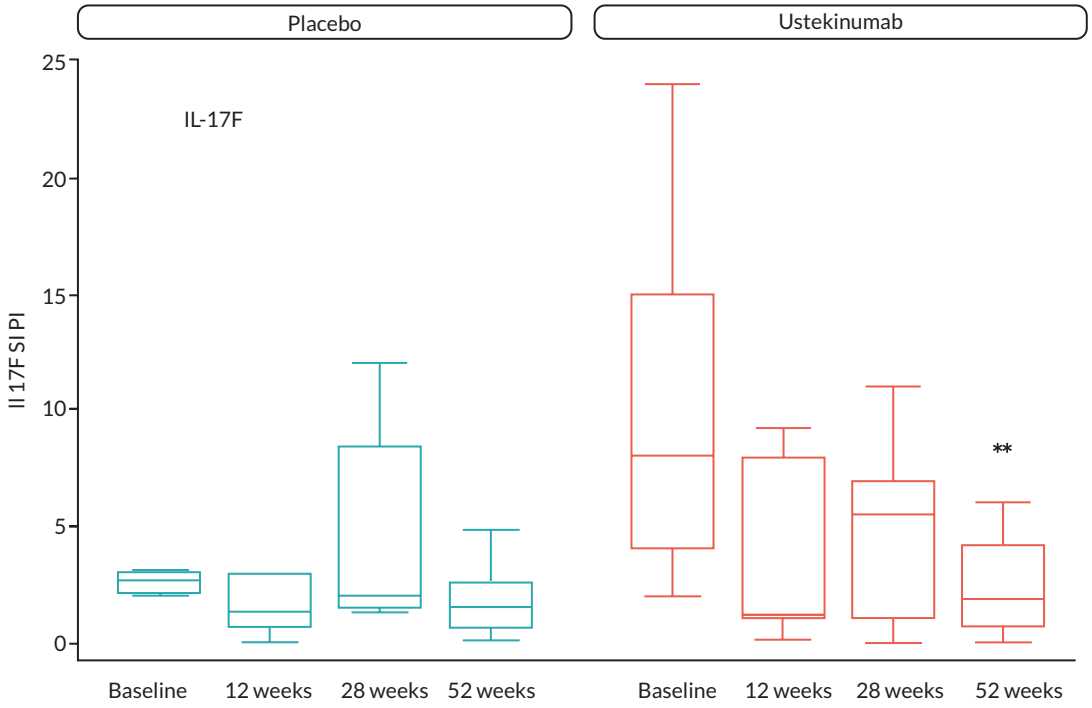


FIGURE 18 Box plot of cell producing IL-17 in response to stimulation with proinsulin in individuals treated with ustekinumab (orange) and control (blue) IL-17F response. Note: Stimulation Index (SI) = mean number of spots in proinsulin stimulated well/mean number of spots in unstimulated well. Individuals with a baseline SI of < 2 were removed. $^{**}p < 0.01$. Line represents median, box represents IQR and whiskers 95% range.

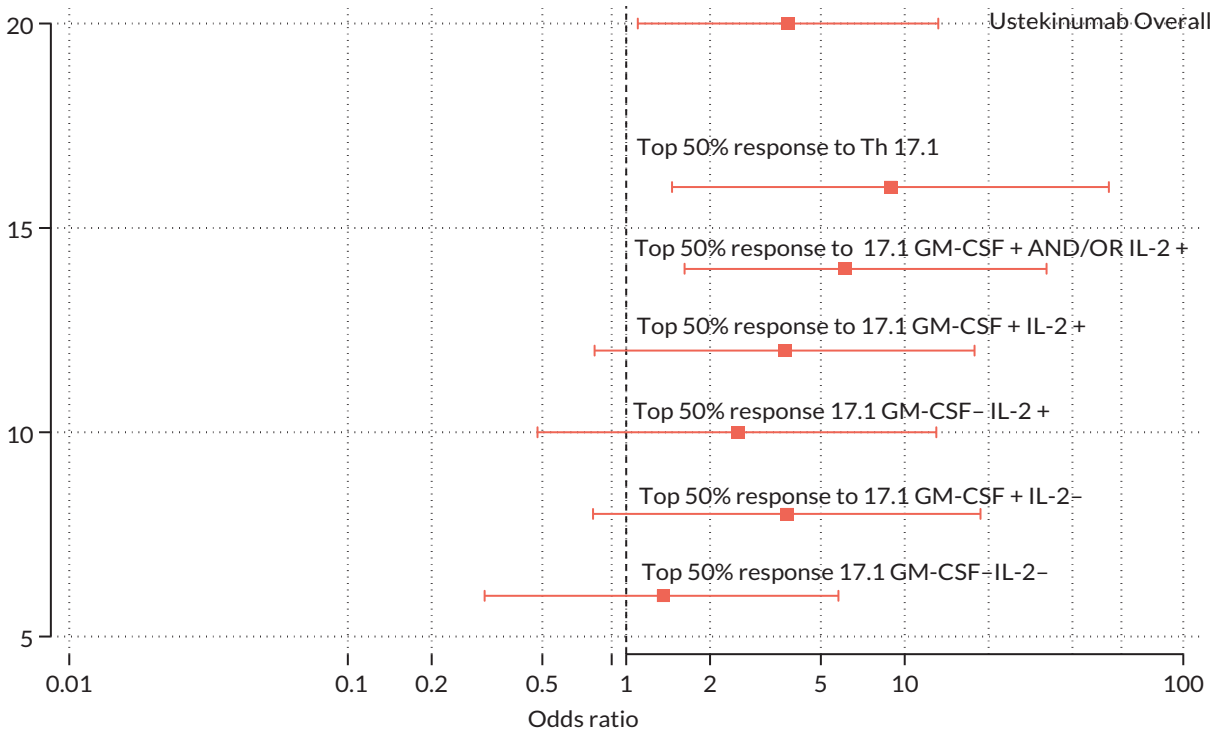


FIGURE 19 Relationship between C-peptide loss and treatment-induced changes in immune response. Note: odds of having an AUC C-peptide that did not fall between weeks 28 and 52 for ustekinumab overall (vs. control) and then by immunological subgroups in those on ustekinumab.

Association of C-peptide changes with age-appropriate participant-reported outcome measures

Rank-order correlation was used to explore the association of C-peptide obtained from MMTT $AUC_{0–120}$ (nmol/l/minute) with participant-reported outcomes (PedsQL, PedsQL Diabetes, DTSQ, HypoFear-Behaviour, HypoFear-Worry and HypoFear-Total) at baseline, 28 and 52 weeks. Correlations between PROMs and C-peptide were small and not significant at baseline and week 52. At week 28, higher C-peptide was associated with less worry about hypoglycaemia (Spearman's $\rho = -0.27$, $p = 0.04$), but the correlations between other PROMs and C-peptide at week 28 were not significant (*Table 20*).

Although not statistically significant, Spearman's Rho indicated a small correlation of higher C-peptide with better generic quality of life (PedsQL), diabetes-specific quality of life (PedsQL Diabetes) and satisfaction with diabetes treatment (DTSQ) at baseline, 28 and 52 weeks. At 28 and 52 weeks, higher C-peptide was associated with less behaviour to avoid hypoglycaemia (HypoFear-Behaviour), less worry about hypoglycaemia (HypoFear-Worry) and less fear of hypoglycaemia (HypoFear-Total). At baseline, though not significant, higher C-peptide was associated with more behaviour to avoid hypoglycaemia and more fear of hypoglycaemia in total.

Comparison of participant- and parent proxy-completed participant-reported outcome measures

Rank-order correlation indicated that there were significant positive correlations between the participant- and parent-completed PROMs (PedsQL, PedsQL Diabetes, DTSQ, HypoFear-Behaviour, HypoFear-Worry and HypoFear-Total) for most of the PROMs and at nearly all the different time points of assessment (*Table 21*). Higher scores in the participant-completed PROMs were associated with higher scores in the parent proxy-completed versions.

The magnitude of the correlations between participant- and parent-completed PedsQL, PedsQL Diabetes scores was moderate to strong at all time points. The magnitude of the correlations between participant- and parent-completed DTSQ, HypoFear-Behaviour, HypoFear-Worry and HypoFear-Total was weak to moderate. There were some associations between the scores derived from participant- and parent-completed versions of the PROMs, but there could be some randomness affecting one or both sets of the scores, or perhaps there were other factors affecting both sets of scores.

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TABLE 20 Correlation (Spearman's Rho) between C-peptide and PROMs (participant)

MMTT $_{0-120}$ mean AUC and PROMs as reported by participants	Baseline correlation significant (95% CI) *N*	Week 28 correlation significant (95% CI) *N*	Week 52 correlation significant (95% CI) *N*
AUC_MEAN and PedsQL	0.029 0.815 (−0.219 to 0.274) *n* = 67	0.158 0.237 (−0.112 to 0.406) *n* = 58	0.114 0.383 (−0.15 to 0.362) *n* = 61
AUC_MEAN and PedsQL Diabetes	0.038 0.757 (−0.206 to 0.277) *n* = 70	0.161 0.223 (−0.107 to 0.407) *n* = 59	0.105 0.401 (−0.148 to 0.345) *n* = 66
AUC_MEAN and DTSQ	0.081 0.520 (−0.172 to 0.323) *n* = 66	0.193 0.162 (−0.087 to 0.445) *n* = 43	0.202 0.115 (−0.058 to 0.436) *n* = 59
AUC_MEAN and HypoFear-Behaviour	0.182 0.14 (−0.068 to 0.411) *n* = 67	−0.193 0.146 (−0.436 to 0.076) *n* = 58	−0.11 0.386 (−0.353 to 0.147) *n* = 64
AUC_MEAN and HypoFear-Worry (Higher C-peptide, less worry about hypo at week 28)	−0.045 0.714 (−0.285 to 0.201) *n* = 69	−0.269[a] 0.042 (−0.499 to −0.003) *n* = 58	−0.163 0.198 (−0.399 to 0.094) *n* = 64
AUC_MEAN and HypoFear-Total	0.079 0.518 (−0.166 to 0.314) *n* = 70	−0.242 0.067 (−0.477 to 0.025) *n* = 58	−0.165 0.193 (−0.401 to 0.092) *n* = 64

a Significant at 0.05 level.

TABLE 21 Correlation (Spearman's Rho) between participant- and parent-completed PROMs

PROMs	Baseline correlation significant (95% CI) *N* *N*	Week 28 correlation significant (95% CI) *N*	Week 52 correlation significant (95% CI) *N*
PedsQL	0.680[a] < 0.001 (0.515 to 0.796) *n* = 64	0.437[a] < 0.001 (0.196 to 0.628) *n* = 59	0.455[a] < 0.001 (0.21 to 0.646) *n* = 56
PedsQL Diabetes	0.533[a] < 0.001 (0.329 to 0.689) *n* = 67	0.610[a] < 0.001 (0.417 to 0.750) *n* = 61	0.544[a] < 0.001 (0.332 to 0.704) *n* = 61
DTSQ	0.299[b] 0.021 (0.039 to 0.521) *n* = 59	0.251 0.070 (-0.029 to 0.494) *n* = 53	0.498[a] < 0.001 (0.258 to 0.680) *n* = 54
HypoFear-Behaviour	0.262[b] 0.036 (0.010 to 0.483) *n* = 64	0.274[b] 0.034 (0.014 to 0.499) *n* = 60	0.091 0.487 (−0.174 to 0.344) *n* = 60

TABLE 21 Correlation (Spearman's Rho) between participant- and parent-completed PROMs (*continued*)

PROMs	Baseline correlation significant (95% CI) *N* *N*	Week 28 correlation significant (95% CI) *N*	Week 52 correlation significant (95% CI) *N*
HypoFear-Worry	0.234 0.059 (−0.016 to 0.456) *n* = 66	0.451[a] < 0.001 (0.213 to 0.638) *n* = 59	0.445[a] < 0.001 (0.205 to 0.634) *n* = 59
HypoFear-Total	0.261[b] 0.033 (0.015 to 0.477) *n* = 67	0.469[a] < 0.001 (0.237 to 0.651) *n* = 60	0.408[a] 0.001 (0.164 to 0.604) *n* = 60
DTSQc	NA	NA	0.352[b] 0.011 (0.079 to 0.575) *n* = 52

a Correlation is significant at the 0.01 level (two-tailed).
b Correlation is significant at the 0.05 level (two-tailed).

Wilcoxon signed-rank tests were used to explore differences between scores derived from participant- and parent-completed PROMs (PedsQL, PedsQL Diabetes, DTSQ, HypoFear-Behaviour, HypoFear-Worry and HypoFear-Total). There were some differences between the two sets of scores at the different time points of assessments, but the direction of the differences was not necessarily in the same direction (*Table 22*).

Although participant- and parent-completed PedsQL Diabetes scores were significantly correlated at baseline, 28 and 52 weeks, parent scores were significantly lower than the participant scores at baseline and 28 weeks. The difference at 52 weeks was in the same direction but did not reach statistical significance. Parents' perception of their child's quality of life was worse than that of the participants in terms of those diabetes-specific aspects.

Parents had lower HypoFear-Behaviour scores than participants at weeks 28 and 52, although the difference between the two sets of scores was not significant at 12 months. Participants might consider themselves as taking more actions to avoid hypoglycaemia than their parents.

Parents had significantly higher HypoFear-Worry scores than participants at baseline, 28 and 52 weeks. Parents might have more concerns about their children having hypoglycaemia than the participants themselves.

Parents had significantly higher HypoFear-Total scores than teens at baseline and 28 weeks, but the difference did not reach statistical significance at 52 weeks. Parents might have more fear about their children having hypoglycaemia than the participants themselves.

Treatment group comparison by dried blood spot

We explored the use of C-peptide concentrations collected by DBS as an alternative way to conducting MMTTs to examine the efficacy of ustekinumab at week 52 as compared to the control. Participants returned DBS samples weekly from screening to week 28 and then monthly thereafter for another 6 months. Those returning both pre and post treatment were included in the analysis. DBS data were analysed by a mixed-effect model for repeated measures with a random intercept, adjusted by age, C-peptide AUC_{0-60} at baseline, length of follow-up (days from screening) and number of doses (1–7). Details of the result will be reported in a separate paper.

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TABLE 22 Differences between scores from the participant- and parent-completed PROMs

	Parent–participant				
	Positive difference	Negative difference	Ties	*z*	*p*-value
Baseline					
PedsQL	34	30	0	−0.007	0.995
PedsQL Diabetes	23	43	1	−3.236	0.001[a]
DTSQ	29	26	4	0.958	0.338
HypoFear-Behaviour	31	33	0	0.043	0.965
HypoFear-Worry	51	15	0	4.29	< 0.0001[a]
HypoFear-Total	48	18	1	3.948	< 0.0001[a]
DTSQc					
Week 28					
PedsQL	28	27	4	0.013	0.99
PedsQL Diabetes	22	38	1	−2.374	0.018[a]
DTSQ	22	24	7	0.005	0.996
HypoFear-Behaviour	21	36	3	−2.39	0.017[a]
HypoFear-Worry	43	12	4	4.617	< 0.0001[a]
HypoFear-Total	35	24	1	2.393	0.017[a]
DTSQc					
Week 52					
PedsQL	35	20	1	0.54	0.589
PedsQL Diabetes	26	34	1	−1.472	0.141
DTSQ	30	22	2	−0.142	0.887
HypoFear-Behaviour	23	37	0	−1.94	0.052
HypoFear-Worry	41	16	2	3.27	0.001[a]
HypoFear-Total	34	26	0	1.318	0.188
DTSQc	22	26	4	−1.455	0.146

a Significant at the 0.05 level (two-tailed).

Treatment group comparison of urinary C-peptide creatinine ratio with dried blood spot

We have also explored the use of UCPCR as an alternative way to MMTT to examine the efficacy of ustekinumab at week 52 as compared to the control. UCPCR data were available for 69 participants (control: 24, ustekinumab: 45) at baseline and 62 (control: 21, ustekinumab: 41) at week 52.

A comparison of UCPCR with DBS and MMTT values by visits showed a different pattern of change between UCPCR and the other two tests (*Table 23*). As units of measurement were different for the three tests, the rates of change from baseline were calculated for each test and compared (*Figure 20*). These findings are consistent with our previous report that UCPCR does not correlate with MMTT in the first 6–9 months after diagnosis and is insensitive to change, especially in the first 28 weeks.[39]

TABLE 23 Mean C-peptide concentration (95% CI) by MMTT, DBS and UCPCR by visits

	Mean MMTT $_{0-120}$ AUC nmol/l/minute *n*	Mean DBS $_{0-60}$ AUC nmol/l/minute *n*[a]	UCPCR (T120) nmol/mmol/l *n*
Baseline	0.90 (0.78, 1.01) *n* = 72	0.44 (0.38, 0.49) *n* = 53	1.15 (0.97, 1.34) *n* = 69
Week 28	0.50 (0.38, 0.62) *n* = 61	0.31 (0.27, 0.35) *n* = 49	1.08 (0.86, 1.30) *n* = 55
Week 52	0.43 (0.34, 0.53) *n* = 68	0.26 (0.20, 0.32) *n* = 32	0.81 (0.65, 0.97) *n* = 62

a Sampled within 30 days of MMTT.

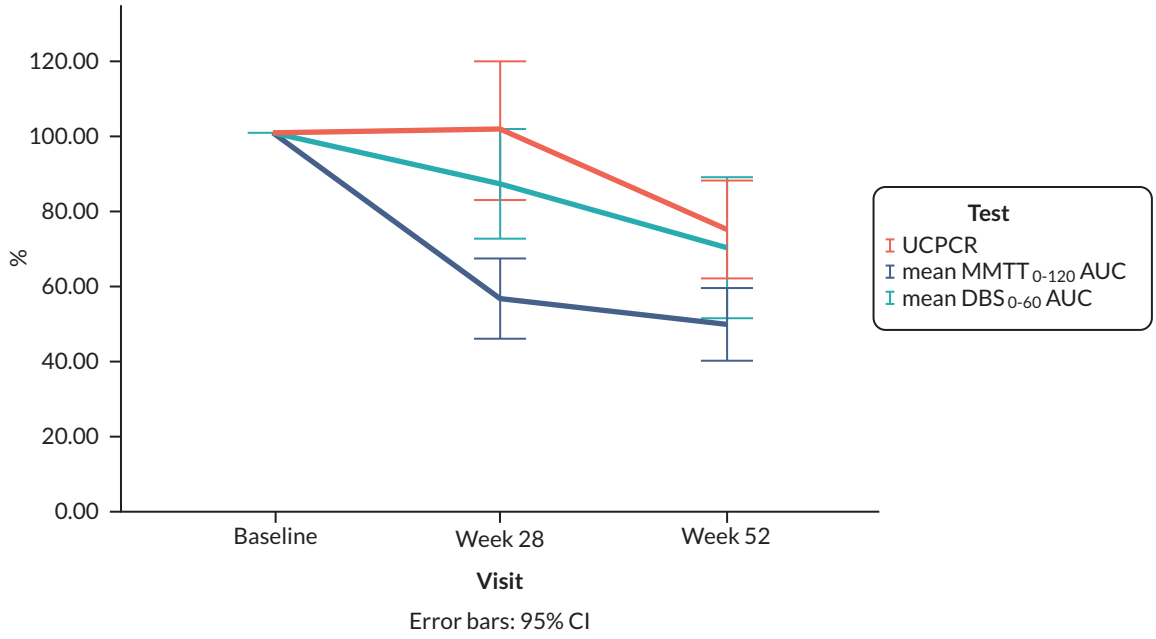


FIGURE 20 Mean rate of change from baseline by visit by test.

COVID-19: vaccination and infection

Antibody test results were available for 54 participants (control: 17, ustekinumab: 37). Those with fold change of antibodies to nucleocapsid of > 4 were classified as COVID-19 positive.

Eighteen per cent (3/17) of those in the control group and 24% (9/37) in the ustekinumab group were COVID-19 positive by serotyping using the above definition. This difference between treatment groups did not reach statistical significance (χ^2 0.04, df = 1, p = 0.84).

Handling of missing data

Every attempt was made to minimise missing data, encouraging participants to provide week 52 data even if they were no longer taking ustekinumab. Patterns and levels of missing data were examined. According to the pre-specified SAP, multiple imputation would be considered if there were more than 5% and < 10% (> 3 and < 7 participants) missing.

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Data were missing for 10 participants (4 withdrawals, 4 with no baseline exogenous insulin use and 2 with missing HbA1c at baseline), affecting > 10% of the participants. A decision was made to perform multiple imputation, purely as a sensitivity check for the primary analysis.

We multiply imputed missing data with a model incorporating baseline MMTT C-peptide, gender, age, baseline insulin use (IU units/kg body weight/day) and HbA1c. Imputation was performed separately by randomised group according to a Markov chain Monte Carlo algorithm with 10 imputations. Analyses of covariance were performed on each imputed data set separately after which results were pooled using Rubins rules.

Multiple imputation showed that the conclusion about treatment group difference (see *Mixed Meal Tolerance Test stimulated 2-hour C-peptide area under the curve at week 52*) might be sensitive to missing values as the geometric ratio of ustekinumab to control changed to 1.36 (95% CI 0.81 to 1.63; $p = 0.27$) and did not reach statistical significance. The model may be sensitive to missing data.

Sensitivity analyses

Primary outcome: Mixed Meal Tolerance Test C-peptide area under the curve at week 52

Sensitivity analyses were performed to confirm robustness of the conclusions about the analysis of the primary outcome to PDs.

There was one participant (allocated to receive the control treatment) whose allocation was accidentally unblinded. Sensitivity analysis by excluding this participant showed the same conclusion as that reported in *Mixed Meal Tolerance Test stimulated 2-hour C-peptide area under the curve at week 52* with a geometric mean ratio of ustekinumab to control as 1.49 (95% CI 1.08 to 2.06; $p = 0.02$) at week 52. This was expected as the participant did not take part in the week 52 visit.

There was one participant (allocated to receive ustekinumab) whose week 52 visit was delayed by > 6 months. Sensitivity analysis by excluding this participant showed a similar conclusion with a geometric mean ratio of ustekinumab to control as 1.45 (95% CI 1.02 to 2.05; $p = 0.04$).

One participant (allocated to receive the control treatment) had a hereditary blood disorder with an extremely low baseline of HbA1c (8 mmol/ml), a covariate for modelling the primary outcome. Sensitivity analysis by excluding this participant showed a similar conclusion with a geometric mean ratio of ustekinumab to control as 1.43 (95% CI 1.01 to 2.02; $p = 0.04$) at week 52.

The model for analysing the primary outcome reported in *Analysis of primary and secondary outcomes* was robust to small numbers of people with some PDs and extreme values in key covariates, for example HbA1c.

Positively skewed outcomes: glycated haemoglobin, extraneous use of insulin and insulin dose-adjusted glycated haemoglobin

Data for HbA1c, extraneous use of insulin and IDAAC were positively skewed. Models with these outcomes log-transformed were built and assessed alongside the simpler linear models.

There were no discrepancies between the linear and the log-transformed models at 3-, 6- and 12-month HbA1c in treatment group comparison in terms of the direction of differences and statistical significances (see *Report Supplementary Material 7*). The simpler linear models were chosen for reporting in *Analysis of primary and secondary outcomes* for ease of interpretation and parsimony.

There were no discrepancies between the linear and the log-transformed models at 12-, 28- and 52-week exogenous insulin use in treatment group comparison in terms of the direction of differences and statistical significances (see *Report Supplementary Material 7*). The simpler linear models were chosen for reporting in *Analysis of primary and secondary outcomes* for ease of interpretation and parsimony.

There were no discrepancies between the linear and the log-transformed models at 12-, 28- and 52-week IDAAC in treatment group comparison in terms of the direction of differences and statistical significances (see *Report Supplementary Material 7*). The simpler linear models were chosen for reporting in *Analysis of primary and secondary outcomes* for ease of interpretation and parsimony.

Safety

Forty-two (89%) patients who received ustekinumab and 22 (88%) who received the control had at least one AE during the study (*Table 24*). The distribution of AEs across the grading levels was similar between the two groups. All were rated as mild to moderate in severity. None were rated as severe.

When evaluating the AEs deemed likely to be attributable to the study drug by a blinded medic, a higher proportion of participants in the ustekinumab group had AEs deemed likely to be related to the study drug in each level of attributability (*Table 25*). The bulk of the events were mild (n = 124) with only 12 events of moderate severity across both treatment groups.

These moderate AEs attributable to the study drug were experienced by seven participants (two control; five ustekinumab). The moderately severe AEs experienced by the two control group participants were general disorders

TABLE 24 Safety experience of participants: AE severity by treatment group

	Control (n = 25)		Ustekinumab (n = 47)	
Severity	Number of events	Number of participants (%)	Number of events	Number of participants (%)
Mild	113	22 (88)	232	41 (87)
Moderate	12	8 (32)	21	15 (32)
Severe	0	0	0	0
Total	125	22 (88)	253	41 (87)

TABLE 25 Participants experiencing AEs attributable to study drug: AE severity by the level of attributability by treatment group

		Control (n = 25)		Ustekinumab (n = 47)	
Attributability[a]	Severity	Number of events	Number of participants (%)	Number of events	Number of participants (%)
Possibly related	Mild	22	5 (20)	96	15 (32)
	Moderate	3	2 (8)	9	5 (11)
	Severe	0	0	0	0
Probably related	Mild	1	1 (4)	3	2 (4)
	Moderate	0	0	0	0
	Severe	0	0	0	0
Definitely related	Mild	0	0	2	2 (4)
	Moderate	0	0	0	0
	Severe	0	0	0	0

a Three records with missing attributability assessment.

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and administration site conditions (*n* = 2 events) or gastrointestinal disorders (*n* = 1 event). The moderately severe AEs experienced by the ustekinumab group participants were gastrointestinal disorders (*n* = 3 events), infections and infestations (*n* = 2 events), nervous system disorders (*n* = 1 event), respiratory, thoracic and mediastinal disorders (*n* = 1 event), musculoskeletal and connective tissue disorders (*n* = 1 event) or general disorders and administration site conditions (*n* = 1 event).

Adverse events were also categorised according to System Organ Class (*Table 26*). The most frequently observed AEs were infections and infestations with an equal proportion (68%) of participants in the ustekinumab (*n* = 32) and the control group (*n* = 17) experiencing some infections and infestations during the study. A higher proportion of the participants in the ustekinumab group (34%, *n* = 16) had general disorders and administration site conditions than the control group (28%, *n* = 7). There was a higher proportion of the participants in the control group who had AEs in all other system organ classes.

In evaluating the evidence of infection, we found 37/117 AEs categorised in the infection and infestation class deemed to be possibly related to treatment allocation. These 37 events were experienced by 17 participants. A higher proportion of participants in the ustekinumab group (30%, *n* = 14) than those in the control group (12%, *n* = 3) experienced one AE deemed to be possibly related to the study drug. Thirty-four of these events were mild. Two moderate AEs were experienced by one ustekinumab participant. They were fever and an upper respiratory tract infection (URTI).

There were six events of injection reaction experienced by five participants (ustekinumab: 9% *n* = 4, control: 4%, *n* = 1). All six events were mild and resolved with no sequelae.

There was no record of hypersensitivity reactions and no record of posterior leucoencephalopathy syndrome.

One participant in the ustekinumab group experienced a moderate SAE (non-glycaemic fit). The event occurred 5 months after the participant discontinued treatment and withdrew from the study.

There were 10 COVID-19 infections experienced by 10 participants (ustekinumab: 18% *n* = 8; control: 7%, *n* = 2). Nine COVID-19 events were assessed to be mild, one (experienced by a control participant) was deemed to be moderate. All 10 COVID-19 events were resolved with no sequelae.

TABLE 26 Number of AEs and participants for each System Organ Class by treatment group

	Control (*n* = 25)		Ustekinumab (*n* = 47)	
System Organ Class	Number of events	Number of participants (%)	Number of events	Number of participants (%)
Infections and infestations	37	17 (68)	80	32 (68)
Immune system disorders	7	6 (24)	16	8 (17)
Nervous system disorders	26	13 (52)	60	15 (32)
Respiratory, thoracic and mediastinal disorders	2	1 (4)	1	1 (2)
Gastrointestinal disorders	22	11 (44)	29	18 (38)
Skin and SC tissue disorders	10	8 (32)	12	9 (19)
Musculoskeletal and connective tissue disorders	8	7 (28)	9	9 (19)
General disorders and administration site conditions	13	7 (28)	22	16 (34)
Others (miscellaneous)	3	3 (12)	24	9 (19)
Total	128	22 (88)	253	42 (89)

Chapter 5 Discussion

In summary, the results from the USTEK1D study suggest that teenagers (aged 12–18) who have recently been diagnosed with T1D and started on insulin when treated with ustekinumab have 49% (95% CI 8% to 206%) higher levels of MMTT-stimulated insulin C-peptide after 52 weeks (primary end point) than those in the control group [geometric ratio of ustekinumab to control = 1.49 (95% CI 1.08 to 2.06; *p* 2.06)]. C-peptide preservation from week 28 to week 52 was correlated with a reduction in a highly specific subset of T cells expressing the cytokines IL-17 and IFN-γ, as well as a smaller subject co-expressing IL-2 and GM-CSF, representing as few as 0.1% of circulating CD4 T cells. This provides the first randomised controlled trial (RCT) evidence in humans that IL-17-secreting T cells are relevant to the disease process, supporting data from observational and preclinical studies. The results are generally consistent with the pilot study in adults performed by Marwaha *et al.* that formed the basis for the design of the current study.[25]

No significant differences in metabolic end points (HbA1c, insulin use, IDAA1c, CGM parameters), hypoglycaemic episodes or PROMs were seen between the groups. This apparent failure to demonstrate statistically significant clinical benefits is likely due to two factors. Firstly, the study did not have adequate power to demonstrate such differences. Data from the Trial Outcome Marker Initiative[38] indicate that two to three times as many participants are required to show significant differences in these parameters and greater numbers for hypoglycaemia. In this context, it may be relevant to note that some of the point estimates for clinical outcomes were in the direction of benefit: for HbA1c with insulin use as a covariate (not pre-specified, but found to be relevant), point estimates at 28 and 52 weeks were 2–3 mmol/mol lower in the ustekinumab group and that participants in the ustekinumab group reported a lower overall incidence per person-year of all types of hypoglycaemia (39.38) than those in the control group (43.80). Secondly, the preservation of C-peptide was apparently delayed – with the major effect occurring between weeks 28 and 52 rather than the first 28 weeks. This meant that around 45% of insulin production had already been lost by the time any preservation benefit took effect. Higher amounts of preserved beta cell function are required for effects on postprandial glucose control, which is a major determinant of HbA1c and glucose variability.[40–42] Lesser amounts of C-peptide have been reported to be beneficial for reduction in hypoglycaemia, but these data come from long-standing diabetes in which absolute C-peptide levels are very low and hypoglycaemia is more common than in the newly diagnosed period.[42]

Included in this study were novel measurements of clinical end points that at the time of protocol design had not previously been included in immunotherapy trials – notably CGM and PROMs (parents and participants). These are now beginning to be introduced into newer studies[43] and the data from USTEK1D alongside these newer studies will allow power calculations to be done to incorporate these into future study designs.

In ancillary mechanistic studies, we were able to demonstrate the immunological changes anticipated from the known actions of ustekinumab – notably a reduction in Th1 (IFN-γ-secreting) and Th17 (IL-17-secreting T cells). These changes appeared delayed – becoming maximal between 28 and 52 weeks which seemed later than reported in the literature where the drug has been used in other diseases such as ulcerative colitis.[44,45] This may be an artefact due to limited early time points being estimated but may also relate to the action of ustekinumab being on the cytokines that control the development of these cells (IL-12 and IL-23) rather than a direct action on the cells themselves. Hence, the time course of change will depend on the half-life of the cells. Our analyses were more detailed than previous studies in ulcerative colitis exploring additional cytokines and combinations of these. Therefore, we were able to show that the impact on Th1 cells alone was minimal, but there was a significant change in Th17.1 cells (expressing both IL-17 and IFN-γ), which constitute < 1% of circulating T cells. In particular, we saw for the first time change in a finer subset of Th17.1 cells co-expressing the cytokines GM-CSF and IL-2, suggesting that they are highly activated. These cells represent around 0.1% (1 in 1000) of circulating T cells. Although not formally corrected for multiple testing, these changes were highly significant ($p < 0.0001$). T cells expressing GM-CSF have been found to be pathogenic in other diseases such as multiple sclerosis as well as T1D[46–49] Note that there was no impact on the majority of circulating T cells including regulatory T cells, which is likely to contribute to the lack of significance generalised immunosuppression with ustekinumab (see safetydiscussion below). It should also be noted that the suppression of these T-cell subsets was not complete. At the end of therapy, the levels were not significantly different between the control and ustekinumab groups: the significant change within the group within the ustekinumab arm which by change started with higher levels of these cells. This potentially leaves room for more powerful interventions on this subset, although any additional risk of harm would need to be assessed.

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Additionally, we were able to show an association between reductions in the Th17.1 and the smaller Th17.1/GM-CSF/IL-2 subsets with preservation of C-peptide in the period 28 and 52 weeks. This finding should be interpreted with caution as it is highly exploratory and not corrected for multiplicity but provides support for the concept that these cells are relevant to the causal pathway. Immunological assays involving markers of the disease process using blood samples are challenging in T1D. The autoimmune process seems largely confined to the pancreas and draining lymph nodes, with estimates of the frequency islet-specific T cells being around 1 in 10^4 cells, which is at the limits of detection of current techniques. However, we were able to see a reduction in proinsulin-specific T cells secreting IL-17 A (and to a lesser extent IL-17F) in the ustekinumab arm using FluoroSpot assays which are sensitive to around 1 in 10^5 cells. This is the first time this has been demonstrated in immunotherapy of T1D. Only around 50% of participants had a response to this specific antigen at baseline and so could be included in the analysis.

An expected but striking feature of treatment with ustekinumab was its tolerability and safety. No SAEs were reported during the treatment phases in the study and, overall, there was no excess of AEs in the ustekinumab arm, although there was possibly an increase in mild infections in events judged to be possible treatment-emergent. This is consistent with the experience in over 100,000 years of patient exposure in other conditions since the marketing of ustekinumab in 2009 in which the risk of serious infections was very low and lower than other commonly used biologics such as anti-TNF. The study was conducted over the COVID-19 pandemic period. Consistent with the lack of immune compromisation with ustekinumab was the finding that 22% of participants experienced COVID-19 during the treatment as judged by seroconversion, of whom 13 were clinically symptomatic (all mild). Rates were not significantly different between the treatment groups (24% vs. 17%, $p = 0.84$) and there was no evidence of impact on the primary end point. The high level of safety observed justifies the choice of using the highest licensed dosing regime (for ulcerative colitis) – 90 mg every 8 weeks – higher than licensed for use in psoriasis.

In addition to a well-established safety and excellent tolerability profile, ustekinumab is particularly easy to use, being given during the maintenance phase just once every 2 months SC. The highly selective impact of ustekinumab on the T-cell population is likely relevant to its safety. This is even more important in T1D than in other autoimmune diseases as alternative therapy exists in the form of insulin replacement, and hence safety and tolerability need to be as good if not better than standard therapy.

Strengths of the current study are the high eligible to randomised ratio, the similarity of the randomised sample to the national profile in gender and ethnicity, the low loss to follow-up rate (6%) – despite the prevailing pandemic conditions – minimisation to improve the balance of baseline C-peptide and age between treatment groups, and that the study was blinded. Differences were seen in the pre-specified primary end point analysed by ITT, avoiding the risk of multiplicity. Although none of the secondary analyses were significant, the ancillary mechanistic analysis was strongly consistent with an immune effect of the ustekinumab and was generally supportive of an effect on beta cell function. Recruitment was completed nearly within the predicted time frame (27 vs. 24 months). Limitations and weaknesses are discussed below.

End of trial

At the end of the trial, sites were provided with unblinding information for their participants and were asked to contact them using a template letter to let them know what treatment they had been allocated and the early findings of the study. The Trial Office e-mail was included in the letter so that participants could contact the team if they had any queries.

Limitations

The trial has several limitations which need to be taken into account in the interpretation of the results. As a phase II study, the main limitation is the relatively small sample size. The final observed difference in the primary end point between the groups was slightly smaller than the assumption made in the power calculation and necessarily the CI was large [geometric ratio of ustekinumab to control = 1.49 (95% CI 1.08 to 2.06)] – between an 8% and 106% difference – resulting in

imprecision. Although loss to follow-up was low (*n* = 4, 6%), six participants had insufficient baseline data to calculate the adjusted primary end point resulting in 14% of individuals (*n* = 10) missing from the final analysis. Dropout was similar between the treatment arms. Overall, considering the ustekinumab was well-blinded and the primary end-point objective, the risk of systematic bias in the primary end point is considered to be low.

An important limitation is the relatively lower numbers of participants attending the week-28 review point and MMTT (76%). The estimate of this end point – which suggested a delayed effect of the ustekinumab – may therefore be unreliable.

Sensitivity analysis suggested the result was robust to inclusion or exclusion of small numbers of people with extreme values of PDs, but missing data imputation suggested that the model would be sensitive to missing data if dissimilar between the groups. None of the secondary end points were significant and hence clearly supportive of the primary end-point result, but these could be considered to be underpowered. In two cases (HbA1c and hypoglycaemia), there was a suggestion that the point estimate was in the same direction as the primary end point, but this was not the case for insulin dose, CGM parameters and PROMs. All assessments beyond the primary outcome, especially the immunological analysis which involved over 100 separate comparisons, should be viewed with caution.

Generalisability

Thirty-five per cent of participants approached were eventually randomised into the trial. The ethnicity mix of the final trial population was very similar to the national balance from the NPDA 2019–20. The trial was slightly enriched in males versus the background population (60% vs. 54%) and had a lower percentage of 16- to 17-year-olds (18% vs. 30%). The mean HbA1c at 52 weeks was 56 mmol/mol, which is lower than similar age and duration in the NPDA (57–66), suggesting some bias towards a more compliant population as might be expected. The loss of C-peptide from baseline over 52 weeks in the control group was higher (65%) than in the paediatric treatment group of the Trial Outcome Markers Initiative in T1D compilation of trials (37–50%). It is not easy to estimate the likely compliance with treatment in the general population, but generally compliance was high and the ustekinumab treatment regime itself is not too onerous. Hence, in general, we would suggest that the trial likely has good external validity and generalisability, within the confines of the imprecision of the evaluation.

Equality, diversity and inclusion

Participant demographics

The trial sought to include patients aged 12–18 years from all ethnic backgrounds, but we were unable to offer translation services to fully inform potential participants and their parents about the trial's requirements if they were unable to understand verbal and written English.

Type 1 diabetes is most commonly diagnosed in Caucasian populations in the UK. The proportions of the main ethnic groups represented in the trial were reflective of the patterns seen in the diagnosis and treatment of T1D in 12- to 18-year-olds in the UK. Of those randomised, there was a comparable distribution of ethnicities across both treatment groups.

The ethnicity balance (82% white) is reflective of the national balance and increased frequency of T1D in Caucasians (80% white in NPDA 2019–20).

The percentage of 16- to 18-year-olds was fewer than predicted (18% vs. 40% predicted) which appeared to be due to less older teens being available to be approached rather than failing to consent for screening. The percentage of 16- to 17-year-olds newly diagnosed with T1D in 2019–20 (vs. 12- to 17-year-olds) in the NPDA was 31%. The NHS system varies across the UK when over 16-year-olds are diagnosed, as some go straight to adult services while others remain with a paediatric service. Most of our trial sites were paediatric, so we were unable to recruit as many aged 16 years and over for the trial.

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The male-to-female ratio (60% male) was slightly more skewed towards males than in the NPDA report (NPDA: 54% male age 12–17).

Hence, overall, the randomised cohort was reasonably well reflective of the national cohort of newly diagnosed 12- to 17-year-olds with T1D.

Trial team demographics

The TMG (*n* = 19) was made up of people with key expertise, of whom 10 were male.

All six patient and public involvement (PPI) representatives on our committees were female. Five had been diagnosed with T1D and the sixth was the mother of two children diagnosed with T1D.

There were 10 male PIs at our 16 trial sites (one of which was later replaced by a female due to retirement) and the gender mix for the allocated Research Nurses at sites was 2 males : 30 females.

Patient and public involvement

During trial design

Young people and their families were involved in the design of the trial to ensure that we could properly inform, recruit and retain participants for the duration of the trial while still capturing the data required to address the aims of the trial. Open meetings involving 15–20 families were held at the initial stage to define key design points in the protocol that influenced trial involvement. Three families with children with T1D aged 14–16 years 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 recruitment video created in partnership with eHealth Digital Media Ltd (http://ehealthdigital.co.uk) was reviewed by two to three young people with T1D and their families from the DRUC Public Reference Panel. Their comments were included in formulating the final documents.

During trial set-up and participant recruitment

We appointed two patients or parents of patients (referred to as PPI representatives in this section) with T1D to each committee (TMG, DSMB, TSC). They were encouraged to liaise with each other outside meetings and the Trial Manager was their point of contact for queries or honoraria payments. The chairperson of each committee was instructed to ensure all meetings were inclusive and jargon-free wherever possible. Every meeting had a PPI item on the agenda to allow them the opportunity to say or ask anything.

Honoraria were paid at £75 per half day as per the INVOLVE guidelines at the time and covered meeting preparation as well as the time of the meeting itself.

Our TMG PPI representatives included one young adult with T1D (aged 18 years at the time of the committee set-up) and one mother of two young children with T1D. Our TSC and DSMB PPI representatives all had a diagnosis of T1D themselves.

Patient and public involvement representative(s) were involved in:

1. Commenting on the protocol and patient-facing materials (TMG).
2. Attending the initial REC committee meeting to answer questions from the committee (parent PPI rep from TMG).
3. Troubleshooting to support recruitment and retention of participants (all committees).
4. Reporting the final results to the trial participants (TMG).
5. Preparing the lay summary for the final report (all committees).
6. Disseminating findings to a wider audience (TMG).
7. Helping set the agenda for future research in this field (all committees).

Reviewed documents were returned by PPI representatives using tracked changes where relevant and reports were discussed in detail during committee meetings with the opportunity to question any unclear text or data. In the majority of cases, edits made by PPI representatives were accepted by the committee and embedded into the next or final draft.

The final results were presented by the CI to the committees and the PPI representatives were asked to comment on the findings and offer any opinions.

Reflections on patient and public involvement input

We found the expertise of the trials' PPI representatives to be exceptionally helpful and the trial benefitted from their first-hand experience of the clinical care they receive themselves or for their children. We sought permission from the REC to allow one PPI representative to attend to offer a 'service user' opinion of the trial design. We were fortunate to have on board an exceptional PPI representative who had two children diagnosed with T1D at the time. The REC committee almost entirely focused their questions on her opinions of the trial design, the sensitivities of asking about pregnancy testing and the potential burden of the trial on young patients and parents. She reassured them that the design we proposed would be completely acceptable to families in a way that the clinical and academic members of the team could not.

We found no negative effects caused by the influence of PPI representatives. Their time and opinions were always valued, and we are grateful to the funder for allowing us to compensate them for their time and efforts.

We were fortunate to have the DRUC Public Reference Panel as well as other more direct links to identify the PPI representatives we invited to the committees. Unfortunately, we lost contact with two PPI representatives (one TMG and one TSC), but the trial was over halfway through at this time and we elected not to replace them as the remaining members were contributing well.

Interpretation of primary and secondary outcomes

Within the power limitations of a phase II trial, the conclusion from the primary end point that ustekinumab reduces the loss of beta cell function as measured by stimulated C-peptide levels appears robust, although the size and clinical significance of the effect are less certain. Replication in a Canadian controlled study in adults with a very similar protocol (UST1D2, NCT03941132) is currently underway.

The effect on clinical (secondary) end points remains unclear, although some impact would be expected. The treatment was very well tolerated with a very low risk of harms consistent with clinical findings with ustekinumab in other diseases. The mechanistic evidence that ustekinumab selectively impacts small subsets of Th17 cells was strong (within the confines of an ancillary study).

The evidence that Th17 cells are on the causative pathway is suggestive and clinically requires replication but is of interest. The stabilisation of C-peptide loss appeared to occur late (between weeks 28 and 52), which is unusual, but this could have been an artefact of significant missing data at week 28.

Research recommendations

1. Replication of these findings should be sought and should be available from the ongoing UST1D2 study, although this is in an adult population.
2. Other biologic agents targeting other aspects of the Th17 pathway, especially those that have shown greater efficacy in other autoimmune diseases, should be tested in new-onset T1D to determine if their effect is greater and/or occurs earlier. These include drugs targeting the IL-23 receptor specifically via the p19 subunit (Guselkumab, Risankizumab, Tildrakizumab) and others directly targeting IL-17 (Ixekizumab, Secukinumab) or the IL-17 receptor (Brodalumab).

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Ustekinumab should be trialled in combination with other beta cell-preserving agents operating via complementary pathways, for example verapamil.

3. Consideration should be given to trialling ustekinumab in pre-clinical T1D where its excellent tolerability would be of particular value and any delay in onset would be less critical.

Conclusions

In summary, ustekinumab appears to slow down the autoimmune process providing the first clinical trial evidence that IL-17-secreting T cells play a pathogenic role in T1D. Alone, it is insufficient to halt the autoimmune process. Consideration may be given to testing other drugs targeting the IL-17 pathway, using ustekinumab in combination with other agents or using it earlier in the disease pathway (preclinical disease) since it is so well tolerated and simple to use.

Additional information

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CRediT contribution statement

Kymberley Carter (https://orcid.org/0000-0003-0691-6282): Data curation (lead), Investigation (equal), Project administration (lead), Resources (equal), Software (lead), Validation (equal), Visualisation (equal), Writing – original draft (lead), Writing – reviewing and editing (lead).

Wai-Yee Cheung (https://orcid.org/0000-0002-0915-9312): Data curation (equal), Formal analysis (co-lead), Investigation (equal), Methodology (equal), Project administration (equal), Validation (equal), Visualisation (equal), Writing – original draft (co-lead), Writing – reviewing and editing (equal).

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Disclosure of interests

Full disclosure of interests: Completed ICMJE forms for all authors, including all related interests, are available in the toolkit on the NIHR Journals Library report publication page at https://doi.org/10.3310/FQLN7416.

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Patient data statement

This work uses data provided by patients and collected by the NHS as part of their care and support. Using patient data is vital to improve health and care for everyone. There is huge potential to make better use of information from people's patient records, to understand more about disease, develop new treatments, monitor safety and plan NHS services. Patient data should be kept safe and secure, to protect everyone's privacy, and it is important that there are safeguards to make sure that they are stored and used responsibly. Everyone should be able to find out about

how patient data are used. #datasaveslives You can find out more about the background to this citation here: https://understandingpatientdata.org.uk/data-citation.

Data-sharing statement

The data for the USTEKID trial will be held by STU. Requests for access to data should be e-mailed to STU@swansea.ac.uk where they will be reviewed by the unit and the Chief Investigator.

Data for this trial will be managed and shared in a way that safeguards the confidentiality and anonymity of participants and is consistent with the terms of consent signed by participants. Data sharing does not necessarily mean public access. Data can be shared on request by contacting at STU@swansea.ac.uk. The request will be formally reviewed and the requestor informed of the decision.

Ethics statement

All researchers have conducted their research in accordance with the World Medical Association Declaration of Helsinki.

Ethical approval was granted by Wales REC 3 reference 18/WA/0092 (IRAS ID 230113) on 14 June 2018 and the MHRA on 26 June 2018. The EudraCT ID issued was 2018-000015-24.

Information governance statement

Cardiff University as Sponsor is committed to handling all personal information in line with the UK Data Protection Act (2018) and the General Data Protection Regulation (EU GDPR) 2016/679. Under the Data Protection legislation, Cardiff University is the Data Controller, and you can find out more about how we handle personal data, including how to exercise your individual rights and the contact details for our Data Protection Officer at https://www.cardiff.ac.uk/public-information/policies-and-procedures/data-protection.

Publications

Full list of publications, conference papers and seminars resulting from the trial

The trial protocol was published in *BMJ Open* in 2021 and is referenced as follows:

Gregory JW, Carter K, Cheung WY, Holland G, Bowen-Morris J, Luzio S, *et al*. Phase II multicentre, double-blind, randomised trial of ustekinumab in adolescents with new-onset type 1 diabetes (USTEK1D): trial protocol. *BMJ Open* 2021;**11**:e049595. https://doi.org/10.1136/bmjopen-2021-049595.

At the time of submission of this report to the Funder, no other trial-related peer-reviewed papers had been published but papers are planned for publication.

The CI (Colin M Dayan) presented the trial and its early findings at the following conferences:

- British Society for Paediatric Endocrinology and Diabetes (BSPED) November 2023, presentation of trial findings
- American Diabetes Association (ADA) June 2023, presentation of trial findings
- Diabetes Scotland 2022, introducing the trial and its progress
- Royal College of Physicians of Edinburgh 2022, introducing the trial and its progress
- Diabetes UK Press release 2019 aimed at advertising the trial to potential participants

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Appendix 1

TABLE 27 Objectives, outcome measures and analysis methods

Objectives	Outcome measures	Time point(s) of evaluation	Analysis method
Primary objective			
To determine the efficacy of ustekinumab [dose: 2 mg/kg (≤ 40 kg); 90 mg (> 40 kg)] for preserving MMTT stimulated 2-hour C-peptide AUC at week 52 as compared to control in children and adolescents with new-onset T1D	MMTT C-peptide AUC values at week 52	Week 52	ANCOVA adjusted for baseline MMTT C-peptide[a] (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 ≤ 48 mmol/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 control group	Week 52	Generalised linear modelling based on appropriate count models with adjustment by important covariates, for example gender and age, baseline insulin use and HbA1c at week 2
2. To investigate additional efficacy (metabolic) end points 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	ANCOVA adjusted for age, gender baseline MMTT C-peptide[b] baseline insulin use and HbA1c (measured at week 2)
	HbA1c	Weeks 0, 12, 28 and 52	ANCOVA 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 (e.g. log) if required with adjustment by important covariates, for example gender and age, baseline insulin use and HbA1c at week 2
	Insulin dose-adjusted HbA1c (IDAAC)	Week 52	Multiple regression based on appropriate transformation (e.g. log) if required with adjustment by important covariates, for example gender and age and baseline IDAAC

TABLE 27 Objectives, outcome measures and analysis methods (*continued*)

Objectives	Outcome measures	Time point(s) of evaluation	Analysis method
3. To compare alternative metabolic end-point assays to MMTT: including glycaemic variability in glucose monitoring systems –FreeStyle Libre and hypoglycaemia rates	Glycaemic variability parameters downloaded from glucose monitoring, for example • 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[c] (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 AEs of the following categories: • Injection reactions • Hypersensitivity reactions • Hypoglycaemic episodes • Evidence of infection • Evidence of posterior leucoencephalopathy 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	• HypoFear, DTSQ and PedsQL questionnaires completed by participants and their parents	Weeks 2, 28 and 52	ANCOVA adjusted for baseline (week 2) values

a Transformed by log (1 + + *x*).
b Transformed by log (1 + *x*).
c Transformed by log (1 + + *x*).

[1] *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), Bacillus Calmette–Guérin 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 2018–9, nasal spray live flu vaccine recommended for: children aged 2 to*

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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- to 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 human papillomavirus cervical cancer vaccine, Dip/Tet/polio 3 in 1 teenage booster and Men ACWY.*

EME
HSDR
HTA
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