Anti-interleukin-21 antibody and liraglutide for the preservation of β-cell function in adults with recent-onset type 1 diabetes: a randomised, double-blind, placebo-controlled, phase 2 trial

*Matthias von Herrath, Stephen C Bain, Bruce Bode, Jesper Ole Clausen, Ken Coppieters, Leylya Gaysina, Janusz Gumprecht, Troels Krarup Hansen, Chantal Mathieu, Cristobal Morales, Ofri Mosenzon, Stine Segel, George Tsoukas, Thomas R Pieber, on behalf of the Anti-IL-21–liraglutide Study Group investigators and contributors**

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*Anti-IL-21–liraglutide Study Group investigators and contributors are listed in the appendix

Novo Nordisk A/S, Søborg, Denmark (M von Herrath MD, J O Clausen DSc); **Swansea University Medical School, Swansea, UK** (S C Bain MD); **Atlanta Diabetes Associates, Atlanta, GA, USA** (B Bode MD); **Emory University School of Medicine, Atlanta, GA, USA** (B Bode); **Novo Nordisk A/S, Måløv, Denmark** (K Coppieters PhD); **Kazan Federal University, Kazan, Russia** (L Gaysina PhD); **Medical University of Silesia, Katowice, Poland** (J Gumprecht MD); **Steno Diabetes Center Aarhus, Aarhus University Hospital, Aarhus, Denmark** (T K Hansen MD); **Clinical and Experimental Endocrinology, UZ Gasthuisberg, University of Leuven, Leuven, Belgium** (C Mathieu MD); **Endocrinology and Nutrition Department, Virgen Macarena Hospital, Seville, Spain** (C Morales MD); **Diabetes Unit, Department of Endocrinology and Metabolism, Hadassah Medical Centre, Faculty of Medicine, Hebrew University of Jerusalem, Jerusalem, Israel** (O Mosenzon MD); **Novo Nordisk A/S, Aalborg, Denmark** (S Segel MSc); **Department of Medicine, McGill University, Montreal, QC, Canada** (G Tsoukas MD); **Division of Endocrinology and Diabetology, Department of Internal Medicine, Medical**

Summary

Background Type 1 diabetes is characterised by progressive loss of functional β-cell mass, necessitating insulin treatment. We aimed to investigate the hypothesis that combining anti-interleukin (IL)-21 antibody (for low-grade and transient immunomodulation) with liraglutide (to improve β-cell function) could enable β-cell survival with a reduced risk of complications compared with traditional immunomodulation.

Methods This randomised, parallel-group, placebo-controlled, double-dummy, double-blind, phase 2 trial was done at 94 sites (university hospitals and medical centres) in 17 countries. Eligible participants were adults aged 18–45 years with recently diagnosed type 1 diabetes and residual β-cell function. Individuals with unstable type 1 diabetes (defined by an episode of severe diabetic ketoacidosis within 2 weeks of enrolment) or active or latent chronic infections were excluded. Participants were randomly assigned (1:1:1:1), with stratification by baseline stimulated peak C-peptide concentration (mixed-meal tolerance test [MMTT]), to the combination of anti-IL-21 and liraglutide, anti-IL-21 alone, liraglutide alone, or placebo, all as an adjunct to insulin. Investigators, participants, and funder personnel were masked throughout the treatment period. The primary outcome was the change in MMTT-stimulated C-peptide concentration at week 54 (end of treatment) relative to baseline, measured via the area under the concentration-time curve (AUC) over a 4 h period for the full analysis set (intention-to-treat population consisting of all participants who were randomly assigned). After treatment cessation, participants were followed up for an additional 26-week off-treatment observation period. This trial is registered with ClinicalTrials.gov, NCT02443155.

Findings Between Nov 10, 2015, and Feb 27, 2019, 553 adults were assessed for eligibility, of whom 308 were randomly assigned to receive either anti-IL-21 plus liraglutide, anti-IL-21, liraglutide, or placebo (77 assigned to each group). Compared with placebo (ratio to baseline 0·61, 39% decrease), the decrease in MMTT-stimulated C-peptide concentration from baseline to week 54 was significantly smaller with combination treatment (0·90, 10% decrease; estimated treatment ratio 1·48, 95% CI 1·16–1·89; p=0·0017), but not with anti-IL-21 alone (1·23, 0·97–1·57; p=0·093) or liraglutide alone (1·12, 0·87–1·42; p=0·38). Despite greater insulin use in the placebo group, the decrease in HbA_{1c} (a key secondary outcome) at week 54 was greater with all active treatments (–0·50 percentage points) than with placebo (–0·10 percentage points), although the differences versus placebo were not significant. The effects diminished upon treatment cessation. Changes in immune cell subsets across groups were transient and mild (<10% change over time). The most frequently reported adverse events included gastrointestinal disorders, in keeping with the known side-effect profile of liraglutide. The rate of hypoglycaemic events did not differ significantly between active treatment groups and placebo, with an exception of a lower rate in the liraglutide group than in the placebo group during the treatment period. No events of diabetic ketoacidosis were observed. One participant died while on liraglutide (considered unlikely to be related to trial treatment) in connection with three reported adverse events (hypoglycaemic coma, pneumonia, and brain oedema).

Interpretation The combination of anti-IL-21 and liraglutide could preserve β-cell function in recently diagnosed type 1 diabetes. The efficacy of this combination appears to be similar to that seen in trials of other disease-modifying interventions in type 1 diabetes, but with a seemingly better safety profile. Efficacy and safety should be further evaluated in a phase 3 trial programme.

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University of Graz, Graz, Austria (Prof T R Pieber MD)

Correspondence to:
Prof Thomas R Pieber, Division of Endocrinology and Diabetology, Department of Internal Medicine, Medical University of Graz, A8036 Graz, Austria
thomas.pieber@medunigraz.at

See **Online** for appendix

Research in context

Evidence before this study

No formal literature search was done. All known and relevant papers were considered, and references are cited on the basis of the authors' knowledge of the scientific literate published up until the date of submission of the final revised version of the Article (Jan 12, 2021). Prevention of type 1 diabetes would require early modulation of the pathways that lead to autoimmune destruction of β cells in the pancreatic islets of Langerhans. In the past decade, insights into the disease mechanisms in type 1 diabetes have led to clinical trials of several novel preventive therapies. New strategies designed to regulate the immune system include the use of antigen-based immunotherapies and immunomodulatory or immunosuppressive agents. However, side-effects associated with systemic immune suppression, the transient nature of the observed efficacy, or both, have prevented the regulatory approval of these therapies. A single agent or approach seems unlikely to halt disease progression in all people with type 1 diabetes.

Added value of this study

We hypothesised that an agent with low-grade and transient immune-modifying effects combined with a therapy to improve β-cell function would offer efficacy-related benefits on β-cell survival, but with lower risk of the complications generally associated with immune suppression. In this phase 2, double-blind, randomised controlled trial in 308 adult patients with recent-onset diabetes and residual C-peptide secretion, combination treatment with anti-interleukin (IL)-21 and liraglutide for 54 weeks was well tolerated and resulted in sustained endogenous insulin secretion and improved glucose metabolism compared with placebo. To our knowledge, this study is the largest trial of a disease-modifying intervention in adults with recent-onset type 1 diabetes and, unlike most other studies, included a fairly long (26-week) off-drug follow-up period, during which the effect of the combination treatment diminished and no lasting adverse changes to the immune system were identified.

Implications of all the available evidence

Combination therapy with agents such as anti-IL-21 and liraglutide could constitute a potential novel disease-modifying therapy by preserving endogenous β-cell function. β-cell preservation seen in this trial is similar to that shown in other disease-modifying trials in type 1 diabetes. Although the reported adverse events were few and mild, suggesting a favourable safety profile, the long-term safety and efficacy of this combination therapy remains to be assessed in a phase 3 trial programme. Future studies are needed to address the long-term effects of the treatment and its benefits in patients with recent-onset type 1 diabetes.

Introduction

Type 1 diabetes is an autoimmune disease characterised by progressive loss of functional β-cell mass. The incidence of type 1 diabetes is increasing by 3% annually in high-income countries, and more than 1·1 million children and adolescents live with the condition.[1] The single treatment option for most people diagnosed with the disease remains life-long administration of exogenous insulin; however, despite the availability of advanced insulin analogues, many individuals with type 1 diabetes do not meet the recommended treatment goals.[2] Consequently, mortality among people with this disease is three-times greater than in the general population.[3]

Disease-modifying therapeutic interventions in type 1 diabetes have focused on disease prevention in individuals at high risk and the preservation of residual β-cell function soon after diagnosis.[4–11] Both strategies have the potential to lead to better long-term glycaemic control, with lower rates of hypoglycaemia and diabetes-related complications. β-cell function can be estimated on the basis of C-peptide concentration, and patients with higher C-peptide concentrations have better glycaemic control, and fewer and less pronounced long-term complications.[12,13] Clinical trials[4–6,10,11] have shown that the rate of decline of C-peptide concentration after diagnosis can be attenuated; however, in all trials, the C-peptide preservation effect eventually disappeared, sometimes during or shortly after therapy, and C-peptide concentrations again declined. Although these observations suggest that prolonged treatment is necessary, the potential advantage of this situation is that, unless an intervention induces irreversible changes to the immune system, the non-permanent nature of the intervention's effects might mean that long-term benefits do not necessarily come at the expense of frequent side-effects related to immune suppression such as infections,[14] including Epstein-Barr virus reactivation.[15]

We hypothesise that a disease-modifying therapy combining milder immunomodulation with a β cell-focused agent to improve cell function and prevent β-cell apoptosis under immune stress[16] could ensure β-cell survival with a reduced risk of complications compared with traditional immunomodulation in patients with newly diagnosed type 1 diabetes.

Anti-interleukin (IL)-21 antibody is a promising candidate for immunotherapy in type 1 diabetes because the IL-21 pathway has been linked to diabetes progression in animal models[17,18] and in humans,[19,20] putatively because of the central role of IL-21 in promoting trafficking of $CD8^+$ T lymphocytes from lymph nodes and the exocrine pancreas to the pancreatic islets.[21] Furthermore, non-clinical investigations[21] have shown a minor effect of IL-21 blockade on the immune repertoire. GLP-1 receptor agonists such as liraglutide have been proposed to relieve β-cell stress and prevent apoptosis,[22] protect against cytokine-mediated inhibitory effects on glucose-stimulated insulin secretion,[16] and ameliorate the

proinsulin-to-insulin processing defects seen in type 1 diabetes and type 2 diabetes.[23] Moreover, GLP-1 receptor agonists have proven beneficial effects on glycaemic control, bodyweight, and cardiovascular risk.[24,25] Thus, pursuing the concept of combination therapy—integrating immunomodulation and a component aimed at another mechanistically distinct target[26,27]—the combination of IL-21 blockade and a GLP-1 receptor agonist was assessed and has shown promising results in a mouse model.[28]

To investigate this approach in a clinical setting, we assessed the disease-modifying potential of a monoclonal anti-IL-21 antibody and liraglutide, in combination and as monotherapies, all as adjuncts to insulin, in a placebo-controlled phase 2 trial in adults recently diagnosed with type 1 diabetes.

Methods

Study design and participants

This randomised, parallel-group, placebo-controlled, double-dummy, double-blind, phase 2 trial was done at 94 sites (university hospitals and medical centres) in 17 countries (appendix pp 2–3). Eligible participants were adults aged 18–45 years with recently diagnosed type 1 diabetes and residual β-cell function. To be included, participants had to have a diagnosis of type 1 diabetes within 20 weeks before screening, a peak C-peptide concentration of at least 0·2 nmol/L (mixed-meal tolerance test [MMTT]), and have antibodies against glutamic acid decarboxylase and either islet antigen-2 or zinc transporter-8, or both. Individuals were excluded if their type 1 diabetes was considered unstable (defined by an episode of severe diabetic ketoacidosis within 2 weeks of enrolment) or if they had active or latent chronic infections. A complete list of eligibility criteria is provided in the appendix (pp 15–16).

The trial was approved by independent ethics committees and institutional review boards at each participating site and was done in accordance with Good Clinical Practice guidelines and the Declaration of Helsinki. All participants provided written informed consent before eligibility screening. The trial did not have a data monitoring committee. The full study protocol and statistical analysis plan are available online at ClinicalTrials.gov.

For the **protocol and statistical analysis plan** see https://clinicaltrials.gov/ct2/show/NCT02443155

Randomisation and masking

At week 0 (baseline), participants were randomly assigned 1:1:1:1 to treatment with anti-IL-21 and liraglutide combination, anti-IL-21, liraglutide, or placebo. Randomisation was stratified by the peak MMTT-derived C-peptide concentration at baseline (≥0·2 nmol/L to ≤0·6 nmol/L or >0·6 nmol/L). Outcome and safety data were collected by site investigators via electronic case report forms as per the study protocol. Investigators, participants, and funder (Novo Nordisk) personnel were masked throughout the treatment period. After all participants had completed the treatment period, Novo Nordisk personnel were unmasked to treatment allocation for an internal analysis done to inform the future clinical development programme. Investigators and participants remained masked until all data were collected and verified.

Procedures

Monoclonal anti-IL-21 antibody at a dose of 12 mg/kg and matching placebo were administered intravenously every 6 weeks during visits to trial sites. Liraglutide and matching placebo were self-administered as subcutaneous injections once per day; there were no indications that treatment non-compliance differed substantially between groups. The liraglutide dose was escalated from 0·6 mg to a target of 1·8 mg per day in increments of 0·6 mg every 2 weeks. In case of intolerable adverse events related to dose escalation, the dose could be reduced to 1·2 mg.

Participants received treatment for 54 weeks and were subsequently followed up for 26 weeks after treatment cessation (for a total follow-up time of 80 weeks). All participants were on a treat-to-target insulin regimen throughout the trial. Participants were withdrawn from the trial if treatment was discontinued. Investigational drug use was assessed by comparison of dispensed versus returned drug at site visits where the drug dispensing was done according to the protocol. Insulin therapy was recorded based on participant diaries.

Outcomes

The primary outcome was change in C-peptide secretion at week 54, measured via the area under the concentration-time curve (AUC) for MMTT-stimulated C-peptide concentration over 4 h at week 54 relative to baseline ($AUC_{0–4\ h,\ C\text{-}peptide,\ week\ 54}/AUC_{0–4\ h,\ C\text{-}peptide,\ baseline}$). MMTTs were scheduled at baseline and at weeks 12, 24, 36, 54, 65, and 80.

The key secondary efficacy outcomes were: ratio to baseline in the AUC of C-peptide over 4 h at week 80 and over 2 h at week 54 and week 80; ratio to baseline in the Cmax of C-peptide over 2 h and 4 h at week 54 and week 80; and change from baseline to week 54 and week 80 in HbA_{1c}, fasting plasma glucose, fasting C-peptide, and total daily insulin dose in units per kg (3-day average). Autoantibodies against insulin (radioimmunoassay-based), glutamic acid decarboxylase (ELISA-based), zinc transporter-8 (ELISA-based), and islet antigen-2 (ELISA-based) were measured at the start and monitored throughout the trial by use of commercial assays (RSR, Cardiff, UK); analyses were done at a central laboratory (Quintiles, Livingston, UK). The frequency and phenotype of circulating immune cell subsets (B cells, T cells, natural killer cells, and myeloid cells) were measured via peripheral blood mononuclear cells and flow cytometry and were defined as supportive secondary biomarker outcomes assessed as the change from baseline to week 54 and week 80.

The key safety outcomes were: the number of treatment-emergent hypoglycaemic events (nocturnal hypoglycaemia defined as events that occurred between 0001 h and 0559 h [both inclusive] was also assessed as a post-hoc outcome) according to the American Diabetes Association (ADA)[29] and Novo Nordisk definitions from the first dose of the study drug to week 54 and week 80; and the number of treatment-emergent events of diabetic ketoacidosis reported from the first dose to week 80. Hypoglycaemic events reported according to the ADA classification[29] are comprised of any type of events (ie, severe, asymptomatic, documented symptomatic, pseudohypoglycaemia, and probable symptomatic).

Supportive pharmacokinetic outcomes reported here, all related to anti-IL-21, were: the anti-IL-21 AUC over a dosing interval at a steady state (defined as after last dose); terminal half-life after the last dose of anti-IL-21; volume distribution at a steady state; clearance at steady state; the mean residence time; accumulation ratio of anti-IL-21 defined as $AUC_{48–54\ weeks}/AUC_{0–6\ weeks}$; anti-IL-21 concentration before and 1 h after dosing at a steady state.

Other additional secondary efficacy outcomes of exploratory nature were reported in the appendix (pp 17, 19) because they were considered relevant in the interpretation of the key outcomes. These additional secondary efficacy outcomes were: ratio to baseline in the AUC of glucose over 2 h and 4 h and change in fasting glucagon from baseline to week 54 and week 80.

Some additional safety outcomes of exploratory or regulatory nature were reported in the appendix (pp 11–14, 18, 21, 22) because they were considered relevant in the interpretation of the key outcomes and in light of the GLP-1 receptor agonist drug class investigated. These additional safety outcomes were: change in bodyweight, blood pressure, pulse rate, and amylase and lipase concentrations from baseline to week 54 and week 80; number of treatment-emergent hyperglycaemic episodes reported and number of treatment-emergent adverse events reported from first dose of the study drug to week 54 and week 80 (a relevant subset is reported here; all adverse events are reported at ClinicalTrials.gov or available in the redacted clinical study report and datasets in accordance with Novo Nordisk data sharing commitments); and the number of treatment-emergent events of diabetic ketoacidosis reported from first dose of the study drug to week 54.

Post-hoc analysis was done for the total number of treatment-emergent hyperglycaemic events.

Several additional secondary efficacy outcomes of exploratory nature and additional safety outcomes of exploratory or regulatory nature will be reported elsewhere, and because of the exploratory purpose of additional secondary outcomes, the results were not reported here. The redacted clinical study report and datasets will be available in accordance with Novo Nordisk data sharing commitments.

Additional secondary efficacy outcomes of exploratory nature from baseline to week 54 and week 80 not reported here were: ratio to baseline for the Cmax of glucose over 2 h and 4 h and change in the number of insulin injections per day (3-day average); number of weeks off bolus; outcomes derived from 7 point self-measured plasma glucose profiles; change in patient-reported outcome scores (SF-36, Experience of Treatment Benefits and Barriers, Diabetes Treatment Satisfaction Questionnaire). Additional safety outcomes of exploratory or regulatory nature not reported here were: the number of participants experiencing treatment-emergent injection or infusion site reactions from the first dose of the study drug and during the treatment period (54 weeks) caused by anti-IL-21–liraglutide–placebo injection–infusion; and from baseline to week 54 and 80: diabetes complications (retinopathy and estimated glomerular filtration rate); change in laboratory safety variables (haematology, biochemistry, coagulation, lipids, IgE, urine dipsticks, cytokine panel, and hormones), vital signs (electrocardiogram, blood pressure, pulse rate, and amylase and lipase concentrations); change in anti-IL-21 antibodies; and change in anti-liraglutide antibodies. Other supportive biomarker outcomes not reported here were: change in total IL-21 and change in autoantibodies against glutamic acid decarboxylase 65, zinc-transporter 8, islet antigen-2, and insulin autoantibodies from baseline to week 54 and week 80; and change in serum vitamin D (1,25 dihydroxycalciferol) from baseline to week 54.

Statistical analysis

This trial was powered for the comparison of combination treatment versus placebo for the primary outcome. The assumed ratio to baseline was 0·98 (–2%) for combination treatment and 0·65 (–35%) for placebo, corresponding to an assumed treatment ratio of 1·50 (treatment effect of –33 percentage points). The SD on the log-transformed primary outcome was assumed to be 0·5 for combination treatment and 1·0 for placebo. With 60 participants completing the trial in each of these two groups, the power would be 80·4% to detect a statistically significant treatment ratio. To account for non-completers, 77 participants were randomly assigned to each of the four treatment groups.

For the primary outcome, AUCs at available timepoints from baseline to end of treatment (week 54) were log-transformed and analysed by use of a mixed model for repeated measurements combined for all four treatments, including all available assessments for participants in the full analysis set (intention-to-treat population consisting of all participants who were randomly assigned with at least one available post-baseline value). Missing data were assumed to be missing at random. Treatment, C-peptide stratum, and sex were included as factors and log of the baseline $AUC_{0–4\ h}$ and age at baseline were covariates. The interaction between all variables and time was included

as a fixed effect. Estimated geometric mean ratios to baseline (percentage changes) and treatment ratios with 95% CIs were derived from the model. In a prespecified (exploratory) subgroup analysis of the primary outcome, the interaction between C-peptide stratum and treatment was added to the model.

We used a similar model in the analysis of the other efficacy outcomes (also assessed in the full analysis set [intention-to-treat population] for all participants who were randomly assigned with at least one available post-baseline value). The change from baseline in total daily insulin dose (average of doses reported on the 3 days before the trial site visits) was analysed by use of a normal linear regression model with treatment, stratum, and sex as factors and the baseline value and age at baseline as covariates.

For reporting of pharmacokinetic data, the pharmacokinetics analysis set (all randomly assigned participants with valid pharmacokinetic measurements) was used, and only descriptive results were reported.

For reporting of safety data, the safety analysis set (all participants who received at least one dose of study treatment) was used. Change from baseline in bodyweight, systolic and diastolic blood pressure, and pulse rate were analysed in a similar model as the efficacy outcomes. The total numbers of treatment-emergent severe or blood glucose-confirmed symptomatic events and nocturnal severe or blood glucose-confirmed symptomatic hypoglycaemic events were analysed by use of negative binominal regression with a log-link function, with the logarithm of exposure time as an offset. Treatment, C-peptide stratum, and sex were included as factors and age was a covariate. Event rates (safety outcomes) were calculated as events per 100 participant-years of exposure, as per standard Novo Nordisk reporting. In a post-hoc analysis, the total number of treatment-emergent

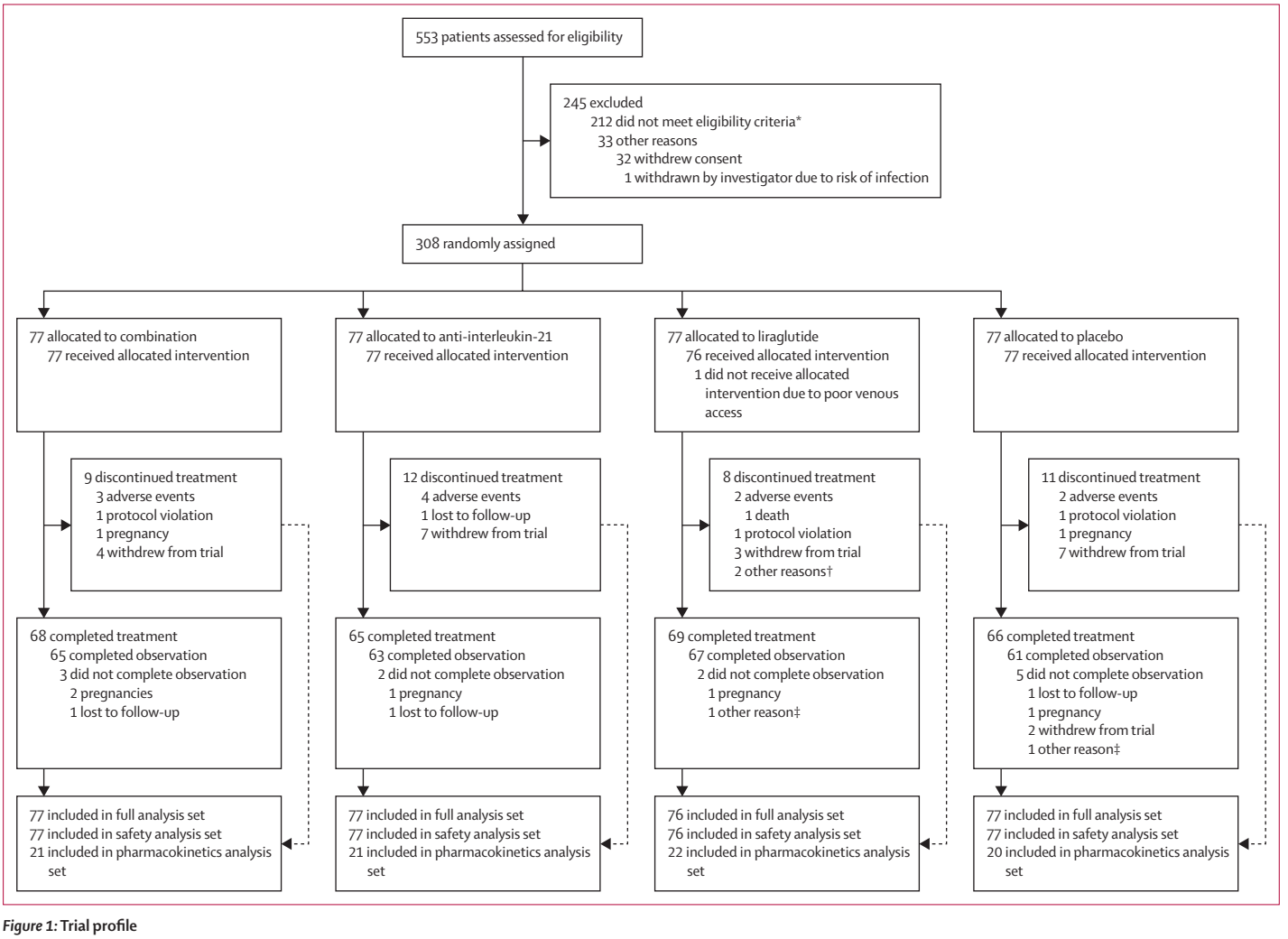

Figure 1: **Trial profile**

Did not complete observation indicates that the participant did not complete the off-treatment follow-up period. *56 patients had absence of islet-specific autoantibodies, 46 had laboratory abnormalities at screening, 45 had a stimulated peak C-peptide concentration of less than 0·2 nmol/L, 32 were positive for tuberculosis, 22 were positive for hepatitis B, and 11 did not meet one or more eligibility criteria. †One patient did not tolerate liraglutide 1·2 mg, and one was unable to receive the intervention because of poor venous access. ‡Moved to another city and did not complete visits.

hyperglycaemic events (plasma glucose >16·7 mmol/L [300 mg/dL]) was analysed by use of negative binominal regression. No correction for multiplicity was applied for any of the analyses. All analyses were done with SAS (version 9.4).

This trial is registered with ClinicalTrials.gov, NCT02443155.

Role of the funding source

The funder of the study was involved in study design, data collection, data analysis, data interpretation, and writing of the report.

Results

Between Nov 10, 2015, and Feb 27, 2019, 553 adults were assessed for eligibility, of whom 245 were excluded and 308 were eligible and randomly assigned to receive either anti-IL-21 and liraglutide, anti-IL-21, liraglutide, or placebo, with 77 allocated to each group (figure 1). 307 participants received treatment and were included in the full analysis set (intention-to-treat population) and the safety analysis set; one participant (in the liraglutide group) did not receive treatment due to poor venous access and was excluded from the full analysis and safety analysis sets. 84 participants in total were included in the pharmacokinetics analysis set, which was considered sufficient to obtain an adequate precision for pharmacokinetics outcomes. Between eight and 12 participants in each group did not complete the treatment period (figure 1).

Demographics and clinical characteristics were similar across the treatment groups at baseline (table 1). The mean age across the full analysis set was 28·4 years (SD 7·3) and 65% (201) of 307 participants were male.

	Combination (n=77)	Anti-interleukin-21 (n=77)	Liraglutide (n=76)	Placebo (n=77)
Age, years	28·0 (7·5)	28·6 (7·9)	28·0 (7·1)	29·0 (7·0)
Sex				
Female	21 (27%)	32 (42%)	25 (33%)	28 (36%)
Male	56 (73%)	45 (58%)	51 (67%)	49 (64%)
Bodyweight, kg	69·0 (14·2)	71·4 (13·2)	74·0 (13·8)	72·8 (19·8)
BMI, kg/m²	22·9 (3·8)	23·7 (3·4)	24·2 (3·8)	24·0 (5·0)
Systolic blood pressure, mm Hg	116 (11)	115 (12)	116 (11)	116 (11)
Diastolic blood pressure, mm Hg	71 (8)	71 (8)	72 (9)	70 (9)
Pulse rate, beats per min	69 (10)	70 (11)	69 (9)	68 (9)
Duration of type 1 diabetes, weeks	11·6 (5·7)	11·5 (5·3)	10·8 (4·8)	10·2 (4·7)
HbA_{1c}, %	7·1% (1·5)	7·0% (1·3)	7·2% (1·5)	7·3% (1·3)
HbA_{1c}, mmol/mol	54 (16)	53 (14)	55 (16)	56 (14)
Fasting plasma glucose, mmol/L	6·6 (2·1)	6·6 (1·9)	7·4 (2·7)	6·7 (2·3)
Fasting C-peptide,* nmol/L	0·22 (67·2%)	0·23 (66·1%)	0·24 (70·4%)	0·23 (83·7%)
Fasting plasma glucagon,* pg/mL	78·0 (27·8%)	83·2 (29·6%)	80·9 (27·6%)	80·0 (26·6%)
Peak C-peptide concentration (stimulated by mixed-meal tolerance test)				
≥0·2 to ≤0·6 nmol/L	31 (40%)	27 (35%)	32 (42%)	30 (39%)
>0·6 nmol/L	46 (60%)	50 (65%)	44 (58%)	47 (61%)
Mean total daily insulin dose, U/kg	0·32 (0·21)	0·33 (0·19)	0·30 (0·17)	0·32 (0·21)
Mean daily bolus insulin dose, U/kg	0·17 (0·11)	0·16 (0·11)	0·16 (0·10)	0·16 (0·12)
Mean daily basal insulin dose, U/kg	0·19 (0·12)	0·19 (0·11)	0·16 (0·09)	0·19 (0·11)
Number of severe hypoglycaemic events since diabetes diagnosis				
0	75 (97%)	77 (100%)	76 (100%)	76 (99%)
1	2 (3%)	0	0	1 (1%)
Amylase,* U/L	47 (38·8%)	50 (37·9%)	51 (35·5%)	47 (40·5%)
Lipase,* U/L	27 (38·9%)	29 (38·8%)	27 (42·8%)	28 (42·9%)
Islet-specific autoantibodies				
1	24 (31%)	20 (26%)	22 (29%)	28 (36%)
2	22 (29%)	27 (35%)	21 (28%)	24 (31%)
3	31 (40%)	30 (39%)	33 (43%)	25 (32%)

Data are n (%) or mean (SD), unless stated otherwise. Baseline is defined as at the time of randomisation or the most recent pre-randomisation value (ie, screening visit). The full analysis set was defined as all participants who were randomly assigned (intention-to-treat population). *Shown as geometric mean (coefficient of variation).

Table 1: **Demographics and baseline characteristics for the full analysis set**

An initial increase in MMTT-derived stimulated C-peptide secretion ($AUC_{0-4\,h}$) was observed with combination therapy (anti-IL-21 and liraglutide) and with liraglutide alone; however, by the end of treatment at week 54 and the end of the post-treatment observation period at week 80, the secretion had decreased in all groups (figure 2). The primary outcome, estimated decrease in stimulated C-peptide secretion from baseline to week 54, was significantly smaller with combination therapy (ratio to baseline 0·90; 10% decrease) than with placebo (0·61; 39% decrease; estimated treatment ratio 1·48, 95% CI 1·16–1·89; p=0·0017; figure 2). At week 54, the MMTT-stimulated C-peptide secretion was about 48% greater with combination therapy (AUC_{0-4h} 1·84 h×nmol/L) than with placebo (1·24 h×nmol/L; figure 2). Change from baseline to week 54 in MMTT-stimulated C-peptide secretion was not significantly different between the monotherapies (anti-IL-21 or liraglutide alone) and placebo (figure 2). Cmax for C-peptide decreased from baseline to week 54 in all treatment groups; compared with placebo (ratio to baseline 0·58, 42% decrease), the decrease was significantly smaller with the combination therapy (0·95, 5% decrease; estimated treatment ratio 1·64, 95% CI 1·28–2·12; p<0·0001), but not with anti-IL-21 alone (0·75, 25% decrease; 1·28, 1·00–1·65; p=0·052]) or liraglutide alone (0·72, 28% decrease; 1·24, 0·97–1·60; p=0·089; appendix p 17). Changes from baseline in MMTT-stimulated C-peptide secretion were similar when based on 2 h rather than 4 h AUC; when based on the 2 h AUC, C-peptide secretion was greater with anti-IL-21 monotherapy than with placebo (appendix p 17). Further, the findings were corroborated by stimulated plasma glucose values, which were reduced by the liraglutide-containing regimens (appendix p 17); although most of these reductions were non-significant, there was a significant difference at week 54 between the combination treatment and placebo for $AUC_{0-4\,h}$ (estimated treatment ratio 0·88, 95% CI 0·79–0·98; p=0·021). Analysis of fasting C-peptide showed a similar pattern to

that seen for the primary outcome at week 54 (figure 3). Fasting C-peptide concentration had remained fairly steady in the combination therapy group by week 54, whereas it had significantly decreased by 36% in the placebo group (1·55, 1·22–1·96; p=0·0003); differences between the monotherapy groups and placebo were not significant (figure 3).

In a prespecified subgroup analysis, we identified a significant differential treatment effect on the primary outcome depending on baseline C-peptide concentration (<0·6 nmol/L or >0·6 nmol/L; appendix pp 4–5). Notably, among participants with a baseline value of more than 0·6 nmol/L, change from baseline in stimulated C-peptide secretion at week 54 was similar in the combination therapy and liraglutide groups (none of the active treatment groups differed significantly from placebo in this subgroup).

With combination therapy of anti-IL-21 and liraglutide, the required total daily insulin dose decreased from baseline to week 54 by 12% (0·04 U/kg bodyweight; appendix p 6); this decrease was significant when compared with placebo (dose increase of 28%; 0·09 U/kg; p=0·0006). Despite greater insulin use in the placebo group in this treat-to-target trial (appendix p 6), the decrease in HbA_{1c} at week 54 was greater with all active treatments (–0·50 percentage points) than with placebo (–0·10 percentage points; figure 4), although the treatment differences were not significant. Fasting glucagon concentration did not change in any of the groups (appendix p 17). Bodyweight (a protocol-defined safety endpoint) significantly decreased from baseline to week 54 with combination treatment and with liraglutide alone (*vs* placebo; appendix p 18).

At week 80 (ie, after 26-week off-treatment observation period), changes from baseline in fasting C-peptide secretion (figure 3), HbA_{1c} (figure 4), and total daily insulin dose (appendix p 6) did not differ significantly between the active treatments and placebo; stimulated C-peptide secretion was significantly reduced with liraglutide versus placebo at 80 weeks (–65% *vs* –49%; p=0·0065), but the other active treatment groups did not differ significantly from placebo (figure 2; appendix p 19).

There were no treatment-related between-group differences in the numbers of patients with insulin autoantibodies or autoantibodies against glutamic acid decarboxylase, zinc transporter-8, or islet antigen-2 throughout the trial (data not shown). Overall, there were only small and transient changes (<10%) in the frequency of conventional T cells (including regulatory T cells), natural killer cells, and myeloid cells, with little effect on

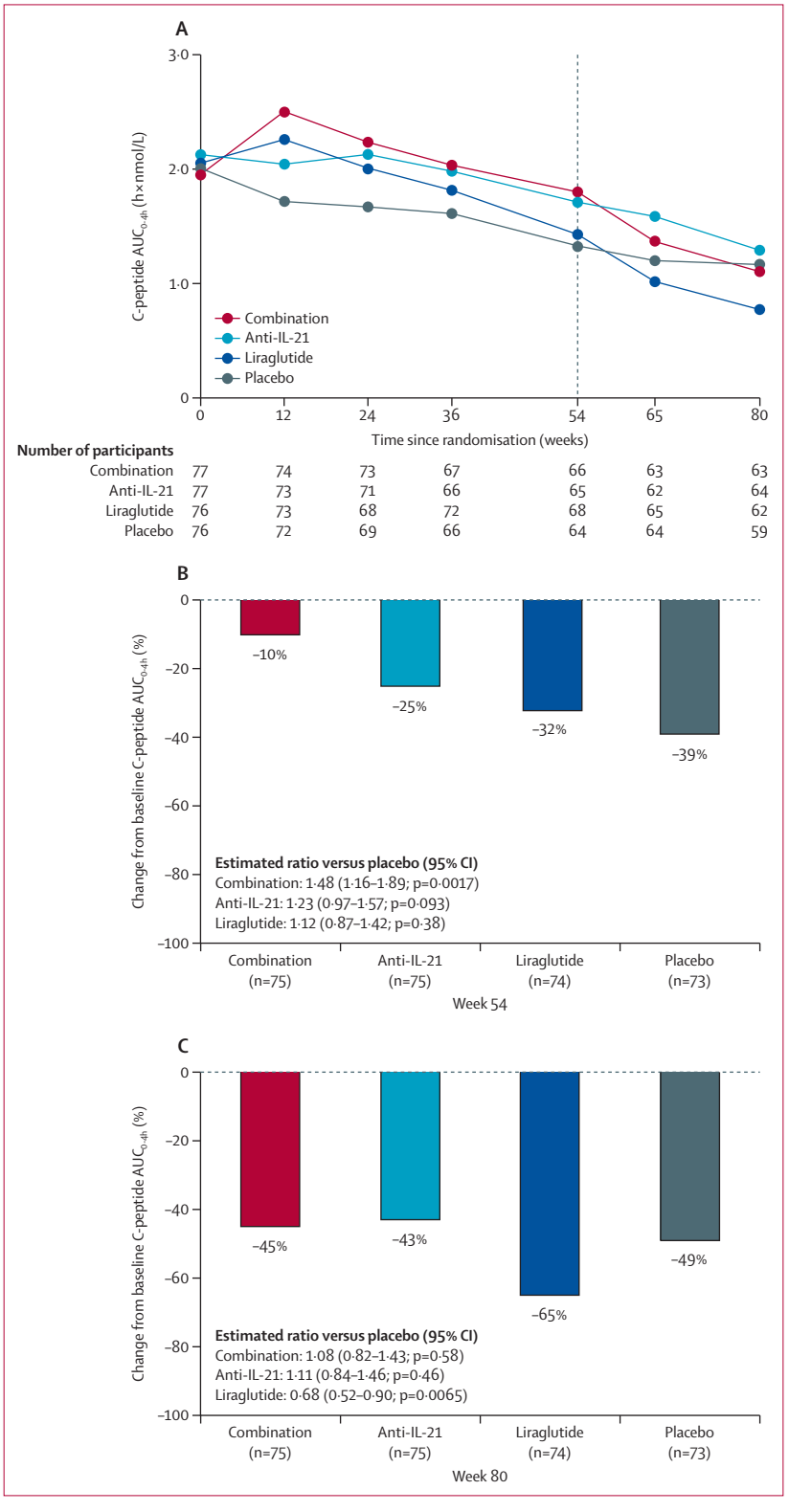

Figure 2: **Change from baseline in MMTT-stimulated C-peptide secretion**
(A) Observed geometric means over time (dotted line shows the end of treatment) and (B) estimated geometric mean changes from baseline at the end of treatment (week 54) and (C) at the end of the post-treatment observation period (week 80). Participants with at least one post-baseline value contribute to the statistical analysis; not all participants in the full analysis set had a post-baseline value. Data were log transformed. AUC=area under the time-concentration curve. IL=interleukin. MMTT=mixed-meal tolerance test.

follicular T-helper cells or B cells across timepoints and between treatment groups (appendix pp 7–10); no safety issues related to these minor changes were identified.

Treatment with liraglutide did not affect anti-IL-21 pharmacokinetic properties (appendix p 20). Adverse events and tolerability profiles (table 2; appendix p 21) were consistent with the previous report[30] on anti-IL-21 treatment in humans and the well established safety profiles of GLP-1 receptor agonists in patients with type 2 diabetes.[31] Accordingly, the most frequently reported adverse events included gastrointestinal disorders, which are a known class effect of exogenous GLP-1 receptor agonists. Apart from gastrointestinal disorders, the most frequently reported adverse events did not differ between active treatments and placebo (appendix p 21). One participant died during the trial (while on liraglutide treatment) following three reported adverse events (hypoglycaemic coma, which led to hospital admission and presentation with pneumonia and brain oedema). These three events were considered unlikely to be related to the assigned study treatment.

Adverse events leading to participant withdrawal from the trial were infrequent across all groups (table 2). Of 13 adverse events in 11 patients leading to withdrawal, two were severe (hypoglycaemic coma and brain oedema in the participant who died). Of the participants who completed the treatment period, most (49 [72%] of 68 in the combination group, 54 [82%] of 65 in the anti-IL-21 group, 53 [77%] of 69 in the liraglutide group, and 58 [88%] of 66 in the placebo group) received 1·8 mg of liraglutide (or the placebo equivalent). The remaining participants (19 [28%] in the combination group, 12 [18%] in the anti-IL-21 group, 16 [23%] in the liraglutide group, and 8 [12%] in the placebo group) who completed treatment received 1·2 mg liraglutide (or equivalent placebo) or had no information available because of issues with the participant-completed electronic diary used for data collection. No safety concerns related to hypersensitivity reactions, injection-site or infusion-site reactions, development of anti-drug antibodies, neoplasms, pancreatitis, or thyroid disease were identified (data not shown but available online at ClinicalTrials.gov).

At baseline, across treatment groups, 186 (61%) of 307 participants were positive for cytomegalovirus IgG and 234 (76%) of 307 were positive for Epstein-Barr virus IgG. During the trial, there was no recurrence of cytomegalovirus infection; however, five participants positive for Epstein-Barr IgG developed IgM antibodies to the virus (one on combination treatment, one on anti-IL-21, and three on placebo). All adverse events related to the five positive tests for Epstein-Barr IgM were mild events.

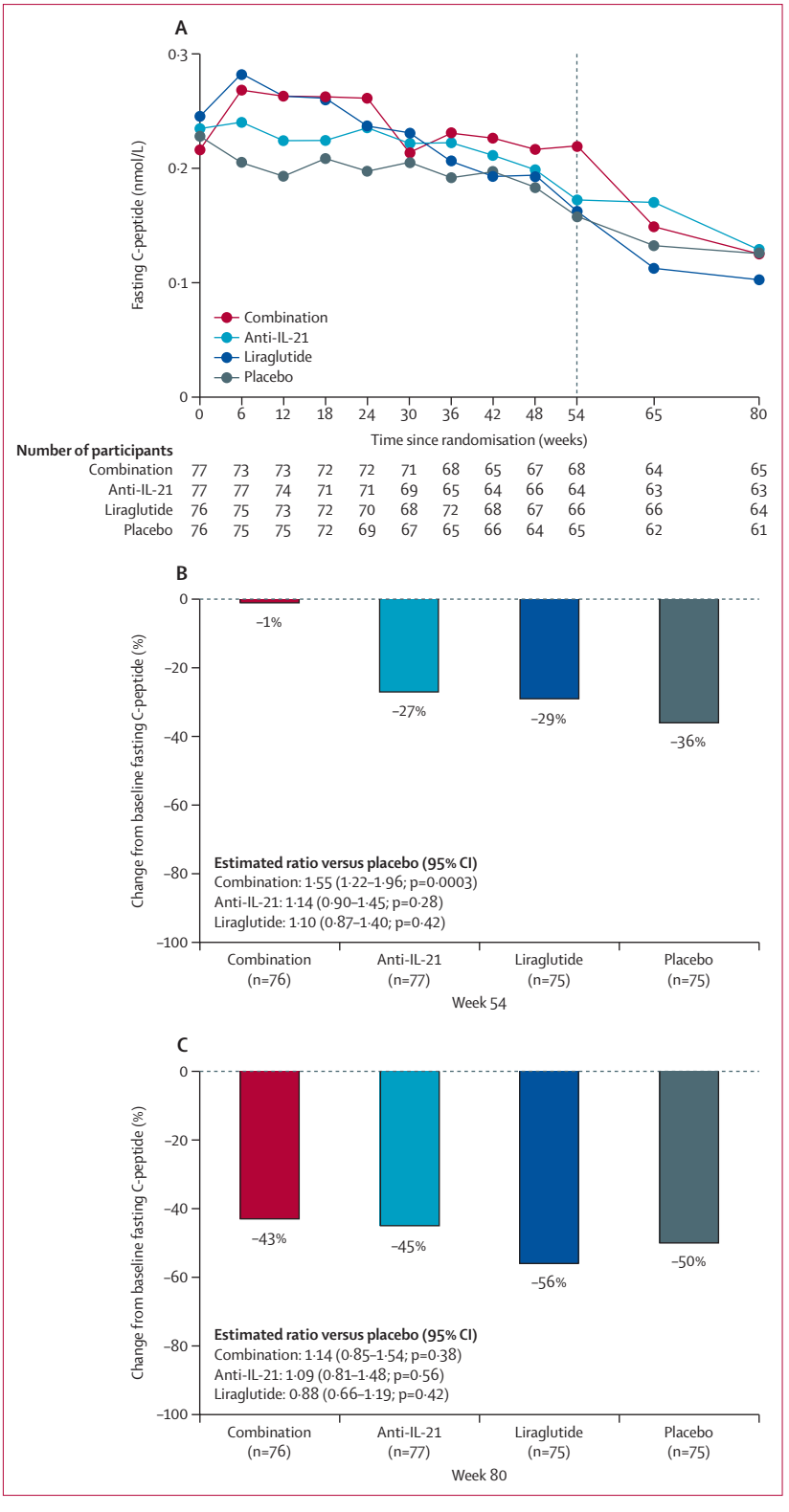

***Figure 3*: Change from baseline in fasting C-peptide secretion**
(A) Observed geometric means over time (dotted line shows the end of treatment) and (B) estimated geometric mean changes from baseline at the end of treatment (week 54) and (C) at the end of the post-treatment observation period (week 80). Participants with at least one post-baseline value contribute to the statistical analysis; not all participants in the full analysis set had a post-baseline value. Data were log transformed. IL=interleukin.

Three participants reported severe hypoglycaemic events during the treatment period (one on combination treatment and two on anti-IL-21 alone); none were nocturnal. The rate of severe or blood glucose-confirmed symptomatic hypoglycaemic events during the treatment period was lower with the active treatments than with placebo (table 2); although the difference versus placebo was not significant, with an estimated treatment ratio of 0·66 (95% CI 0·39–1·12) for the combination treatment and 0·69 (0·41–1·16; appendix p 22) for anti-IL-21 alone. For liraglutide versus placebo the difference was significant, with an estimated treatment ratio of 0·50 (0·30–0·85). During the post-treatment observation period, there were no differences in rates of hypoglycaemic events between the active treatment groups and placebo (appendix p 22). During the treatment period, the rate of hyperglycaemic events did not differ significantly between the active treatment groups and placebo; no events of diabetic ketoacidosis were observed (table 2). During the post-treatment observation period, the rate of hyperglycaemic events was significantly higher for combination therapy and for liraglutide alone compared with placebo (appendix p 22). No unexpected or clinically important differences were observed across groups in clinical laboratory variables or vital signs (data not shown). Blood pressure, pulse rate, and amylase and lipase concentrations changed in the combination therapy and liraglutide alone groups in accordance with the well known class effects of GLP-1 receptor agonists (appendix p 18).

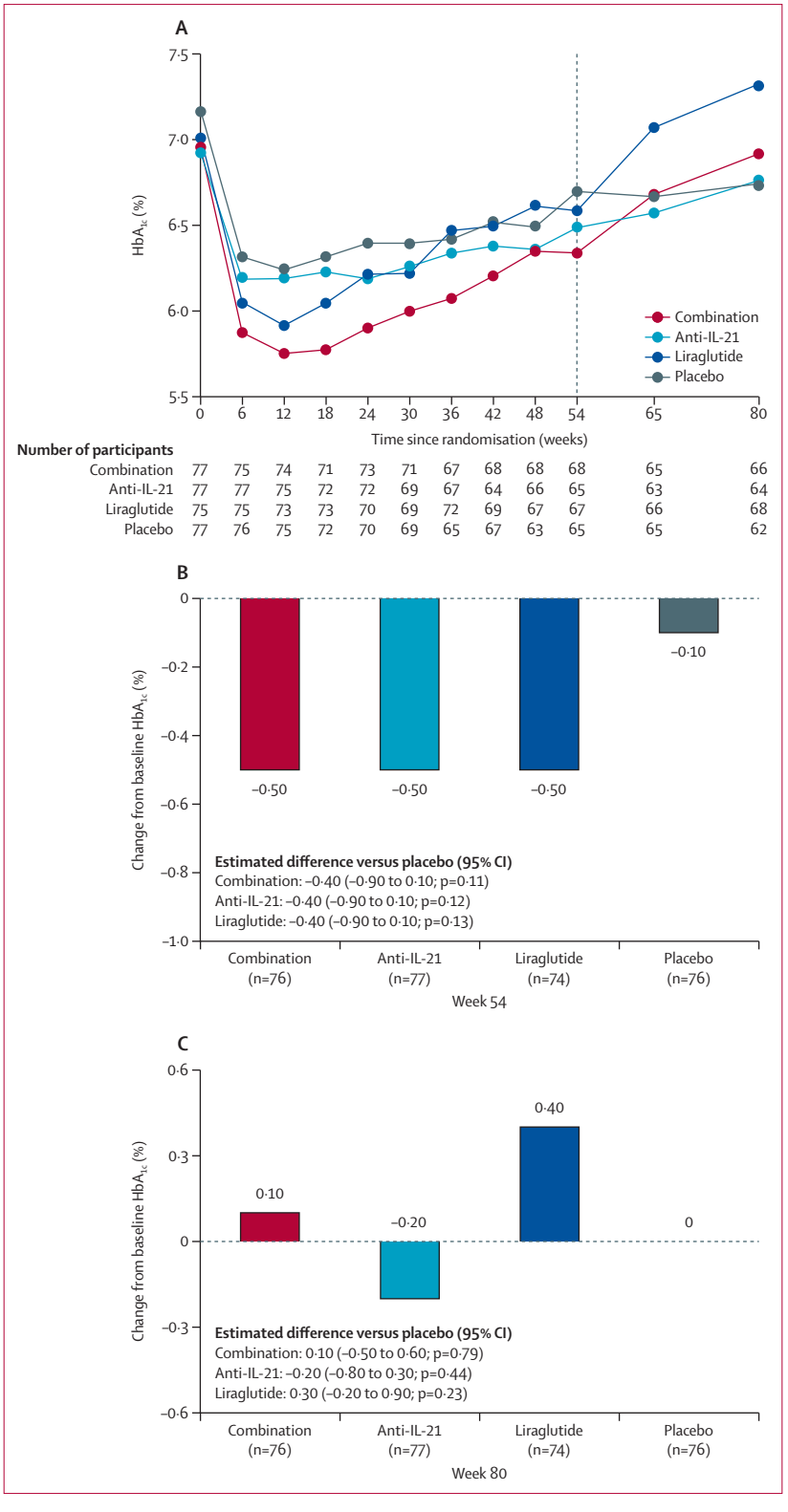

Figure 4: **Change from baseline in HbA_{1c}**
(A) Observed means over time (dotted line shows the end of treatment) and (B) estimated mean changes from baseline at the end of treatment (week 54) and (C) at the end of the post-treatment observation period (week 80). Participants with at least one post-baseline value contribute to the statistical analysis; not all participants in the full analysis set had a post-baseline value. Data were not log-transformed. IL=interleukin.

Discussion

In this phase 2 trial, we showed that 54-week treatment with the combination of a monoclonal anti-IL-21 antibody and the GLP-1 receptor agonist liraglutide was significantly better than placebo at preserving endogenous insulin secretion, as shown by a higher MMTT-stimulated C-peptide secretion. This effect was accompanied by nearly complete maintenance of fasting baseline C-peptide secretion and a reduction in the need for exogenous insulin by almost a third. A non-significant reduction by about a third in hypoglycaemia and a non-significant reduction in HbA_{1c} were also observed, despite the treat-to-target trial design. Notably, the benefit of the combination therapy seemed to be more pronounced in participants with a lower baseline C-peptide concentration (≤0·6 nmol/L), possibly reflecting the beneficial effect of anti-IL-21 in preserving the remaining β-cell function. In those with a higher baseline C-peptide concentration (reflecting more residual β-cell function), the combination treatment and liraglutide alone were equally beneficial, suggesting that in this group the

	Combination (n=77)		Anti-interleukin-21 (n=77)		Liraglutide (n=76)		Placebo (n=77)	
	Participants with events	Events per 100 participant-years of exposure	Participants with events	Events per 100 participant-years of exposure	Participants with events	Events per 100 participant-years of exposure	Participants with events	Events per 100 participant-years of exposure
Patient-years of exposure	75·9	..	75·0	..	75·2	..	74·5	..
All adverse events	59 (77%)	572	64 (83%)	436	65 (86%)	545	63 (82%)	489
Considered possibly or probably related to study drug (assessed before unmasking)								
Anti-IL-21 versus placebo	25 (33%)	88	20 (26%)	72	22 (29%)	125	24 (31%)	87
Liraglutide versus placebo	37 (48%)	177	24 (31%)	72	50 (66%)	209	27 (35%)	109
Serious adverse event	6 (8%)	8	3 (4%)	5	7 (9%)	13	7 (9%)	12
Adverse event leading to withdrawal from the study	3 (4%)	4	4 (5%)	4	2 (3%)	3	2 (3%)	2
Most frequently reported adverse event*								
Nasopharyngitis	18 (23%)	36	23 (30%)	57	22 (29%)	55	22 (29%)	47
Nausea	19 (25%)	44	6 (8%)	12	41 (54%)	81	9 (12%)	17
Vomiting	13 (17%)	30	0	0	17 (22%)	44	3 (4%)	5
Diarrhoea	12 (16%)	21	8 (10%)	19	13 (17%)	27	8 (10%)	12
Headache	9 (12%)	20	8 (10%)	12	9 (12%)	13	10 (13%)	19
Oropharyngeal pain	10 (13%)	15	11 (14%)	20	3 (4%)	7	7 (9%)	11
Decreased appetite	14 (18%)	20	2 (3%)	3	11 (15%)	17	1 (1%)	1
Hypoglycaemic events								
ADA classification†	73 (95%)	4419	73 (95%)	4560	69 (91%)	4287	73 (95%)	4579
Severe events	1 (1%)	1	2 (3%)	3	0	0	0	0
Severe or blood glucose-confirmed symptomatic events‡	43 (56%)	522	55 (71%)	525	46 (61%)	419	51 (66%)	675
Hyperglycaemic events§	32 (42%)	398	31 (40%)	341	29 (38%)	289	36 (47%)	391
Diabetic ketoacidosis	0	0	0	0	0	0	0	0

Data are numbers of participants with at least one specified event. The safety analysis set was defined as all participants who received at least one dose of study treatment (intention-to-treat population). ADA=American Diabetes Association. *Events with an overall rate of at least 10 events per 100 participant-years of exposure. †Any events of hypoglycaemia according to the ADA classification.[29] ‡Severe or blood glucose-confirmed symptomatic hypoglycaemic events are either severe as defined in accordance with the ADA classification[29] or confirmed by a plasma glucose concentration of less than 3·1 mmol/L and with symptoms consistent with hypoglycaemia. §Hyperglycaemic events were defined and confirmed by plasma glucose values of more than 16·7 mmol/L.

Table 2: **Treatment-emergent adverse events and glycaemic events in the safety analysis set**

effect of liraglutide did not depend on the β cell-preserving effect of anti-IL-21. Further research is warranted to explore the patient subgroups most likely to benefit from this combination.

Importantly, no safety concerns were identified during the trial, with the treatments being well tolerated and with no indications of generalised immune suppression on the basis of the assessed immune biomarkers, including multiple cell populations.

The overall purpose of the combination treatment was to achieve safe preservation of β-cell function. It is well recognised that even a small amount of residual endogenous insulin secretion, as measured by low concentrations of C-peptide, has important clinical benefits such as lower rates of hypoglycaemia and diabetes-related complications such as retinopathy.[12,32,33] These benefits seem to be independent of, or at least additional to, the effects of improved HbA_{1c} levels.[4–6]

The efficacy of the combination therapy seen in the present trial seems to be similar to that reported in trials of other disease-modifying interventions,[10,34] and is greater than that of each of the individual components (anti-IL-21 and liraglutide) given as monotherapy. Interestingly, the C-peptide curve in this study resembles the one seen in another recent study[35] with albiglutide. The observed safety profile of anti-IL-21 combined with liraglutide seems favourable compared with the safety profiles observed in previous trials of interventions intended to preserve β-cell function in patients with recent-onset type 1 diabetes, wherein side-effects seemed to be more severe and with long-term (months to years) changes to the immune system resulting in risk of, for example, reactivation of Epstein-Barr virus infection.[14,15]

Although the effects were less pronounced and not statistically significant, anti-IL-21 alone also seemed to have some potential beneficial effect on the preservation of C-peptide secretion as well as key glycaemic variables (HbA_{1c} and severe or blood glucose-confirmed hypoglycaemic events). This finding supports a future role for anti-IL-21 treatment either as a monotherapy or in combination with other agents for disease modulation in type 1 diabetes.

Identification of the exact mechanisms by which liraglutide and anti-IL-21 in combination lead to

preservation of C-peptide secretion was not the purpose of this trial and requires further research. However, evidence suggests that IL-21 blockade reduces the pancreatic influx of new CD8+ effector T cells, thereby modulating the inflammatory process in the pancreas.[21] Similarly, liraglutide has the potential to relieve β-cell stress and ameliorate the proinsulin-to-insulin processing defects seen in type 1 diabetes.[16,22,23] Thus, in addition to preserving glucose-induced insulin secretion under immune stress, liraglutide might also directly preserve β-cell health. Notably, however, another GLP-1 receptor agonist, albiglutide, did not preserve β-cell function compared with placebo during another 1-year trial[35] in patients with newly diagnosed type 1 diabetes. Additional studies are needed to address these questions, possibly on organoids since no human in-vivo β-cell mass assessments are currently available.

During the treatment period, the combination therapy was more efficacious than placebo in sustaining endogenous C-peptide secretion capacity, with the placebo group most likely reflecting natural disease course. Unlike most previous studies in disease-modifying interventions for type 1 diabetes, this trial included an off-drug observation period of 26 weeks immediately after the 54-week treatment period. Upon cessation of treatment, the beneficial effects diminished rapidly as the ongoing autoimmune process presumably resumed. Arguably, this finding is positive because the treatments did not induce permanent changes to the immune system, as seen with other immunomodulatory interventions. Therefore, on one hand, the need for continued treatment is not a full reset or cure from the autoimmune attack; yet, on the other, it will give the patient more control over treatment because the effects appear to cease directly upon cessation of treatment, which is reflected in the favourable side-effect profile.

There appeared to be a more rapid decline in C-peptide secretion during the 26-week observation period (ie, after treatment cessation) in the combination therapy and liraglutide alone groups than in the treatment period, which might reflect the observed increase in hyperglycaemia after cessation of liraglutide (with or without anti-IL-21). Hyperglycaemia might have been caused by a delayed up-titration or otherwise suboptimal titration of the insulin dose in these groups in particular. This notion is corroborated by the well established glycaemic efficacy of GLP-1 receptor agonists such as liraglutide, perhaps requiring tighter insulin titration than was specified in the trial protocol or applied at the trial sites. Whatever the cause, we speculate that hyperglycaemia might have led to increased glucose toxicity towards the β cells and resulted in the more rapid decrease in C-peptide secretion seen with the liraglutide-containing regimens. Moreover, we hypothesise that further damage to the β cells could also arise from liraglutide withdrawal because of an increase in self-presentation of the β-cell autoantigen proinsulin.

C-peptide and plasma glucose outcomes were assessed via 4h AUC values by default; 2h AUC values were also derived, and for the primary outcome (stimulated C-peptide secretion), the results and statistical inferences were overall similar across the two AUC approaches; however, anti-IL-21 alone was significantly better at preserving C-peptide secretion than placebo when assessed via the 2 h AUC, but not via the 4 h AUC. Notably, the 4 h AUC was chosen as the default because previous evidence suggested that the maximum concentration of C-peptide is reached about 2 h after a meal.

Whether the benefits of combination therapy can be sustained after 54 weeks will require further investigation. Future trials should also address the period after treatment withdrawal with a specific focus on glycaemia.

The weight loss seen with liraglutide-containing regimens is in line with licenced use of liraglutide in weight management and constitutes an additional benefit as a type 1 diabetes intervention, considering that type 1 diabetes can be associated with excess bodyweight, but this weight loss might also be a problem for patients with type 1 diabetes who are underweight.

The limitations of this study relate to the duration of treatment (1 year) and the enrolled patient population. Efficacy of the study treatment beyond 1 year was not tested. Furthermore, the study population were participants with recent-onset type 1 diabetes (diagnosis within 20 weeks of enrolment) and residual β-cell function (as determined by a baseline C-peptide concentration of <0·2 nM), and the efficacy was not evaluated in patients with early-stage type 1 diabetes. Finally, the long-term safety beyond 80 weeks cannot be addressed on the basis of this trial. Additional studies are required to clarify these unknowns.

In conclusion, treatment with the combination of anti-IL-21 and liraglutide for 54 weeks was well tolerated and resulted in sustained endogenous insulin secretion in response to an MMTT and improved glucose metabolism compared with placebo. These results suggest that this combination has the potential to offer a novel and valuable disease-modifying therapy for patients with recently diagnosed type 1 diabetes. However, the efficacy and safety need to be further investigated in a phase 3 programme.

Contributors

MvH and KC developed the ideas and concept of the study, were involved in the study design and data interpretation, and contributed to the writing of the report. SS was the principal statistician, did the data analyses, and contributed to the revision of the report. JOC was the international medical director for the study funder (Novo Nordisk) on the trial. SCB, BB, LG, JG, TKH, CMa, CMo, OM, GT, and TRP were clinical site heads, contributed to the writing and revision of the report, and were involved in data analysis. All authors had full access to all the data in the study upon request and had final responsibility for the decision to submit for publication. SS and TRP have accessed and verified all the data in the study.

Declaration of interests

MvH, JOC, KC, and SS are employees of Novo Nordisk and SS also holds shares in the company. MvH and KC hold a patent related to this work

(publication number WO 2015/169789) that has been issued and is owned by Novo Nordisk. SCB reports personal fees from AstraZeneca, Boehringer Ingelheim, Eli Lilly, Merck Sharp & Dohme, Novo Nordisk, Sanofi-Aventis, the All Wales Medicines Strategy Group, and the UK National Institute for Health and Care Excellence; he has also received funding for the development of educational programmes from Medscape and is a shareholder of Glycosmedia. BB reports grants and personal fees (for consulting and lectures) from Novo Nordisk. JG reports personal fees from Eli Lilly, Boehringer Ingelheim, Sanofi-Aventis, Merck Sharp & Dohme, Merck, AstraZeneca, Mundipharma, Polfa Tarchomin, Bioton, Servier, Berlin-Chemie, Adamed, and Novo Nordisk. CMa reports grants and personal fees from Sanofi-Aventis, Eli Lilly, Novartis, Boehringer Ingelheim, and ActoBio Therapeutics, and personal fees from AstraZeneca, Roche, Medtronic, and Pfizer. OM and TRP report grants and personal fees from Novo Nordisk and AstraZeneca. OM also reports personal fees from Eli Lilly, Sanofi-Aventis, Merck Sharp & Dohme, Boehringer Ingelheim, and Teva. TRP also reports personal fees from Adocia, Arecor, Eli Lilly, and Sanofi-Aventis. LG, TKH, CMo, and GT declare no competing interests.

Data sharing

Individual participant data will be shared in datasets in a deidentified or anonymised format. Datasets from clinical research funded by Novo Nordisk and completed after 2001 for product indications approved in the EU and the USA will be shared. The redacted clinical study report will be available in accordance with Novo Nordisk data sharing commitments. The data will be available permanently after research completion and approval of product and product use in the EU and the USA. Data will be shared with bona fide researchers submitting a research proposal and requesting access to data. Data will be made available for analyses as approved by the independent review board (IRB) in accordance with the IRB charter. The access request proposal form and the access criteria can be found on the Novo Nordisk Trials website. The data will be made available on a specialised SAS data platform.

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