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**

Lancet Diabetes Endocrinol 2021; 9: 212–24

Published Online March 1, 2021 https://doi.org/10.1016/S2213-8587(21)00019-X

See Comment page 191

*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.

Funding Novo Nordisk.