Liraglutide and semaglutide: Pooled post hoc analysis to evaluate risk of dementia in patients with type 2 diabetes

Clive Ballard[1] | Caroline Holm Nørgaard[2] | Sarah Friedrich[3] | Lina Steinrud Mørch[4] | Thomas Gerds[5] | Daniel Vega Møller[6] | Lotte Bjerre Knudsen[7] | Kajsa Kvist[6] | Bernard Zinman[8] | Ellen Holm[9] | Christian Torp-Pedersen[10] | Charlotte Thim Hansen[6]

[1] The University of Exeter College of Medicine and Health, Exeter, United Kingdom

[2] University of California Irvine, Irvine, CA, USA

[3] University Medical Center Göttingen, Goettingen, Germany

[4] Cancer Surveillance and Pharmacoepidemiology, Danish Cancer Society, Copenhagen, Denmark

[5] Copenhagen University, Østerbro, Denmark

[6] Novo Nordisk, Søborg, Denmark

[7] Novo Nordisk, Måløv, Denmark

[8] Lunenfeld–Tanenbaum Research Institute, Mount Sinai Hospital, University of Toronto, Toronto, ON, Canada

[9] Nykøbing Falster Hospital, Nykøbing Falster, Denmark

[10] Nordsjællands University Hospital, Hillerød, Denmark

Correspondence
Clive Ballard, The University of Exeter College of Medicine and Health, Exeter, United Kingdom.
Email: c.ballard@exeter.ac.uk

Abstract

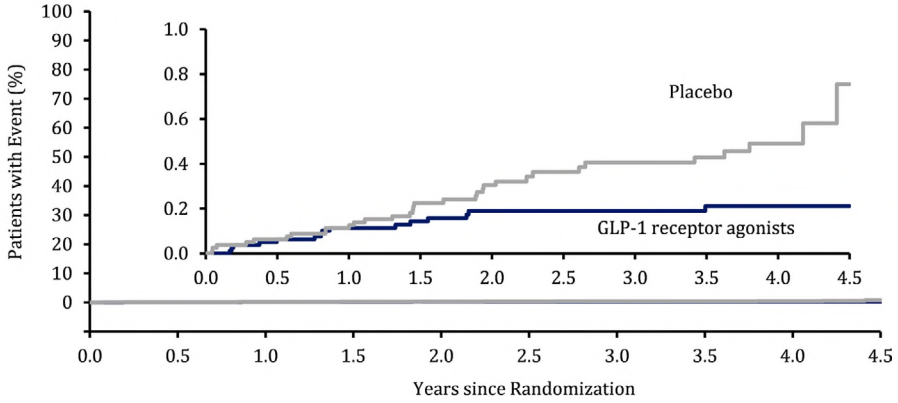
Background: Glucagon-like peptide 1 receptor agonists (GLP-1 RA) have previously shown improved measures of memory and reduced phospho-tau burden in preclinical animal models relevant to progressive cognitive impairment (Hansen. *J Alzheimers Dis.*2015;46:877-88; Hansen. *Brain Res.*2016;1634:158-70). Liraglutide and semaglutide are structurally similar GLP-1 RAs associated with potent glucose-lowering effect, body weight loss and cardiovascular benefits shown in large cardiovascular outcomes trials (CVOTs) (Marso. *N Engl J Med.*2016;375:311-22; Marso. *N Engl J Med.*2016;375:1834-44; Husain. *N Engl J Med.*2019;381:841-51). In order to investigate the potential effects of GLP-1 RA on dementia in a clinical setting, a *post-hoc* analysis was conducted based on pooled data from three CVOTs.

Method: LEADER, SUSTAIN 6 and PIONEER 6 were randomised, double-blind, multicentre, placebo-controlled CVOTs evaluating the cardiovascular effect of liraglutide or semaglutide vs. placebo, added to standard of care. The trials included patients with type 2 diabetes and established or high risk of cardiovascular disease. A *post-hoc* analysis on pooled data from the three CVOTs was considered appropriate due to the similarities in trial design, patient population and treatment effects. Across all trials 15,820 patients with median follow-up of 3.6 years were included in this analysis. Dementia-related adverse events (AEs) were identified using Standardised MedDRA (version 21.1) Query for "dementia" narrow search terms. AE data collection across the trials differed in line with the regulatory requirements at the time of trial conduct. In LEADER and PIONEER 6 only serious AEs were systematically collected, while all AEs were collected in SUSTAIN 6. A time-to-event analysis based on the Cox proportional-hazards model using treatment as covariate was used to estimate the hazard ratio for developing dementia.

Result: Across the three CVOTs, 15 GLP-1 RA-treated patients and 32 placebo-treated patients were identified with development of dementia (Figure). *Post-hoc* analysis on the pooled data showed a significant estimated hazard ratio of 0.47 $[0.25; 0.86]_{95\%CI}$ in favour of the GLP-1 RA treatment versus placebo.

Conclusion: *Post-hoc* analysis based on pooled data from three double-blinded CVOTs suggests, albeit with a low number of events, a reduced risk of dementia with liraglutide or semaglutide treatment in patients with type 2 diabetes.

Figure. Time to dementia with GLP- 1 receptor agonists versus placebo in pooled data from CVOTs



No. at risk										
GLP-1RA	7907	7852	7763	6479	6064	4441	4373	4312	1716	483
Placebo	7913	7843	7740	6438	6016	4394	4321	4251	1700	460

FIGURE 1