Effect of dulaglutide in promoting abstinence during smoking cessation: a single-centre, randomized, double-blind, placebo-controlled, parallel group trial

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Summary

Background Quitting smoking is difficult due to barriers such as craving for cigarettes and post-cessation weight gain. Recent experimental data suggest a role of glucagon-like peptide-1 (GLP-1) in the pathophysiology of addiction in addition to appetite regulation and weight control. We hypothesized that a pharmacological intervention with the GLP-1 analogue dulaglutide during smoking cessation may improve abstinence rates and reduce post-cessation weight gain.

Methods This is a single-centre, randomized, double-blind, placebo-controlled, parallel group, superiority study conducted in the University Hospital Basel in Switzerland. We included adult smokers with at least moderate cigarette dependence who wanted to quit. Participants were randomly assigned to a 12-week treatment with dulaglutide 1.5 mg once weekly or placebo subcutaneously in addition to standard of care including behavioural counselling and oral varenicline pharmacotherapy of 2 mg/day. The primary outcome was self-reported and biochemically confirmed point prevalence abstinence rate at week 12. Secondary outcomes included post-cessation weight, glucose metabolism, and craving for smoking. All participants who received one dose of study drug were included in the primary and safety analyses. The trial was registered on ClinicalTrials.gov (NCT03204396).

Findings Between June 22, 2017, and December 3, 2020, 255 participants were enrolled and randomly assigned to each group (127 in the dulaglutide group and 128 in the placebo group). After 12 weeks, 63% (80/127) participants on dulaglutide and 65% (83/128) on placebo treatment were abstinent (difference in proportions −1.9% [95% Confidence interval (CI) −10.7, 14.4], p-value (p) = 0.859). Dulaglutide decreased post-cessation weight (−1 kg [standard deviation (SD) 2.7]), while weight increased on placebo (+1.9 kg [SD 2.4]). The baseline-adjusted difference in weight change between groups was −2.9 kg (95% CI −3.59, −2.3, p < 0.001). Haemoglobin A1c (HbA1c) level declined on dulaglutide treatment (baseline-adjusted median difference in HbA1c between groups −0.25% [interquartile range (IQR) −0.36, −0.14], p < 0.001). Craving for smoking declined during treatment without any difference between the groups. Treatment-emergent gastrointestinal symptoms were very common in both groups: 90% (114/127) of participants on dulaglutide and 81% (81/128) on placebo).

Interpretation Dulaglutide had no effect on abstinence rates but prevented post-cessation weight gain and decreased HbA1c levels. GLP-1 analogues may play a role in future cessation therapy targeting metabolic parameters such as weight and glucose metabolism.

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Keywords: Cigarette smoking; Glucagon like peptide-1 receptor agonists; Weight gain; Craving for smoking; Varenicline

Research in context

Evidence before this study

Glucagon like peptide-1 (GLP-1) analogues have weight- and blood glucose-lowering properties which are of great interest in the context of smoking cessation. In addition, GLP-1 appears to modulate addictive behaviours, including nicotine addiction, as demonstrated by several studies in rodents. Whether these preclinical results translate to patients is unclear. We searched PubMed using the terms "GLP-1" AND "smoking" OR "cigarette" OR "nicotine" from May 2016 to August 2022 and reviewed all publications of clinical trials. To date, a pilot clinical trial (n = 84) has shown that treatment with the GLP-1 analogue exenatide, compared to placebo, may modulate nicotine craving and increases short-term cigarette abstinence rates.

Added value of this study

In this randomized controlled smoking cessation trial, nearly two-thirds of 255 smokers successfully quit smoking, but in contrast to the above-mentioned study, there was no difference in abstinence rate or craving for smoking between dulaglutide and placebo. Importantly, we demonstrated that the GLP-1 analogue dulaglutide counteracted post-cessation weight gain and reduced HbA1c levels after 12 weeks of treatment.

Implications of all the available evidence

While our data provided no evidence that dulaglutide modulates addictive behaviour in smokers, it addresses an important barrier of smoking cessation: post-cessation weight gain. A weight-control intervention with GLP-1 analogues during smoking cessation could motivate more smokers to quit while preventing metabolic complications of smoking cessation such as obesity and diabetes.

Introduction

Smoking cessation prevents cardiovascular diseases[1] and increases both life expectancy and quality of life.[2,3] Most smokers wish to quit,[4] but the chance of successful smoking cessation remains small[5] and one-year abstinence rates do not exceed 30% even if smokers make use of the most effective treatment with combined behavioural- and pharmacotherapy.[6,7]

Barriers of smoking cessation are linked to the psychoactive properties of nicotine causing physical dependence[8] and withdrawal symptoms.[9] Another important barrier represents post-cessation weight gain.[10,11] On average, smoking quitters show an increase in mean body weight of four to five kg within 12 months.[12] Fear of gaining weight may discourage smokers from quitting while post-cessation weight gain, in turn, may mitigate the health benefits of smoking cessation.[13] Especially excessive weight gain (>5 kg) is linked to higher incidences for cardiovascular diseases, including hypertension and diabetes.[14,15] In fact, the increased short-term risk of type 2 diabetes associated with smoking cessation is directly proportional to weight gain.[16,17]

Although post cessation weight gain does not cancel out the beneficial effects of smoking cessation,[18] new strategies are desirable to maximize smoking cessation rates while addressing adverse metabolic effects of smoking cessation (e.g., weight gain, diabetes).

Glucagon like peptide-1 (GLP-1) analogues may bring together all requested properties: they stimulate insulin secretion and reduce energy intake, body weight and cardiovascular risk.[19–21] Moreover, recent findings suggest a role of GLP-1 in reward regulation and the pathophysiology of addiction.[22,23] In mice, the GLP-1 analogue exenatide has shown to abolish nicotine reward and to decrease nicotine intake.[24] In humans, a preliminary study investigating exenatide for smoking cessation in individuals with prediabetes or overweight found increased smoking abstinence rates compared to placebo (46.3% versus 26.8%) after six weeks.[25] Furthermore, craving for smoking and post-cessation weight tended to be lower on exenatide compared to placebo.

The aim of this study was to investigate the GLP-1 analogue dulaglutide as a novel strategy for smoking cessation. Assuming a dual effect of dulaglutide (blunting nicotine reward/craving for smoking and reducing post-cessation weight gain), we expected an increase in abstinence rates by adding this component of medical therapy.

Methods

Study design

This is an investigator-initiated, single-centre, randomized, double-blind, placebo-controlled, parallel group, superiority study conducted at the University Hospital Basel in Switzerland. The trial and study protocol have been published on ClinicalTrials.gov (NCT03204396).

The study was conducted in compliance with the ethical principles of the Declaration of Helsinki and the International Conference on Harmonization guidelines on Good Clinical Practice, and the protocol was approved by the local ethic committee (Ethikkommission Nordwest-und Zentralschweiz) as well as the Swiss Agency for Therapeutic Products (Swissmedic). Consolidated standards of reporting trials (CONSORT) were followed.

Participants

Smokers who wanted to quit were recruited. Main inclusion criteria were: age 18–75 years, daily smokers with at least moderate cigarette dependence (defined by a Fagerstroem score[26–28] of at least five points) who agreed to receive concomitant behavioural counselling and pharmaco-treatment with varenicline. Exclusion criteria included pregnancy, severe renal insufficiency, unstable psychiatric conditions and pre-existing treatment with GLP-1 analogues. For detailed information on eligibility criteria and the Fagerstroem Test, see Supplementary Appendix. Gender was self-reported by participants. Participants were included after full explanation of study procedures and obtaining written informed consent.

Randomization and masking

Participants were 1:1 randomized according to a computer-generated randomization list (randomly selected, varying block sizes; no stratification) produced by the Clinical Trial Unit of the University Hospital Basel. Participants were assigned to a sequentially numbered study identification (ID) (in chronological order), which was activated by investigators after inclusion and corresponded to the predefined randomization list. Only unblinded study nurses were able to see the assigned study intervention (placebo versus dulaglutide) of the participants. Participants, health-care providers and data collectors were blinded to treatment allocation. As injection devices of dulaglutide and placebo were not identical, injections were performed by unblinded study staff otherwise not involved in the trial and participants wore blindfolds during the drug injection and were not able to see the injection site or the injection device. For further details, see Supplementary Appendix.

Procedures

Procedures and timeline are displayed in Fig. S1 and Table S1 of the Supplementary Appendix.

The experimental intervention was 0.5 ml dulaglutide while the control intervention was 0.5 ml sodium chloride (NaCl 0.9%). The trial medication was injected weekly subcutaneously with a first dulaglutide dose of 0.75 mg/0.5 ml for week 1 and 1.5 mg/0.5 ml for weeks 2–12.

The standard of care included behavioural counselling and treatment with the nicotinic receptor partial agonist varenicline according to national guidelines.[29] For titration regimen of varenicline and details of the behavioural counselling, see Supplementary Appendix.

At baseline, demographic data, cigarette dependence (Fagerstroem score) and craving for smoking (assessed by a visual analogue scale [VAS], range 0–10, 0 = no craving, 10 = maximal craving; and by the German version of the questionnaire on smoking urges [QSU-G],[30] see Supplementary Appendix) were assessed. A short physical examination and haemoglobin A1c (HbA1c) measurement were performed. Smoking and nicotine exposure were assessed by end-expiratory carbon monoxide (CO) measurement (Micro+™ Smokerlyzer®)[31] and a cotinine test in the spot urine (Urine Cotinine All Test COT 3 in 1, graduations of "negative", ≥50, ≥100, ≥200 ng/ml).[32]

During the following weekly visits, smoking status, craving for smoking by VAS, CO measurement and adverse events were assessed by the study team. Additionally, weight was measured at week 4, 8 and 12 and craving for smoking by QSU-G at week 4 and 12.

At week 12, smoking status, craving for smoking and adverse events were assessed and a short physical examination, HbA1c testing, CO and urine cotinine measurement took place.

Outcomes

The objective of this trial was to determine the effect of the GLP-1 analogue dulaglutide in addition to standard of care (varenicline and behavioural counselling) on smoking abstinence rates at week 12 compared to placebo and standard of care. The primary outcome was the point prevalence abstinence rate defined as self-reported 7-days smoking abstinence and end-expiratory exhaled CO measurements of 10 ppm or less, at week 12.

The main secondary outcome was the change in body weight in kilograms at week 12 relative to baseline.

Further secondary outcomes were change in glucose homeostasis (HbA1c %), craving for smoking (VAS and QSU-G,[30] see Supplementary Appendix), smoking reduction (defined as number of cigarettes per day and reduction of end-expiratory exhaled CO more than 50% at week 12 compared to baseline), and tolerability of treatment (expected gastrointestinal symptoms such as nausea or abdominal pain were assessed by VAS; e.g. 0 = no nausea, 10 = maximal nausea). All outcomes were measured at week 12.

Statistical analysis

Sample size estimation and power considerations

We assumed that the abstinence rate on standard therapy is 33% at week 12 and that dulaglutide treatment increases the rate by 18 percentage points, i.e. that the point prevalence abstinence rate increases to 51%. Using a Pearson $\chi 2$-Test with $\alpha = 0.05$ and a power of 80% the targeted sample size was 255 adult smokers. We did not adjust the sample size for potential loss to follow-up, but rather considered lost participants as being persistent smokers. For further information, including rational for assumptions, see Supplementary Appendix.

Analysis sets

The full analysis set consisted of all 255 randomized participants and was analysed according to the intention-to-treat principle, in the following referred to as intention to treat set (ITT-S).

The per protocol analysis set (PP–S) consisted of 204 (101 dulaglutide, 103 placebo) participants of the ITT-S who received at least 80% of the study medication (10/12 doses). For further details, see Fig. 1.

Statistical methods

Analyses were conducted using the statistics program R[33] Version 4.2.1. The primary analysis assessed the difference in the point prevalence abstinence rates at week 12 on dulaglutide compared to placebo using the ITT-S. The difference in proportions was tested using Pearson's $\chi 2$-test and the 95% confidence interval (CI) was calculated, using the Wilson score method with continuity correction. Several pre-specified supplementary analyses were performed to further examine the effect of dulaglutide on the primary outcome (see Supplementary Appendix).

Secondary binary outcomes were analysed according to the primary outcome. Weight change was analysed using a linear regression, adjusting for weight at baseline. All other continuous outcomes showed a skewed distribution and were analysed using quantile regression for the median, adjusting for baseline values.

Missing data in outcomes related to abstinence were assumed not missing at random but for reasons closely linked to the (continued) smoking status. Hence, participants with missing values in the primary outcome

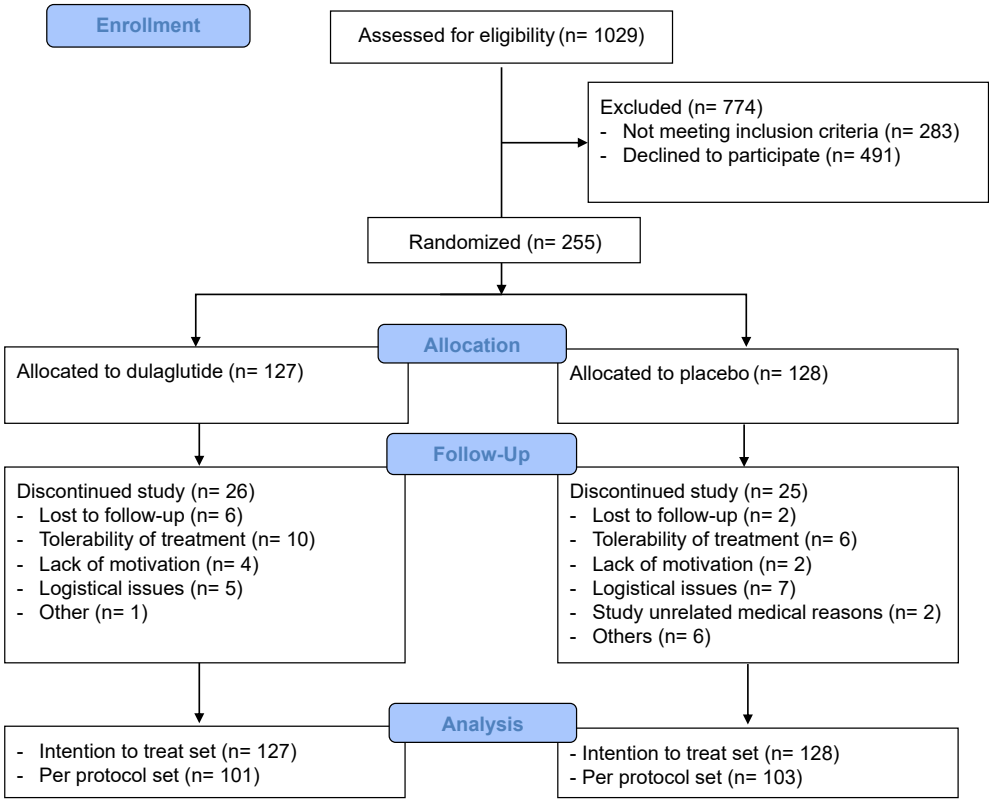

***Fig. 1:* Consort flow diagram.** Consolidated standards of reporting trials diagram of the progress through the phases of this single-centre, randomized, double-blind, placebo-controlled, parallel group, superiority study including smokers who want to quit and receive once-weekly placebo or dulaglutide subcutaneously for 12 weeks. The intention to treat set (ITT-S) consists of all randomized participants. The per protocol analysis set (PP-S) consists of all participants in the ITT-S without any major protocol violations and who received at least 80% of the study medication (10/12 doses).

were considered smokers. The range of all possible outcomes was examined by post-hoc best- and worst-case sensitivity analyses (Supplementary Appendix). For continuous secondary outcomes with more than 10% missing values, data was imputed using an expectation-maximization with bootstrapping algorithm (EMB), implemented in the R package Amelia[34] (Table S2 and technical details, Supplementary Appendix).

Intention-to-treat analyses

We tested three separate possible effects of dulaglutide assessed by outcomes related to smoking behaviour, weight change and glucose homeostasis. To adjust for multiple testing, we applied the Bonferroni-Holm procedure to each group of outcomes in order to keep the corresponding family-wise error rate at 5% and report adjusted p-values (p) (more details see Supplementary Appendix).

All analyses were predefined in a statistical analysis plan unless explicitly indicated as post-hoc. For details, see Supplementary Appendix.

Data of the post-intervention follow-up phase are not yet available and will be published at a later date.

When Pfizer stopped varenicline distribution due to nitrosamine impurities in 2021, participants were informed about the ongoing discussions and made aware of possible risks. Weighing up the risk (harms from nitrosamines and failure to quit smoking), all study participants decided to continue the therapy (as it was recommended by the FDA) and were able to obtain sufficient medication for the remaining treatment phase.

Role of the funding source

The funders had no role in study design, data collection, data analysis, data interpretation, or writing of the report. SL and BW had access to all data and had final responsibility for the decision to submit for publication.

Results

Between June 22nd, 2017, and December 3rd, 2020, 255 participants (ITT-S) were enrolled and randomized to treatment with dulaglutide (n = 127) or placebo (n = 128), see Fig. 1.

Participants were predominantly female (60.8%) with a mean age of 43.2 years (standard deviation [SD] 13.1), mean body mass index (BMI) of 27.1 kg/m^2 (SD 5.0) and had a normal-range median HbA1c of 5.4% (interquartile range [IQR] 5.1, 5.7). Mean Fagerstroem score was 7.0 points (SD 1.5) and median lifetime smoking exposure was 20 pack years (IQR 11.0, 35.0). Baseline characteristics were well balanced between groups, except for a slightly higher percentage of female participants in the dulaglutide group (Table 1). The PP-S consisted of 204 participants (Table S3 of the Supplementary Appendix).

For the primary outcome, 31 participants had missing values and were counted smokers (13 in the placebo and 18 in the dulaglutide group). At week 12, almost two thirds of participants had quit smoking: 80/127 (63%) participants on dulaglutide and 83/128 (65%) on placebo. Results were consistent in the PP-S with slightly higher abstinence rates in both groups, see Supplementary Appendix. There was no difference between the groups; estimated difference in proportions was –1.9 (95% CI –10.7, 14.4%, p = 0.859). For results of best-case and worst-case scenarios see Supplementary Appendix. The median time to quit was 15.5 days in the dulaglutide group and 17 days in the placebo group (Supplementary Appendix, Fig. S2). Abstinence with a stricter definition (negative urine cotinine level at week 12 required additionally) was reached in 59/127 (46%) participants on dulaglutide and 64/128 (50%) on placebo (difference in proportions –3.5, 95% CI –9.5, 16.6%, p = 0.659) (data not shown). Adherence to behavioural counselling and varenicline was balanced between the two groups. A positive association of total varenicline dose and abstinence was observed, but the data provided no evidence that the effect of dulaglutide on abstinence might depend on the varenicline dose (Supplementary Appendix).

Overall, we observed a weight reduction on dulaglutide treatment (–1 kg, SD 2.7) and an increase in weight on placebo (+1.9 kg, SD 2.4). The baseline-adjusted difference in weight change between groups was –2.9 kg (95% CI [–3.59, –2.3], p < 0.001), see Fig. 2A. Weight change from baseline to week 12 according to randomized treatment and smoking status at week 12 are illustrated in Fig. 2B and Fig. S3 and further details are given in the Supplementary Appendix.

The dulaglutide effect on weight was not associated with baseline BMI nor HbA1c levels. Results were similar in the PP-S, see Supplementary Appendix.

Median HbA1c levels declined on dulaglutide (baseline: 5.3% [IQR 5.1, 5.7]; at week 12: 5.1% [IQR 4.9, 5.5]; change –0.2 [IQR –0.4, –0.1]; n = 110), while we observed no notable change on placebo (baseline: 5.4% [IQR 5.1, 5.6]; at week 12: 5.3% [IQR 5.0, 5.7]; change 0.0 [IQR –0.2, 0.2]; n = 115). The baseline-adjusted median difference in HbA1c between dulaglutide and placebo was –0.25% (IQR –0.36, –0.14, p < 0.001, Fig. 3).

New onset prediabetes (defined as HbA1c between 5.7% and 6.4%) was observed exclusively in quitters and was more frequent on placebo (n = 9, 7%) than dulaglutide (n = 2, 1.6%) (absolute risk difference: 5.5 [95% CI –0.3, 11.2] %; post-hoc analysis, no p calculated). No one was diagnosed with new onset diabetes (HbA1c >6.4%). Comparable results on HbA1c were observed in the PP-S, see Supplementary Appendix.

	Overall (n = 255)	Dulaglutide (n = 127)	Placebo (n = 128)
Demographics, clinical parameters, laboratory values			
Gender			
Female - n (%)	155 (60.8)	83 (65.4)	72 (56.3)
Male – n (%)	100 (39.2)	44 (34.6)	56 (43.8)
Mean Age (SD) - y	43.2 (13.1)	42.7 (13.8)	43.2 (13.1)
Caucasian - n (%)	247 (96.9)	126 (99.2)	121 (94.5)
Mean systolic blood pressure (SD) -mmHg	120.8 (14.2)	119.5 (13.6)	122.2 (14.7)
Mean diastolic blood pressure (SD) - mmHg	78.3 (8.4)	77.6 (8.5)	78.9 (8.3)
Mean heart rate (SD)- bpm	75.1 (10.3)	75.3 (10.8)	75.0 (9.8)
Mean weight (SD) – kg	80.1 (17.9)	79.0 (17.9)	81.2 (17.9)
Mean BMI (SD) - kg/m^2	27.1 (5.0)	27.1 (5.1)	27.1 (5.0)
BMI category			
BMI <25 kg/m^2 - n (%)	95 (37.3)	46 (18)	49 (19.2)
BMI 25–29.9 kg/m^2 - n (%)	97 (38.0)	52 (20.4)	45 (17.6)
BMI >30 kg/m^2 - n (%)	63 (24.7)	29 (11.4)	34 (13.3)
Median HbA1c [IQR] - %	5.4 [5.1, 5.7]	5.3 [5.1, 5.7]	5.4 [5.1, 5.6]
Median end-expiratory exhaled CO [IQR] - ppm	19 [13, 27]	18 [13, 25]	19 [13, 27.8]
Smoking status			
Median no. of cigarettes per day [IQR]	20 [15, 20]	18 [14, 20]	20 [5, 25]
Median no. of pack years smoked [IQR]	20 [11, 35.0]	19 [10, 34.5]	20.5 [12.8, 36]
Mean Fagerstroem (SD) - total sum score	7.0 (1.5)	6.9 (1.3)	7.0 (1.6)
Mean VAS Craving (SD) - total sum score	6.1 (2.7)	5.9 (2.7)	6.3 (2.7)
Mean QSU-G (SD) - total sum score	110.2 (35.5)	106.5 (34.9)	113.9 (35.8)
Tobacco related diseases, n (%)			
Pulmonal disease	57 (22.4)	24 (18.9)	33 (25.8)
Cardiovascular disease	65 (25.5)	29 (22.8)	36 (28.1)
Cerebrovascular disease	10 (3.9)	7 (5.5)	3 (2.3)
Cancer	17 (6.7)	8 (6.3)	9 (7.0)
Gastrointestinal disease	28 (11.0)	13 (10.2)	15 (11.7)
Osteoporosis	10 (3.9)	5 (3.9)	5 (3.9)
Other comorbidities, n (%)			
Diabetes mellitus	13 (5.1)	6 (4.7)	7 (5.5)
Dyslipidemia	42 (16.5)	23 (18.1)	19 (14.8)
Psychiatric disease	71 (27.8)	36 (28.3)	35 (27.3)
Medication if > 5%; n (%)			
Medication (total)	178 (69.8)	88 (69.3)	90 (70.3)
Antihypertensive	51 (20.0)	25 (19.7)	26 (20.3)
Contraceptives	25 (9.8)	14 (11.0)	11 (8.6)
Acetylsalicylic acid	19 (7.5)	8 (6.3)	11 (8.6)
Proton pump inhibitors	26 (10.2)	12 (9.4)	14 (10.9)
Lipid-lowering drugs	29 (11.4)	17 (13.4)	12 (9.4)
Antipsychotics, neuroleptics	23 (9.0)	12 (9.4)	11 (8.6)

Percentages may not total 100 because of rounding. BMI = body mass index; n = numbers, y = years, IQR = interquartile range, SD = standard deviation, VAS = visual analog scale, QSU-G = german version of the questionnaire on smoking urges.

Table 1: **Baseline characteristics.**

Craving for smoking assessed by VAS reduced by two thirds and QSU-G scores were halved, without any difference between dulaglutide and placebo (baseline-adjusted median difference at week 12: VAS score 0 [IQR –0.71, 0.71 points, p = 1.000] and QSU-G –3.07 [IQR –12.26, 6.13 score points; p = 1.000]). Comparing persistent smokers and quitters, there was a greater reduction in craving in quitters. Time course of craving according to treatment and smoking status and results of the PP-S are shown in the Supplementary Appendix and Figs. S4-S6.

The number of cigarettes per day decreased during the treatment phase without any difference between the groups: the baseline-adjusted median difference

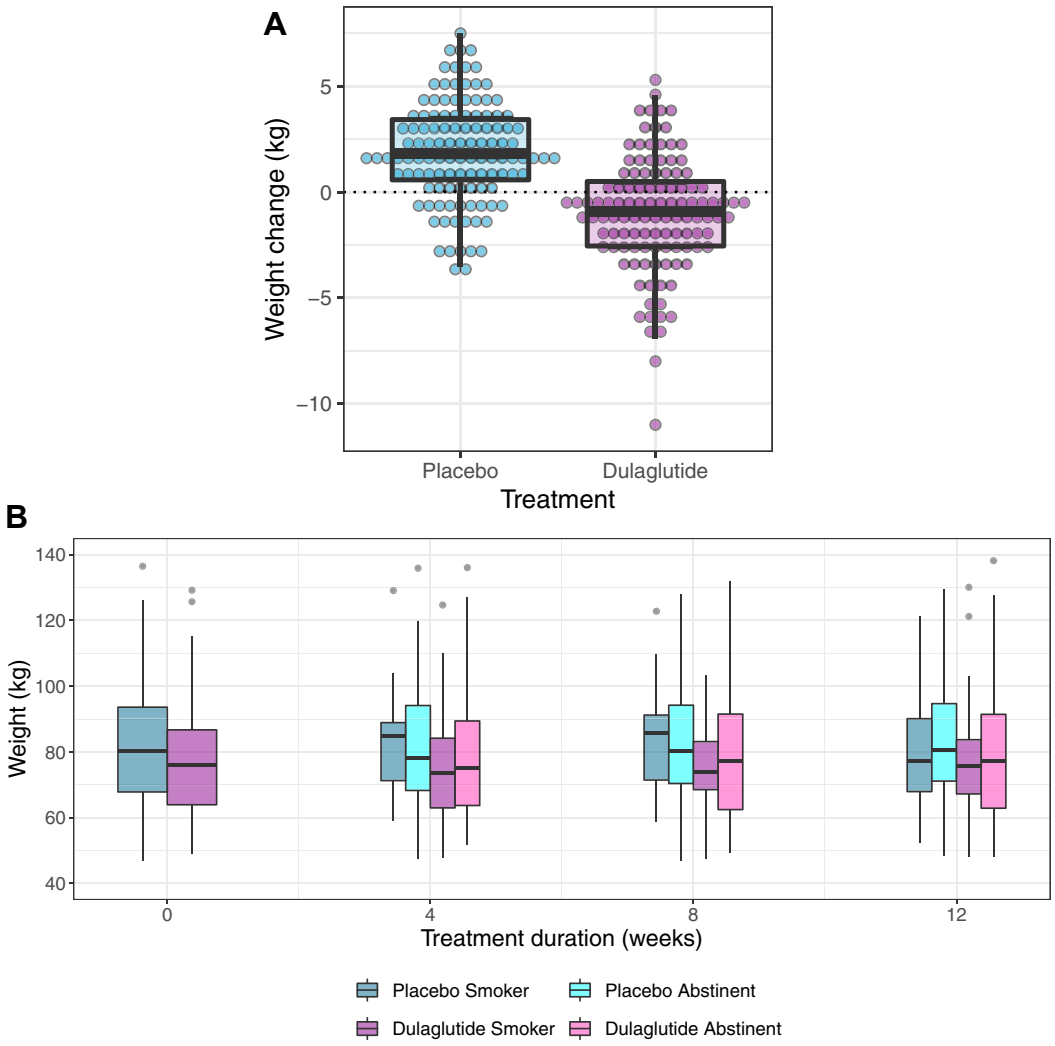

***Fig. 2*: Panel A. Change in weight (kg) from baseline to end of treatment according to treatment (intention to treat set [ITT-S]). Panel B. Change in weight (kg) from baseline to end of treatment according to treatment group and smoking status at weeks 0, 4, 8, 12 (ITT-S).** Panel A: Figure shows the change of weight in kg (y-axis) from baseline to end of treatment according to the treatment group (x-axis). Thick line indicates the median; box indicates the interquartile range (IQR); whiskers include all points within the range of 1.5x the IQR; dots outside the whiskers represent all points outside 1.5x the IQR. Purple and blue colors represent the treatment group (dulaglutide and placebo, respectively). Panel B: The y-axis shows the weight in kg, the x-axis represents the treatment weeks 0, 4, 8, 12. Box plots are subdivided into 4 groups (persistent) smokers and quitters on placebo or dulaglutide, respectively. Thick line indicates the median; box indicates the IQR; whiskers include all points within the range of 1.5x the IQR; dots outside the whiskers represent all points outside 1.5x the IQR. Purple and blue colors represent the treatment group (dulaglutide and placebo, respectively), brightness indicates smoking status (bright = abstinent, dark = smoker).

between dulaglutide and placebo was −3.11 (IQR −6.99, 0.77) (p = 0.721). For persistent smokers, the number of cigarettes per day decreased on dulaglutide from median (IQR) 20 (15, 25) (n = 46) at baseline to 6 (IQR 2, 10) (n = 30) at the end of treatment (change: −12 [−15, −8]; n = 29) and on placebo from 20 [15–25]; n = 45 at baseline to 12 [7–15]; n = 29 at the end of treatment (change: −8 [−12, −5]; n = 29). In parallel with number of cigarettes per day, CO-reductions were observed without any difference between the groups, see Supplementary Appendix.

Gastrointestinal symptoms were already reported by many participants at baseline (34/127; 27% participants in dulaglutide and 33/128; 26% in placebo group). During treatment, gastrointestinal symptoms peaked in weeks 1–3 and were very common in both groups (90% of participants on dulaglutide and 81% on placebo reported gastrointestinal symptoms at any time during

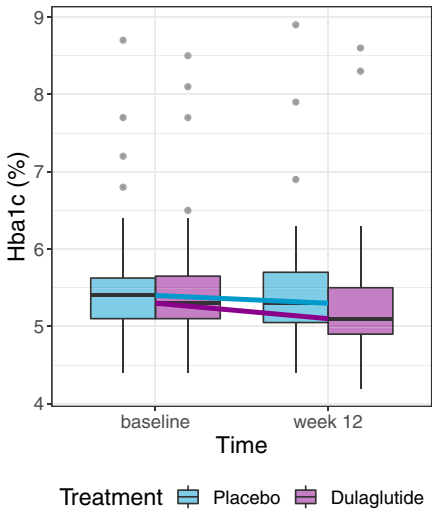

Fig. 3: **Change in HbA1c from baseline to end of treatment according to treatment (intention to treat set [ITT-S]).** Figure shows the change of HbA1c in % (y-axis) from baseline to end of treatment according to the treatment group (x-axis). Thick line indicates the median; box indicates the interquartile range (IQR); whiskers include all points within the range of 1.5x the IQR; dots represent all points outside 1.5x the IQR. Purple and blue colors represent the treatment group (dulaglutide and placebo, respectively).

treatment). In the dulaglutide group, they were more severe and required therapy more often (e.g. proton-pump inhibitors, antiemetic): 28 (22%) participants on dulaglutide and 14 (11%) on placebo (Table S4 and Fig. S7). Nausea was the most common complaint; in the dulaglutide group, participants were roughly 2.5 times as likely to report severe nausea as compared to placebo. Despite the high number of gastrointestinal symptoms, participants rarely withdrew due to adverse events (dulaglutide n = 10; placebo n = 6) and none of these adverse events was serious. More than 80% of adherent participants remained on the standard dulaglutide dose of 1.5 mg (Figs. 1 and S8).

In 106 participants on dulaglutide and 121 on placebo, other adverse events were recorded (Table S4). Most of these events were mild to moderate with upper respiratory tract infections as the most frequent manifestation.

In total, 9 serious adverse events were recorded (5 in the dulaglutide, 4 in the placebo group) (see Table S4). All of them were judged unrelated to the study drug.

Discussion

Our trial investigating the GLP-1 analogue dulaglutide during smoking cessation found high point prevalence abstinence rates above 60% after 12 weeks without any difference in the treatment groups. Further analyses indicated a positive effect of dulaglutide on post-cessation weight gain and on glucose metabolism, but not on craving for smoking.

Considering abstinence rates of a similar trial evaluating the efficacy of varenicline and behavioural counselling in more than 2000 smokers showed an abstinence rate of 33.5% after 12 weeks.[35] While some randomized trial evidence suggested that smoking cessation could be increased by adding a second component of medical therapy, i.e. nicotine replacement therapy to varenicline,[36] our data showed no additional benefit of combining varenicline and dulaglutide. However, our assumption of a point prevalence abstinence rate of 51% was exceeded by far (up to 65% and 77% in the ITT-S and PP-S, respectively). We assume that the unexpectedly high abstinence rate was achieved through the intense, weekly face-to-face contact with the study staff and feedback on CO measurement in addition to the intervention by the smoking cessation counselors. According to a recent Cochrane Systematic Review based on a pooled estimate from 65 trials, behavioural support as an adjunct to pharmacotherapy is likely to increase the chance of abstinence by about 10%–20%.[37] Future studies should investigate the optimal type and frequency of behavioural support in combination with pharmacotherapy to achieve highest smoking cessation rates.

Post-cessation weight gain occurs in 80% of people being as high as 2.3 kg after two months.[12] In our study, dulaglutide was able to counteract the expected post-cessation weight gain and even led to a weight reduction at 12 weeks. Our findings confirm the preliminary results of a pilot randomized controlled study with exenatide, suggesting that GLP-1 analogues may be effective in controlling weight in the setting of smoking cessation.[25] As weight gain is an important reason for not quitting and or relapsing,[10,11,38] the option of a weight stabilizing therapy allows an individualized treatment and may motivate more smokers to quit and avoid early relapses due to unwanted weight gain. Moreover, excess weight gain is linked to alterations in lipid and glucose metabolism, blood pressure and coagulation.[39] Of note, the well-described short-term risk of type 2 diabetes in quitters is primarily seen in people who gain substantial weight.[15,16] In our study of mainly participants without diabetes (94.9%), dulaglutide compared to placebo had a small, but significant glucose lowering effect resulting in HbA1c reductions. This effect was most relevant for quitters: only 2 participants on dulaglutide developed new onset prediabetes compared to 9 in the placebo group. Other antidiabetic medication such as metformin, which has positive effects on glucose metabolism and weight in individuals with and without diabetes, may also be beneficial in the smoking cessation setting. However, no other antidiabetic medication is as effective on HbA1c and weight reductions as GLP-1 analogues. Moreover, GLP-1 analogues have consistently been shown to affect hard endpoints and to reduce cardiovascular events and

death.[19,40] These drugs seem therefore predestined for use during smoking cessation, where cardiovascular risk reduction is a main focus. Lastly, weight control is also an important factor in terms of improving lung function after smoking cessation. According to the international European Community Respiratory Health Survey, men who give up smoking but gain 1 kg per year show no longer benefits in lung function.[41]

Based on preclinical data showing an attenuated reward effect of nicotine[24] and other addictive drugs by GLP-1 analogues,[23] we expected dulaglutide to decrease craving for smoking and increase abstinence rates compared to placebo. However, our results showed no such effects and are not consistent with the hypothesis that GLP-1 analogues influence nicotine reward-seeking behaviours. This contrasts with a previous pilot randomized controlled study by Yammine et al.[25] who treated 84 smokers with the GLP-1 analogue exenatide or placebo in addition to nicotine replacement therapy. After a 6-week treatment period, smoking abstinence was higher on exenatide than on placebo (46.3% versus 26.8%). Additionally, slight improvements in craving and withdrawal symptoms were noted on exenatide versus placebo. Explanations for the divergent results may include the combination with a different smoking cessation treatment (nicotine replacement versus varenicline) and the choice of the study drug (exenatide versus dulaglutide). Dulaglutide is one of the larger GLP-1 molecules[42] and its blood brain barrier permeability may be lower than that of the smaller molecule exenatide thus having a lower central effect on reward.[43] Another explanation may be the different study populations - older and predominantly male population of African American ethnicity versus a younger, mostly female Caucasian population in our study. Moreover, Yammine et al. only included prediabetic or overweight smokers who might respond differently to GLP-1 analogues than our cohort of participants without diabetes, although our data provided no evidence for an association of BMI or HbA1c with the dulaglutide effect on abstinence. Finally, one may also speculate that the exceptionally high abstinence rate masked the dulaglutide effect on craving and abstinence. In the same line, the high abstinence rate could also explain why successful weight control on dulaglutide had no further effect on abstinence in this study.

No unexpected adverse events occurred on dulaglutide. Gastrointestinal symptoms were very common and pre-existed in a quarter of participants at baseline. During the study, the percentage of participants with gastrointestinal symptoms was higher on dulaglutide versus placebo and also higher than in previous studies of dulaglutide in a diabetic population (up to 30%).[44] For varenicline, nausea and gastrointestinal complaints are also the most common adverse events and occur in about 28% of participants.[35,45,46] Not surprisingly, the highest rate of symptoms was recorded after 2 weeks - when both dulaglutide and varenicline induced gastrointestinal adverse effects peak.[45,47] In terms of symptom intensity, participants on dulaglutide achieved higher VAS scores and they required drug therapy more often. Nonetheless, only 10 participants on dulaglutide and 6 on placebo discontinued the study drug because of treatment tolerability, which is similar to discontinuation rates reported in other dulaglutide trials.[40] Lastly, the high rate of symptoms recorded in this study may also be owed to the study design with active query of symptoms at a higher monitoring frequency than in other studies.[40,43]

This study has the following limitations. First, the treatment phase was limited to 12 weeks. Whether the short-term effect on weight and HbA1c impacts the later risk of diabetes remains unclear. Most probably, a longer treatment duration is needed to obtain sustained effects on metabolic parameters. Additionally, rebound weight gain after dulaglutide treatment termination may be an important issue and may put the positive 12-week results in a different light. The evaluation of the follow-up results will provide information on this at a later date. Second, we cannot determine whether and how the high rate of gastrointestinal symptoms contributed to weight change. Third, the results may be different with a more potent GLP-1 analogue, such as semaglutide (which was not yet approved in Switzerland at the time of the study start). Forth, the study design with weekly visits required a high level of motivation and time commitment explaining the high percentage of screened smokers who declined to participate. This particular setting of the study may have contributed to high abstinence rates, but the available data do not allow us to determine the contribution of specific factors. Fifth, the study drug injection was performed by unblinded study staff. Although all measures were taken to prevent exchanges between blinded and unblinded staff and participants, interaction cannot be completely ruled out. Lastly, this was a single centre study and the generalizability of our findings may therefore be limited. The strengths of our study include the randomized controlled design with a representative number of participants, which allowed advancing our understanding of GLP-1 effects on craving for smoking, post-cessation weight and glucose metabolism that have been little studied so far.

In conclusion, this study achieved very high abstinence rates and highlights the value of close behavioral support in combination with pharmacotherapy. Dulaglutide had no effect on abstinence rates and craving, but reduced post-cessation weight and HbA1c levels.

A pharmacological intervention during smoking cessation that targets weight gain and glucose metabolism is of high interest in terms of cardiovascular risk reduction and potentially improved lung function. In addition, as post-cessation weight gain is one of the

main barriers of smoking cessation, the prospect of a weight control intervention with GLP-1 analogues may motivate more smokers to try to quit and, at best, to improve long term abstinence.

Contributors

SL collected, analysed and interpreted the data, did the literature search and wrote the manuscript. NJ contributed to the study design and collection of data. TB and AM were involved in the conceptualisation, interpreted the data and contributed to the manuscript. DRV planned, performed and interpreted the statistical analyses and contributed to the manuscript. COS, TV, KB, MS, SAU, JK, FB, LNL and CB contributed to data collection. BS and LGH were involved in the study design and contributed to the manuscript. TEE contributed to the methodology. MCC contributed to the methodology, interpreted the data and contributed to the manuscript. BW designed the study, wrote the protocol, collected, analysed and interpreted data, and supervised all steps of the conduct of the study. All authors edited and approved the final manuscript.

Data sharing statement

We may share de-identified, individual participant-level data that underlie the results reported in this article and related documents, including the study protocol and the statistical analysis plan. Data will be available with the publication of our main manuscript on receipt of a request detailing the study hypothesis and statistical analysis plan. All requests should be sent do the corresponding author. The steering committee of this study will discuss all requests and decide based on the scientific rigor of the proposal whether data sharing is appropriate. All applicants are asked to sign a data access agreement.

Declaration of interests

BS declares receiving an unrestricted grant from Moderna (2022) for a study outside the submitted work. All other authors declare no competing interests.

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Appendix A. Supplementary data

Supplementary data related to this article can be found at https://doi.org/10.1016/j.eclinm.2023.101865.

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