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ORIGINAL ARTICLE

Neuropsychiatric safety with liraglutide 3.0 mg for weight management: Results from randomized controlled phase 2 and 3a trials

Patrick M. O'Neil PhD[1] | Vanita R. Aroda MD[2] | Arne Astrup MD DMSc[3] | Robert Kushner MD[4] | David C. W. Lau MD PhD[5] | Thomas A. Wadden PhD[6] | Jason Brett MD[7] | Ana-Paula Cancino MD MSc[8] | John P. H. Wilding DM FRCP[9] | on behalf of the Satiety and Clinical Adiposity – Liraglutide Evidence in individuals with and without diabetes (SCALE) study groups

[1]Weight Management Center, Department of Psychiatry and Behavioral Sciences, Medical University of South Carolina, Charleston, South Carolina

[2]Department of Internal Medicine, Endocrinology, Diabetes & Metabolism, MedStar Health Research Institute, Georgetown University School of Medicine, Hyattsville, Maryland

[3]Department of Nutrition, Exercise and Sports, University of Copenhagen, Frederiksberg C, Denmark

[4]Department of Internal Medicine, Northwestern University Feinberg School of Medicine, Chicago, Illinois

[5]Departments of Medicine and Biochemistry & Molecular Biology, University of Calgary Cumming School of Medicine, Calgary, Alberta, Canada

[6]Department of Psychiatry, Perelman School of Medicine at the University of Pennsylvania, Philadelphia, Pennsylvania

[7]Novo Nordisk Inc., Plainsboro, New Jersey

[8]Novo Nordisk A/S, Søborg, Denmark

[9]Department of Obesity and Endocrinology, Obesity and Endocrinology Clinical Research Group, University of Liverpool, Liverpool, UK

Correspondence
Patrick M. O'Neil, Department of Psychiatry and Behavioral Sciences, Weight Management Center, Medical University of South Carolina, 67 President Street, IOP South, Ste. 410, P.O. Box 250861, Charleston, SC 29425.
Email: oneilp@musc.edu

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Aims: Liraglutide, a GLP-1 receptor agonist, regulates appetite via receptors in the brain. Because of concerns regarding the potential of centrally-acting anti-obesity medications to affect mental health, pooled neuropsychiatric safety data from all phase 2 and 3a randomized, double-blind trials with liraglutide 3.0 mg were evaluated *post hoc*.

Methods: Data from the liraglutide weight-management programme were pooled. Across trials, individuals with a body mass index ≥30 or ≥27 kg/m^2 with weight-related comorbidities were randomized to once-daily subcutaneous liraglutide 3.0 mg (n = 3384) or placebo (n = 1941), both with a 500 kcal/d deficit diet, plus exercise. Adverse events related to neuropsychiatric safety were collected in all trials. Additionally, in the phase 3a trials, validated mental-health questionnaires were prospectively and systematically administered.

Results: In the pooled analysis of 5325 randomized and exposed individuals, rates of depression (2.1 vs 2.1 events/100 person-years) and anxiety (1.9 vs 1.7 events/100 person-years) through adverse event reporting were similarly low in liraglutide and placebo groups. Nine (0.3%) individuals receiving liraglutide and 2 (0.1%) receiving placebo reported adverse events of suicidal ideation or behaviour. In phase 3a trials, mean baseline Patient Health Questionnaire-9 scores of 2.8 ± 3.0 vs 2.9 ± 3.1 for liraglutide vs placebo improved to 1.8 ± 2.7 vs 1.9 ± 2.7, respectively, at treatment end; 34/3291 individuals (1.0%) receiving liraglutide 3.0 mg vs 19/1843 (1.0%) receiving placebo reported suicidal ideation on the Columbia-Suicide Severity Rating Scale.

Conclusions: Results of this exploratory pooled analysis provide no cause for concern regarding the neuropsychiatric safety of treatment with liraglutide 3.0 mg in patients similar to those included in the examined trials. Although there was a small numerical imbalance in suicidal ideation with liraglutide through adverse event reporting, no between-treatment imbalances in suicidal ideation/behaviour or depression were noted through prospective questionnaire assessments.

KEYWORDS

antiobesity drug, GLP-1 analogue, liraglutide, obesity therapy, randomized trial

1 | INTRODUCTION

Obesity is a global health problem[1] and is associated with multiple comorbidities,[2,3] premature mortality,[4] impaired health-related quality of life[5] and individual, societal and economic costs.[6] While initially effective for many individuals, diet or behaviour modification alone is often difficult to sustain and many individuals regain weight upon discontinuation.[2] Pharmacotherapy for chronic weight management may serve as an adjunct to lifestyle intervention in enabling individuals to achieve and sustain clinically relevant weight loss.

Given that many of the approved anti-obesity medications are centrally-acting appetite suppressants, neuropsychiatric safety has become an area of interest.[7–9] Rimonabant, the first selective central cannabinoid (CB1) receptor antagonist, was never approved by the Food and Drug Administration (FDA) because of concerns regarding psychiatric adverse events, including depression, anxiety and suicidal ideation.[10] Rimonabant was withdrawn by the European Medicines Agency (EMA) in 2009, leading to termination of development of several CB1-receptor blockers for the treatment of obesity.[11,12] However, many potential treatments aimed at varied molecular targets in the central nervous system (CNS) are still under development.[8,9,11] Adding to the complexity of the situation is the fact that, in general, obese individuals have a higher prevalence of neuropsychiatric disorders, such as depression, compared to the general population.[13,14]

Liraglutide is a glucagon-like peptide-1 (GLP-1) receptor agonist that regulates appetite centrally via receptors in the hypothalamus and other areas of the brain.[15] Weight loss with liraglutide is mediated by reduced appetite and energy intake rather than by increased energy expenditure.[16] The clinical development programme for liraglutide concerning weight management comprised one phase 2 dose-finding trial, which demonstrated weight loss with liraglutide doses up to 3.0 mg over 2 years,[17] and a large global phase 3a programme called SCALE (Satiety and Clinical Adiposity – Liraglutide Evidence in individuals with and without diabetes). The SCALE programme was designed to investigate the efficacy and safety of liraglutide 3.0 mg in 4 randomized, double-blind, placebo-controlled trials (1 during 3 years, 2 during 56 weeks and 1 during 32 weeks) in over 5300 adults. Treatment with liraglutide 3.0 mg led to observed mean weight loss from baseline, ranging from 5.7% to 8.0% (6.0-8.4 kg) depending on the SCALE trial, whereas mean weight loss in the placebo group ranged from 0.1% to 2.6% (0.1-2.8 kg).[18–22] Liraglutide, administered at a once-daily subcutaneous dose of 3.0 mg, is now approved for weight management in several regions, including North America and Europe.

This *post hoc* analysis evaluates pooled neuropsychiatric safety data from the 5 randomized, double-blind and placebo-controlled trials described above, including data from 2 mental health questionnaires that were used in the 4 SCALE trials. Because of the evolving regulatory and safety concerns described above, psychiatric disorders were identified as medical events of special interest in the phase 3a liraglutide 3.0 mg clinical development programme, providing an opportunity for prospective evaluation of depression and suicidality.

2 | METHODS

This is a *post hoc* analysis and comprehensive report of pooled neuropsychiatric safety data from the liraglutide weight management programme. The 5 trials were performed at clinical research sites in accordance with the Declaration of Helsinki[23] and Good Clinical Practice guidelines,[24] and the respective protocols were approved by local institutional review boards or ethics committees. All participants provided written informed consent before the trials began. See Table S1, Supporting Information online, for further information about the trials, including inclusion/exclusion criteria and primary endpoints; full methodology details have been reported previously.[17–22]

2.1 | Participants

Each trial enrolled men and women with a body mass index (BMI) of ≥27 kg/m^2 and with at least 1 weight-related comorbidity, or a BMI of ≥30 kg/m^2 (Table S1, Supporting Information). Key exclusion criteria included type 1 or 2 diabetes (except for the SCALE Diabetes trial which specifically enrolled individuals with type 2 diabetes), the use of medications causing significant weight gain or loss, previous bariatric surgery, or a history of chronic pancreatitis or idiopathic acute pancreatitis. Psychiatric illness was not excluded in the phase 2 trial, as this was not a regulatory requirement at the time, but individuals were excluded from the phase 3a trials for the following reasons: history of major depressive disorder within the last 2 years; a Patient Health Questionnaire-9 (PHQ-9) score ≥ 15 (indicating moderately severe/severe depression) at screening; history of other severe psychiatric disorders; lifetime history of a suicide attempt; or history of suicidal behaviour or suicidal ideation type 4 (active suicidal ideation with some intent to act without specific plan) or type 5 (active suicidal ideation with specific plan and intent) according to the Columbia-Suicide Severity Rating Scale (C-SSRS) during the month before randomization.

2.2 | Interventions

All participants self-administered treatment with once-daily subcutaneous liraglutide or placebo in FlexPen devices (Novo Nordisk A/S, Bagsværd, Denmark), starting at a dose of 0.6 mg with weekly 0.6-mg increments to 3.0 mg. This pooled analysis compared data with liraglutide 3.0 mg and placebo only; additional liraglutide doses were investigated in the phase 2 dose-finding trial (1.2, 1.8 and 2.4 mg) and the SCALE Diabetes trial (1.8 mg), but those doses were not included in this analysis since they are not approved for weight management. Furthermore, for the phase 2 trial, only data up to 1 year were included for liraglutide 3.0 mg and placebo; after that, all liraglutide- or placebo-treated individuals were switched to treatment with liraglutide 2.4 mg and, thereafter, to 3.0 mg.[17] Diet and exercise counselling, provided at approximately monthly intervals, was similar across trials.[17–22] Participants were advised (in groups or individually) to follow a reduced-calorie diet with an energy deficit of ~500 kcal/d below their estimated total energy expenditure, containing a maximum of 30% energy from fat, ~20% from protein and ~50% from carbohydrates. The diet was reinforced by the use of 3-day food diaries,

and pedometers were provided to encourage participants to achieve a recommended minimum of 150 min/wk of physical activity.

2.3 | Neuropsychiatric safety

In each trial, adverse events in the system organ classes of "psychiatric disorders" and "nervous system disorders" were identified using MedDRA (Medical Dictionary for Regulatory Activities) coding. In the phase 3a trials, psychiatric disorders were classified as medical events of special interest to ensure that brief narratives were collected, also for non-serious adverse events. These narratives were limited to a free-text description of the event by the investigator, such as relevant medical history.

In the phase 3a trials, 2 validated mental health questionnaires were employed for detecting possible depression (PHQ-9)[25] or suicidal ideation and behaviour (C-SSRS).[26] These were completed at screening, randomization and each visit to the clinic during treatment (except the dose-titration visits in the SCALE Maintenance trial) and each took approximately 10 minutes to complete. Suicidal behaviour was defined as: (1) death by suicide, (2) suicidal attempts where there was intention to die or (3) nonfatal, self-injurious acts committed without intent to die.

The PHQ-9 was self-administered and consisted of 9 questions used for detecting possible depression and monitoring treatment.[25] The C-SSRS (available at http://www.cssrs.columbia.edu/) was administered as an interview by the investigator or sufficiently trained medical personnel.[26] The investigator reviewed the PHQ-9 and C-SSRS questionnaires for completeness, together with any reported adverse events at each visit.

2.4 | Statistical analyses

All available randomized individuals who received at least 1 treatment dose of liraglutide 3.0 mg or placebo from the 5 randomized, controlled weight management trials were included in the analyses. For the change from baseline to end-of-treatment in the PHQ-9 total score, a treatment difference was estimated, using an ANCOVA model that included the baseline PHQ-9 total score as a covariate and treatment and trial as factors. None of the trials was powered to identify differences in adverse event rates; hence, adverse events were analysed using descriptive statistics and no testing for significance was undertaken.

3 | RESULTS

3.1 | Participant characteristics

Baseline characteristics of the 5325 randomized and exposed individuals are displayed in Table 1, and were generally comparable for liraglutide 3.0 mg and placebo. At baseline, 9.1% of individuals in the liraglutide 3.0 mg group and 10.6% of those in the placebo group had a self-reported history of depression, and 7.2% vs 7.8% had a self-reported history of anxiety. None had a history of suicide attempt or self-injury.

TABLE 1 Demographics and baseline characteristics

Pooled trials[a]	Liraglutide 3.0 mg N = 3384	Placebo N = 1941
Sex, n (%)		
Female	2449 (72.4)	1374 (70.8)
Male	935 (27.6)	567 (29.2)
Age, years	46.6 (12.2)	46.6 (11.8)
Race, n (%)		
White	2845 (84.1)	1651 (85.1)
Black/African-American	348 (10.3)	202 (10.4)
Asian	115 (3.4)	53 (2.7)
American Indian or Alaska Native	9 (0.3)	4 (0.2)
Native Hawaiian or other Pacific Islander	5 (0.1)	4 (0.2)
Other	62 (1.8)	27 (1.4)
Ethnicity, n (%)		
Hispanic	341 (10.1)	193 (9.9)
Body weight, kg	106.1 (21.4)	106.2 (22.2)
Body mass index, kg/m^2	37.9 (6.4)	37.8 (6.5)
HbA1c, %[b]	5.6 (0.4)	5.6 (0.4)
Fasting plasma glucose, mmol/L[b]	5.3 (0.6)	5.4 (0.6)
History of psychiatric disorder, n (%)	454 (13.4)	307 (15.8)
Depression (except suicide and self-injury)	309 (9.1)	206 (10.6)
Suicide and self-injury	0 (0.0)	0 (0.0)
Anxiety	243 (7.2)	151 (7.8)
Receiving antidepressants, n (%)	306 (9.0)	197 (10.1)
Receiving anxiolytics, n (%)	91 (2.7)	53 (2.7)
Dyslipidaemia, n (%)	1166 (34.5)	618 (31.8)
Hypertension, n (%)	1296 (38.3)	755 (38.9)
Dyslipidaemia and hypertension, n (%)	716 (21.2)	376 (19.4)
History of cardiovascular disease, n (%)	311 (9.2)	172 (8.9)
SCALE Diabetes (individuals with T2DM)	**n = 423**	**n = 212**
Duration of T2DM, years	7.5 (5.7)	6.7 (5.1)
HbA1c, %	7.9 (0.8)	7.9 (0.8)
Fasting plasma glucose, mmol/L	8.8 (1.9)	8.6 (1.8)

Abbreviations: HbA1C, glycated haemoglobin; SCALE, Satiety and Clinical Adiposity – Liraglutide Evidence; SD, standard deviation; T2DM, type 2 diabetes mellitus.

Data are presented as mean (SD), unless otherwise stated, and are reported for randomized individuals who were exposed to at least 1 dose of liraglutide or placebo. Individuals from France were not required to report race. Ethnicity was not collected in the phase 2 trial. Anxiety includes the high-level terms "anxiety symptoms" and "anxiety disorders not elsewhere classified." Dyslipidaemia and hypertension were based on reported medical history. Cardiovascular disease was based on standardized (Medical Dictionary for Regulatory Activities; MedDRA) queries regarding ischaemic heart disease, cardiac failure, central nervous system haemorrhages, cerebrovascular conditions, and embolic and thrombotic events.

[a]Including data from the 104-week phase 2 trial and the 4 phase 3a SCALE trials (1 of 160 weeks' duration, 2 of 56 weeks' duration and 1 of 32 weeks' duration). SCALE Obesity and Prediabetes had 2 parts: a 56-week period for individuals with and without prediabetes. Individuals with prediabetes at screening continued in the second part of the trial for up to 160 weeks of treatment.

[b]Individuals without T2DM.

3.2 | Neuropsychiatric safety data by adverse event reporting

3.2.1 | Adverse events

Adverse events in the system organ classes of psychiatric and nervous system disorders in the pooled analysis across all 5 trials are shown in Table 2. Overall rates of psychiatric disorder were similar for liraglutide 3.0 mg and placebo. Most events were non-serious and did not lead to participant withdrawal. Rates of depression, anxiety and insomnia were similarly low in both treatment groups (Table 2), though insomnia rates were marginally higher in the liraglutide group.

3.2.2 | Suicidal ideation and behaviour

Nine of 3384 individuals (0.3%, 0.2 events/100 person-years) in the liraglutide 3.0 mg group vs 2 of 1941 (0.1%, <0.1 events/100 person-years) in the placebo group reported adverse events of suicidal ideation or behaviour. All except 3 individuals continued treatment and all except 1 recovered from the events. The condition of the individual who did not recover was considered chronic but stable at the end of the study. Importantly, at the final trial visit, it was discovered that this participant had a history of suicide attempt 12 years prior to study enrolment, and thus, based on exclusion criteria, should not have been enrolled. Weight loss for each individual at the time of the event is shown in Table S2, Supporting Information. Of the 11 individuals reporting suicidal ideation or behaviour, all except 1 in each treatment group (liraglutide, suicidal ideation event; placebo, suicide attempt) reported having a past history of psychiatric disorders (including major depression, depression, anxiety and insomnia) or life stressors accompanying the events (Table S2, Supporting Information). Ten of the 11 individuals were from the SCALE Obesity and Prediabetes trial and 9 had prediabetes. Two of the 11 individuals reported 2 events each, giving 13 events in total. Of these 13 events, 7 occurred after the first year of the SCALE Obesity and Prediabetes trial.

3.3 | Neuropsychiatric safety data through prospective collection of mental health questionnaires

Two validated mental health questionnaires were employed in the phase 3a trials, the PHQ-9 and the C-SSRS.

3.3.1 | Patient Health Questionnaire-9 (PHQ-9)

Mean ± SD PHQ-9 scores at baseline were 2.8 ± 3.0 (range, 0-14) with liraglutide 3.0 mg vs 2.9 ± 3.1 (range, 0-17) with placebo. Mean PHQ-9 scores improved (decreased) to 1.8 ± 2.7 vs 1.9 ± 2.7, respectively, at end-of-treatment (using last-observation-carried-forward imputation), with an estimated treatment difference (95% confidence interval) of −0.02 (−0.17 to 0.12). The mean maximum post-baseline

TABLE 2 Pooled psychiatric and nervous system disorders reported during treatment

	Liraglutide 3.0 mg			Placebo		
	N = 3384			N = 1941		
Pooled trials[a]	N (%)	E	R	N (%)	E	R
Psychiatric disorders						
Overall events	412 (12.2)	557	11.0	206 (10.6)	273	10.8
Serious events	5 (0.1)	6	0.1	4 (0.2)	4	0.2
Events leading to withdrawal	11 (0.3)	14	0.3	14 (0.7)	15	0.6
Selected types of events						
Depression	101 (3.0)	107	2.1	48 (2.5)	52	2.1
Serious events	1 (<0.1)	1	<0.1	1 (<0.1)	1	<0.1
Anxiety	92 (2.7)	96	1.9	41 (2.1)	44	1.7
Serious events	1 (<0.1)	1	<0.1	1 (<0.1)	1	<0.1
Insomnia	122 (3.6)	143	2.8	45 (2.3)	50	2.0
Serious events	0 (0.0)	0	0.0	0 (0.0)	0	0.0
Nervous system disorders						
Overall events	1024 (30.3)	1869	36.9	507 (26.1)	874	34.6
Serious events	18 (0.5)	19	0.4	11 (0.6)	13	0.5
Events leading to withdrawal	30 (0.9)	36	0.7	9 (0.5)	9	0.4
Selected types of events						
Headache	534 (15.8)	820	16.2	273 (14.1)	422	16.7
Serious events	0 (0.0)	0	0.0	1 (<0.1)	1	<0.1
Memory impairment	7 (0.2)	7	0.1	1 (<0.1)	1	<0.1
Serious events	0 (0.0)	0	0.0	0 (0.0)	0	0.0

Abbreviations: N, number of individuals; %, based on total N; E, number of events; R, event rate per 100 person-years; SCALE, Satiety and Clinical Adiposity – Liraglutide Evidence.

Data were for individuals in the safety analysis set (all exposed individuals) and show specific preferred terms from the Medical Dictionary for Regulatory Activities (MedDRA) database.

[a]Including data from the phase 2 trial up to 52 weeks and 4 phase 3a SCALE trials (1 of 160 weeks' duration, 2 of 56 weeks' duration and 1 of 32 weeks' duration). SCALE Obesity and Prediabetes had 2 parts: a 56-week period for individuals with and without prediabetes; individuals with prediabetes at screening continued in the second part of the trial for up to 160 weeks of treatment.

scores were 4.2 ± 3.7 and 4.0 ± 3.8 for liraglutide vs placebo, respectively. Examining the highest PHQ-9 score observed at any time during treatment for each participant, 8.3% vs 8.5% of individuals scored ≥10 (moderate depression or worse) and 1.9% vs 2.0% scored ≥15 (moderately severe depression or worse) with liraglutide 3.0 mg vs placebo. Treatment groups were similar in terms of proportion of participants showing improvement or worsening from baseline to their maximum total PHQ-9 score at any time of treatment (Table 3).

Mental health questionnaire information for individuals reporting suicide-related adverse events is shown in Table S3, Supporting Information. PHQ-9 total scores at baseline indicated no depression or mild depression for all 11 individuals. Eight of the 11 individuals showed increases during treatment in maximum PHQ-9 score from baseline, with 2 scores in the moderately severe or severe depression category. Question 9 of the PHQ-9 asks the respondent to report how often over the previous 2 weeks he or she has "been bothered by thoughts that you would be better off dead or of hurting yourself in some way?" Of the 11 individuals reporting suicide-related events, the maximum post-baseline response to this question was a 0 ("not at all") for 5 in the liraglutide group and both of those in the placebo group, a 1 ("several days") for 3 in the liraglutide group, and a 3 ("nearly every day") for 1 liraglutide group member (see Supporting Information for details).

3.3.2 | Columbia-Suicide Severity Rating Scale (C-SSRS)

On the C-SSRS at baseline, 110 individuals (3.3%) in the liraglutide 3.0 mg group vs 67 (3.6%) in the placebo group reported suicidal behaviour and/or ideation at some time during their life. Most instances were of suicidal ideation, while 6 (0.2%) vs 2 (0.1%) individuals, respectively, reported suicidal behaviour. The above individuals were not excluded from the trials as the reported behaviour did not occur in the month before randomization, as per exclusion criteria. During treatment, 34 individuals (1.0%) receiving liraglutide 3.0 mg vs 19 individuals (1.0%) receiving placebo reported suicidal ideation on the C-SSRS (Table 4). Most of these individuals (26/34, 76% in the liraglutide group and 19/19, 100% in the placebo group) did not report accompanying suicidal ideation adverse events.

For the 11 individuals reporting suicidal ideation or behaviour adverse events, only 1 of 9 individuals in the liraglutide 3.0 mg group reported suicidal ideation at baseline on the C-SSRS. Neither of the 2 individuals in the placebo group did so, and no individual in either group reported suicidal behaviour on the C-SSRS at baseline. The individual who reported suicidal ideation at baseline was not excluded as the ideation did not occur in the month before randomization. The C-SSRS captured suicidal ideation during treatment in 8 of the 11 individuals who reported such events (Table S3, Supporting Information). The 3 individuals for whom events were not captured by C-SSRS included 1 in the liraglutide group who reported depression with suicidal ideation, and 2 individuals in the placebo group who reported a suicide attempt and a major depressive episode with contemplation about suicide, respectively. The C-SSRS did not capture the suicidal behaviour in either of the 2 individuals who reported a suicide attempt.

TABLE 3 PHQ-9 results post-baseline for pooled phase 3a trials[a]

Baseline PHQ-9 category	End of treatment PHQ-9 category (n (%)) for Liraglutide 3.0 mg (N = 3291) / Placebo (N = 1843)				
	None	Mild	Moderate	Moderately severe	Severe
None					
Liraglutide 3.0 mg	1824 (55.4)	564 (17.1)	95 (2.9)	16 (0.5)	5 (0.2)
Placebo	1039 (56.4)	284 (15.4)	49 (2.7)	16 (0.9)	5 (0.3)
Mild					
Liraglutide 3.0 mg	207 (6.3)	313 (9.5)	89 (2.7)	21 (0.6)	6 (0.2)
Placebo	120 (6.5)	177 (9.6)	44 (2.4)	6 (0.3)	2 (0.1)
Moderate					
Liraglutide 3.0 mg	22 (0.7)	61 (1.9)	28 (0.9)	9 (0.3)	4 (0.1)
Placebo	11 (0.6)	35 (1.9)	27 (1.5)	5 (0.3)	1 (0.1)
Moderately severe[b]					
Liraglutide 3.0 mg	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)
Placebo	2 (0.1)	1 (0.1)	0 (0.0)	1 (0.1)	0 (0.0)

Abbreviations: PHQ-9, Patient Health Questionnaire-9; SCALE, Satiety and Clinical Adiposity – Liraglutide Evidence.

Data were for individuals in the safety analysis set (all exposed individuals), and show the shift from randomization to maximum PHQ-9 total score during treatment. Blue shading represents improvement and grey shading represents worsening. No shading denotes no change. No individuals were in the severe category at randomization.

Total for no change was 2167 (65.8%) in the liraglutide group and 1247 (67.7%) in the placebo group. Total improved was 290 (8.8%) vs 169 (9.2%). Total worsened was 809 (24.6%) vs 412 (22.4%). Total missing was 25 (0.8%) vs 15 (0.8%). The total score of the 9 items ranges from 0 to 27; total scores of 0 to 4 represent no depression, of 5 to 9 represent mild depression, of 10 to 14 represent moderate depression, of 15 to 19 represent moderately severe depression and of 20 to 27 represent severe depression. A PHQ-9 score ≥ 15 at screening was exclusionary.

[a]Including data from the 4 phase 3a SCALE trials (1 of 160 weeks' duration, 2 of 56 weeks' duration and 1 of 32 weeks' duration). SCALE Obesity and Prediabetes had 2 parts: a 56-week period for individuals with and without prediabetes; individuals with prediabetes at screening continued in the second part of the trial for up to 160 weeks of treatment.

[b]Three individuals changed to the moderately severe category (which was exclusionary at screening) between screening and baseline.

TABLE 4 C-SSRS results post-baseline

Pooled phase 3a trials[a]	Liraglutide 3.0 mg N = 3291	Placebo N = 1843
Number of participants completing C-SSRS	3270	1832
N (%) with suicidal ideation on the C-SSRS	34 (1.03)	19 (1.03)
1. Wish to be dead	30 (0.91)	18 (0.98)
2. Active suicidal ideation, non-specific thoughts	15 (0.46)	8 (0.43)
3. Active suicidal ideation, any method (no plan) without intent	11 (0.33)	3 (0.16)
4. Active suicidal ideation, some intent to act, without specific plan	2 (0.06)	1 (0.05)
5. Active suicidal ideation, specific plan and intent	1 (0.03)	2 (0.11)

Abbreviations: C-SSRS, Columbia-Suicide Severity Rating Scale; N (%), number and percentage of individuals; SCALE, Satiety and Clinical Adiposity – Liraglutide Evidence.

Data were for individuals in the safety analysis set (all exposed individuals) and represent responses obtained at any time during treatment. The number and percentage of specific ideation types sum to more than that of any ideation because individuals may have more than 1 type over time.

[a]Including data from the 4 phase 3a SCALE trials (1 of 160 weeks' duration, 2 of 56 weeks' duration and 1 of 32 weeks' duration). SCALE Obesity and Prediabetes had 2 parts: a 56-week period for individuals with and without prediabetes; individuals with prediabetes at screening continued in the second part of the trial for up to 160 weeks of treatment.

3.4 | Neuropsychiatric safety data following treatment discontinuation

All of the SCALE trials, except the SCALE Sleep Apnoea trial, had a 12-week off-treatment observational follow-up period to evaluate withdrawal or rebound effects of discontinuing liraglutide treatment. No neuropsychiatric safety signals, through adverse event reporting, PHQ-9 or C-SSRS data collection at the end of the 12-week time period, were evident to indicate any withdrawal or rebound effects.

4 | DISCUSSION

This was a pooled *post hoc* analysis of neuropsychiatric safety data across weight management trials with liraglutide 3.0 mg. The overall incidence of depression, anxiety and insomnia adverse events was similarly low (≤3.6%) in both liraglutide 3.0 mg and placebo treatment groups, with a small numerical imbalance not favouring liraglutide in insomnia events and in suicidality ideation/behaviour. However, there were no differences in depression or suicidality indicators when prospectively assessed in the phase 3a programme, which excluded individuals with a history of severe psychiatric disorders or suicidal ideation/behaviour, as reflected by detailed analysis of PHQ-9 scores and categories and C-SSRS data. Furthermore, there was no indication of withdrawal or rebound adverse effects when liraglutide treatment was discontinued.

Nine (0.3%) vs 2 (0.1%) individuals reported suicidal ideation or behaviour adverse events; 8 of the 11 individuals continued treatment and symptoms resolved in 10. The individual who did not recover from suicidal ideation was randomized in error, as she had a history of a suicide attempt 12 years previously; her condition was considered chronic but stable at the end of the trial. Nine of the 11 individuals had prediabetes, which, as with diabetes, has been shown to be associated with symptoms of depression[27]; however, no one from the SCALE Diabetes trial reported suicidal ideation/behaviour events. Nine of the 11 individuals had a history of psychiatric disorders or life stressors accompanying the events. Overall, no evidence suggests that a positive history of these types of events should be a contraindication for treatment with liraglutide.

Several studies have revealed positive associations between BMI and some psychiatric disorders, including depression and anxiety,[14] with some differences between men and women.[13] In one epidemiological study, individuals with obesity were 1.5 times more likely than those of normal weight to report such disorders occurring during their lifetime or in the past year, and anxiety rates were increased not only in individuals with obesity, but also in those who were moderately overweight.[28] Individuals with obesity are also more likely to experience insomnia, according to a recent review.[29] There appears to be a reciprocal link between depression and obesity,[30] whereby obesity can increase the risk of depression and, conversely, depression can predict the development of obesity.[31] It is therefore important that pharmacological treatment options for chronic weight management that will not exacerbate depression and can be used safely with antidepressants are available. As with this trial, no signal for neuropsychiatric events was detected in trials of liraglutide at doses up to 1.8 mg for management of hyperglycaemia in individuals with type 2 diabetes, including the LEADER trial (Liraglutide Effect and Action in Diabetes: Evaluation of Cardiovascular Outcome Results),[32,33] or in postmarketing surveillance. Nevertheless, and in accordance with regulatory guidance, US prescribing information states that patients treated with liraglutide 3.0 mg should be monitored for depression or suicidal thoughts, and treatment should be discontinued if symptoms develop; treatment should also be avoided in patients with a history of suicidal attempts or active suicidal ideation. However, no such text is included in the European summary of product characteristics.

We note that the information obtained from adverse-event reporting and that from questionnaires used in the SCALE trials were not always concordant, even though the data were collected during the same visits throughout the trials. For example, while a similar proportion of individuals in the liraglutide 3.0 mg group (1.0%) and the placebo group (1.0%) reported suicidal ideation on the C-SSRS, far fewer individuals in both treatment groups reported adverse events of suicidal ideation or behaviour. Furthermore, although 8 of the 11 individuals who reported suicidal ideation or behaviour adverse events had increases in maximum total PHQ-9 scores during treatment, these increased scores were in the moderately severe or severe depression range in only 2 cases. The suicidal ideation events were detected by the C-SSRS for 8 of the 11 individuals, all in the liraglutide group, whereas neither adverse event of suicidal behaviour (attempt) was detected by C-SSRS. Thus, longitudinal assessment of neuropsychiatric safety in clinical trials may benefit from the combination of adverse event reporting and validated questionnaires, as shown here.

A limitation of this analysis is that it was performed in a population that was selected according to trial-specific eligibility criteria, and does not necessarily cover the full spectrum of patients who might be treated outside of clinical trials, as individuals at high-risk for psychiatric disorders were excluded. Furthermore, the trial was not powered to quantify a treatment effect on the event rate of psychiatric disorders, suggesting the importance of further investigation. While the PHQ-9 and the C-SSRS are validated mental-health questionnaires and may be useful as rapid assessment screening tools, their limitations, as compared to longer structured assessments, should also be noted. Strengths of the analysis include the overall large sample size and the substantial exposure to liraglutide 3.0 mg in the blinded trials, as well as the systematic prospective collection of neuropsychiatric safety data by trained staff.

In conclusion, the results of this exploratory pooled analysis of neuropsychiatric safety data from the liraglutide 3.0 mg weight management clinical development programme do not provide any clear cause for concern regarding liraglutide 3.0 mg treatment in patients who are similar to those included in the examined trials. Although there was a small numerical imbalance in suicidal ideation with liraglutide, as indicated through adverse event reporting, no between-treatment imbalances in suicidal ideation/behaviour or depression were noted through prospective questionnaire assessments. The long-term safety and efficacy of anti-obesity medications are important as individuals with obesity often require sustained therapy to achieve and maintain weight loss. Neuropsychiatric safety should be an integral component of any clinical risk/benefit assessment, and the data provided here contribute to thoughtful and objective decision-making and dialogue between patients and clinicians.

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Conflict of interest

P. O. has received funding for research from Orexigen Therapeutics, Weight Watchers International and Novo Nordisk, honoraria from Novo Nordisk and Medscape/WebMD, and has been an advisory board member for Orexigen Therapeutics, Janssen and Pfizer. V. A. has received funding for research from AstraZeneca/BMS, Calibra, Eisai, Elcelyx, Janssen, Novo Nordisk, Sanofi and Theracos and has received consultancy fees from Adocia, ADA, AstraZeneca, Janssen, Medscape, Novo Nordisk, Sanofi and Tufts, all within the last 12 months. A. A. has been an advisory board member for BioCare, consultant for Basic Research, Gelesis, Novo Nordisk, Omega ACO, Pathway Genomics, Pfizer, Sanofi-Aventis and S-Biotek and is a recipient of travel expenses and/or modest honoraria (<$2,000) for lectures given at national and international meetings, often with support from one or more corporate sponsors. He is co-inventor of a number of patents owned by the University of Copenhagen, in accordance with Danish law. He is a member of the board and a shareholder in the consultancy company Dentacom Aps, Denmark, and is a co-founder and co-owner of the University of Copenhagen spin-out company, Mobile Fitness A/S, Denmark. He is also co-founder, co-owner and a member of the board of the University of Copenhagen spin-out company Flaxslim ApS, Denmark. R. K. serves on the advisory boards for Novo Nordisk, Weight Watchers, Retrofit and Zafgen, and has received grant support, on behalf of Northwestern University, from Aspire Bariatrics, Eisai and Novo Nordisk. D. L. has received research funding from AstraZeneca, Boehringer-Ingelheim and Novo Nordisk, and has received consultancy fees from Amgen, AstraZeneca, Boehringer-Ingelheim, Novo Nordisk, Sanofi and Shire, and lecture fees from Amgen, AstraZeneca, Boehringer-Ingelheim, Merck and Novo Nordisk. T. W. serves on advisory boards for Novo Nordisk, Nutrisystem and Weight Watchers and has received grant support, on behalf of the University of Pennsylvania, from Eisai Co. and Novo Nordisk. J. B. and A. C. are employed by and hold stock in Novo Nordisk. J. W. has received grant funding (via his institution), consultancy and lecture fees (institutional and personal) from Novo Nordisk, and consultancy and lecture fees from AstraZeneca, Boehringer Ingelheim, Eli Lilly, Janssen, Orexigen and Sanofi (both institutional and personal) in relation to treatments for obesity and/or diabetes.

Author contributions

Novo Nordisk provided overall management of the trials, performed the statistical analyses and verified the accuracy of the presented data. Novo Nordisk was also responsible for the overall trial designs, and provided a formal review of the manuscript, but the authors had final authority, including choice of journal. Under the direction of the authors and according to an agreed outline, the medical writer, Angela Stocks, drafted the initial version of the manuscript. A. A. participated in the concept and design of the phase 2 trial. A. A. and T. W. were signatory investigators on the phase 2 trial and the SCALE Maintenance trial, respectively, and P. O., V. A., R. K., D. L. and J. W. were also trial investigators. All authors were involved in the analysis or interpretation of data, and all critically reviewed the manuscript and approved the final version for submission. All authors also agreed to be accountable for all aspects of the work.

ORCID

Patrick M. O'Neil http://orcid.org/0000-0002-0388-4046

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SUPPORTING INFORMATION

Additional Supporting Information may be found online in the supporting information tab for this article.

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