Efficacy and Safety of Twincretin Survodutide, a Dual Glucagon-Like Peptide-1 and Glucagon Receptor Agonist as an Anti-Obesity and Anti-Diabetes Medication: A Systematic Review and Meta-Analysis

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Abstract

Survodutide is a twincretin having dual glucagon-like peptide-1 and glucagon receptor agonist activity, conceptually based on endogenous peptide oxyntomodulin. This systematic review and meta-analysis (SRM) holistically analyzed the body weight lowering, glycemic efficacy, and safety of survodutide. Electronic databases were searched for RCTs involving diabetes and/or obesity patients receiving once-weekly subcutaneous survodutide in intervention arm and placebo/active comparator in control arm. Co-primary outcomes were the percent changes in body weight and HbA1c. Secondary outcomes were to evaluate absolute changes in absolute weight, blood pressure, fatty-liver disease parameters, and adverse events (AEs). Data from 3 RCTs (1088 patients) having follow-up duration ranging from 4–11 months were analyzed. Survodutide at 2.4 mg [MD (mean difference) −7.79% (95% confidence interval [CI]: −11.54, −4.07); $I^2 = 98\%$; $P < 0.01$] and 3.6 mg [MD − 9.08% (95% CI: −11.63, −6.54); $I^2 = 96\%$; $P < 0.001$] was associated with significantly greater percent reductions in body weight compared to placebo. The corresponding absolute body-weight reduction with survodutide 2.4 mg and 3.6 mg was − 9.14 kg (95% CI: −13.76, −4.53) and − 10.23 kg (95% CI: −15.43, −5.04), respectively. Survodutide of 2.4 mg was associated with significant HbA1c reduction [MD: −0.88% (95% CI − 1.72, −0.05); $I^2 = 99\%$; $P = 0.040$]. Survodutide of 2.4 mg [odds ratio (OR): 2.93 (95% CI: 1.66, 5.18); $I^2 = 0\%$; $P < 0.001$] and 3.6 mg [OR: 4.61 (95% CI: 2.33, 9.12); $I^2 = 0\%$; $P < 0.001$] was associated with significantly higher treatment-emergent AEs, compared to placebo, although severe AEs were not increased. Gastrointestinal AEs were the predominant AEs and were dose dependent. Treatment discontinuation due to AEs was significantly higher with survodutide and was dose dependent. Survodutide demonstrates impressive weight and glucose-lowering properties over short-term clinical use. The optimal dose for clinical use ranges from 2.4 to 4.8 mg/week.

Keywords: Fatty liver, meta-analysis, obesity, survodutide, systematic review, twincretin, type-2 diabetes

Introduction

Survodutide is conceptually based on the endogenous peptide oxyntomodulin.[1] Oxyntomodulin is a natural gut peptide hormone, which happens to be a weak dual agonist of glucagon-like peptide-1 receptor (GLP1R) and glucagon receptor (GCR).[1,2] Oxyntomodulin promotes weight loss through effects on appetite and satiety, along with increasing energy expenditure.[1] Survodutide is a 29-amino acid peptide derived from glucagon, incorporating potent GLP1R agonistic activities.[3] It contains a C-18 diacid which mediates binding to albumin, thereby prolonging the half-life to

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enable once-weekly subcutaneous dosing.[3] The utilization of GCR agonism aims to enhance body weight-lowering effects by increasing energy expenditure in addition to the anorectic action of GLP1R agonists.[2,3] Another drug that works on the same mechanism and is under development is cotadutide, which activates GLP1 receptor and GCR in a ratio of 5:1.[4] Several randomized controlled trials (RCTs) have been published evaluating the role of survodutide as an anti-diabetes, anti-obesity, and anti-fatty-liver medication.[5-7] Survodutide has also been studied in patients with advanced liver disease and cirrhosis.[8]

To date, no systematic review and meta-analysis (SRM) has been published evaluating the efficacy and safety of survodutide. Therefore, we undertook this SRM to holistically analyze and summarize the clinical efficacy and safety of this novel twincretin in diabetes, obesity, and fatty-liver disease (metabolic syndrome).

Methods

The SRM was carried out according to the recommendations of the Cochrane Handbook for Systematic Reviews of Interventions.[9] The predefined protocol has been registered in PROSPERO, having a registration number of CRD42024573985. All RCTs published till July 2024 were considered for this SRM. This meta-analysis has been reported in accordance with the Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA).[10] Since ethical approval already exists for the individual studies included in the meta-analysis, no separate approval was required for this study.

The PICOS criteria was used to screen and select the studies for this meta-analysis, with patients (P) being people living with type-2 diabetes (T2DM) and/or obesity and/or fatty-liver disease; intervention (I) being use of survodutide in the intervention arm; control (C) being patients either on placebo/active control medicine; outcomes (O) being evaluated were impact on HbA1c, percent weight reduction, percent reduction in liver fat, blood glucose parameters, lipid parameters, other fatty-liver disease parameters, and any adverse effects.

The primary outcomes were to evaluate the percent reduction in body weight and changes in HbA1c from baseline. The secondary outcomes of this SRM were to evaluate the alterations in absolute weight, percent reduction in liver fat from baseline, fatty-liver parameters, systolic blood pressure (SBP), diastolic blood pressure (DBP), heart rate, and adverse events (AEs). The outcomes were analyzed based on whether the control group received an active comparator – labelled here as the active control group (ACG) or a placebo – labelled as the passive control group (PCG).

Search method, study selection, and data extraction

Electronic databases of Medline (Via PubMed), Embase (via Ovid SP), Cochrane central register of controlled trials (CENTRAL), ctri.nic.in, clinicaltrials.gov, global health, and Google Scholar were searched using Boolean search strategy: (survodutide). Data extraction was performed independently by two authors using data extraction forms. Whenever there was more than one publication of a single cohort of patients and authors, the outcomes were grouped from each report into one for analyses. Data on the primary and secondary outcomes as stated above was extracted. Patient characteristics from the different RCTs included for analysis were noted in tabular form. The first and the last authors of this SRM resolved all disagreements.

Assessment of risk of bias in included studies

Three authors independently assessed the risk of bias using the risk of bias assessment tool in Review Manager (RevMan) Web Version (The Cochrane Collaboration, Oxford, UK, 2024) software. We specifically looked for adequate sequence generation (selection bias), allocation adequately concealed (selection bias), knowledge of the allocated interventions adequately prevented during the study or not, participants and personnel blinding (performance bias), blinding of the outcome assessors (detection bias), whether the incomplete outcome data issue was adequately addressed or not (attrition bias) and lastly involvement of the industry in the planning and execution of the work (other bias).[11] Details have been elaborated in previous publication from our group.[12]

Measures of treatment effect and heterogeneity assessment

For continuous variables, the outcomes were expressed as mean differences (MD). For dichotomous outcomes (treatment success), results were expressed as risk ratios (RR) with 95% confidence intervals (CIs). For AEs, results were expressed as post-treatment absolute risk differences. RevMan Web was used for comparing MD of the different primary and secondary outcomes between survodutide and the control groups of the included studies. Heterogeneity was assessed using forest plot generated for the outcomes. Heterogeneity was analyzed using the Chi^2 test on N-1 degrees of freedom, with an α of 0.05 used for statistical significance and with the I^2 test.[9] The importance of the observed value of I^2 depends on the magnitude and direction of treatment effects and the strength of the evidence for heterogeneity (e.g. P value from the Chi^2 test, or a confidence interval for I^2).[10] Details have been elaborated elsewhere.[12]

Grading of the results and data synthesis

An overall grading of the evidence (certainty of the evidence) related to outcomes of this SRM was performed using the Grades of Recommendation, Assessment, Development, and Evaluation (GRADE) approach.[13] Details have been elaborated in previous publications from our group.[12,14] Data was pooled as a random effect model for the analysis of outcomes, which were expressed as 95% CIs. Forrest plots were plotted with the left side of the graph favouring

survodutide and the right side of the graph favouring control using RevMan Web software. $P < 0.05$ was considered statistically significant.

Results

A total of 13 articles were found after the initial search [Supplementary Figure 1]. Three duplicates were removed. Following the screening of the titles and abstracts, the search was reduced to four articles whose full texts were reviewed in detail.[3,5-7] Finally, data from 3 RCTs (1088 patients) which fulfilled all inclusion and exclusion criteria was included in this SRM [Supplementary Figure 1].[5-7] The study by Klein *et al*.[3] was excluded as it was not an RCT.

The details of the studies included in this SRM have been elaborated in Table 1. The prevalence of T2DM in the 3 RCTs analyzed in this SRM ranged from 0–100% [Table 1]. All the patients in the study by Blüher *et al*.[6] had T2DM. None of the patients in the study by le Roux *et al*.[7] had T2DM. Thirty-nine percent of patients in the study by Sanyal *et al*.[5] had T2DM. Survodutide has been studies in different doses ranging from 0.3–6.0 mg once-weekly subcutaneous injection in the different RCTs over a period of 16–48 weeks [Table 1]. However, in terms of clinical efficacy, the 3 RCTs examined in this SRM most frequently used dosages of 2.4 mg/week, 3.6 mg/week, and 4.8 mg/week. Hence, the use of survodutide at these three doses has been most extensively studied in this SRM. The maximum dose of survodutide that has been studied till date is 6 mg/week in the setting of metabolic dysfunction associated steatotic liver disease (MASLD) by Sanyal *et al*. In all the clinical trials, survodutide weekly injections were started at a dose of 0.3 mg/week, and the dose of increased by 0.3 mg every 2 weeks to reach the therapeutic dose target for treatment.

Table 1: Characteristics of patients in the different randomized controlled trials evaluated in this systematic review and meta-analysis on the use of survodutide

Parameter	Sanyal *et al*.[5] (*n*=293)	Blüher *et al*.[6] (*n*=411)	le Roux *et al*.[7] (*n*=384)
Age (years)	50.8±12.8	57.3±9.8	49.1±12.9
Female sex	53%	43.3%	68%
Weight (kg)	100.84±22.37	96.6±21.6	105.7±20·4
WC (cm)	113.81±13.91	110.3±18.2	113.4±14.5
BMI (kg/m^2)	35.81±6.41	33.9±6.0	37.1±6.1
T2DM	39%	100%	0%
HbA1c (%)	6.96±0.96	8.07±0.84	–
SBP (mm Hg)	129.4±14.1	–	125.6±13.4
DBP (mm Hg)	80.7±8.5	–	81.3±7.8
AST (U/L)	47.3±36.5	–	–
MRI-PDFF (%)	19.57±7.51	–	–
Follow-up duration	48 weeks	16 weeks	46 weeks

WC=waist circumference, BMI=body mass index, SBP=systolic blood pressure, DBP=diastolic blood pressure, T2DM=type-2 diabetes, MRI-PDFF=magnetic resonance imaging proton density fat fraction

Risk of bias in the included studies

The summaries of the risk of bias of the 3 RCTs included in this SRM have been elaborated in Supplementary Figure 2a and b. Random sequence generation, allocation concealment, performance bias, detection bias, reporting bias, and attrition bias were low in all three studies (100%). Source of funding, especially by the pharmaceutical industry, authors from the pharmaceutical organizations, and conflict of interests were looked into the "other bias" section. Other bias was judged to be high in all the 3 RCTs (100%).

Effect of survodutide on primary outcomes

Body weight

Survodutide use at doses of 2.4 mg/week [MD (mean difference) −7.79% (95% CI: −11.54, −4.07); $I^2 = 98\%$; $P < 0.001$] and 3.6 mg/week [MD: −9.08% (95% CI: −11.63, −6.54); $I^2 = 96\%$; $P < 0.001$] was associated with a significantly greater dose-dependent percent reduction in body weight from baseline, as compared to placebo [Table 2]. In terms of absolute weight in kg, survodutide use at 2.4 mg/week [MD: −9.14 kg (−13.76, −4.53); $I^2 = 99\%$; $P < 0.001$] and 3.6 mg/week [MD: −10.23 kg (−15.43, −5.04); $I^2 = 99\%$; $P < 0.001$] was associated with significantly greater dose-dependent reduction in body weight from baseline, as compared to placebo [Table 2]. Blüher *et al*.[6] showed that the use of survodutide at doses of 2.4 mg/week [OR: 18.13 (5.70, 58.60); $P < 0.001$] and 3.6 mg/week [OR: 18.33 (5.74, 58.60); $P < 0.01$] was associated with significantly greater chances of having >5% weight loss from baseline, as compared to placebo.

HbA1c

As compared to placebo, survodutide use at doses of 2.4 mg/week was associated with a significant reduction in HbA1c [MD: −0.88% (95% CI: −1.72, −0.05); $I^2 = 99\%$; $P = 0.040$] [Table 2]. The reduction in HbA1c with survodutide 3.6 mg/week was higher as compared to placebo but statistically not significant [MD: −0.95% (95% CI: −2.09, 0.19); $I^2 = 100\%$; $P = 0.101$] [Table 2]. This was primarily due to significant data heterogeneity, as evidenced by an I^2 value of 100%. HbA1c reduction is expected to be minimal in people without diabetes as compared to those with diabetes.

Effect of survodutide on secondary outcomes

Waist circumference

As compared to placebo, survodutide use at doses of 2.4 mg/week [MD: −9.05 cm (−13.06, −5.04); $I^2 = 93\%$; $P < 0.001$] and 3.6 mg/week [MD: −10.78 cm (−13.59, −7.97); $I^2 = 80\%$; $P < 0.001$] was associated with dose-dependent progressively greater reduction of waist circumference from baseline [Table 2].

Systolic and diastolic blood pressure

As compared to placebo, survodutide use at doses of 2.4 mg/week [MD: −5.67 mmHg (−6.81, −4.53); $I^2 = 0\%$; $P < 0.012$] and 4.8 mg/week [MD: −6.17 mmHg (−7.24, −5.09); $I^2 = 0\%$; $P < 0.001$] was associated with a greater reduction of SBP from

Table 2: Impact of survodutide on body weight, glycaemic, and metabolic parameters expressed as change from baseline (CFB) in this systematic review and meta-analysis

Outcome variables (Continuous)	Survodutide dose	No. of RCT included (ref)	No. of participants analyzed		Pooled effect size, MD (95% CI)	I^2 (%)	*P*
			Survodutide arm	Placebo arm			
CFB in body weight (kg)	2.4 mg	3 (5, 6 ,7)	182	190	−9.14 kg [−13.76, −4.53]	99	0.0001
	3.6 mg	2 (6, 7)	110	116	−10.23 kg [−15.43, −5.04]	99	0.0001
Percent CFB in body weight (%)	2.4 mg	2 (6, 7)	109	116	−7.79% [−11.54, −4.07]	98	<0.001
	3.6 mg	2 (6, 7)	110	116	−9.08% [−11.63, −6.54]	96	<0.00001
CFB in WC (cm)	2.4 mg	2 (5, 6)	131	131	−9.05 cm [−13.06, −5.04]	93	<0.00001
	4.8 mg	2 (5, 6)	136	131	−10.78 cm [−13.59, −7.97]	80	<0.00001
CFB in systolic BP (mmHg)	2.4 mg	2 (5, 6)	131	131	−5.67 mmHg [−6.81, −4.53]	0	<0.00001
	4.8 mg	2 (5, 6)	136	131	−6.17 mmHg [−7.24, −5.09]	0	<0.00001
CFB in diastolic BP (mmHg)	2.4 mg	2 (5, 6)	131	131	−2.54 mmHg [−3.23, −1.85]	0	<0.00001
	4.8 mg	2 (5, 6)	136	131	−2.85 mmHg [−3.60, −2.11]	0	<0.00001
CFB in HR (bpm)	2.4 mg	2 (5, 6)	151	151	1.63 bpm [−1.51, 4.78]	0	0.31
	4.8 mg	2 (5, 6)	148	151	3.33 bpm [0.15, 6.51]	0	0.04
CFB in HbA1c (%)	2.4 mg	3 (5, 6, 7)	202	210	−0.88% [−1.72, −0.05]	99	0.04
	3.6 mg	2 (6, 7)	125	136	−0.95% [−2.09, 0.19]	100	0.10
CFB in ALT (U/L)	2.4 mg	2 (5, 6)	151	151	−16.91 U/L [−40.89, 7.08]	94	0.17
Percent CFB in ALT (%)	2.4 mg	2 (5, 6)	151	151	−25.10% [−65.26, 15.06]	97	0.22

ALT=alanine aminotransferase, BP=blood pressure, bpm=beats/min, BW=body weight, CFB=change from baseline, CI=confidence interval, HbA1c=glycated haemoglobin, HR=hear rate, MD=mean difference, RCT=randomized controlled trial, WC=waist circumference, ref=reference number

baseline [Table 2]. As compared to placebo, survodutide use at doses of 2.4 mg/week [MD: −2.54 mmHg (−3.23, −1.85); I^2 = 0%; P < 0.01] and 4.8 mg/week [MD: −2.85 mmHg (−3.60, −2.11); I^2 = 0%; P < 0.001] was associated with a greater reduction of DBP from baseline [Table 2].

Heart rate

As compared to placebo survodutide use at dose of 4.8 mg/week [MD: 3.33 beats per minute (bpm) (0.15, 6.51); I^2 = 0%; P = 0.041] and not 2.4 mg/week [MD: 1.63 bpm (−1.51, 4.78); I^2 = 0%; P = 0.310] was associated with a mild but significant increase in heart rate from baseline [Table 2].

Biochemical and radiologic measures of fatty liver

Survodutide use at 2.4 mg/week was associated with comparable reduction in absolute [MD: −16.91 U/L (−40.89, 7.08); I^2 = 94%; P = 0.171] and percent reduction [MD: −25.10% (−65.26, 15.06); I^2 = 97%; P = 0.223] in alanine aminotransferase (ALT) from baseline, as compared to placebo [Table 2]. Sanyal *et al*.[5] showed that use of survodutide use at doses of 2.4 mg/week [OR: 10.9 (4.81, 24.72); P < 0.001], 4.8 mg/week [OR: 12.80 (5.60, 29.72); P < 0.001], and 6 mg/week [OR: 8.40 (3.74, 18.88); P < 0.001] was associated with significantly higher chances of having > 30% reduction in liver fat content when assessed using magnetic resonance imaging proton density fat fraction (MRI-PDFF), as compared to placebo. Blüher *et al*.[6] showed that survodutide use at doses of 2.4 mg/week [MD: −0.13 (−0.21, −0.05); P = 0.002] and 4.8 mg/week [MD: −0.16 (−0.29, −0.02); P = 0.02] was associated with significantly greater reductions in Fib-4 score (a biochemical measure of fatty liver using age, aspartate amino-transferase, ALT, and platelet count for calculation), as compared to placebo.

Safety

Survodutide use at doses of 2.4 mg/week [odds ratio (OR): 2.93 (95% CI: 1.66, 5.18); I^2 = 0%; P < 0.001] and 3.6 mg/week [OR: 4.61 (95% CI: 2.33, 9.12); I^2 = 0%; P < 0.001] but not 4.8 mg/week [OR: 2.14 (95% CI: 0.80, 5.73); I^2 = 40%; P = 0.132] was associated with a significantly higher occurrence of treatment-emergent AEs (TAEs), as compared to placebo [Table 3]. As compared to placebo, the use of survodutide was associated with similar occurrence of severe adverse events (SAEs) at doses of 2.4 mg/week [OR: 0.55 (95% CI: 0.21, 1.43); I^2 = 0%; P = 0.222], 3.6 mg/week [OR: 0.72 (95% CI: 0.13, 4.06) I^2 = 33%; P = 0.710], and 4.8 mg/week [OR: 1.13 (95% CI: 0.46, 2.76); I^2 = 0%; P = 0.801] [Table 2]. Survodutide use at doses 2.4 mg/week and 3.6 mg/week and 4.8 mg/week was not associated with increased occurrence of headache or depression [Table 3].

Gastrointestinal adverse events

As compared to placebo, the use of survodutide was associated with dose-dependent progressively increased occurrence of nausea at doses of 2.4 mg/week [OR: 6.11 (95% CI: 3.83, 9.73); I^2 = 0%; P < 0.001], 3.6 mg/week [OR: 10.31 (95% CI: 3.86, 27.54]; I^2 = 0%; P < 0.001], and 4.8 mg/week [OR: 13.49 (95% CI: 5.89, 30.89); I^2 = 0%; P < 0.001] [Table 3]. As compared to placebo, the use of survodutide was associated with dose-dependent progressively increased occurrence of vomiting at doses of 2.4 mg/week [OR: 9.64 (95% CI: 4.43, 20.96]; I^2 = 0%; P < 0.001], 3.6 mg/week [OR: 7.41 (95% CI: 4.05, 13.53); I^2 = 0%; P < 0.001], and 4.8 mg/week [OR: 7.19 (95% CI: 4.28, 12.06); I^2 = 0%; P < 0.001] [Table 3]. As compared to placebo, the use of survodutide was not associated with increased occurrence of constipation or cholelithiasis/cholecystitis [Table 3].

Treatment discontinuation due to adverse events

As compared to placebo, treatment discontinuation due to AEs was significantly higher and dose dependent with survodutide at doses of 2.4 mg/week [OR: 5.01 (95% CI: 2.20, 11.42); $I^2 = 33\%$; $P < 0.001$], 3.6 mg/week [OR: 5.63 (95% CI: 2.21, 14.33) $I^2 = 0\%$; $P < 0.01$], and 4.8 mg/week [OR: 9.70 (95% CI: 3.69, 25.52); $I^2 = 0\%$; $P < 0.001$] [Table 3].

The summary of findings of the key outcomes of this SRM has been elaborated in Table 4. All the major outcomes with use of survodutide 2.4 mg/week were supported by moderate to high quality of evidence [Table 4].

Discussion

The development of survodutide, a dual receptor agonist, shows considerable promise in managing obesity and T2DM. This is the first SRM to highlight the glycaemic efficacy and impacts on body weight, blood pressure, and fatty-liver disease parameters, along with tolerability and AE profile of survodutide in the management of different aspects of metabolic syndrome like obesity, T2DM, and MASLD. This SRM highlights the impressive body weight and blood glucose-lowering properties of survodutide.

Use of even the lowest dose of survodutide analyzed in this SRM (2.4 mg/week) was associated with an impressive 9% reduction in body weight along with an impressive 0.9% reduction in HbA1c from baseline over 4–11 months. This reduction is body weight is comparable to that noted with tirzepatide and semaglutide.[15] In a previous SRM, we documented that use of tirzepatide exclusively in people with T2DM was associated with around 8.63 kg mean reduction in body weight along with 0.75% reduction in HbA1c.[16,17] The HbA1c reduction with survodutide 2.4 mg/week is especially impressive in the context that only 48% of the studies patients had T2DM, and also, the baseline HbA1c among people with T2DM analyzed in this SRM ranged from 7–8% only. Hence, a greater quantum of HbA1c reduction can be expected in people with T2DM having higher baseline HbA1c and also with higher doses of survodutide.

Survodutide also has a positive role in MASLD, evidenced by significant reductions in ALT, liver fat content, and FIB-4 score. Moreover, Sanyal *et al*.[5] also demonstrated clinical benefits concerning fibrosis improvement (34% of the participants in the survodutide 6.0 mg group vs. 22% of those in the placebo group) in MASH/MASLD. To date, the therapeutic options

Table 3: The results of safety outcome findings in this systematic review and meta-analysis

Outcome variables	Survodutide dose	No. of RCT included (ref)	No. of participants with outcome/ participants analyzed		Pooled effect size, OR (95% CI)	I^2 (%)	*P*
			Survodutide arm	Placebo arm			
Any TAE	2.4 mg	3 (5, 6, 7)	180/202	157/210	2.93 [1.66, 5.18]	0	0.0002
	3.6 mg	2 (6, 7)	113/126	89/136	4.61 [2.33, 9.12]	0	<0.0001
	4.8 mg	2 (5, 6)	137/149	126/151	2.14 [0.80, 5.73]	40	0.13
Serious AE	2.4 mg	3 (5, 6, 7)	7/202	13/210	0.55 [0.21, 1.43]	0	0.22
	3.6 mg	2 (6, 7)	6/126	8/136	0.72 [0.13, 4.06]	33	0.71
	4.8 mg	2 (5, 6)	11/149	10/151	1.13 [0.46, 2.76]	0	0.80
AE leading to treatment discontinuation	2.4 mg	3 (5, 6, 7)	36/202	8/210	5.01 [2.20, 11.42]	33	0.0001
	3.6 mg	2 (6, 7)	27/126	6/136	5.63 [2.21, 14.33]	0	0.0003
	4.8 mg	2 (5, 6)	37/149	5/151	9.70 [3.69, 25.52]	0	<0.00001
Nausea	2.4 mg	3 (5, 6, 7)	111/202	37/210	6.11 [3.83, 9.73]	0	<0.00001
	3.6 mg	2 (6, 7)	70/126	20/136	7.41 [4.05, 13.53]	0	<0.00001
	4.8 mg	2 (5, 6)	98/149	32/151	7.19 [4.28, 12.06]	0	<0.00001
Vomiting	2.4 mg	3 (5, 6, 7)	56/202	8/210	9.64 [4.43, 20.96]	0	<0.00001
	3.6 mg	2 (6, 7)	36/126	5/136	10.31 [3.86, 27.54]	0	<0.00001
	4.8 mg	2 (5, 6)	60/149	7/151	13.49 [5.89, 30.89]	0	<0.00001
Diarrhoea	3.6 mg	2 (6, 7)	27/126	13/136	2.55 [1.25, 5.22]	0	0.01
	4.8 mg	2 (5, 6)	55/149	25/151	3.23 [1.84, 5.68]	27	<0.0001
Constipation	2.4 mg	2 (5, 6)	32/151	15/151	2.58 [0.78, 8.61]	65	0.12
	4.8 mg	2 (5, 6)	32/149	15/151	2.61 [0.48, 14.09]	82	0.26
Cholelithiasis/ cholecystitis	2.4 mg	2 (5, 7)	1/124	1/133	1.08 [0.11, 10.55]	0	0.95
	4.8 mg	1 (6)	1/72	0/74	3.13 [0.13, 78.0]	–	0.49
Headache	2.4 mg	2 (5, 7)	16/124	13/133	1.29 [0.58, 2.90]	0	0.53
	3.6 mg	1 (7)	2/49	1/59	2.47 [0.22, 28.07]	–	0.47
	4.8 mg	1 (5)	16/72	12/74	1.48 [0.64, 3.39]	–	0.36
Depression	2.4 mg	1 (5)	0/73	2/74	0.20 [0.01, 4.18]	–	0.30
	4.8 mg	1 (5)	0/72	2/74	0.20 [0.01, 4.24]	–	0.30

AE=adverse event, CI=confidence interval, RCT=randomized controlled trial, NA=not applicable, OR=odds ratio, TAE=treatment-emergent adverse event, ref=reference number

Table 4: Summary of findings of the key outcomes of the use of survodutide 2.4 mg/week in this systematic review and meta-analysis

Outcomes	Anticipated absolute effects* (95% CI)		Relative effect (95% CI)	No of participants (studies)	Certainty of the evidence (GRADE)
	Risk with placebo	Risk with survodutide			
Weight reduction with Survodutide 2.4 mg	The mean weight reduction with Survodutide 2.4 mg was −1.43 kg	MD: 9.14 kg lower (13.76 lower to 4.53 lower)	–	372 (3 RCTs)	⊕⊕⊕[a] Moderate
HbA1c reduction with Survodutide 2.4 mg	The mean HbA1c reduction with Survodutide 2.4 mg was −0.01%	MD: 0.88% lower (1.72 lower to 0.05 lower)	–	412 (3 RCTs)	⊕⊕⊕[a] Moderate
TAE with Survodutide 2.4 mg	748 per 1000	897 per 1000 (831 to 939)	OR: 2.93 (1.66 to 5.18)	412 (3 RCTs)	⊕⊕⊕⊕ High
SAE with Survodutide 2.4 mg	62 per 1000	35 per 1000 (14 to 86)	OR: 0.55 (0.21 to 1.43)	412 (3 RCTs)	⊕⊕⊕⊕ High
ADR leading to discontinuation Survodutide 2.4 mg	38 per 1000	166 per 1000 (80 to 311)	OR: 5.01 (2.20 to 11.42)	412 (3 RCTs)	⊕⊕⊕⊕ High
Nausea with Survodutide 2.4 mg	176 per 1000	566 per 1000 (450 to 675)	OR: 6.11 (3.83 to 9.73)	412 (3 RCTs)	⊕⊕⊕⊕ High
Vomiting with Survodutide 2.4 mg	38 per 1000	276 per 1000 (149 to 454)	OR: 9.64 (4.43 to 20.96)	412 (3 RCTs)	⊕⊕⊕⊕ High

CI=confidence interval, MD=mean difference, OR=odds ratio, TAE=treatment-emergent adverse events, SAE=severe adverse events, ADR=adverse drug reaction, HbA1c=glycated haemoglobin. *The risk in the intervention group (and its 95% confidence interval) is based on the assumed risk in the comparison group and the relative effect of the intervention (and its 95% CI).; GRADE Working Group grades of evidence; High certainty: We are very confident that the true effect lies close to that of the estimate of the effect; Moderate certainty: We are moderately confident in the effect estimate: The true effect is likely to be close to the estimate of the effect, but there is a possibility that it is substantially different; Low certainty: Our confidence in the effect estimate is limited: The true effect may be substantially different from the estimate of the effect; Very low certainty: We have very little confidence in the effect estimate: The true effect is likely to be substantially different from the estimate of effect; [a]one point reduced in view of high data heterogeneity (I^2>90%; see Table 1)

for MASLD are limited. As survodutide, along with its GLP-1 receptor agonism, also acts on glucagon receptors expressed on hepatocytes, it is considered to be more effective than GLP-1 receptor agonism alone for treating MASLD. This dual agonist offers extrahepatic benefits of GLP-1 receptor agonism (glucose control, reduced appetite, and weight loss) and direct hepatic effects associated with glucagon receptor agonism (increased energy expenditure, lipolysis, and mobilization of hepatic fat).[18,19]

The anti-obesity and anti-hyperglycaemic outcomes of survodutide 2.4 mg/week compare impressively to other dual agonists for the glucagon-like peptide 1 receptor (GLP-1R) and the glucagon receptor (GCGR) under development like mazdutide and cotadutide. In a recently published SRM, mazdutide use over 12–24 weeks was associated with around 6% reduction in body weight from baseline as compared to placebo.[20] In another SRM, the use of cotadutide was associated with around 3.31 kg additional reduction in body weight as compared to placebo.[21] The side effects are predominantly gastrointestinal and appear to be similar to other GLP1 receptor agonism based therapies.

Limitations of this SRM are that it has primarily analyzed data from different phase-2 RCTs. Hence, the absolute number of patients analyzed for each of the doses of survodutide remained small. Also, maximum analysis was possible with survodutide 2.4 mg/week dose followed by 4.8 mg/week dose. More studies are needed with higher doses of survodutide (3.6–6 mg/week) to document their impact on different aspects of metabolic syndrome. Strengths of this SRM include being the first SRM to highlight the efficacy and safety profile of the twincretin survodutide. Also, our analysis suggests that survodutide 2.4–4.8 mg/week may be the most optimal therapeutic dose in diabesity. It is noteworthy to mention that the current impressive weight loss and blood glucose-lowering results with survodutide have primarily been noted with the lower dose of 2.4 mg/week. Hence, even better anti-obesity and anti-hyperglycaemic outcomes may be expected with the use of higher doses of survodutide in future trials.

As the prevalence of obesity continues to rise globally, the development and utilization of these advanced pharmacotherapies are crucial. They not only offer hope for better individual health outcomes but also have the potential to alleviate the broader societal and economic burdens associated with metabolic syndrome (diabesity and its complications). Survodutide and other dual receptor agonists are revolutionizing the therapeutic landscape, offering new hope and improved outcomes for patients dealing with obesity and its associated complications.

Conclusion

To conclude, it may be said that survodutide demonstrates impressive blood glucose-lowering, weight-lowering, and

fatty-liver reduction properties over short-term clinical use. Future research should focus on long-term outcomes and direct comparisons with other dual receptor agonists to better delineate survodutide's place in the therapeutic landscape of metabolic syndrome.

Acknowledgement

The predefined protocol has been registered in PROSPERO, having a registration number of CRD42024573985.

Author contributions

The study was conceptualized by DD and AKH. Literature search done by AJ, LN and MS. Data analysis was done by DD, AD and AKH. All authors contributed to manuscript preparation.

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Conflicts of interest

There are no conflicts of interest.

Use of artificial intelligence

Artificial intelligence was not used in any form for analysis or writing of this research article.

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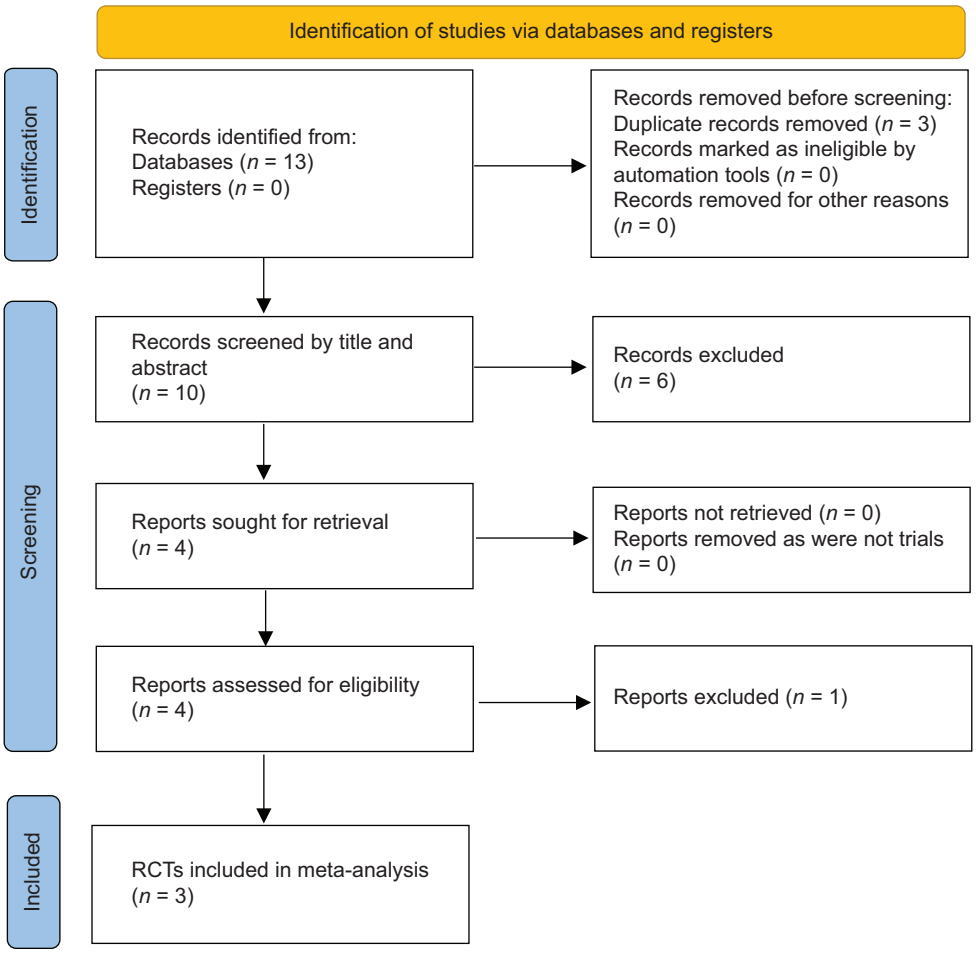
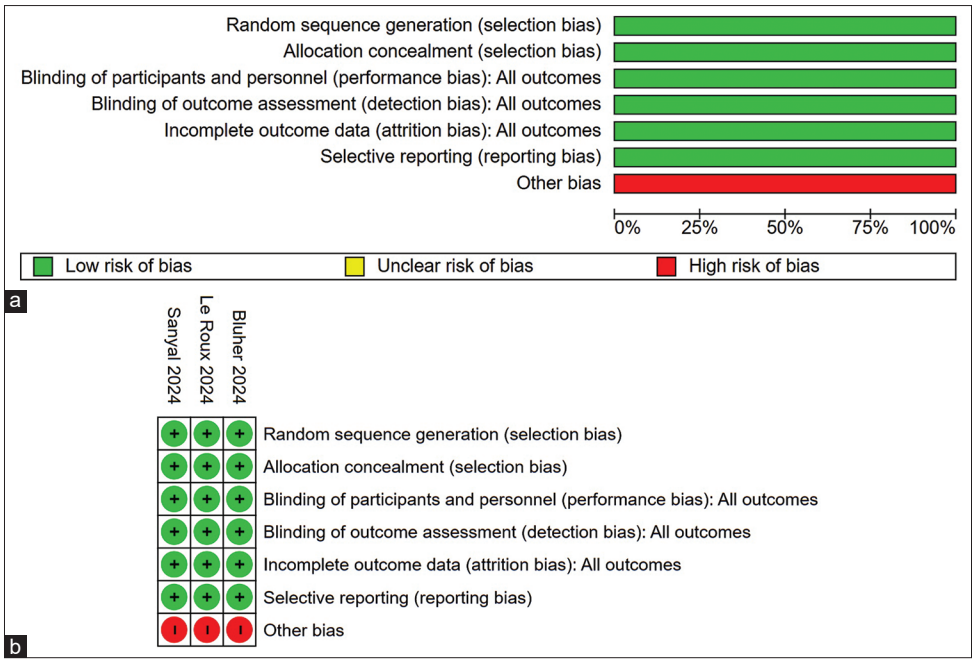


Supplementary Figure 1: Flowchart elaborating on study retrieval and inclusion in the meta-analysis. RCT: Randomized controlled trial



Supplementary Figure 2: (a) Risk of bias graph: review authors' judgements about each risk of bias item presented as percentages across all included studies; (b) risk of bias about each risk of bias item for each included study