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ARTICLE

Dose–response effects on HbA_{1c} and bodyweight reduction of survodutide, a dual glucagon/GLP-1 receptor agonist, compared with placebo and open-label semaglutide in people with type 2 diabetes: a randomised clinical trial

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Abstract

Aims/hypothesis The aim of this study was to assess the dose–response effects of the subcutaneous glucagon receptor/glucagon-like peptide-1 receptor dual agonist survodutide (BI 456906) on HbA_{1c} levels and bodyweight reduction.

Methods This Phase II, multicentre, randomised, double-blind, parallel-group, placebo-controlled study, conducted in clinical research centres, assessed survodutide in participants aged 18–75 years with type 2 diabetes, an HbA_{1c} level of 53–86 mmol/mol (7.0–10.0%) and a BMI of 25–50 kg/m^2 on a background of metformin therapy. Participants were randomised via interactive response technology to receive survodutide (up to 0.3, 0.9, 1.8 or 2.7 mg once weekly [qw; dose group (DG) 1–4, respectively] or 1.2 or 1.8 mg twice weekly [DG 5 and 6, respectively]), placebo or semaglutide (up to 1.0 mg qw). Participants and all those involved in the trial conduct/analysis were blinded; the semaglutide arm was open-label. The primary endpoint was absolute change from baseline in HbA_{1c} after 16 weeks' treatment. The key secondary endpoint was relative change from baseline in bodyweight after 16 weeks' treatment.

Results A total of 413 participants were randomised (DG1, *n*=50; DG2, *n*=50; DG3, *n*=52; DG4, *n*=50; DG5, *n*=51; DG6, *n*=50; semaglutide, *n*=50; placebo, *n*=60). The full analysis set comprised 411 treated participants (DG6, *n*=49; placebo, *n*=59). Adjusted mean (95% CI) HbA_{1c} decreased from baseline (mean ± SD 64.7±9.2 mmol/mol [8.07±0.84%] after 16 weeks' treatment: DG1 (*n*=41), −9.92 mmol/mol (−12.27, −7.56; −0.91% [−1.12, −0.69]); DG2 (*n*=46), −15.95 mmol/mol (−18.27, −13.63; −1.46% [−1.67, −1.25]); DG3 (*n*=36), −18.72 mmol/mol (−21.15, −16.29; −1.71% [−1.94, −1.49]); DG4 (*n*=33), −17.01 mmol/mol (−19.59, −14.43; −1.56% [−1.79, −1.32]); DG5 (*n*=44), −17.84 mmol/mol (−20.18, −15.51; −1.63% [−1.85, −1.42]); DG6 (*n*=36), −18.38 mmol/mol (−20.90, −15.87; −1.68% [−1.91, −1.45]). The mean reduction in HbA_{1c} was similar with low-dose survodutide (DG2: −15.95 mmol/mol [−1.46%]; *n*=46) and semaglutide (−16.07 mmol/mol [−1.47%]; *n*=45). Mean (95% CI) bodyweight decreased dose-dependently up to −8.7% (−10.1, −7.3; DG6, *n*=37); survodutide ≥1.8 mg qw produced greater bodyweight reductions than semaglutide (−5.3% [−6.6, −4.1]; *n*=45). Adverse events (AEs) were reported for 77.8% of survodutide-treated participants (mainly gastrointestinal), 52.5% receiving placebo and 52.0% receiving semaglutide.

Conclusions/interpretation Survodutide reduced HbA_{1c} levels and bodyweight after 16 weeks' treatment in participants with type 2 diabetes. Dose-related gastrointestinal AEs could be mitigated with slower dose escalations.

Trial registration ClinicalTrials.gov NCT04153929 and EudraCT 2019-002390-60.

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Research in context

What is already known about this subject?

- Glucagon-like peptide-1 receptor (GLP-1R) agonists are approved for the treatment of type 2 diabetes and obesity
- Glucagon receptor (GCGR) agonism can increase energy expenditure and lipolysis
- GCGR/GLP-1R dual agonists can reduce bodyweight by reducing food intake and increasing energy expenditure and may be more efficacious than GLP-1R mono-agonists

What is the key question?

- Are multiple rising doses of the GCGR/GLP-1R dual agonist survodutide tolerated and efficacious in participants with type 2 diabetes compared with placebo or open-label semaglutide?

What are the new findings?

- After 16 weeks, survodutide produced greater HbA_{1c} and bodyweight reductions than placebo or semaglutide
- High dose survodutide (≥1.2 mg twice weekly) reduced bodyweight by ≥5% in >50% of participants and by ≥10% in >25% of participants
- The survodutide tolerability profile was as expected for the mechanism of action; gastrointestinal-related adverse events were most frequently reported

How might this impact on clinical practice in the foreseeable future?

- GCGR/GLP-1R dual agonism shows potential for greater therapeutic efficacy than GLP-1R mono-agonism, supporting the development of survodutide for the treatment of type 2 diabetes and obesity

Keywords Bodyweight loss · Dual incretin agonist · Glucagon · Glucagon-like peptide-1 · Obesity · Pharmacotherapy · Semaglutide · Survodutide · Type 2 diabetes

Abbreviations

AE	Adverse event
APRI	Aspartate aminotransferase to platelet ratio
biw	Twice weekly
bpm	Beats per min
DG	Dose group
ELF	Enhanced liver fibrosis
EoT	End of treatment
Fib-4	Fibrosis-4
GCGR	Glucagon receptor
GI	Gastrointestinal
GIPR	Glucose-dependent insulinotropic polypeptide receptor
GLP-1R	Glucagon-like peptide-1 receptor
MCPMod	Multiple comparisons procedure with modelling
MMRM	Mixed model for repeated measures
NAFLD	Non-alcoholic fatty liver disease
NASH	Non-alcoholic steatohepatitis
PGI-S	Patient Global Impression of Severity
qw	Once weekly
SMBG	Self-monitoring of blood glucose
TEAE	Treatment-emergent adverse event
TFEQ-R18 V2	Three-Factor Eating Questionnaire
VAS	Visual analogue scale

Introduction

Glucagon-like peptide-1 receptor (GLP-1R) agonists, such as liraglutide and semaglutide, have been developed for the treatment of both type 2 diabetes and obesity. These therapies have produced placebo-corrected bodyweight decreases of up to 5.4% (liraglutide 3 mg) [1] and 12.4% (semaglutide 2.4 mg), and HbA_{1c} reductions of –12.0 to –17.5 mmol/mol (–1.1 to –1.6%) (liraglutide 1.8 mg and semaglutide 1 mg, respectively) in adults with type 2 diabetes [2, 3]. Apart from the well-characterised gastrointestinal (GI) adverse events (AEs), GLP-1R agonists are generally well tolerated [2–4]. However, dual agonists, such as glucose-dependent insulinotropic polypeptide receptor (GIPR)/GLP-1R and glucagon receptor (GCGR)/GLP-1R dual agonists, have the potential for enhanced therapeutic efficacy and improved tolerability compared with GLP-1R mono-agonists, owing to their multiple mechanisms of action [5, 6].

In addition to the glucose-lowering effects associated with GLP-1R agonism, GCGR agonism, via receptors in the liver, may lead to increased energy expenditure [7, 8]. This effect can be seen at doses that do not activate the sympathetic nervous system, thereby avoiding potentially harmful effects on the cardiovascular system [7]. GCGR signalling also leads to stimulation of hepatic glucose production (via glycogenolysis and gluconeogenesis), stimulation of lipolysis and amino acid breakdown, and suppression of hepatic fat accumulation [9].

The efficacy of GCGR/GLP-1R dual agonism has been demonstrated by oxyntomodulin, an endogenous proglucagon derivative [10]. Oxyntomodulin has been shown to reduce bodyweight and food intake in rodents and humans [11, 12] and to increase energy expenditure in people with obesity [13], via activity at both receptors. However, oxyntomodulin requires frequent dosing owing to its very short half-life; therefore, research into longer acting GCGR/GLP-1R dual agonists is warranted.

Survodutide (BI 456906) is a novel subcutaneous GCGR/GLP-1R dual agonist in development for the treatment of people with type 2 diabetes, obesity and non-alcoholic steatohepatitis (NASH). Addition of a C18 fatty acid into the acylated peptide, as a half-life-extending principle, allows for weekly administration of survodutide [14]. Preclinical studies of survodutide in murine models showed that survodutide simultaneously engages the GLP-1R and GCGR to produce reductions in bodyweight, gastric emptying and energy intake, increasing energy expenditure and improving glucose tolerance [14]. In Phase I studies (ClinicalTrials.gov NCT03175211, NCT03591718), survodutide was generally well tolerated and showed no unexpected safety or tolerability concerns in healthy volunteers and people with overweight/obesity; multiple ascending doses of survodutide over 16 weeks produced mean bodyweight decreases of up to 14.1% (2.4 mg survodutide twice weekly [biw] vs −0.3% with placebo) [15].

Here we report the results of a Phase II study (ClinicalTrials.gov NCT04153929) assessing the effects on HbA_{1c} levels and bodyweight of multiple rising doses of survodutide compared with placebo and open-label weekly semaglutide in participants with type 2 diabetes. The safety and tolerability of survodutide were also assessed. As a proof-of-clinical concept study, this trial aimed to demonstrate that survodutide lowers HbA_{1c} levels and bodyweight and to examine the dose–response relationship in this participant population to inform the design of further studies.

Methods

Study design and participants This study had a multicentre, randomised, double-blind within dose groups (DGs), parallel-group, placebo-controlled design, with six dose-escalation schemes for survodutide (BI 456906, Boehringer Ingelheim Pharma GmbH & Co. KG, Germany; electronic supplementary material [ESM] Fig. 1). The study included an open-label semaglutide group, which served as a reference control to permit comparison of response curves and support assumptions for the design of Phase III studies. Participants were assigned to one of six survodutide DGs (0.3 mg once weekly [qw; DG1], up to 0.9 mg qw [DG2], up to 1.8 mg qw [DG3], up to 2.7 mg qw [DG4], up to 1.2 mg biw [2.4 mg total; DG5] or up to 1.8 mg biw [3.6 mg total; DG6]), placebo or semaglutide (up to 1.0 mg qw). The trial was conducted in clinical research centres, including hospitals and healthcare centres. Each investigational site had a principal investigator who was responsible for the conduct of the study. See the ESM for a list of study sites and investigators.

Eligible participants were aged 18–75 years, had been diagnosed with type 2 diabetes for ≥6 months, had an HbA_{1c} value of 53–86 mmol/mol (7.0–10.0%) and a BMI of 25–50 kg/m^2 at screening and had been treated with a stable dose of metformin of ≥1000 mg/day (immediate or extended release) for ≥3 months before screening. Exclusion criteria are listed in the ESM Methods. The full protocol is available at https://clinicaltrials.gov/ct2/show/NCT04153929.

Randomisation and blinding Randomisation to survodutide or placebo was in a 5:1 ratio within DGs (planned randomisation: survodutide, n=50 per DG; placebo, n=60); it was planned to randomise 50 participants to the semaglutide group. The trial was double-blind within DG1–6. Further details of randomisation and blinding are provided in the ESM Methods.

Endpoints The primary endpoint was the absolute change in HbA_{1c} from baseline after 16 weeks' treatment. Secondary endpoints were related to changes in bodyweight from baseline after 16 weeks' treatment: the relative change in bodyweight (key secondary endpoint), absolute change in bodyweight, absolute change in waist circumference and proportion of participants with a ≥5% and ≥10% decrease in bodyweight. Further efficacy endpoints are described in the ESM Methods.

Pharmacodynamic endpoints were the changes from baseline in exploratory biomarkers related to liver function and fatty liver disease (plasma levels of cytokeratin 18 and Pro-C3 and enhanced liver fibrosis [ELF] score), glucose metabolism (adiponectin and fasting insulin and C-peptide levels) and target receptor engagement (amino acid and glucagon levels). Exploratory NASH-related scores (Fibrosis-4 [Fib-4] score, aspartate aminotransferase/platelet ratio [APRI] and non-alcoholic fatty liver disease [NAFLD] fibrosis score) were assessed as safety-related endpoints.

The attainment of steady state and dose proportionality of survodutide were assessed as pharmacokinetic endpoints.

Procedures After completion of the 16 week treatment period, all participants had an end-of-treatment (EoT) visit (week 17). Participants then entered a 4-week follow-up period and completed the study. Details of treatment administration are provided in the ESM Methods.

HbA_{1c} was assessed at screening, weeks 1, 5, 8, 12 and 16, EoT and follow-up and analysed centrally. Bodyweight was measured at every visit (screening, weeks 1–8, 12 and 16, EoT and follow-up). Waist circumference was measured at screening, weeks 1 and 6 and EoT. Waist circumference was measured at the midpoint between the lowest rib and the iliac crest. Participants were provided with a glucose monitoring device for weekly use at home during the study. Participant-reported outcomes (Three-Factor Eating Questionnaire [TFEQ-R18 V2], Patient Global Impression of Severity [PGI-S] and a hunger visual analogue scale [VAS]) were assessed at weeks 1, 5 and 8 and EoT in a fasted state. Blood sampling for pharmacokinetics was carried out at every visit (weeks 1–8, 12 and 16, EoT and follow-up) and blood sampling for exploratory biomarkers was carried out at weeks 1, 5, 8 and 12, EoT and follow-up. Safety assessments are described in the ESM Methods.

Statistical analyses The trial planned to screen 615 people and randomise 410 participants at 80 study sites in multiple countries. The sample size calculation was based on an assumed maximum effect size for survodutide vs placebo of a 0.5–0.6% change (SD 1%) in HbA_{1c} for the primary endpoint, similar to that seen in a Phase II trial of semaglutide [16]. In this study, HbA_{1c} was measured in per cent. In order to report HbA_{1c} results in mmol/mol, HbA_{1c} (%) was converted to HbA_{1c} (mmol/mol) before analysis using the following equation: HbA_{1c} (mmol/mol) = 10.929 × (HbA_{1c} [%] – 2.15). Full details of the statistical analyses are provided in the ESM Methods.

Study ethics This trial was approved by the relevant institutional review boards, independent ethics committees and competent authorities, according to national and international regulations. The study was conducted in compliance with ethical principles laid down in the Declaration of Helsinki, in accordance with the International Council for Harmonisation Guideline for Good Clinical Practice (ICH GCP). All participants provided written informed consent, according to the ICH GCP and regulatory and legal requirements of the participating countries.

Trial registration This trial was registered at ClinicalTrials.gov (NCT04153929) and EudraCT (2019-002390-60).

Results

Study participants and compliance Participants were recruited between 9 June 2020 and 7 June 2021; the last participant completed the trial on 5 November 2021. In total, 669 people were screened, 413 were randomised and 411 were treated (DGs 1, 2 and 4, *n*=50 each; DG3, *n*=52; DG5, *n*=51; DG6, *n*=49; semaglutide up to 1.0 mg qw, *n*=50; placebo, *n*=59; ESM Fig. 2). Of the 411 participants treated, 80 (19.5%) prematurely discontinued treatment, 53 (12.9%) owing to an AE. Important protocol deviations were reported for 62 of all randomised participants (15.0%), with two-thirds (*n*=41) due to restricted medication use. All 411 participants treated were analysed for efficacy (full analysis set: all randomised participants who received one or more dose of the study drug and had analysable data for one or more efficacy endpoint) and safety (treated set: all randomised participants who received one or more dose of the study drug). Baseline characteristics and demographics were similar between DGs (*N*=411); 83.7% of participants were White and mean ± SD age was 57.3±9.8 years, BMI 33.9±6.0 kg/m^2 and HbA_{1c} 64.7±9.2 mmol/mol (8.1±0.8%) (Table 1). The population included in this study was representative of a large study population of people with type 2 diabetes with respect to age and HbA_{1c} levels [17]; however, most participants were White and had a higher bodyweight, due to the inclusion criteria of this trial.

Primary endpoint Absolute HbA_{1c} (mixed model for repeated measures [MMRM] estimates; primary endpoint) decreased from baseline after 16 weeks' treatment with survodutide, with a markedly weaker treatment effect observed in DG1 (0.3 mg qw) than in the other DGs; no obvious dose-dependent effects were observed between DG2–6 (Fig. 1). The results of the multiple contrast test showed that the contrasts of all predefined dose–response models were significant in terms of non-flat dose–response for the absolute change from baseline in HbA_{1c} after 16 weeks of treatment at a one-sided α=0.025. According to the final multiple comparisons procedure with modelling (MCPMod) averaging model, the predicted dose–response reached a plateau at 1.8 mg qw survodutide, with no increase in treatment effect seen at doses higher than this (ESM Fig. 3a). After 16 weeks' treatment with survodutide, adjusted mean (95% CI) HbA_{1c} levels decreased from a baseline (mean ± SD) of 64.7±9.2 mmol/mol (8.07±0.84%; *N*=411) as follows: DG1 (*n*=41), −9.92 mmol/mol (−12.27, −7.56; −0.91% [−1.12, −0.69]); DG2 (*n*=46), −15.95 mmol/mol (−18.27, −13.63; −1.46% [−1.67, −1.25]); DG3 (*n*=36), −18.72 mmol/mol (−21.15, −16.29; −1.71% [−1.94, −1.49]); DG4 (*n*=33), −17.01 mmol/mol (−19.59, −14.43; −1.56% [−1.79, −1.32]); DG5 (*n*=44), −17.84 mmol/mol (−20.18, −15.51; −1.63% [−1.85, −1.42]); DG6 (*n*=36), −18.38 mmol/mol

Table 1 Participant baseline characteristics and demographics

Characteristic	DG1: Survodutide 0.3 mg qw (*n*=50)	DG2: Survodutide 0.9 mg qw (*n*=50)	DG3: Survodutide 1.8 mg qw (*n*=52)	DG4: Survodutide 2.7 mg qw (*n*=50)	DG5: Survodutide 1.2 mg biw (*n*=51)	DG6: Survodutide 1.8 mg biw (*n*=49)	Semaglutide 1.0 mg qw (*n*=50)	Placebo (*n*=59)	Total (*N*=411)
Sex									
Male	26 (52.0)	28 (56.0)	27 (51.9)	33 (66.0)	27 (52.9)	27 (55.1)	34 (68.0)	31 (52.5)	233 (56.7)
Race and ethnicity									
White	42 (84.0)	44 (88.0)	42 (80.8)	43 (86.0)	41 (80.4)	42 (85.7)	43 (86.0)	47 (79.7)	344 (83.7)
Asian	4 (8.0)	5 (10.0)	8 (15.4)	4 (8.0)	5 (9.8)	3 (6.1)	5 (10.0)	8 (13.6)	42 (10.2)
Black or African American	3 (6.0)	1 (2.0)	2 (3.8)	2 (4.0)	4 (7.8)	3 (6.1)	2 (4.0)	3 (5.1)	20 (4.9)
American Indian or Alaska Native	1 (2.0)	0	0	0	0	1 (2.0)	0	0	2 (0.5)
Native Hawaiian or Other Pacific Islander	0	0	0	0	0	0	0	1 (1.7)	1 (0.2)
Missing	0	0	0	1 (2.0)	1 (2.0)	0	0	0	2 (0.5)
Age, years	56.1±10.2	58.2±9.6	55.3±10.3	59.6±8.5	58.3±8.8	57.7±9.4	55.8±10.5	57.5±10.5	57.3±9.8
HbA_{1c}, mmol/mol	64.9±8.3	62.8±8.8	65.5±9.4	65.9±10.6	65.1±10.3	63.6±7.8	64.3±9.2	65.6±9.2	64.7±9.2
HbA_{1c}, %	8.09±0.76	7.89±0.80	8.14±0.86	8.18±0.97	8.11±0.94	7.97±0.71	8.03±0.82	8.15±0.85	8.07±0.84
Time from type 2 diabetes diagnosis, years	6.1±4.7	7.7±7.3	7.0±5.6	7.9±5.7	8.8±7.1	7.4±5.3	7.9±4.7	7.9±5.6	7.6±5.8
Weight, kg	97.6±19.7	100.1±19.8	95.9±22.8	96.6±22.8	95.0±22.1	98.3±24.4	96.7±20.0	93.0±21.0	96.6±21.6
BMI, kg/m^2	33.8±6.1	34.9±5.2	33.6±5.8	34.0±6.8	33.0±5.0	34.9±7.0	33.4±6.1	33.4±5.9	33.9±6.0
Waist circumference, cm	110.6±12.8	111.5±15.6	107.2±20.0	110.7±16.4	109.0±18.2	115.1±28.7	108.1±13.5	110.4±16.5	110.3±18.2

Data are presented as *n/N* (%) or mean ± SD. Sex and race were self-reported

(−20.90, −15.87; −1.68% [−1.91, −1.45]). The decrease from baseline was significantly greater for all survodutide groups compared with placebo (−1.62 mmol/mol [−3.83, 0.59]; −0.15% [−0.35, 0.05]; *n*=49) at all tested time points ($p<0.0001$ for all DGs and time points except DG1 week 5 [$p=0.0004$]). After 16 weeks' treatment, low-dose survodutide treatment (0.9 mg qw [DG2]) reduced HbA_{1c} to approximately the same extent as semaglutide (*n*=45) up to 1.0 mg qw (−15.95 mmol/mol [−1.46%] vs −16.07 mmol/mol [−1.47%], respectively). Descriptive statistics of the primary endpoint revealed similar results to the MMRM analysis (ESM Fig. 3b); survodutide reduced mean ± SD HbA_{1c} by up to 19.5 mmol/mol (1.88%) in both DG3 (*n*=36) and DG6 (*n*=36) after 16 weeks, with a low dose (DG2, *n*=46) again showing similar results to the reductions seen with semaglutide (*n*=45) up to 1.0 mg qw (−14.9±10.2 mmol/mol [−1.37±0.93%] vs −16.4±9.2 mmol/mol [−1.50±0.84%], respectively).

Secondary endpoints The relative and absolute reduction from baseline in bodyweight was greater with increasing survodutide dose, with bodyweight loss seen in all survodutide DGs in a dose-dependent manner (Fig. 2, ESM Fig. 4). After 16 weeks of treatment, the relative decrease in bodyweight from baseline (key secondary endpoint) for DG2–6 was significantly greater than for placebo ($p<0.001$), with a maximum adjusted mean (95% CI) MMRM estimate for relative bodyweight reduction of −8.7% (−10.1, −7.3; DG6, *n*=37; Fig. 2). Survodutide doses of ≥1.8 mg qw produced greater adjusted mean (95% CI) bodyweight reductions than semaglutide up to 1.0 mg qw (DG3 [*n*=36] vs semaglutide [*n*=45]: −6.6% [−7.9, −5.3] vs –5.3% [−6.6, −4.1]). Results

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