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Survodutide for treatment of obesity: rationale and design of two randomized phase 3 clinical trials (SYNCHRONIZE™-1 and -2)

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Abstract

Objective: The objective of this study was to describe the rationale and design of two multinational phase 3 clinical trials of survodutide, an investigational glucagon and glucagon-like peptide-1 receptor dual agonist for the treatment of obesity with or without type 2 diabetes (T2D; SYNCHRONIZE-1 and -2).

Methods: In these ongoing double-blind trials, participants were randomized to once-weekly subcutaneous injections of survodutide or placebo added to lifestyle modification. Survodutide doses are uptitrated to 3.6 or 6.0 mg, and dose flexibility is permitted. Participants ($n = 726$) in SYNCHRONIZE-1 (NCT06066515) have a baseline BMI ≥ 30 kg/m^2 or ≥27 kg/m^2 with at least one obesity-related complication but without T2D; participants ($n = 755$) in SYNCHRONIZE-2 (NCT06066528) have a baseline BMI ≥ 27 kg/m^2 and T2D. The primary endpoints are percentage change in body weight and proportion of participants achieving ≥5% body weight reduction from baseline to week 76. Secondary endpoints include change in systolic blood pressure and measures of glycemia. A SYNCHRONIZE-1 substudy is evaluating

changes in body composition and liver fat content using magnetic resonance imaging.

Conclusions: These trials are designed to provide robust evaluation of the efficacy, safety, and tolerability of survodutide for the treatment of obesity in the presence or absence of T2D.

INTRODUCTION

Approximately 1 billion people globally are living with obesity [1, 2], a burgeoning pandemic that has created an urgent medical need for safe and effective antiobesity treatments. Obesity is a chronic disease associated with metabolic and inflammatory changes that can lead to the damage of organs and tissue [3]. The reduction of weight, primarily visceral adiposity, is a key component of obesity treatment and can reduce the complications of obesity [4–7]. Factors beyond weight reduction, such as the various mechanisms of pharmacological weight management agents, may significantly impact treatment outcomes. Therefore, different approaches to obesity treatment may be necessary depending on the impact of obesity on health in individual patients.

Clinical guidelines for managing obesity recommend lifestyle modification, including diet and exercise, as the first-line intervention for inducing weight reduction [4–7]. However, because obesity is a neurometabolic disease, sustained weight reduction can be difficult to achieve with lifestyle intervention alone. Antiobesity medications (AOMs) are recognized as an effective therapeutic option in conjunction with a healthy diet and physical activity for obesity management. Currently, only a few medications are licensed for treating obesity, the most effective being compounds that include receptor agonist activity for the glucagon-like peptide-1 (GLP-1) hormone: notably, semaglutide, a GLP-1 receptor mono-agonist, and tirzepatide, a GLP-1/glucose-dependent insulinotropic polypeptide receptor dual agonist [8, 9]. GLP-1 receptor agonists act centrally to modify appetitive drive and signals [10]. They also appear to have beneficial effects on obesity complications and end-organ damage independent of weight reduction [11–13].

Survodutide (BI 456906) is an investigational dual agonist of the glucagon receptor and the GLP-1 receptor being developed for treatment of obesity and its complications, including metabolic dysfunction-associated steatohepatitis (MASH) [14]. Survodutide is a unimolecular acylated peptide with pharmacokinetics that enable once-weekly dosing in humans [15]. Concurrent activation of both the glucagon and GLP-1 signaling pathways is hypothesized to provide additional clinical benefits for managing obesity beyond greater weight reduction, owing to the role of glucagon in reducing energy intake, increasing energy expenditure, and directly reducing hepatic fat content [16]. These effects have been demonstrated in preclinical studies of survodutide [14], with liver antifibrotic and anti-inflammatory clinical benefits observed in a phase 2 trial in people with MASH [17]. In a phase 2 trial in people with body mass index (BMI) ≥ 27 kg/m^2 without type 2 diabetes (T2D), survodutide elicited dose-dependent mean reductions in body weight of up to 18.7% after 46 weeks and concomitant metabolic effects [18].

Based on these promising preliminary results, a comprehensive phase 3 clinical development program is evaluating survodutide for treating obesity. This program includes two multinational trials in people with obesity: one in people without T2D (SYNCHRONIZE-1) and one in people with T2D (SYNCHRONIZE-2). Similar trials are being

Study Importance

What is already known?

- Antiobesity medications (AOMs) in conjunction with lifestyle changes are recommended for the treatment of obesity, but only a few AOMs are available to combat this highly prevalent and heterogenous disease.
- Survodutide is a dual glucagon and glucagon-like peptide-1 (GLP-1) receptor agonist under investigation for the treatment of obesity in people with BMI ≥ 30 kg/m^2 or ≥27 kg/m^2 with at least one obesity-related complication.

What do these studies add?

- These two phase 3 randomized clinical trials (SYNCHRONIZE-1 and -2) are designed to provide robust evidence on the efficacy for body weight reduction and metabolic health improvement, safety, and tolerability of survodutide in multinational cohorts of people with obesity with or without type 2 diabetes.

How might these results change the direction of research or the focus of clinical practice?

- Glucagon receptor agonism has the potential to augment the antiobesity effects of GLP-1 receptor agonists by increasing satiety and, potentially, energy expenditure, among other metabolic effects.
- The results of SYNCHRONIZE-1 and -2 will provide important insights into the efficacy, safety, and tolerability of this glucagon and GLP-1 receptor dual agonist, informing its potential as a treatment for obesity.

conducted in China (SYNCHRONIZE-CN) and Japan (SYNCHRONIZE-JP) to evaluate survodutide in these Asian populations. Furthermore, an ongoing cardiovascular outcomes trial (SYNCHRONIZE-CVOT) is assessing the cardiovascular safety and efficacy of survodutide in people with obesity and increased cardiovascular risk. We describe here the rationale and design of the SYNCHRONIZE-1 and -2 trials, the objectives of which are to evaluate body weight reduction as a primary endpoint and a surrogate endpoint for reduced risk of several obesity complications.

METHODS

Overall trial designs

SYNCHRONIZE-1 and -2 are 76-week, multinational, randomized, double-blind, placebo-controlled phase 3 clinical trials evaluating the efficacy, safety, and tolerability of survodutide as an adjunct to a reduced-calorie diet and increased physical activity to reduce body weight in people with obesity. A SYNCHRONIZE-1 substudy is evaluating changes in body composition and liver fat content by magnetic resonance imaging (MRI).

SYNCHRONIZE-1 (ClinicalTrials.gov: NCT06066515) is being conducted in individuals without concomitant T2D at 118 clinical sites in 14 countries (Australia, Belgium, Canada, China, Finland, Germany, Japan, South Korea, Netherlands, New Zealand, Poland, Sweden, the United Kingdom, and the United States). The MRI substudy involves participants from 45 of these sites across 11 countries, with sites selected by the MRI central reading vendor and participants selected based on their acceptance of the additional assessment and lack of contraindication to MRI.

SYNCHRONIZE-2 (NCT06066528) is being conducted in individuals with concomitant T2D at 143 sites in 19 countries (the 14 aforementioned countries plus Czechia, Denmark, Greece, Hungary, and Spain).

The trial protocols were approved by institutional review boards and/or independent ethics committees at each site, according to national and international regulations. The trials are being conducted according to the Declaration of Helsinki, the International Council for Harmonization (ICH) harmonized tripartite guideline for Good Clinical Practice, and relevant country-specific regulations. All participants provided written informed consent prior to entering the trials.

Participants

The key inclusion and exclusion criteria for these two trials are summarized in Table 1; full criteria are detailed in the online Supporting Information. Briefly, in SYNCHRONIZE-1, participants included male and female individuals aged ≥18 years with either BMI ≥ 30 kg/m^2 or BMI ≥ 27 kg/m^2 and hypertension, dyslipidemia, obstructive sleep apnea, cardiovascular disease, and/or MASH (previously called nonalcoholic steatohepatitis), as well as at least one previous unsuccessful dietary attempt to lose body weight by self-report. Individuals were ineligible if they had a >5% body weight change or treatment with AOMs within the previous 3 months, previous or planned metabolic/bariatric surgery, glycated hemoglobin (HbA1c) ≥ 6.5% (≥48 mmol/mol), a history of type 1 diabetes or T2D, or treatment with a glucose-lowering drug within the previous 3 months. Individuals with obesity that was documented to result from a defined endocrinological (e.g., Cushing syndrome) or a genetic cause (e.g., melanocortin 4 receptor deficiency, leptin deficiency, Prader-Willi syndrome) were also ineligible.

In SYNCHRONIZE-2, eligible individuals were male and female individuals aged ≥18 years with BMI ≥ 27 kg/m^2, at least one previous unsuccessful dietary attempt to lose body weight, a diagnosis of T2D, HbA1c ≥ 6.5% and <10% (≥48 and <86 mmol/mol), and current glucose-lowering treatment with either diet and exercise alone or glucose-lowering drugs (other than insulin, amylin analogues, drugs with GLP-1 receptor agonist activity, and dipeptidyl peptidase 4 inhibitors). Individuals with AOM treatment, a body weight change >5% within the previous 3 months, or a defined endocrinological or genetic cause of obesity were excluded.

Randomization, treatment, and assessments

In both trials, participants were randomized 1:1:1 to receive once-weekly subcutaneous injections of survodutide 3.6 mg, survodutide 6.0 mg, or matching placebo in addition to lifestyle modification (Figure 1). Randomization was implemented in blocks by a computer-generated random sequence using an interactive response system. In SYNCHRONIZE-1, randomization was stratified by participation in the MRI substudy (yes/no); in SYNCHRONIZE-2, it was stratified by HbA1c (<8.5% or ≥8.5%) and background glucose-lowering treatment (physical activity counseling only or monotherapy with metformin, sodium-glucose co-transporter-2 [SGLT2] inhibitor, or sulfonylurea vs. glitazone or combination treatment with no more than three of the following: metformin, SGLT2 inhibitor, sulfonylurea, or glitazone). Survodutide doses are uptitrated to 3.6 or 6.0 mg with a dose-escalation scheme that has been extended compared to the earlier phase 2 trial [18], with some additional flexibility for uptitration included. As described later in this paper, this scheme is designed to reduce the likelihood of gastrointestinal symptoms, which contribute significantly to discontinuation of medications with GLP-1 receptor agonist activity in clinical practice. After escalation, the dose is maintained until the end of treatment (the dose-maintenance period). Participants, investigators, and all other individuals involved in trial conduct are blinded to treatment assignment.

During the dose-escalation period, a structured mitigation strategy that includes flexible dosing is in place to manage gastrointestinal symptoms as needed. If a participant experiences significant gastrointestinal symptoms, the following steps are undertaken in a sequential and additive manner: counseling on dietary changes to reduce symptoms; prescription of medication(s) for symptom control at the investigator's discretion; and temporary interruption of study drug for one to

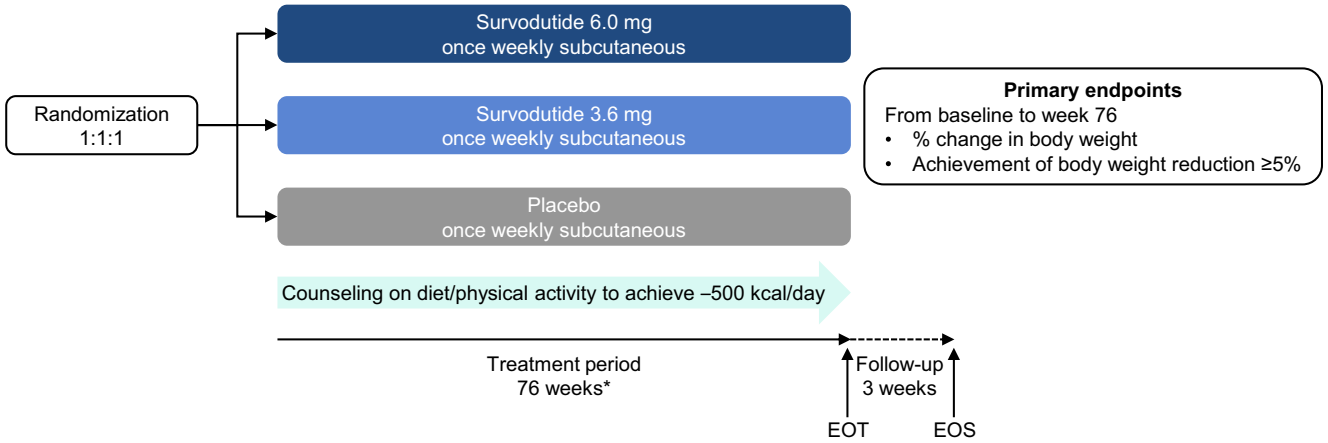

FIGURE 1 Design of the SYNCHRONIZE-1 and -2 trials. These are multinational, randomized, double-blind, placebo-controlled phase 3 clinical trials evaluating the efficacy, safety, and tolerability of survodutide as an adjunct to a reduced-calorie diet and increased physical activity to reduce body weight in people with obesity without T2D (SYNCHRONIZE-1) or with T2D (SYNCHRONIZE-2). *The treatment period includes an initial dose-escalation period that may be extended if one or two re-escalation attempts are needed due to occurrence of gastrointestinal symptoms. Abbreviations: EOS, end of study; EOT, end of treatment; T2D, type 2 diabetes.

TABLE 1 Key eligibility criteria for the SYNCHRONIZE-1 and -2 trials.

	SYNCHRONIZE-1	SYNCHRONIZE-2
Key inclusion criteria		
Adult male or female individuals[a] aged ≥18 y	X	X
BMI ≥ 30 or BMI ≥ 27 kg/m^2 and ≥1 weight-related comorbidity (e.g., hypertension, dyslipidemia, obstructive sleep apnea, CVD, MASH), without T2D	X	N/A
BMI ≥ 27 kg/m^2 with T2D[b]	N/A	X
HbA1c ≥ 6.5% (≥48 mmol/mol) and <10% (<86 mmol/mol)	N/A	X
Current treatment with diet and exercise alone or stable treatment (≥3 mo prior to screening) with metformin, SGLT2i, acarbose, sulfonylurea, or glitazone as single-agent therapy or up to 3 antihyperglycemia medications (i.e., metformin, SGLT2i, acarbose, sulfonylurea, or glitazone)	N/A	X
≥1 self-reported unsuccessful dietary effort to lose weight	X	X
Key exclusion criteria		
Obesity-related		
Self-reported change in body weight >5% within 3 mo prior to screening	X	X
Treatment with medication indicated for obesity within 3 mo prior to screening	X	X
Previous or planned (during trial period) treatment for obesity with surgery or weight loss device or prior surgery of the GI tract that could affect body weight	X	X
Obesity induced by other endocrinological disorders or monogenetic or syndromic forms of obesity	X	X
Diabetes-related		
HbA1c ≥ 6.5% (≥48 mmol/mol)	X	N/A
History of T1D or T2D or treatment with glucose-lowering agent started within 3 mo before screening	X	N/A
Treatment with any medication for T2D not listed in inclusion criteria within 3 mo before screening (i.e., insulin, amylin analogues, GLP-1RA, GLP-1RA/insulin/GIP combinations, and DPP-4i)	N/A	X
New initiation of any other glucose-lowering investigational drug within 3 mo prior to screening	N/A	X
Uncontrolled and potentially unstable diabetic retinopathy or maculopathy, verified by an eye examination within 3 mo before screening or between screening and randomization	N/A	X
Mental health		
Answered "yes" to any of the suicide-related behaviors or non-suicidal self-injurious behavior questions, relating to the past 2 y or during the screening period; suicidal ideation within 3 mo prior to screening or during screening	X	X
Reported a history of psychiatric inpatient hospitalization (due to significant active or unstable major depressive disorder or other severe psychiatric disorder) within the past year before screening, or are	X	X

TABLE 1 (Continued)

	SYNCHRONIZE-1	SYNCHRONIZE-2
not stabilized on psychiatric medication (i.e., change of medication type or dosage adjustment within 8 wk prior to screening), or major depressive symptoms (PHQ-9 score ≥ 15) at screening or during the screening period		
Medical		
Treatment with medications which may cause significant weight change started within 3 mo prior to screening	X	X
Impaired renal function (eGFR < 30 mL/min/1.73 m^2 [CKD-EPI_{cr}]) at screening or requiring dialysis	X	X
Known clinically significant gastric emptying abnormality	X	X
Uncontrolled hypo- or hyperthyroidism	X	X
History of chronic or acute pancreatitis or elevation of serum lipase or amylase >2× ULN	X	X
Uncontrolled hypertension (mean SBP ≥ 160 mm Hg and/or mean DBP ≥ 100 mm Hg) at screening	X	X
Recent evidence (within 3 mo to screening) of acute or unstable CV events and/or acute peripheral vascular event	X	X
Corrected QT (Fridericia) mean interval greater than 500 ms at screening or personal/family history of long QT syndrome	X	X
HF with NYHA functional class IV	X	X
Serum AST and/or ALT elevation ≥3× ULN or total serum bilirubin concentration ≥1.2× ULN	X	X
History or evidence of chronic liver disease other than MASLD	X	X
History of infection with HIV or positive HIV test at screening	X	X
Major surgery within 3 mo prior to screening or planned during the trial	X	X
Personal/family history of medullary thyroid carcinoma or MEN2	X	X
Calcitonin ≥100 pg/mL (≥29.26 pmol/L) at screening	X	X
Confirmed malignancy within 5 y prior to screening (except basal or squamous cell carcinoma of the skin that has been treated successfully)	X	X
History of organ transplantation (except corneal transplants [keratoplasty]) or awaiting organ transplant	X	X
Hematological condition that may interfere with HbA1c measurement	X	X
Women who are pregnant or nursing or who plan to become pregnant during the trial	X	X
Known or suspected hypersensitivity to the IMP or related products	X	X

Abbreviations: ALT, alanine aminotransferase; AST, aspartate aminotransferase; CKD-EPI_{cr}, Chronic Kidney Disease Epidemiology Collaboration creatinine equation; CV, cardiovascular; CVD, cardiovascular disease; DBP, diastolic blood pressure; DPP4i, dipeptidyl peptidase 4 inhibitor; eGFR, estimated glomerular filtration rate; GI, gastrointestinal; GIP, glucose-dependent insulinotropic polypeptide; GLP-1RA, glucagon-like peptide-1 receptor agonist; HbA1c, glycated hemoglobin; HF, heart failure; ICH, International Council for Harmonization; IMP, investigational medicinal product; MASH, metabolic dysfunction-associated steatohepatitis; MASLD, metabolic dysfunction-associated steatotic liver disease; MEN2, multiple endocrine neoplasia syndrome type 2; N/A, not applicable; NYHA, New York Heart Association; PHQ-9, Patient Health Questionnaire-9; SBP, systolic blood pressure; SGLT2i, sodium-glucose co-transporter-2 inhibitor; T1D, type 1 diabetes; T2D, type 2 diabetes; ULN, upper limit of normal.

[a]Women of childbearing potential must be ready and able to use highly effective methods of birth control per ICH guideline M3 (R2) that result in a low failure rate of less than 1% per year when used consistently and correctly.

[b]T2D defined as HbA1c ≥ 6.5% (≥48 mmol/mol) ≥180 days prior to screening.

two doses followed by resumption at the assigned dose. After reaching 3.6 mg and up to 32 weeks post randomization, delay of uptitration or reduction of dose by one level for 2 to 4 weeks is also permitted.

Following randomization, participants are assessed either onsite or remotely every 2 to 4 weeks during dose escalation and every 6 weeks during dose maintenance until the end of treatment (week 76). At randomization and all onsite visits, participants receive advice from a dietitian (or similarly qualified health care professional) on dietary and physical activity changes needed, with caloric intake adapted to achieve an energy deficit of ∼500 kcal/day relative to estimated total energy expenditure at baseline (determined by the Schofield equation [19]).

SYNCHRONIZE-1 has two substudies. In one, a subset of participants will undergo MRI and MRI-proton density fat fraction (MRI-PDFF) assessment to measure body composition and liver fat content, respectively, at baseline and week 76. In the other, a subset of participants administer the injection at different sites to compare the effect of injection-site location on pharmacokinetics, pharmacodynamics, and development of adverse events; investigating the possibility of injection site-dependent differences is a regulatory requirement

for subcutaneously administered peptides and small proteins. These participants are asked to return to the site for additional blood sampling 24 h after the first dose. All other participants inject the study drug into the abdomen without additional sampling.

Endpoints

The primary endpoints in SYNCHRONIZE-1 and -2 are the percentage change in body weight and the percentage of participants achieving ≥5% body weight reduction from randomization to week 76. These endpoints are regulatory requirements [20, 21] based on evidence that weight reduction improves clinical outcomes in people with obesity. The key secondary endpoints (also evaluated as change from randomization to week 76) are achievement of body weight reductions of ≥10%, ≥15%, or ≥20% and absolute change in body weight, HbA1c (SYNCHRONIZE-2 only), waist circumference, systolic blood pressure, Capacity to Resist domain score on the Eating Behavior Patient-Reported Outcome (EB PRO) measure [22], and EB PRO total score. The EB PRO measure consists of 12 items across two domains (Desire to Eat: 6 items; Capacity to Resist: 6 items) and a total eating behavior score. Additional secondary endpoints include various measures of glycemia, plasma lipids, and liver function. Table 2 shows all primary and secondary endpoints for each study.

Additional exploratory endpoints include, but are not limited to, other changes in body weight and BMI (e.g., percentage of participants achieving ≥25% body weight reduction from baseline to week 76 or achieving BMI < 25 kg/m^2 at week 76 or BMI reduction from baseline to week 76 of ≥7 points); change in Distance to Goal (defined as the difference between the baseline BMI and target BMI); glycemic parameters (e.g., HbA1c, homeostatic model assessment for insulin resistance [HOMA-IR] and β-cell function [HOMA-β]); kidney function (e.g., estimated glomerular filtration rate) and urinary albumin: creatinine ratio; liver function (e.g., fibrosis biomarkers, i.e., NAFLD fibrosis score and Fibrosis-4 [FIB-4]); daily energy intake, patient-related outcomes (including 36-Item Short-Form Survey [SF-36] v2 acute and Impact of Weight on Quality of Life [IWQOL]-Lite-Clinical Trials [CT] scores); pharmacokinetics; safety endpoints such as heart rate; and clinical outcomes, including hospitalizations, cardiovascular outcomes, and all-cause mortality. All additional endpoints are shown in the online Supporting Information.

In the SYNCHRONIZE-1 subset of participants undergoing MRI for assessment of body composition and MRI-PDFF liver fat content, additional secondary endpoints include total fat volume, visceral fat volume, lean body volume, subcutaneous fat volume, and liver fat content.

In both trials, safety and tolerability are assessed based on reported adverse events, physical examinations, vital signs, laboratory tests (including, but not limited to, calcitonin, amylase/lipase, kidney function tests, and liver enzymes), and 12-lead electrocardiograms. Adverse events prespecified as being of special interest are potentially severe drug-induced liver injury, thyroid malignancies, C-cell hyperplasia, systemic or serious cutaneous hypersensitivity or anaphylactic

TABLE 2 Primary and secondary endpoints for the SYNCHRONIZE-1 and -2 trials.

Endpoints from baseline to week 76	SYNCHRONIZE-1	SYNCHRONIZE-2
Primary endpoints		
Percentage change in body weight	X	X
Achievement of body weight reduction ≥5%	X	X
Key secondary endpoints		
Body weight reduction ≥10%	X	X
Body weight reduction ≥15%	X	X
Body weight reduction ≥20%	X	X
Absolute change in the following:		
Body weight (kg)	X	X
HbA1c (%)	N/A	X
Waist circumference (cm)	X	X
SBP (mm Hg)	X	X
Capacity to Resist domain score of the EB PRO measure	X	X
EB PRO total score	X	X
Additional secondary endpoints		
Absolute change in the following:		
BMI (kg/m^2)	X	X
DBP (mm Hg)	X	X
HbA1c (mmol/mol)	N/A	X
HbA1c (% and mmol/mol)	X	N/A
Fasting plasma glucose (mg/dL)	X	X
Fasting plasma insulin (mIU/L)	X	X
Total cholesterol (mg/dL)	X	X
HDL cholesterol (mg/dL)	X	X
LDL cholesterol (mg/dL)	X	X
VLDL cholesterol (mg/dL)	X	X
Triglycerides (mg/dL)	X	X
Free fatty acids (mg/dL)	X	X
ALT (U/L)	X	X
AST (U/L)	X	X
Body composition[a] (% and L)		
Total fat volume	X	N/A
Lean body volume	X	N/A
Visceral fat volume	X	N/A

(Continues)

TABLE 2 (Continued)

Endpoints from baseline to week 76	SYNCHRONIZE-1	SYNCHRONIZE-2
Subcutaneous fat volume	X	N/A
Relative change in liver fat content (%)	X	N/A

Abbreviations: ALT, alanine aminotransferase; AST, aspartate aminotransferase; DBP, diastolic blood pressure; EB PRO, Eating Behavior Patient-Reported Outcome; HbA1c, glycated hemoglobin; HDL, high-density lipoprotein; LDL, low-density lipoprotein; N/A, not applicable; SBP, systolic blood pressure; VLDL, very low-density lipoprotein.
[a]Body composition will be assessed by MRI in a subset of ~120 participants.

reactions, acute gallbladder disease, and severe hypoglycemia requiring third-party assistance.

Study oversight and organization

These trials are sponsored by Boehringer Ingelheim (Ingelheim am Rhein, Germany). They are designed and overseen by an executive committee composed of independent experts and sponsor-employed scientists and physicians with relevant clinical and methodological expertise. An independent data-monitoring committee for the program regularly reviews safety data and recommends continuation, modification, or termination of the trials. An independent clinical-event committee prospectively adjudicates major adverse cardiovascular events (including nonfatal myocardial infarction, nonfatal stroke, ischemia-related coronary revascularization, and cardiovascular death), non-cardiovascular death, heart failure events (including hospitalization for heart failure, emergency department visit, urgent care visit, or urgent outpatient heart failure visit), acute pancreatitis, thyroid malignancies and C-cell hyperplasia, and pancreatic cancer.

Statistical analysis

All efficacy and safety analyses will be based on the treated set (all randomized participants who received ≥1 dose of study drug; modified intention-to-treat). In each trial, it was planned to randomize ~600 participants (~200 per treatment group). In SYNCHRONIZE-1, ~25 participants per group would be required to provide 90% power at a two-sided significance level (α) of 0.025 to show superiority of survodutide over placebo for the primary endpoint of percentage change in body weight from baseline to week 76, assuming a placebo effect of 3%, a survodutide effect of 14%, standard deviations of 6% for placebo and 10% for survodutide, and 20% of participants permanently discontinuing treatment. In SYNCHRONIZE-2, ~54 participants per group would be required to provide 90% power at a two-sided α of 0.025 to show superiority of survodutide over placebo for the primary endpoint of percentage change in body weight from baseline to week 76, assuming a placebo effect of 3%, a survodutide effect of 10%, standard deviations of 6% for placebo and 10% for survodutide, and 20% of participants permanently discontinuing treatment. For the other primary endpoint in both trials, the percentage of participants achieving ≥5% body weight reduction (a magnitude associated with improved clinical outcomes), ~66 participants per group would be required to provide 90% power at α of 0.025 to show superiority of survodutide over placebo, assuming a placebo rate of 30% of participants and a survodutide rate of 60% for both trials. Based on these assumptions, a total sample size of 600 participants would have 99% power for both primary endpoints. The sample sizes are primarily defined to support safety, i.e., these sample sizes combined with that of the SYNCHRONIZE-CVOT trial (ClinicalTrials.gov: NCT06077864) enable collection of sufficient safety data to meet the regulatory requirement for ≥4500 patients treated for at least 1 year [20]. For the body composition and injection-site substudies in SYNCHRONIZE-1, we planned to randomize ~120 and ~180 total participants, respectively.

In both trials, the primary efficacy analysis will be conducted using the treatment regimen estimand. This estimand incorporates the effects of any early treatment discontinuation, the use of AOMs prohibited by the protocol, and the effects of a prolonged dose-escalation period. Efficacy analyses will also be conducted using the efficacy estimand. This estimand represents the treatment effect that would be expected if all participants had adhered to the prescribed treatment and did not receive any prohibited antiobesity therapy. It includes the effect of any prolonged dose-escalation phase. Both estimands will be used to evaluate the primary and key secondary endpoints. For the treatment regimen estimand, missing data will be multiple-imputed by a retrieved-dropout approach. Data will be analyzed using ANCOVA, with treatment, region, baseline body weight, and the randomization stratification factors as covariates for the continuous primary endpoint, and logistic regression with fixed categorical effects of region, treatment, and the stratification factors and the fixed continuous effect of baseline body weight for the categorical endpoint. For the efficacy estimand, a mixed model for repeated measures will be used for analysis with fixed categorical factors of treatment at each visit and region at each visit, and continuous factors of baseline at each visit, using visit as repeated measures, participant as random effect, and unstructured covariance matrix to model within-participant measurements. A multiple testing procedure for the primary endpoints and all key secondary endpoints will be implemented using a graphical approach that controls the familywise error rate within each estimand at an overall two-sided α of 5%.

Adverse events will be reported descriptively, with no hypothesis testing planned, and coded using the Medical Dictionary for Regulatory Activities (https://www.meddra.org/).

Trial status

Recruitment of participants for both SYNCHRONIZE-1 and -2 began on November 15, 2023, and is now completed, with 726 and 755 total

participants randomized, respectively. It is estimated that both trials will be completed in early 2026 (i.e., the last visit for the last participant in each trial), with analyzed results available later in 2026.

DISCUSSION

These two 76-week, multinational, randomized, controlled phase 3 clinical trials are designed to assess the efficacy, safety, and tolerability of survodutide for chronic weight management in nearly 1500 people living with obesity with or without T2D. The World Obesity Federation estimated that 988 million people worldwide had obesity (defined as BMI ≥ 30 kg/m^2) in 2020, representing 14% of the global population at the time. It predicted an increase to ∼1.9 billion (24%) by 2035 [1]. More recently, the NCD Risk Factor Collaboration estimated that ∼1.0 billion people worldwide had obesity in 2022 [2]. This high and growing prevalence of obesity highlights the need for effective AOMs to treat obesity and improve health outcomes [4]. Indeed, the frequent coexistence and interrelatedness of the metabolic/inflammatory complications of obesity have led to the recent focus on cardio-kidney-metabolic medicine as a means of enhancing and coordinating clinical care in this area [23]. Additionally, many obesity-related conditions extend beyond the cardio-kidney-metabolic focus, including osteoarthritis, obstructive sleep apnea, and other highly prevalent diseases.

Body weight reduction of as little as 5% has clinical benefits for certain obesity complications, but greater reductions of 10% to 20% may be needed to improve or mitigate the severity of many other common complications [8, 24]. Prior to the highly effective GLP-1 receptor agonist-based compounds (i.e., semaglutide and tirzepatide), AOMs typically elicited <10% weight reduction, and some were associated with serious side effects [8], including neuropsychiatric disorders (i.e., rimonabant) [25], adverse cardiovascular effects (i.e., fenfluramine and sibutramine) [25], and cancer (i.e., lorcaserin) [26]. Semaglutide and tirzepatide can elicit average weight reductions of ∼15% to 20% [27, 28]. Furthermore, in people with obesity, semaglutide significantly reduces risk for major adverse cardiovascular events in those with cardiovascular disease [11] and improves heart failure-related symptoms, physical limitations, and exercise function in those with heart failure with preserved ejection fraction [12, 13], whereas tirzepatide improves apneic episodes in those with obstructive sleep apnea [29]. Some of these benefits appeared to emerge before significant weight reduction, suggesting that they may be at least partially weight-independent.

Glucagon/GLP-1 receptor dual agonism has the potential to provide a new opportunity for treating obesity via several mechanisms [30]. GLP-1 receptor mono-agonists impact body weight by decreasing energy intake via direct central effects on appetitive drives and signals [10]. Glucagon receptor agonism also appears to reduce food intake via mechanisms likely distinct from those activated by GLP-1 receptor agonism [30], although such effects are less clear in humans [31]. Importantly, glucagon receptor signaling may influence the energy-expenditure component of energy-balance regulation [31, 32]. In both preclinical models and early clinical trials, glucagon receptor activation increased total energy expenditure [31, 32]. Thus, glucagon/GLP-1 receptor dual agonism is promising, allowing for a possible compensation for the higher-than-expected decrease in metabolic rate seen with weight reduction efforts [33, 34]. Additionally, lipolytic effects of glucagon receptor agonism in the liver [35] may improve hepatic and systemic metabolism and contribute to the substantial reductions in hepatic inflammation and fibrosis observed in people with MASH receiving survodutide [17]. Similar anti-inflammatory and antifibrotic properties may also prove beneficial for other end-organ complications, including atherosclerotic cardiovascular disease and heart failure.

Because glucagon receptor agonism and GLP-1 receptor agonism have opposing effects on blood glucose levels, the precise balance of these activities in dual agonists is important to avoid worsening glycemic control, particularly early in treatment, before substantial weight reduction has occurred. Survodutide has agonist activity at the human glucagon and GLP-1 receptors in a ratio of ∼1:8 in vitro [14]. In addition to the robust weight-reducing effects seen in the phase 2 clinical trial in people with obesity without T2D [18], a separate phase 2 trial in people with T2D found that glycemic control improved early after initiation of survodutide and improved further over time with increasing weight reduction [36].

Body weight reduction in people with obesity and T2D is typically less than that in those without T2D, for reasons that are not fully understood [37]. The exclusive focus of the SYNCHRONIZE-2 trial on people with T2D will provide important data on the efficacy and safety of survodutide for this patient population. Weight reduction in people with both obesity and T2D can improve glycemic control and reduce the need for glucose-lowering medications, with the potential to achieve sustained HbA1c levels below 6.5% [5].

The SYNCHRONIZE-1 substudy on body composition (using MRI) and liver fat (using MRI-PDFF) will provide further insight into the effects of survodutide on liver fat, as well as adipose and muscle tissue. Although intentional body weight reduction with diet, AOMs, or surgery primarily decreases adipose tissue, ∼25% of the weight lost is fat-free (i.e., lean) mass, about one-half of which is skeletal muscle mass [38–40]. This phenomenon is also seen with AOMs that include GLP-1 receptor agonist activity, raising some concerns regarding the potential for impairing physical function and inducing frailty or sarcopenia, given the magnitude of weight reduction [33], although these concerns are not uniformly shared [40]. Overall, these compounds appear to improve physical function as measured by the SF-36 v2 and IWQOL-Lite-CT patient-reported outcome measures [28, 41]. Both measures are incorporated into the full SYNCHRONIZE-1 and -2 trials. Notably, the SYNCHRONIZE-1 body composition substudy is employing MRI rather than less-informative techniques such as dual energy x-ray absorptiometry, which has been used in many previous body composition analyses of antiobesity therapies.

The most common side effects of AOMs with GLP-1 receptor agonist activity are gastrointestinal disturbances such as nausea, vomiting, diarrhea, and constipation [42, 43]. Although these disturbances are often mild and transient, some individuals are unable to tolerate them and consequently discontinue treatment. How and whether the prevalence of such adverse events differs with glucagon/GLP-1 dual receptor agonists compared to other agents with GLP-1

receptor agonist activity is unclear. Adverse events in phase 1 and 2 trials of survodutide were mainly gastrointestinal in nature and were most frequently reported during dose escalation, which involved a more rapid uptitration (every 2 weeks) [15, 18, 36] than that in trials of similar agents. In SYNCHRONIZE-1 and -2, uptitration is less frequent, with the option to temporarily stop dosing in participants who experience more severe or intolerable gastrointestinal adverse events. This slower and more flexible uptitration approach is designed to mitigate gastrointestinal adverse events and enable more participants to reach and maintain their target doses.

There are several other noteworthy aspects of the SYNCHRONIZE-1 and -2 trial designs. First, the higher dose of 6.0 mg is greater than that in the phase 2 obesity trial (4.8 mg), a dose that reduced mean body weight by 18.7% (placebo-adjusted 16.4%) after 46 weeks, with no indication of a weight plateau at that time point [18]. Thus, it will be of interest to observe the magnitude of weight reduction and impact on tolerability of longer treatment and higher dosage (6.0 mg for 76 weeks) in the SYNCHRONIZE trials. Second, both trials are deploying a recently developed measure of eating behavior designed specifically for people with obesity (i.e., EB PRO) [22]. This measure was developed by academic, clinical, and industry experts in chronic weight management, behavior, clinical psychology, and PRO methodology (including employees of the sponsor) to provide a more comprehensive assessment of patient-reported eating behavior in people with obesity. Most of the commonly used instruments, developed primarily to assess eating disorders, focus on limited aspects of eating behavior such as cravings or are lengthy and somewhat cumbersome to administer. The EB PRO measure was validated using data from the phase 2 trial of survodutide in obesity [22]. As eating behaviors can be strongly affected by AOMs with GLP-1 receptor agonist activity [44–46], documenting such behaviors during treatment may lead to a better understanding of the physiological mechanism(s) driving medication-induced weight reduction. Finally, individuals receiving other GLP-1 receptor agonists or dipeptidyl peptidase 4 inhibitors are excluded from both trials to ensure that participants are not taking other, similar therapies that can independently affect body weight and glycemia.

Limitations of the SYNCHRONIZE-1 and -2 trial designs should also be noted. First, both trials are mainly evaluating body weight-related endpoints up to 76 weeks, limiting the extent to which the long-term clinical outcomes and safety of survodutide treatment can be assessed. The SYNCHRONIZE-CVOT trial is evaluating the cardiovascular safety of survodutide over a longer period in nearly 5000 participants with obesity and increased cardiovascular risk. Second, individuals with uncontrolled hypertension, recent cardiovascular events, or significant mood disorders, including depression, were excluded from SYNCHRONIZE-1 and -2, potentially limiting generalizability.

CONCLUSION

Early clinical studies of unimolecular glucagon/GLP-1 receptor dual agonists suggest that this mechanistic combination can provide added and complementary benefits for treating the disease of obesity via a range of metabolic effects, including lipolysis in the liver and a possible effect on energy expenditure. The results of the SYNCHRONIZE-1 and -2 trials of the glucagon/GLP-1 receptor dual agonist survodutide will provide data on the efficacy, safety, and tolerability of this molecule, informing its potential clinical role for the treatment of obesity and its many complications.

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DATA AVAILABILITY STATEMENT

To ensure independent interpretation of clinical study results and enable authors to fulfill their role and obligations under the International Committee of Medical Journal Editors (ICMJE) criteria, Boehringer Ingelheim grants all external authors access to relevant clinical study data. In adherence with the Boehringer Ingelheim Policy on Transparency and Publication of Clinical Study Data, scientific and medical researchers can request access to clinical study data, typically, 1 year after the approval has been granted by major regulatory authorities or after termination of the development program. Researchers should use the link (https://vivli.org/) to request access to study data and visit the following link for further information: https://www.mystudywindow.com/msw/datasharing.

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SUPPORTING INFORMATION

Additional supporting information can be found online in the Supporting Information section at the end of this article.

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