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ORIGINAL RESEARCH

Survodutide for Obesity in Chinese Adults: Phase 3 Randomized Trial Design and Baseline Characteristics (SYNCHRONIZE™-CN)

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ABSTRACT

***Introduction*:** We aimed to describe the rationale, design, and overall baseline characteristics of the trial evaluating the efficacy, safety, and tolerability of survodutide in Chinese adults with overweight or obesity (SYNCHRONIZE™-CN, NCT06214741).

***Methods*:** In this 76-week, multicenter, randomized, double-blind, placebo-controlled, phase 3 trial, Chinese participants were randomized 1:1:1 to once-weekly subcutaneous survodutide (3.6 mg or 4.8 mg) or placebo plus lifestyle intervention. Participants with either body mass index (BMI) ≥ 28 kg/m^2 or BMI ≥ 24 kg/m^2 and at least one obesity-related complication were eligible. The primary endpoints were the percentage change in body weight and achievement of body weight reduction ≥ 5% from baseline to week 52.

***Results*:** At baseline, participants (N = 306) had a mean age of 36.9 years, body weight 93.9 kg,

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waist circumference 105.6 cm, BMI 33.2 kg/m^2, triglycerides 2.2 mmol/L. 49% were women. 72.9% had at least one obesity-related complication, with metabolic dysfunction-associated steatotic liver disease (48.4%), dyslipidemia (42.2%), hypertension (27.8%), and type 2 diabetes mellitus (16.7%) being the most prevalent, followed by obstructive sleep apnea (4.6%) and cardiovascular diseases (4.2%). In total, 19.6% had prediabetes.

Conclusions: This trial was designed to provide a robust evaluation of efficacy and safety of survodutide for the treatment of obesity or overweight in Chinese adults.

Trial Registration: Clinical Trials.gov identifier, NCT06214741.

Keywords: Glucagon; Glucagon-like peptide-1; Obesity; Randomized controlled trial

Key summary points

Why carry out this study?

The prevalence of obesity and related complications (e.g., hypertension, dyslipidemia, and type 2 diabetes mellitus [T2DM]) is rising rapidly worldwide, especially in China, where lower body mass index cut-offs are adopted

The use of anti-obesity medications is relatively limited in China, with only a few approved agents available by the time when the trial initiated, underscoring the urgent need for effective and well-tolerated pharmacological interventions for this ethnic group

SYNCHRONIZE™-CN was a phase 3 randomized controlled trial which evaluated the efficacy, safety, and tolerability of survodutide, an investigational dual agonist of the glucagon and glucagon-like peptide-1 receptors, in Chinese adults with obesity or overweight and at least one obesity-related complication. Here, the rationale, design and overall baseline characteristics are reported for the first time

What was learned from the study?

Among the 306 participants treated in this trial at baseline, 72.9% had at least one obesity-related complication, with metabolic dysfunction-associated steatotic liver disease (MASLD; 48.4%), dyslipidemia (42.2%), hypertension (27.8%), and T2DM (16.7%) being the most common, and 19.6% of participants had prediabetes. Among the 51 participants with T2DM at baseline, a higher proportion presented with complications, particularly dyslipidemia (70.6%), MASLD (58.8%), hypertension (51.0%), and cardiovascular disease (21.6%)

The overall baseline characteristics of participants is more representative of the severe cases of overweight or obesity in the Chinese population, indicating high disease burden and further highlighting the need for more effective and safer medications

INTRODUCTION

Obesity has evolved into a tricky public health issue worldwide, with its prevalence steadily increasing. According to the World Obesity Atlas, 764 million adults were affected by obesity in 2020, and it is predicted to increase to more than 1 billion by 2030, using standard World Health Organization criteria (body mass index [BMI] ≥ 25 kg/m^2 and ≥ 30 kg/m^2 for overweight and obesity, respectively) [1, 2]. Notably, substantial studies demonstrate that at given BMI levels, East Asian populations exhibit higher body fat percentages than white individuals, as well as increased incidence of cardiovascular risk factors and higher rates of mortality from any cause [3–5]. This results in lower BMI thresholds: ≥ 24 kg/m^2 as overweight and ≥ 28 kg/m^2 as obesity in China [3–5]. On the basis of these standards, 16.4% of Chinese adults have obesity and 34.3% are overweight, indicating a high prevalence in China [6].

Overweight and obesity contributed to deaths related to noncommunicable diseases, with the proportion increasing from 5.7% in 1990 to 11.1% in 2019 [6]. Furthermore, patients with

obesity are prone to diverse obesity-related complications, further exacerbating the disease burden [7]. A real-world study found that, among Chinese adults classified as overweight or obese on the basis of the Chinese criteria, the most common complications were fatty liver disease (49.0% and 81.8%, respectively), followed by prediabetes (30.7% and 36.9%, respectively), dyslipidemia (31.3% and 42.4%, respectively), and diabetes (9.2% and 14.6%, respectively) (American Diabetes Association criteria) [8]. A meta-analysis also revealed that in patients with overweight and obesity in China, the prevalence of nonalcoholic fatty liver disease (NAFLD, now termed metabolic dysfunction-associated steatotic liver disease [MASLD]) was as high as 60% and 63%, respectively [9]. Similarly, another meta-analysis found that 64% of patients diagnosed with MASLD had obesity [10].

Comprehensive obesity treatment goals encompass weight loss as well as the management of obesity-related complications, improvements in multi-organ health, and better long-term outcomes [11–13]. Lifestyle interventions as the first-line treatment typically result in a mean weight loss of 5–8% over a short period, which is often insufficient to achieve the goal. In such circumstances, anti-obesity medications (AOMs) offer a therapeutic option to achieve further weight loss in addition to lifestyle interventions [14]. However, the use of AOMs in China is currently relatively limited, with only a few approved agents available [15]. Traditional medications (e.g., orlistat, phentermine/topiramate, naltrexone/bupropion) result in less than 10% placebo-corrected weight loss and are limited by psychiatric disturbances and cardiotoxicity [16, 17]. Currently, the approved AOMs for obesity treatment in China include glucagon-like peptide-1 (GLP-1) receptor mono-agonists such as beinaglutide, liraglutide, and semaglutide. Additionally, dual agonists such as the GLP-1 receptor and glucose-dependent insulinotropic polypeptide (GIP) receptor agonist tirzepatide, as well as the GLP-1 receptor and glucagon (GCG) receptor agonist mazdutide, have also been licensed [18].

Survodutide, an investigational unimolecular peptide dual agonist of the GCG and GLP-1 receptors, is being evaluated for the treatment of obesity and metabolic dysfunction-associated steatohepatitis (MASH, previously known as nonalcoholic steatohepatitis) [19]. Glucagon is another hormone which plays a role in adipocyte mass regulation and metabolic health, and that recent clinical trial results in phase 2 in people with MASH (NCT04771273) shows improvements in liver health consistent with mechanisms known from preclinical research, such as: direct hepatic effects including increasing gluconeogenesis, glycogenolysis, and lipolysis; reducing oxidative stress, hepatic lipogenesis, steatosis, and hepatic lipid accumulation; and improving mitochondrial function [20, 21]. Additionally, GCG receptor agonism may exert its effects potentially through enhanced hepatic synthesis of fibroblast growth factor 21 and other centrally mediated mechanisms [22, 23]. GLP-1 receptor agonism elicits a glucose lowering effect by stimulating insulin secretion, suppressing GCG release, and promoting weight loss by inhibiting appetite, delaying gastric emptying, and reducing food intake [22, 24]. The GCG and GLP-1 receptor dual agonism indicates additional benefits of survodutide beyond weight loss. In a phase 2 clinical trial (NCT04667377), treatment with survodutide for 46 weeks revealed body weight reductions in a dose-dependent manner and concomitant metabolic benefits, with a mean weight loss of up to 18.7% in adults with BMI ≥ 27 kg/m^2 without type 2 diabetes mellitus (T2DM; according to actual treatment) [25]. Another phase 2 clinical trial (NCT04153929) showed that survodutide with 16-week treatment dose-dependently decreased glycated hemoglobin (HbA_{1c}) in adults with overweight or obesity and T2DM, with a mean HbA_{1c} reduction of up to 1.7% observed with a once-weekly dose of 1.8 mg survodutide [26]. Additionally, in another phase 2 clinical trial (NCT04771273), decreased liver fat content (LFC), along with improvements in MASH and liver fibrosis, was observed after 48 weeks of treatment with survodutide in adults with biopsy-confirmed MASH [27].

Considering the promising results and the current prevalence of obesity in China, a phase 3 clinical trial evaluating survodutide for obesity treatment among Chinese adults was launched. Similar clinical trials include the

global SYNCHRONIZE™–1 (NCT06066515) and SYNCHRONIZE™–2 (NCT06066528) trials, which involved Chinese participants, as well as the SYNCHRONIZE™-JP (NCT06176365) trial in Japan [28]. In SYNCHRONIZE™–1, survodutide achieved significantly greater reductions in body weight than placebo in adults with obesity without diabetes [29]. Here, we aimed to describe the rational, design, and overall baseline characteristics of the phase 3 trial (SYNCHRONIZE™-CN, NCT06214741), which is evaluating the efficacy, safety, and tolerability of survodutide versus placebo in addition to lifestyle intervention in Chinese adults with overweight or obesity and at least one obesity-related complication.

METHODS

Trial Design

SYNCHRONIZE™-CN was a 76-week, multicenter, randomized, double-blind, three-arm, parallel-group, placebo-controlled, superiority, phase 3 trial across 30 sites in China. The trial protocol was approved by the respective Institutional Review Boards or Independent Ethics Committees of all participating centers (leading site: Ethics Review Committee of Peking University People's Hospital; approval number: 2023PHA128-001; full list in Table S1), in accordance with national and international regulations, including the Declaration of Helsinki, the International Council for Harmonization Harmonized Guideline for Good Clinical Practice, and the trial sponsor's standard operating procedures. Written informed consent was signed by all participants before entering the trial.

Participants

Eligible participants were aged ≥ 18 years with a BMI ≥ 28 kg/m^2 or a BMI ≥ 24 kg/m^2 and ≥ 1 obesity-related complication, such as T2DM (defined by HbA_{1c} and fasting plasma glucose [FPG] criteria), MASH, obstructive sleep apnea (OSA), cardiovascular diseases (CVD), dyslipidemia, or hypertension. Oral glucose tolerance testing was not included because of its operational complexity and participant burden in this 76-week trial. HbA_{1c} and FPG were selected as complementary measures reflecting long-term and short-term glycemic status, respectively, while enhancing feasibility and participant compliance. Additionally, participants were required to have ≥ 1 self-reported unsuccessful dietary attempt for weight loss [28]. Key exclusion criteria included > 5% weight loss or the use of AOMs during the 3 months prior to screening, prior or intended bariatric surgery, and previous gastrointestinal (GI) surgery that could interfere with body weight [28]. The key inclusion and exclusion criteria are presented in Table 1, and full criteria are presented in Table S2.

Randomization, Treatments, and Assessments

Eligible participants were randomly assigned in a 1:1:1 ratio to survodutide (3.6 mg or 4.8 mg) or placebo via subcutaneous injection once weekly, along with a reduced-calorie diet and increased physical activity (Fig. 1). Randomization codes were generated using a validated system. Treatment assignments were concealed from all parties including investigators, independent reviewers, participants, and all others responsible for trial conduct, analysis, or related activities. Randomization was stratified by T2DM status (presence or absence) and whether participants underwent magnetic resonance imaging (MRI) assessment. The trial comprised a dose escalation period of approximately 20 weeks, followed by a dose maintenance period of approximately 56 weeks. Dose escalation was performed over 16 to 20 weeks after randomization and consisted of stepwise dose increases every 4 weeks from the starting dose of 0.3 mg and consecutive escalation doses of 0.6, 1.2, 2.4, 3.6, and 4.8 mg. Maintenance dosages of 3.6 mg and 4.8 mg survodutide were continued until the end of the trial.

Planned up-titration and flexibility to interrupt or reduce the dose were implemented in this trial for mitigation of tolerability issues where needed. Dose reductions were possible between weeks 16 and 28 of treatment if

a predefined, structured approach of measures including dietary counseling, symptomatic medications, and a brief treatment pause were not sufficient. If dose reduction was done, a maximum of 28 weeks of the dose escalation period could be permitted to allow for 1 or 2 re-escalation attempts, and accordingly, the maintenance period would be shorter than 56 weeks.

During the dose escalation period, site visits or remote visits were scheduled every 2–4 weeks and during maintenance, they occurred every 4–6 weeks [28]. A safety assessment visit (follow-up or end-of-study) was scheduled 28 days after the last administration of the study drug (i.e., 21 days after week 76 or end-of-treatment visit). At randomization and during scheduled in-clinic visits, all participants received counseling on diet (a recommended daily energy shortfall of about 500 kcal relative to the total energy expenditure estimate) from a nutrition specialist or healthcare professional with equivalent qualification, as well as counselling on physical activity (a recommended weekly total of ≥ 150 min of moderate-intensity physical activity) from a qualified healthcare professional [28]. The trial visit schedule is detailed in Fig. S1.

The trial included two subpopulations stratified by the presence of T2DM and MRI assessment at baseline. The assessments of the T2DM subpopulation aligned with those conducted in the overall trial population. The MRI subpopulation assessed body composition via MRI and LFC via MRI-proton density fat fraction (MRI-PDFF),

Table 1 Key inclusion and exclusion criteria of SYNCHRONIZE™-CN trial

Key inclusion criteria	Aged ≥ 18 years at informed consent signing, men or women
	BMI ≥ 28 kg/m^2 or BMI ≥ 24 kg/m^2 with at least one of the following obesity-related complications at screening: hypertension, dyslipidemia, OSA, CVD, T2DM, and/or MASH
	≥ 1 self-reported unsuccessful dietary attempt for weight loss
Key exclusion criteria	Obesity-related:
	Self-reported body weight change > 5% during the 3 months prior to screening
	Use of any anti-obesity medication during the 3 months prior to screening
	Prior or intended (during the trial) surgical or device-based obesity treatment, or previous GI surgery that may impact body weight
	Presence of obesity attributable to other endocrinopathies, or confirmed monogenetic, or syndromic obesity
	Diabetes-related for participants with T2DM:
	Use of any medication for T2DM (e.g., insulin, GLP-1RA, amylin analogues, GLP-1RA/insulin/GIP combinations, and DPP-4i) during the 3 months prior to screening
	Starting any other investigational glucose-lowering drug during the 3 months before screening
	Presence of diabetic retinopathy or maculopathy which is uncontrolled or potentially unstable, via eye examinations during the 3 months before screening or from screening to randomization
	Mental health-related:
	"Yes" response to any question about suicidal behaviors or nonsuicidal self-injurious in the past 2 years (up to randomization); suicidal ideation during the 3 months before screening through randomization
	Psychiatric inpatient hospital admission during the 12 months prior to screening; lack of stabilization on current psychiatric medications; presence of major depressive symptoms (PHQ-9 score ≥ 15) at screening through randomization

Table 1 continued

Other medical conditions:
Use of any medications that may lead to significant weight change during the 3 months before screening
Renal function impairment (eGFR < 30 mL/min/1.73 m^2 at screening by CKD-EPIcr) or need for dialysis
Established gastric emptying disorder of clinical significance
Poorly controlled hypothyroidism or hyperthyroidism
Prior acute or chronic pancreatitis; lipase or pancreatic amylase > 2 × ULN at screening
Elevated mean SBP (≥ 160 mm Hg) and/or DBP (≥ 100 mm Hg) at screening (poorly controlled hypertension)
Documented acute/unstable CV/peripheral vascular event within 3 months prior to screening
Prolonged QTcF (mean 500 ms) at screening or known long QT syndrome history (self or family)
Heart failure, NYHA class IV
Elevated AST/ALT (≥ 3 × ULN) or total bilirubin (≥ 1.2 × ULN)
Documented or suspected chronic liver disease excluding MASLD
Known HIV infection or positive screening test
Undergone major surgery during the 3 months before screening or scheduled surgery during the trial
MTC or MEN2 history (self or family)
Screening calcitonin ≥ 100 pg/mL (≥ 29.3 pmol/L)
History of malignancy during the 5 years before screening excluding successfully treated basal/squamous cell skin cancer
Prior organ transplant surgery or candidate for organ transplantation
Any hematological abnormality impacting HbA_{1c} measurement
Pregnancy, lactation, or planned pregnancy over the trial
Hypersensitivity (documented or suspected) to the IMP or its associated compounds

BMI body mass index, *OSA* obstructive sleep apnea, *CVD* cardiovascular diseases, *T2DM* type 2 diabetes mellitus, *MASH* metabolic dysfunction-associated steatohepatitis, *GI* gastrointestinal, *GLP-1RA* glucagon-like peptide-1 receptor agonists, *GIP* glucose-dependent insulinotropic polypeptide, *DPP-4i* dipeptidyl peptidase 4 inhibitor, *PHQ-9* Patient Health Questionnaire-9, *eGFR* estimated glomerular filtration rate, *CKD-EPIcr* Chronic Kidney Disease Epidemiology Collaboration creatinine equation, *ULN* upper limit of normal, *SBP* systolic blood pressure, *DBP* diastolic blood pressure, *CV* cardiovascular, *QTcF* Fridericia-corrected heart rate, *NYHA* New York Heart Association, *AST* aspartate aminotransferase, *ALT* alanine aminotransferase, *MASLD* metabolic dysfunction-associated steatotic liver disease, *HIV* human immunodeficiency virus, *MTC* medullary thyroid carcinoma, *MEN2* multiple endocrine neoplasia syndrome type 2, HbA_{1c} glycated hemoglobin, *IMP* investigational medicinal product

respectively. These evaluations were conducted prior to randomization and at subsequent visits at week 52 and 76 to investigate changes in body composition and LFC after survodutide treatment (Fig. S1).

Endpoints

The primary endpoint was the percentage change in body weight from baseline to week 52 and achievement of body weight reduction ≥ 5% from baseline to week 52. Key secondary endpoints included achievement of body weight reduction ≥ 10% and ≥ 15%, as well as the absolute change from baseline to week 52 in waist

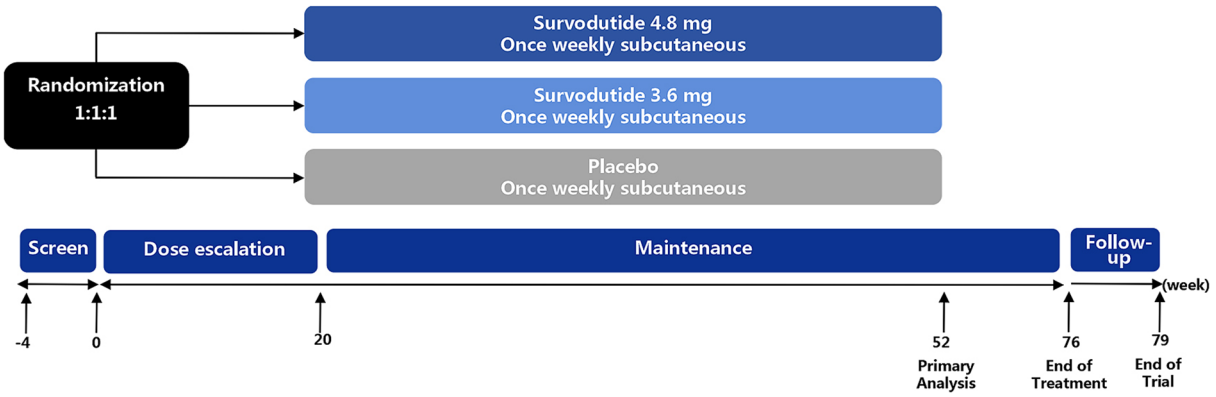

Fig. 1 Design of the SYNCHRONIZE™-CN trial

circumference. The primary and secondary endpoints are presented in Table 2.

Further endpoints included other weight-related changes (e.g., the achievement of body weight reduction ≥ 25%, ≥ 30% from baseline to week 52), T2DM-related changes (e.g., fasting C-peptide), kidney-related changes (e.g., estimated glomerular filtration rate), liver-related changes (e.g., NAFLD fibrosis score), MRI-related changes (e.g., visceral fat volume), and patients-reported outcomes (PROs, e.g., Eating Behavior PRO [EB PRO]) [28]. Details of additional endpoints are provided in Table S3.

Safety was evaluated during the trial through physical examinations, eye examinations, vital signs, 12-lead electrocardiograms, laboratory parameters, mental health assessments, and reporting of adverse events (AEs) [28]. AEs of special interest included potential severe drug-induced liver injury, thyroid malignancies and C cell hyperplasia, systemic and serious cutaneous hypersensitivity or anaphylactic reactions, acute gallbladder disease (e.g., emergent biliary colic, cholecystitis), and severe hypoglycaemia requiring assistance (Level 3) [28].

Study Oversight and Organization

This trial was funded by Boehringer Ingelheim. An executive committee formed by external specialists and sponsor delegates was committed to designing this trial and ensuring its successful execution. An independent data-monitoring committee was responsible for reviewing the trial's status, comprising unblinded safety assessments at predefined time points [28]. It then made recommendations to the sponsor regarding the trial continuation, adjustment, or termination [28]. An independent, external, and blinded clinical event committee was responsible for the prospective adjudication of predefined clinical outcomes: major adverse CV events (including nonfatal MI, nonfatal stroke, ischemia related coronary revascularisation, and CV death), non-CV death, heart failure (HF) events (including hospitalization for HF, emergency room visit, urgent care visit, or urgent outpatient HF visit), acute pancreatitis, thyroid malignancies, and C cell hyperplasia [28].

Statistical Analysis

The treated set, composed of all randomized trial participants who received ≥ 1 dose of survodutide, served as the basis for all efficacy and safety analyses in this trial [28].

Sample size was calculated to demonstrate that survodutide was superior to placebo in two primary endpoints. The assumed effect size and standard deviation (SD) of survodutide and placebo for the two primary endpoints are provided in Table S4. Assuming that 20% of patients permanently discontinued treatment and had the equivalent effect to placebo-treated participants who completed the trial, the treatment effect (SD) for survodutide would be 10.2% (10.2%)

Table 2 Primary and secondary endpoints of SYNCHRONIZE™-CN trial

Primary endpoints	Percentage change in body weight from baseline to week 52
	Achievement of body weight reduction ≥ 5% from baseline to week 52 (yes/no)
Key secondary endpoints	Achievement of body weight reduction ≥ 10% from baseline to week 52 (yes/no)
	Achievement of body weight reduction ≥ 15% from baseline to week 52 (yes/no)
	Absolute change from baseline to week 52 in waist circumstance (cm)
Additional secondary endpoints	Achievement of body weight reduction ≥ 20% from baseline to week 52 (yes/no)
	Absolute change in (from baseline to week 52): body weight (kg), HbA_{1c} (%, mmol/mol), SBP (mmHg), DBP (mmHg), BMI (kg/m^2), FPG (mg/dL), FPI (mIU/L), total cholesterol (mg/dL), HDL-C (mg/dL), LDL-C (mg/dL), VLDL-C (mg/dL), triglycerides (mg/dL), free fatty acids (mg/dL), ALT (U/L), AST(U/L)

HbA_{1c} glycated hemoglobin, *SBP* systolic blood pressure, *DBP* diastolic blood pressure, *BMI* body mass index, *FPG* fasting plasma glucose, *FPI* fasting plasma insulin, *HDL-C* high-density lipoprotein cholesterol, *LDL-C* low-density lipoprotein cholesterol, *VLDL-C* very-low-density lipoprotein cholesterol, *ALT* alanine aminotransferase, *AST* aspartate aminotransferase

after re-calculation. For primary endpoint 1 "Percentage change in body weight from baseline to week 52," based on the assumptions, randomizing 35 participants per arm would provide 90% power to demonstrate superiority for a survodutide dose versus placebo at the two-sided α of 0.025. For primary endpoint 2 "Achievement of body weight reduction ≥ 5% from baseline to week 52," based on the assumptions, randomizing 66 participants per arm would provide 90% power to demonstrate superiority for a survodutide dose versus placebo at the two-sided α of 0.025. These calculations yielded a sample size of 300 participants in total, which provided marginal powers of 99.9% and 98.3% for primary endpoints 1 and 2, respectively, and an overall effective power of 98.2%. The sample size was primarily defined to collect sufficient safety information. The sample size calculations were performed using R software (version 4.2.2).

The main analysis of the primary and key secondary endpoints was performed on the basis of two estimands: the treatment-regimen estimand and the efficacy estimand. The treatment-regimen estimand included the effects of any forbidden anti-obesity treatment, any premature treatment discontinuation, or a prolonged dose escalation phase [28]. The efficacy estimand reflected the expected treatment effect under the assumptions of full treatment adherence, absence of any forbidden anti-obesity treatment, and incorporation of any prolonged dose escalation effects [28]. For the treatment-regimen estimand, missing body weight assessments at week 52 after early treatment discontinuation was imputed under the missingness not at random assumption, leveraging data from retrieved dropouts who discontinued treatment yet stayed in the study with available endpoint measurements. For the continuous primary endpoint, the analysis of covariance model with treatment, T2DM presence at screening, and baseline weight as covariates was fitted to the imputed data, along with completer and retrieved dropouts. The binary primary endpoint, ≥ 5% weight loss from baseline to week 52, was then

be obtained from the imputed data set of the continuous body weight value at week 52. The comparison between survodutide and placebo treatment for this binary primary endpoint was evaluated using the odds ratio from a logistic regression model, adjusting for T2DM presence at screening and baseline weight. For the efficacy estimand, the continuous primary endpoint was analyzed through the mixed model for repeated measures (MMRM). Categorical factors (treatment per visit and baseline T2DM status) and a continuous covariate (baseline weight per visit) was incorporated in the model, where participant served as a random effect, visit was a repeated factor, and within-participant observations were modeled with an unstructured covariance matrix [28]. Missing data were processed in an implicit way through MMRM. Similarly, a multiple imputation approach based on missingness at random and a logistic regression was utilized to compare survodutide and placebo for the binary primary endpoint described above. For the primary and key secondary endpoints, a graphical approach, controlling the familywise error rate at the two-sided α of 5% in the strong sense, was applied to the multiple testing procedure [28]. More details about the graphical approach are presented in Table S5 and Fig. S2.

Baseline characteristics and safety analyses were summarized using descriptive statistics, without hypothesis testing.

RESULTS

Recruitment for this trial began in February 2024. Study follow-up has now been completed, and data analysis is ongoing, with study results expected later.

A total of 306 participants were treated in this trial. At baseline, the mean age was 36.9 years, with 49% being women. The mean body weight was 93.9 kg, with a mean waist circumference of 105.6 cm and a waist-to-height ratio of 0.6. The mean BMI was 33.2 kg/m^2, and almost all participants (93.8%) had a baseline BMI of at least 28 kg/m^2. The mean systolic blood pressure, diastolic blood pressure, and heart rate were 121.1 mmHg, 82.7 mmHg, and 70.8 bpm, respectively. The mean total cholesterol, high-density lipoprotein cholesterol, low-density lipoprotein cholesterol (LDL-C), and triglycerides were 4.9 mmol/L, 1.1 mmol/L, 2.9 mmol/L, and 2.2 mmol/L, respectively. The mean HbA_{1c}, FPG, and fasting plasma insulin were 5.6%, 5.6 mmol/L, and 13.7 mIU/L, respectively. 60 (19.6%) participants had prediabetes, and 16.7% had T2DM. Most participants (72.9%) had at least one obesity-related complication. The most prevalent complications were MASLD (48.4%) (including 5.6% with MASH), followed by dyslipidemia (42.2%), hypertension (27.8%), T2DM (16.7%), OSA (4.6%), and CVD (4.2%). Antihypertension drugs were the most frequently prescribed (16.3%), followed by glucose lowering drugs (8.2%) and lipid-lowering drugs (7.8%).

Among 51 (16.7%) participants in the T2DM subpopulation at baseline, 94.1% had at least two obesity-related complications, with dyslipidemia (70.6%), MASLD (58.8%) (including 7.8% with MASH), hypertension (51.0%), and CVD (21.6%) being the most prevalent complications (besides T2DM), followed by OSA (3.9%).

Among 255 (83.3%) participants in the non-T2DM subpopulation at baseline, 52 (20.4%) participants had prediabetes, and similar characteristics were observed with the overall population (Table 3).

DISCUSSION

SYNCHRONIZE™-CN was a 76-week, multicenter, randomized, double-blind phase 3 clinical trial designed to assess the efficacy, safety, and tolerability of survodutide, a GCG receptor and GLP-1 receptor dual agonist, among more than 300 Chinese adults with obesity or overweight and at least one obesity-related complication. Obesity, a chronic and progressive disease, now represents an urgent public health concern both in China and globally [8].

The development of mono-, dual-, and multi-agonists targeting GLP-1, GIP, GCG, and amylin receptors has transformed obesity treatment [30]. Several emerging agents include GLP-1 receptor mono-agonists (e.g., ecnoglutide, orforglipron), GLP-1 and amylin receptor dual agonist

(e.g., CagriSema, amycretin), GLP-1 and GIP receptor dual agonists (e.g., HRS9531), GLP-1 and GCG receptor dual agonists (e.g., survodutide, pemvidutide), and GLP-1, GIP, and GCG receptor triple agonists (e.g., retatrutide) [13, 23, 30, 31]. Among investigational GLP-1 and GCG receptor dual agonists, only survodutide has completed the phase 3 trial implemented in multiple countries.

The SYNCHRONIZE™-CN trial design and BMI cut-offs based on Chinese criteria were consistent with other phase 3 studies conducted in the Chinese population with overweight or obesity for GLP-1 dual agonists, such as the SURMOUNT-CN trial and GLORY-1 trial [32, 33]. However, this trial had distinctive inclusion criteria compared with the other trials. Both the SURMOUNT-CN and GLORY-1 trials excluded those with overweight and T2DM [32, 33]. The inclusion of obesity-related complications varied across trials. The SYNCHRONIZE™-CN trial included participants with T2DM but does not consider prediabetes or simple fat deposition in the liver (i.e., MASLD) as an obesity-related complication [34, 35]. These distinctions make SYNCHRONIZE™-CN trial more representative of the severe cases of overweight or obesity in the Chinese population.

The baseline characteristics in this trial, including demographics, anthropometrics, and nonglycemic laboratory parameters, were generally similar across the overall population, T2DM, and non-T2DM subpopulations. However, the T2DM subpopulation had a higher proportion of participants with complications, especially dyslipidemia, hypertension, MASLD, and CVD. Owing to the different inclusion criteria described above, the baseline data exhibited some differences from the SURMOUNT-CN and GLORY-1 trials [32, 33]. Specifically, a higher proportion of participants with baseline BMI ≥ 28 kg/m^2 was observed in this trial than in the GLORY-1 trial. The mean baseline LDL-C was similar to that of the SURMOUNT-CN trial but slightly lower than in the GLORY-1 trial. Additionally, 16.7% of participants in this trial had T2DM and had higher baseline HbA_{1c} levels, whereas the other two trials excluded participants with T2DM and reported a mean baseline HbA_{1c} within the normal range. Furthermore, MASH was present in 5.6% of participants in this trial, reflecting a population with more severe metabolic dysfunction and a higher unmet need for weight loss in Chinese adults [32, 33].

The SYNCHRONIZE™-CN was a 76-week trial with the primary endpoint analysis conducted at 52 weeks. Compared with the SURMOUNT-CN trial, where the primary and key secondary endpoints were assessed at week 52, and the GLORY-1 trial, which lasted 48 weeks with primary endpoints at week 32, this trial with survodutide allowed for a longer-term efficacy and safety assessment [32, 33]. This design also facilitated a better understanding of 1-year efficacy, making it more suitable for clinical practice in China. Two estimands were generally adopted to evaluate efficacy in obesity-related research, namely the treatment-regimen estimand and the efficacy estimand [28]. In the SURMOUNT-CN trial, tirzepatide 10/15 mg achieved mean weight loss of 13.6%/17.5% (treatment-regimen estimand) [32]; while mazdutide 4.0/6.0 mg in the GLORY-1 trial achieved 10.1%/12.6% (treatment-policy estimand) [33]. Survodutide in this trial is expected to provide promising evidence on weight loss in Chinese participants, supported by positive results from the phase 2 clinical trial, which demonstrated weight reduction of up to 14.9% over a 46-week treatment (treatment-regimen estimand) [25]. Additionally, important aspects of obesity-related influence in quality of life such as the capacity to resist food cravings were evaluated through the EB PRO to document changes mediated by survodutide. A subpopulation of trial participants underwent MRI assessment to evaluate body composition and LFC, providing critical insights into treatment effects on fat distribution and liver health.

MASH, a typical complication associated with obesity, potentially leads to liver fibrosis and cirrhosis [36, 37]. Survodutide, with its direct-hepatic effects related to GCG receptor agonism [20, 38, 39], had shown promising results in a phase 2 clinical trial (NCT04771273) for adults with MASH and F1-F3 fibrosis confirmed by biopsy [27]. Treatment with 4.8 mg or 6.0 mg of survodutide for 48 weeks led to MASH improvement without fibrosis worsening in 62% and 43% of participants, respectively [27]. Reductions in LFC and improvements in fibrosis were

Table 3 Baseline characteristics

	Overall (*N* = 306)	**T2DM subpopulation (*N* = 51)**	**Non-T2DM subpopulation (*N* = 255)**
Age, years, mean (SD)	36.9 (9.3)	44.6 (9.5)	35.4 (8.5)
Sex, *n* (%)	306 (100)	51 (100)	255 (100)
Women	150 (49.0)	28 (54.9)	122 (47.8)
Men	156 (51.0)	23 (45.1)	133 (52.2)
Body weight, kg, mean (SD)	93.9 (20.5)	91.1 (21.1)	94.5 (20.4)
BMI, kg/m^2, mean (SD)	33.2 (5.5)	32.3 (6.1)	33.4 (5.4)
BMI category, *n* (%)	306 (100)	51 (100)	255 (100)
≥ 24 to < 28 kg/m^2	19 (6.2)	12 (23.5)	7 (2.7)
≥ 28 to < 30 kg/m^2	79 (25.8)	12 (23.5)	67 (26.3)
≥ 30 kg/m^2	208 (68.0)	27 (52.9)	181 (71.0)
Waist circumference, cm, mean (SD)	105.6 (14.1)	104.4 (13.8)	105.9 (14.2)
Waist-to-height ratio, cm/cm, mean (SD)	0.6 (0.1)	0.6 (0.1)	0.6 (0.1)
SBP, mmHg, mean (SD)	121.1 (12.4)	123.7 (12.7)	120.6 (12.3)
DBP, mmHg, mean (SD)	82.7 (8.0)	83.9 (7.1)	82.5 (8.2)
Heart rate, bpm, mean (SD)	70.8 (10.0)	72.2 (10.7)	70.5 (9.8)
Glycemic status, *n* (%)	306 (100)	51 (100)	255 (100)
Normoglycemia	207 (67.6)	9 (17.6)	198 (77.6)
Prediabetes	60 (19.6)	8 (15.7)	52 (20.4)
Glycemic and insulin profile, mean (SD)			
HbA_{1c}, %	5.6 (0.7)	6.7 (1.0)	5.4 (0.4)
HbA_{1c}, mmol/mol	37.9 (8.0)	49.8 (10.8)	35.6 (4.5)
FPG, mmol/L	5.6 (1.0)	7.0 (1.4)	5.3 (0.5)
Fasting plasma insulin, mIU/L	13.7 (10.2)	12.2 (9.4)	14.0 (10.4)
Lipids profile, mean (SD)			
Total cholesterol, mmol/L	4.9 (0.9)	4.9 (1.2)	4.9 (0.9)
HDL-C, mmol/L	1.1 (0.3)	1.1 (0.3)	1.1 (0.2)
LDL-C, mmol/L	2.9 (0.8)	2.8 (1.0)	2.9 (0.8)
Triglycerides, mmol/L	2.2 (2.8)	2.2 (1.5)	2.2 (3.0)
Complications[a], *n* (%)	306 (100)	51 (100)	255 (100)
Dyslipidemia	129 (42.2)	36 (70.6)	93 (36.5)

Table 3 continued

	Overall ($N=306$)	T2DM subpopulation ($N=51$)	Non-T2DM subpopulation ($N=255$)
Hypertension	85 (27.8)	26 (51.0)	59 (23.1)
T2DM	51 (16.7)	51 (100)	0 (0)
MASLD	148 (48.4)	30 (58.8)	118 (46.3)
MASH	17 (5.6)	4 (7.8)	13 (5.1)
OSA	14 (4.6)	2 (3.9)	12 (4.7)
CVD*	13 (4.2)	11 (21.6)	2 (0.8)
Number of complications, *n* (%)	306 (100)	51 (100)	255 (100)
0	83 (27.1)	0 (0.0)	83 (32.5)
1	78 (25.5)	4 (7.8)	74 (29.0)
2	74 (24.2)	8 (15.7)	66 (25.9)
≥ 3	71 (23.2)	39 (76.5)	32 (12.6)
Baseline medications, *n* (%)	306 (100)	51 (100)	255 (100)
Anti-hypertension drugs	50 (16.3)	18 (35.3)	32 (12.5)
Glucose-lowering drugs	25 (8.2)	25 (49.0)	0 (0)
Metformin	23 (7.5)	23 (45.1)	/
SGLT2 inhibitors	9 (2.9)	9 (17.6)	/
Lipid-lowering drugs	24 (7.8)	11 (21.6)	13 (5.1)
Other CVD drugs	1 (0.3)	1 (2.0)	0 (0)

[a]The complications were assessed at screening; *CVD included atrial fibrillation, coronary artery disease, ischaemic stroke, peripheral vascular disorder

T2DM type 2 diabetes mellitus, *SD* standard deviation, *BMI* body mass index, *SBP* systolic blood pressure, *DBP* diastolic blood pressure, HbA_{1c} glycated hemoglobin, *FPG* fasting plasma glucose, *HDL-C* high-density lipoprotein cholesterol, *LDL-C* low-density lipoprotein cholesterol, *MASLD* metabolic dysfunction-associated steatotic liver disease, *MASH* metabolic dysfunction-associated steatohepatitis, *OSA* obstructive sleep apnea, *CVD* cardiovascular disease, *SGLT2* sodium-glucose cotransporter-2 inhibitor

also demonstrated [27]. The promising results highlighted the potential of survodutide, with two ongoing phase 3 clinical trials, LIVERAGE™ (NCT06632444) for MASH and F2-F3 fibrosis, and LIVERAGE™-Cirrhosis (NCT06632457) for compensated MASH cirrhosis.

GI disorders, including nausea, diarrhea, vomiting, constipation, and bloating, represent the most prevalent AEs linked to GLP-1 receptor agonists [28]. These events are associated with the centrally mediated effects and delayed gastric emptying of GLP-1 receptor agonism [40]. These GI-related AEs are transient, mild-to-moderate in intensity, and typically resolve with time, mainly occurring during the rapid dose escalation period [41, 42]. Previous clinical studies and meta-analyses of survodutide had demonstrated a higher incidence of GI-related AEs (e.g., nausea and vomiting) compared with placebo, in line with the established safety profile of GLP-1

receptor agonists [25–27, 43]. Similarly, survodutide is expected to cause GI-related AEs in this trial, with a higher incidence compared with placebo. A Multidisciplinary Expert Consensus suggests that an optimized dose escalation schedule, considering individualized administration, is effective in reducing the occurrence of GI-related AEs and mitigate their severity [44]. In this trial, a slower and more flexible dose escalation schedule was designed compared with the previous phase 2 trial [25] in obesity, allowing an extended dose escalation period with down-titration and subsequent re-escalation where needed. These approaches aimed to mitigate GI-related AEs, reduce discontinuation rates, and allowed more participants to achieve and sustain planed doses [28].

In addition to GI-related events, other safety aspects relevant to the GLP 1 receptor agonist class include acute pancreatitis, acute gallbladder disease, dehydration-related renal impairment secondary to severe GI symptoms, and increases in heart rate, which are generally temporary, easy to monitor, and manageable in clinical trials [45, 46]. Risk mitigation strategies had been incorporated into the study design to minimize potential safety concerns. For example, participants with a history of pancreatitis or clinically relevant pancreatic abnormalities were excluded to mitigate the risk of acute pancreatitis. Additionally, key laboratory parameters and clinical conditions were closely monitored throughout the study to enable early detection of AEs, including renal dysfunction related to dehydration, hepatic effects, such as potential drug-induced liver injury, and gallbladder-related events, which may also be associated with rapid weight loss. The overall risk of survodutide is considered low relative to the expected benefits. These potential safety concerns were carefully monitored and comprehensively evaluated, with detailed safety findings to be reported separately.

This trial was a robust investigation designed to evaluate efficacy, safety, and tolerability of survodutide in adults with overweight or obesity in China. The trial examined whether individuals could benefit from survodutide at lower BMI thresholds. Including participants with T2DM made the trial more reflective of those in medical need in China. Participants using weight-altering or glycemic control medications (i.e., insulin, amylin analogues, GLP-1 receptor agonists, GLP-1receptor agonist/insulin/GIP combinations, and dipeptidyl peptidase 4 inhibitor [DPP-4i]) were excluded to minimize confounding effects. Eating behavior influenced by survodutide were comprehensively assessed using the validated EB PRO tool [47]. The effects of survodutide on LFC and body composition were evaluated in a subpopulation. Sample size goal (>300) was achieved, ensuring sufficient to evaluate efficacy and safety outcomes. The primary and key secondary endpoints would be assessed simultaneously through the treatment-regimen estimand and efficacy estimand with rigorous missing data handling. These stringent designs laid the foundation to obtain credible and reliable trial results, ultimately yielding valuable insights. The data from SYNCHRONIZE™-CN together with data from global trials (SYNCHRONIZE™–1, SYNCHRONIZE™–2, and SYNCHRONIZE™-CVOT) including Chinese participants, will further strengthen the evidence for survodutide in overweight or obesity, particularly in China, of which, the SYNCHRONIZE™–1 trial had demonstrated that survodutide elicited significantly greater reductions in body weight than placebo in adults with obesity without diabetes in a global population involving Chinese participants [29]. These findings indicate that survodutide can be expected to yield consistent favorable efficacy among Chinese participants with overweight or obesity in the SYNCHRONIZE™-CN trial.

This trial has some limitations. Obesity is widely recognized as a complex and relapsing chronic disease, which necessitates long term management [7, 8]. Given its chronic and relapsing nature, even long-duration clinical trials provide only a limited perspective on the long-term effectiveness and safety of treatment in routine clinical practice. Participants with some diseases (e.g., uncontrolled hypertension) were excluded. These exclusions may potentially limit the generalizability of the trial. Meanwhile, a small sample size was noted in the T2DM subpopulation, which may introduce bias and require cautious interpretation of the subsequent analysis results. Most participants included in the trial

had a BMI ≥ 28 kg/m^2, and 72.9% had at least one obesity-related complication. Therefore, the study population may represent individuals with more severe obesity or metabolic abnormalities, with limited generalizability to those with mild obesity or the broader overweight populations.

CONCLUSIONS

The SYNCHRONIZE™-CN trial was designed to provide a robust evaluation of the efficacy, safety, and tolerability of survodutide for the treatment of adults with obesity or overweight and at least one obesity-related complication in China, which was anticipated to generate strong evidence supporting survodutide as a valuable treatment option.

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Data Availability. Boehringer Ingelheim supports independent interpretation of clinical study results and helps all authors to obtain clinical study data related to publication development. All authors will meet ICMJE authorship obligations. In line with the company's transparency and data publication policy, researchers in the scientific and medical communities may receive clinical study data. Typically, this will be permitted 1 year after a major regulatory authority has approved the therapy or after the development program has been terminated. Data access requests should be submitted via the https://vivli.org/ link. Further information is available at www.mystudywindow.com/msw/datasharing.

Declarations

Conflict of Interest. Boehringer Ingelheim was involved in the study design, data collection, data analysis and preparation of the manuscript. Yinan Zhu, Liying Jin, Isabel M. Kloer are employees of Boehringer Ingelheim. Linong Ji reports receiving consulting or lecture fees from Eli Lilly, Novo Nordisk, Merck, Bayer, Sanofi-Aventis, MSD, AstraZeneca, Boehinger Ingelheim, Abbott, Fosun Pharma, Innovent Biologics, Gan & Lee Pharmaceuticals, Sinocare, Sibionics. Liming Chen reports receiving research funding from AstraZeneca, Boehringer-Ingelheim, Eli Lilly, Gan & Lee, Hansoh, Hengrui, and Novo Nordisk. Zhifeng Cheng, Yibing Lu, Yan Yang, and Fangming Fu declare no conflicts of interest.

Ethical Statement. The trial protocol was approved by the respective Institutional Review Boards or Independent Ethics Committees of all participating centers (leading site: Ethics Review

Committee of Peking University People's Hospital; approval number: 2023PHA128-001; full list in Table S1), in accordance with national and international regulations, including the Declaration of Helsinki, the International Council for Harmonization Harmonized Guideline for Good Clinical Practice, and the trial sponsor's standard operating procedures. Written informed consent was signed by all participants before entering the trial. The trial protocol was reported following the guidelines of Standard Protocol Items: Recommendations for Interventional Trials (SPIRIT). The SPIRIT 2025 checklist was provided in **Table S6**. In this trial, assessment scales including Impact of Weight on Quality of Life-Lite Clinical Trials Version (IWQOL-Lite CT) and Columbia-Suicide Severity Rating Scale (C-SSRS) were used with appropriate permissions and in accordance with licensing requirements. The Eating Behavior patients-reported outcome (EB PRO) and Patient Health Questionnaire-9 (PHQ-9) were used in compliance with its open-access terms.

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