

Survodutide for obesity in Chinese adults: phase 3 randomized trial design and baseline characteristics (SYNCHRONIZE™-CN)

Authors:

Linong Ji^{1*}, Liming Chen², Zhifeng Cheng³, Yibing Lu⁴, Yan Yang⁵, Fangming Fu⁶, Yinan Zhu⁷, Liying Jin⁷, Isabel M. Kloer⁸

*first and corresponding author, Email: jiln@bjmu.edu.cn

Affiliation:

1. Peking University People's Hospital, 2. Chu Hsien-I Memorial Hospital of Tianjin Medical University, 3. The Fourth Affiliated Hospital of Harbin Medical University, 4. The Second Affiliated Hospital of Nanjing Medical University, 5. Sichuan Academy of Medical Sciences & Sichuan Provincial People's Hospital (Affiliate Hospital of UESTC), 6. Central Hospital Affiliated to Shandong First Medical University, 7. Boehringer Ingelheim (China) Investment Co. Ltd, Shanghai, People's Republic of China, 8. Boehringer Ingelheim International GmbH, Ingelheim, Germany

Table S1: Full list of Institutional Review Boards or Independent Ethics Committees

Site No.	IRB or IEC (name)	Principal investigator
CHN1	Ethics Review Committee of Peking University People's Hospital	Linong Ji
CHN10	Medical Ethics Committee of The People's Hospital of Xuancheng City	Chongbing Huang
CHN12	Medical Ethics Committee of Shanghai Fifth People's Hospital Affiliated to Fudan University	Jun Liu
CHN13	Medical Ethics Committee of Huzhou Central Hospital	Jianping Yao
CHN14	Medical Ethics Committee of The Second Hospital of Jilin University	Hanqing Cai
CHN15	Medical Ethics Committee of Pinggu District Hospital, Beijing City	Yufeng Li
CHN18	Clinical Trial Ethics Committee of Forth Clinical Hospital of Harbin Medical University	Zhifeng Cheng
CHN19	Medical Ethics Committee of Luoyang Third People's Hospital	Junhang Tian
CHN21	Yichang First People's Hospital Medical Ethics Committee	Jun Zeng
CHN22	Ethics Committee for Drug and Medical Device Clinical Trials of Tianjin Medical University General Hospital	Ming Liu
CHN23	Lishui Municipal Central Hospital Hospital Clinical Trial Ethics Review Committee	Lingchun Lv
CHN25	Medical Ethics Committee of Union Hospital Affiliated to Tongji Medical College of Huazhong University of Science and Technology	Tianshu Zeng
CHN26	Medical Ethics Committee, The First Affiliated Hospital of Henan University of Science and Technology	Hongwei Jiang
CHN27	Siping city Central People's Hospital Drug Clinical Trial Ethics Review Committee	Li Sun
CHN28	Medical Ethics committee of NanFang Hospital of Southern Medical University	Yaoming Xue
CHN29	Medical Ethics Committee of Jinan Central Hospital	Xiaolin Dong
CHN31	Ethics Committee for Clinical Trials of Pharmaceuticals and Medical Devices, The First Affiliated Hospital of Ningbo University	Jialin Li
CHN32	Ethics Committee of Nantong University Affiliated Hospital	Yunjuan Gu

CHN33	Ethics Committee of Changzhou Second People's Hospital	Xinhua Ye
CHN34	Ethics Review Committee for Clinical Trials of Drugs/Medical Devices at Yueyang People's Hospital	Dijun Zhou
CHN35	Tianjin Medical University Chu Hsien-I Memorial Hospital Ethics Committee	Liming Chen
CHN36	Ethics Committee of Pingxiang People's Hospital	Yawei Zhang
CHN37	Medical Ethics Committee, Beijing Chao-Yang Hospital, Capital Medical University	Guang Wang
CHN38	Ethics Committee of The First Hospital of Jilin University	Guixia Wang
CHN5	Ethics Committee of the Second Affiliated Hospital of Chongqing Medical University	Shengbing Li
CHN4	Human Research Ethics Committee,	Ya Li
CHN40	Clinical Research Ethics Committee, Panjin LiaoYou Baoshihua Hospital	Xin Zhang
CHN41	Medical Ethics Committee of the Second Affiliated Hospital of Nanjing Medical University	Yibing Lu
CHN8	Ethics Committee for Clinical Trials of Drugs (Medical Devices) of Sichuan Academy of Medical Sciences and Sichuan Provincial People's Hospital	Yan Yang
CHN9	Clinical Trial Subcommittee of the Ethics Committee, Jincheng General Hospital	Lili Zhang

Abbreviations: IEC, independent ethics committee; IRB, institutional review board; No., number.

Table S2: Full criteria of the SYNCHRONIZE™-CN trial**Inclusion criteria**

Participants are eligible to be included if all the following criteria apply:

1. Male or female, age ≥ 18 years at the time of signing informed consent.
2. BMI ≥ 28 kg/m² at screening or BMI ≥ 24 kg/m² with the presence of at least one of the following weight-related complications:
 - Hypertension (defined as repeated, i.e. at least 3 measurements in resting condition, SBP values of ≥ 140 mmHg and/or DBP values of ≥ 90 mmHg in the absence of anti-hypertensive treatment, or intake of at least 1 anti-hypertensive drug to maintain a normotensive blood pressure)
 - Dyslipidaemia (defined as at least 1 lipid-lowering treatment required to maintain normal blood lipid levels, or LDL cholesterol ≥ 160 mg/dL (≥ 4.1 mmol/L), or triglycerides ≥ 150 mg/dL (≥ 1.7 mmol/L), or HDL cholesterol < 40 mg/dL (< 1.0 mmol/L) for men or HDL cholesterol < 50 mg/dL (< 1.3 mmol/L) for women)
 - Obstructive sleep apnoea
 - CVD (e.g. HF with NYHA functional class II-III, history of ischaemic or haemorrhagic stroke or cerebrovascular revascularisation procedure [e.g. carotid endarterectomy and/or stent], MI, coronary artery disease, or peripheral vascular disease)
 - T2DM diagnosed at least 180 days prior to screening (HbA1c $\geq 6.5\%$ (48 mmol/mol) and $< 10\%$ (86 mmol/mol)), and FPG ≤ 11.1 mmol/L measured by the central laboratory at screening
 - ✧ Currently treated with either: diet and exercise alone or stable treatment (for at least 3 months prior to screening) with metformin, SGLT2 inhibitor, acarbose, sulfonylurea, or glitazone as single agent therapy, or up to 3 anti-hyperglycaemia medications (metformin, SGLT2i, acarbose, sulfonylurea, or glitazone) according to local label
 - MASH, as assessed in medical records by histological liver assessment (within the last 6 months)
3. History of at least one self-reported unsuccessful dietary effort to lose body weight.
4. Signed and dated written informed consent in accordance with ICH-GCP and local legislation prior to admission to the trial.
5. WOCBP¹ must be ready and able to use highly effective methods of birth control per ICH M3 (R2) that result in a low failure rate of less than 1% per year when used consistently and correctly. A list of contraception methods meeting these criteria and instructions on the duration of their use will be provided in the participant information.

¹A woman is considered of childbearing potential, i.e. fertile, following menarche and until becoming postmenopausal unless permanently sterile. Permanent sterilisation methods include hysterectomy, bilateral salpingectomy, and bilateral oophorectomy. Tubal ligation is NOT a method of permanent sterilisation. A postmenopausal state is defined as no menses for 12 months without an alternative medical cause.
6. In the investigator's opinion, participants are well-motivated, capable, and willing to:
 - Learn how to self-inject the IMP, as required for this protocol (persons with physical

limitations who are not able to perform the injections must have the assistance of an individual trained to inject the IMP) OR

- Inject the IMP or accept injection from a designated person
- Follow study procedures for the duration of the study, including, but not limited to: follow lifestyle advice (for example, dietary restrictions and exercise plan), maintain a Diary, complete required questionnaires, and handle the IMP as described in the IFU

Additional criterion applicable for sub-set of participants for MRI assessment of body composition and MRI-PDFF assessment of liver fat:

7. Acceptable quality of the baseline scan as defined by the imaging laboratory prior to randomization.

Exclusion criteria

Participants are excluded if any of the following criteria apply:

Obesity:

1. Body weight change (self-reported) >5% within 3 months before screening.
2. Treatment with any medication for the indication obesity within 3 months before screening.
3. Previous or planned (during the trial period) treatment for obesity with surgery or a weight loss device, or prior surgery of the GI tract that could interfere with body weight. The following are allowed: (1) liposuction and/or abdominoplasty, if performed >1 year before screening, (2) lap banding, if the band has been removed >1 year before screening, (3) intragastric balloon, if the balloon has been removed >1 year before screening, (4) duodenal-jejunal bypass sleeve, if the sleeve has been removed >1 year before screening, (5) appendectomy, (6) simple hernia repair, or (7) cholecystectomy.
4. Have obesity induced by other endocrinologic disorders (for example, Cushing Syndrome) or diagnosed monogenetic or syndromic forms of obesity (for example, melanocortin 4 receptor deficiency, leptin deficiency, or Prader Willi Syndrome).

Diabetes-related for participants with T2DM:

5. Treatment with any medication for the indication of T2DM other than stated in the inclusion criteria within 3 months before screening (i.e. insulin, amylin analogues, GLP-1R agonists, GLP-1R agonist/insulin/GIP combinations, and DPP-4i).
6. New initiation of any other glucose-lowering investigational drug within 3 months prior to screening for this trial.
7. Uncontrolled and potentially unstable diabetic retinopathy or maculopathy, verified by an eye examination within 3 months prior to screening or in the period between screening and randomization.

Mental health:

8. Answered “yes” to any of the suicide-related behaviors (Actual attempt, Interrupted attempt, Aborted attempt, Preparatory act or behavior) or to the non-suicidal self-injurious behavior question on the “Suicidal Behavior” section of the C-SSRS related to the past 2 years before screening visit up to and including the randomization visit.
 9. Answered “yes” to Question 4 (Active Suicidal Ideation with Some Intent to Act,
-

Without Specific Plan) or to Question 5 (Active Suicidal Ideation with Specific Plan and Intent) on the “Suicidal Ideation” section of the C-SSRS from 3 months prior to the screening visit up to and including the randomization visit.

10. Reported a history of psychiatric inpatient hospitalisation (due to significant active or unstable major depressive disorder or other severe psychiatric disorder (e.g. schizophrenia, bipolar disorder, or other serious mood or anxiety disorder) within 1 year before screening, OR are not stabilized on their psychiatric medications (i.e. change of medication type or dosage adjustment within 8 weeks prior to screening visit and until randomization), OR has major depressive symptoms defined as a PHQ-9 score of 15 at screening visit up to and including randomization visit.

Patients with major depressive disorder or generalized anxiety disorder whose disease state is considered stable and expected to remain stable throughout the course of the study, in the opinion of the investigator, may be considered for inclusion if they are not on excluded medications.

Other medical:

11. Any treatment with medications which may cause significant weight change started within 3 months prior to screening (included but not limited to systemic glucocorticoid therapy, TCAs, atypical antipsychotic, mood stabilizers, anti-hypertensive, antihistamines, and anti-epileptics).
- Participants taking these medications for more than 3 months prior to screening with stable body weight are allowed.
12. Impaired renal function, defined as $\text{eGFR} < 30 \text{ mL/min/1.73 m}^2$ (CKD-EPIcr) at screening or trial participants requiring dialysis.
13. Known clinically significant gastric emptying abnormality (e.g. severe diabetic gastroparesis or gastric outlet obstruction).
14. Uncontrolled (as per investigators assessment) hypo- or hyperthyroidism.
15. History of either chronic or acute pancreatitis or elevation of serum lipase or serum pancreatic amylase $> 2 \times \text{ULN}$ as measured by the central laboratory at screening.
16. Uncontrolled hypertension (mean SBP $\geq 160 \text{ mm Hg}$ and/or mean DBP $\geq 100 \text{ mm Hg}$) at screening.
17. Trial participants who demonstrate recent evidence (within 3 months to screening) of acute or unstable cardiovascular events, e.g. hospitalisation for HF, acute coronary syndrome, unstable angina, MI, haemorrhagic or ischaemic stroke, transient ischaemic attack, and/or acute peripheral vascular event.
18. QTc (Fridericia) mean interval greater than 500 ms at screening (triplicate ECG) or personal or family history of long QT syndrome.
19. HF with NYHA functional class IV.
20. Any of the following liver laboratory test abnormalities at screening:
- Serum AST and/or ALT elevation $\geq 3 \times \text{ULN}$
 - Total serum bilirubin concentration $\geq 1.2 \times \text{ULN}$ (except for cases of Gilbert's Syndrome)
21. Any history or evidence of chronic liver disease other than MASLD (e.g. liver cirrhosis,
-

alcoholic liver disease, autoimmune liver disease, primary biliary cholangitis, primary sclerosing cholangitis, Wilson's disease) including ongoing active or chronic viral hepatitis.

Trial participants with the following laboratory findings are excluded:

- HBV: Trial participants with positive HBsAg
- HCV: Trial participants with positive HCV antibody and a positive HCV RNA (All trial participants with positive HCV antibody should be tested for HCV RNA. Trial participants with positive HCV antibody and no history of HCV treatment require a negative HCV RNA test at screening to be eligible for the trial. Trial participants treated for hepatitis C must also have an additional negative RNA test at least 3 years prior to screening in order to be eligible for the trial.)

22. History of HIV infection or positive HIV test at screening.
23. Major surgery (in the opinion of the investigator) performed within 3 months prior to screening or planned during the trial.
24. Personal or family history of MTC or MEN 2.
25. Calcitonin 100 pg/mL (≥ 29.26 pmol/L) at screening.
26. Confirmed diagnosis of malignancy within 5 years prior to screening, except for basal- or squamous-cell carcinoma of the skin that has been treated successfully. Trial participants with a history of other malignancies that have been treated with curative intent and who have no demonstrable disease recurrence within 5 years may also be eligible if approved following discussion with the sponsor. Trial participants under evaluation for malignant disease currently are not eligible for study participation.
27. History of organ transplantation (corneal transplants [keratoplasty] allowed) or awaiting an organ transplant.
28. Haematological condition that may interfere with HbA1c measurement (e.g. haemolytic anaemias, sickle cell disease).
29. Women who are pregnant, nursing or who plan to become pregnant while in the trial.
30. Known or suspected hypersensitivity to the IMP or related products.

Other exclusions:

31. Participants not expected to comply with the protocol requirements or not expected to complete the trial as scheduled (e.g. chronic alcohol or drug abuse or any other condition, that in the investigator's opinion, makes the participant an unreliable trial participant).
 32. Participants who must or wish to continue the intake of prohibited medication or any drug considered likely to interfere with the safe conduct of the trial.
 33. WOCBP who are using oral contraceptives during the screening visit and are not willing to change to non-oral contraceptives at least 7 days prior to first dose of IMP or not willing to add an additional barrier method of contraception during the entire treatment period with IMP and 28 days thereafter.
 34. Currently enrolled in another investigational device or drug trial, or less than 30 days or 5 half-lives, whichever is longer, since ending another investigational device or drug trial or receiving other investigational treatment(s); current or previous enrolment in strictly observational trials is allowed.
-

-
35. Previous randomization in this trial.
36. Confirmed acute SARS-CoV-2 infection based on local testing. Participants who recovered from a SARS-CoV-2 infection may be eligible: 14 days or more from first symptoms or from first PCR test confirmation to randomization, AND at least 7 days without SARS-CoV-2 symptoms. If local criteria are different, they will apply.
37. Any condition not covered by any of the other exclusion criteria, which in the investigator's opinion, might jeopardise the participant's safety or compliance with the protocol.

Additional criteria applicable for sub-set of participants for MRI assessment of body composition and MRI-PDFF assessment of liver fat:

38. Contraindication to MRI including, but not limited to severe claustrophobia, extensive tattoos, inner ear implant, pacemakers incompatible with MRI, other implanted cardiac rhythm management device, intracranial aneurism clips incompatible with MRI, any other metallic, non-MRI compatible implanted devices (e.g. hip replacement), a history of intra-orbital metal fragments that have not been removed, and weight or girth that exceeds scanner capabilities.

Participants who do not fulfil the MRI criteria are eligible for the main trial if the eligibility criteria for the main trial are fulfilled.

Abbreviations: ALT, alanine aminotransferase; AST, aspartate aminotransferase; BMI, body mass index; C-SSRS, Columbia-Suicide Severity Rating Scale; CKD-EPIcr, Chronic Kidney Disease Epidemiology Collaboration creatinine equation; CVD, cardiovascular disease; DBP, diastolic blood pressure; DPP-4i, dipeptidyl peptidase-4 inhibitor; ECG, electrocardiogram; eGFR, estimated glomerular filtration rate; FPG, fasting plasma glucose; GI, gastrointestinal; GIP, glucose-dependent insulintropic polypeptide; GLP-1R, glucagon-like peptide-1 receptor; HbA1c, glycated hemoglobin; HBsAg, hepatitis B surface antigen; HBV, hepatitis B virus; HCV, hepatitis C virus; HDL, high-density lipoprotein; HF, heart failure; HIV, human immunodeficiency virus; ICH, International Council for Harmonisation; ICH-GCP, International Council for Harmonisation Good Clinical Practice; IFU, instructions for use; IMP, investigational medicinal product; LDL, low-density lipoprotein; MASH, metabolic dysfunction-associated steatohepatitis; MASLD, metabolic dysfunction-associated steatotic liver disease; MEN2, multiple endocrine neoplasia type 2; MI, myocardial infarction; MRI, magnetic resonance imaging; MRI-PDFF, magnetic resonance imaging–proton density fat fraction; MTC, medullary thyroid carcinoma; NYHA, New York Heart Association; PCR, polymerase chain reaction; PHQ-9, Patient Health Questionnaire-9; QTc, corrected QT interval; RNA, ribonucleic acid; SARS-CoV-2, severe acute respiratory syndrome coronavirus 2; SBP, systolic blood pressure; SGLT2, sodium-glucose cotransporter 2; SGLT2i, sodium-glucose cotransporter 2 inhibitor; T2DM, type 2 diabetes mellitus; TCAs, tricyclic antidepressants; ULN, upper limit of normal; WOCBP, women of childbearing potential.

Table S3: Further endpoints of the SYNCHRONIZE™-CN trial**Efficacy**Weight related:

- Achievement of body weight reduction $\geq 25\%$ (yes/no) from baseline to Week 52
- Achievement of body weight reduction $\geq 30\%$ (yes/no) from baseline to Week 52
- Percentage change in body weight from baseline to Week 76
- Achievement of body weight reduction $\geq 5\%$ (yes/no) from baseline to Week 76
- Achievement of body weight reduction $\geq 10\%$ (yes/no) from baseline to Week 76
- Achievement of body weight reduction $\geq 15\%$ (yes/no) from baseline to Week 76
- Achievement of body weight reduction $\geq 20\%$ (yes/no) from baseline to Week 76
- Achievement of body weight reduction $\geq 25\%$ (yes/no) from baseline to Week 76
- Achievement of body weight reduction $\geq 30\%$ (yes/no) from baseline to Week 76
- Absolute change from baseline to Week 76 in: body weight (kg), waist circumference (cm), HbA1c (%), mmol/mol, SBP (mmHg), DBP (mmHg), BMI (kg/m²), FPG (mg/dL), FPI (mIU/L), Total cholesterol (mg/dL), HDL cholesterol (mg/dL), LDL cholesterol (mg/dL), VLDL cholesterol (mg/dL), triglycerides (mg/dL), free fatty acids (mg/dL)

T2DM-related:

- Absolute change from baseline to Week 52 and Week 76 in:
 - Fasting C-peptide (ng/mL)
 - ✧ HOMA-IR (units on a scale)
 - For FPG assessed in [mg/dL]: $(\text{FPI [mIU/L]} \cdot \text{FPG [mg/dL]})/405$
 - For FPG assessed in [mmol/L]: $(\text{FPI [mIU/L]} \cdot \text{FPG [mmol/L]})/22.5$
 - ✧ HOMA- β (percentage of normal beta cell function)
 - For FPG assessed in [mg/dL]: $(360 \cdot \text{FPI [mIU/L]})/(\text{FPG [mg/dL]} - 63)$
 - For FPG assessed in [mmol/L]: $(20 \cdot \text{FPI [mIU/L]})/(\text{FPG [mmol/L]} - 3.5)$
 - ✧ CPI (dimensionless ratio)
 - For FPG assessed in [mg/dL]: $(\text{fasting C-peptide [ng/mL]}/\text{FPG [mg/dL]}) \cdot 100$
 - ✧ WHR (dimensionless ratio)
 - Achievement of HbA1c $< 7.0\%$ (yes/no) from baseline to Week 52 and Week 76
 - Achievement of HbA1c $< 6.5\%$ (yes/no) from baseline to Week 52 and Week 76
 - Achievement of HbA1c $< 5.7\%$ (yes/no) from baseline to Week 52 and Week 76
 - For the trial participants with pre-diabetes status at baseline, defined as HbA1c $\geq 5.7\%$ to $< 6.5\%$ (≥ 39 to < 48 mmol/mol) at baseline:
 - ✧ Achievement of normoglycemic status at last administration of IMP + 28 days, defined as achievement of HbA1c $< 5.7\%$ (< 39 mmol/mol) at last administration of IMP + 28 days (yes/no)
 - ✧ Prevention of pre-diabetes progressing to T2DM at last administration of IMP + 28 days, defined as maintenance of HbA1c $< 6.5\%$ (< 48 mmol/mol) at last administration of IMP + 28 days (yes/no)

Kidney related:

-
- eGFR (CKD-EPIcr) slope of change from baseline to Week 52 and Week 76
 - UACR change as a continuous categorical from baseline to Week 24 as a continuous and categorical variable (<30, ≥30 to ≤300, and >300 mg/g) from baseline to Week 24, Week 52 and Week 76
 - Absolute change from baseline to Week 52 and 76 in uric acid (μmol/L)
 - Percentage change from baseline to Week 52 and 76 in uric acid (%)

Liver related:

- Absolute change from baseline to Week 52 and Week 76 in:
 - ✧ GGT (U/L)
 - ✧ NAFLD fibrosis score (units on a scale)

Calculated as:

$$-1.675 + 0.037 \cdot \text{age [years]} + 0.094 \cdot \text{BMI [kg/m}^2] + 1.13 \cdot (\text{if T2DM}) + 0.99 \cdot (\text{AST [U/L]/ALT [U/L]}) - 0.013 \cdot \text{platelets [} \cdot 10^9/\text{L]} - 0.66 \cdot \text{albumin [g/dL]}$$
 - ✧ Fib-4 score (units on a scale)

Calculated as:

$$(\text{age [years]} \cdot \text{AST [U/L]}) / (\text{platelets [} \cdot 10^9/\text{L]} \cdot \sqrt{\text{ALT [U/L]}})$$
 - ✧ APRI (units on a scale)

Based on the ULN for AST, ASTULN, provided by the central lab by sex and age group calculated as:

$$((\text{AST [U/L]}/\text{ASTULN [U/L]})/\text{platelets [} \cdot 10^9/\text{L]}) \cdot 100$$
 - ✧ HSI (units on a scale)

Calculated as:

$$8 \cdot (\text{ALT [U/L]}/\text{AST [U/L]}) + \text{BMI [kg/m}^2] + 2 (\text{if T2DM}) + 2 (\text{if female})$$

HSI is interpreted as a score with typical values between 16 and 60 where higher values indicate a worse condition.
 - ✧ FLI (units on a scale)

Calculated as:

$$(\exp(\lambda)/(1+\exp(\lambda))) \cdot 100 \text{ where}$$

$$\lambda = 0.953 \cdot \ln(\text{triglycerides [mg/dL]}) + 0.139 \cdot \text{BMI [kg/m}^2] + 0.718 \cdot \ln(\text{GGT [U/L]}) + 0.053 \cdot \text{waist circumference [cm]} - 15.745$$

and $\ln()$ is the natural logarithm.

FLI is interpreted as a score between 0 and 100 where higher values indicate a worse condition.
- Relative and absolute change from baseline to Week 52 and Week 76 in liver fat content (%), assessed by MRI-PDFF
- Improvement of liver fat content (yes/no), defined as at least 30% relative reduction in liver fat content after 52 and 76 weeks of treatment compared with baseline, assessed by MRI-PDFF

MRI related:

- Absolute change from baseline to Week 52 and Week 76 in the following parameters, assessed by MRI for body composition: total fat volume (%), total fat volume (L), lean body volume (%), lean body volume (L), visceral fat volume (%), visceral fat volume
-

(L), subcutaneous fat volume (%), subcutaneous fat volume (L)

Effect on daily energy intake:

- Absolute change from baseline to Week 52 and Week 76 in mean daily energy intake (kcal) as derived from the dietician's assessment based on the food diary provided by the participant

PRO related:

- Absolute change from baseline to Week 52 and Week 76 in:
 - ✧ “Capacity to Resist” domain score of Eating Behavior PRO (units on a scale) which will be derived as the sum of items in the domain (possible responses being 0= Not at all, 1= A little, 2= Moderately, 3= A lot, 4= Extremely). The domain score is ranging between 0 and 24 and a higher score indicates a lower capacity to resist.
 - ✧ Eating Behavior PRO total score (units on a scale) which will be derived from “Desire to Eat” and “Capacity to Resist” domain (each domain consists of 6 item) as the sum of all items (possible responses being 0= Not at all, 1= A little, 2= Moderately, 3= A lot, 4= Extremely). The score is ranging between 0 and 48 and a higher score indicates a worse eating behavior (greater desire to eat and/or lower capacity to resist)
 - ✧ IWQOL-Lite-CT version (4 scales) (units on a scale) The IWQOL-Lite-CT was developed to assess weight-related changes in physical and psychosocial functioning in patients with overweight and obesity. The 20-item IWQOL-Lite-CT yields a total score and 3 composite scores: physical (7 items), including physical function (5 items), and psychosocial (13 items)
 - ✧ “Desire to Eat” domain score of the Eating Behavior PRO (units on a scale)
- Achievement of 4 or more points improvement on “Capacity to Resist” domain score of Eating Behavior PRO (yes/or) from baseline to Week 52 and Week 76
- Achievement of 4 or more points improvement on “Desire to Eat” domain score of Eating Behavior PRO (yes/or) from baseline to Week 52 and Week 76
- Achievement of 4 or more points improvement on total Eating Behavior PRO (yes/or) score from baseline to Week 52 and Week 76

Effect of survodutide treatment on standard of care medications:

- Change of medication and dose, measured in 3 categories, assessed at baseline up to Week 52 and Week 76 in:
 - ✧ Antihypertensive medication (decrease, no change, increase)
 - ✧ Lipid-lowering medication (decrease, no change, increase)
 - ✧ Anti-hyperglycaemic medication (decrease, no change, increase) for patients with T2DM at baseline

Long-term clinical outcomes:

- Time to onset of T2DM in trial participants without T2DM at baseline
New onset T2DM is defined as occurrence of any 1 of the following after randomization:
 - ✧ Hyperglycaemia (random glucose ≥ 200 mg/dL [≥ 11.1 mmol/L]) with signs or symptoms of hyperglycaemia
 - ✧ Within a 4-week period, observation of both of the following, or 1 observation of 1
-

abnormal value which is confirmed either from the same sample or 2 separate test samples:

HbA1c $\geq 6.5\%$ [≥ 48 mmol/L]

Fasting glucose ≥ 126 mg/dL [≥ 7.0 mmol/L]

Or

✧ Initiation of any medication for the treatment of T2DM

- Occurrence of first hospitalisation due to any cause (yes/no)
- Occurrence of recurrent (two or more) hospitalisations due to any cause (yes/no)
- Time to first occurrence of hospitalisation for unstable angina
- Time to first occurrence of hospitalisation due to any cause
- Time to first occurrence of any of the adjudicated components of the composite endpoint consisting of hospitalisation for HF or CV death
- Time to all-cause mortality
- Time to first occurrence of any of the adjudicated components of the composite endpoint consisting of CV death, non-fatal MI, non-fatal stroke (3P-MACE)
- Time to first occurrence of any of the adjudicated components of the composite endpoint consisting of CV death, non-fatal stroke, non-fatal MI, or hospitalisation for HF (3P-MACE + HF)
- Time to first occurrence of any of the adjudicated components of the composite endpoint consisting of CV death, non-fatal stroke, non-fatal MI, or ischaemia related coronary revascularisation (4P-MACE)
- Time to first occurrence of any of the adjudicated components of the composite endpoint consisting of non-fatal stroke, non-fatal MI, ischaemia related coronary revascularisation, hospitalisation for HF, or CV death (5P-MACE)
- Time to first occurrence of any of the adjudicated components of the composite endpoint consisting of hospitalisation for HF or urgent care visit for HF
- Time to first occurrence of adjudicated ischaemia related coronary revascularisation
- Time to first occurrence of chronic dialysis¹ or renal transplant or sustained reduction² of $\geq 40\%$ eGFR (CKD-EPI_{cr}), or sustained eGFR² (CKD-EPI_{cr}) < 15 mL/min/1.73 m²
- Time to first occurrence of any of the components of the composite endpoint consisting of onset of sustained macroalbuminuria² (UACR > 300 mg/g [33.9 mg/mmol]), or sustained reduction² of $\geq 40\%$ eGFR (CKD-EPI_{cr}) compared with baseline (randomization), or onset of sustained eGFR² (CKD-EPI_{cr}) < 15 mL/min/1.73 m², or initiation of chronic renal replacement therapy (dialysis¹ or transplantation), or renal death (5-component composite nephropathy endpoint)
- Number of clinically relevant hyperuricaemic events per trial participant which occur between baseline and end of Week 76. A clinically relevant hyperuricaemic event is defined to be either “acute gout”, “gouty arthritis” or the initiation of treatment with serum uric acid lowering therapy (xanthine oxidase inhibitors, uricosuric agents or colchicine)

¹Chronic dialysis is defined as dialysis for at least 90 days.

²A condition is considered sustained if it is determined by measurements of 2 consecutive visits. If the

condition is met only at the last visit or once before the trial participant is discontinued or died, then the respective condition is also considered sustained.

Safety:

- Absolute change from baseline to Week 52 and Week 76 in: Heart rate (bpm), Lipase (U/L), Amylase (U/L)
 - Change from baseline to Week 52 and Week 76 in calcitonin (ng/L)
-

Pharmacokinetics

- Pre-dose concentration of the analyte in plasma immediately before dose N, reported for each scheduled visit with PK assessment
-

Immunogenicity assessment

- Presence of ADAs (including cross-reactive antibodies against endogenous GLP-1 and/or glucagon) and NAbs (including cross-reactive antibodies against endogenous GLP-1 and/or glucagon) at baseline and Weeks 4, 8, 12, 24, 36, 48, 52, 64, 76, and EU/EOS Visit
-

Abbreviations: ADAs, anti-drug antibodies; ALT, alanine aminotransferase; APRI, aspartate aminotransferase to platelet ratio index; AST, aspartate aminotransferase; ASTULN, upper limit of normal for aspartate aminotransferase; BMI, body mass index; bpm, beats per minute; CKD-EPIcr, Chronic Kidney Disease Epidemiology Collaboration creatinine equation; CPI, C-peptide index; CV, cardiovascular; DBP, diastolic blood pressure; eGFR, estimated glomerular filtration rate; EU/EOS, end-of-use/end-of-study; Fib-4, fibrosis-4; FLI, fatty liver index; FPG, fasting plasma glucose; FPI, fasting plasma insulin; GGT, gamma-glutamyl transferase; GLP-1, glucagon-like peptide-1; HbA1c, glycated hemoglobin; HDL, high-density lipoprotein; HF, heart failure; HOMA- β , homeostatic model assessment of β -cell function; HOMA-IR, homeostatic model assessment of insulin resistance; HSI, hepatic steatosis index; IMP, investigational medicinal product; IWQOL-Lite-CT, Impact of Weight on Quality of Life-Lite Clinical Trials Version; LDL, low-density lipoprotein; MACE, major adverse cardiovascular events; 3P-MACE, three-point major adverse cardiovascular events; 4P-MACE, four-point major adverse cardiovascular events; 5P-MACE, five-point major adverse cardiovascular events; MI, myocardial infarction; MRI, magnetic resonance imaging; MRI-PDFF, magnetic resonance imaging–proton density fat fraction; NAbs, neutralizing antibodies; NAFLD, nonalcoholic fatty liver disease; PK, pharmacokinetics; PRO, patient-reported outcome; SBP, systolic blood pressure; T2DM, type 2 diabetes mellitus; UACR, urinary albumin-to-creatinine ratio; ULN, upper limit of normal; VLDL, very-low-density lipoprotein; WHR, waist-to-hip ratio.

Table S4: Assumptions for sample size calculation

Parameter	Survodutide effect (SD)	Placebo (SD)
Percentage change in body weight from baseline to Week 52	12% (10.2%)	3% (6%)
Proportion of 5% body weight reduction from baseline at Week 52	60%	30%

Abbreviations: SD, standard deviation.

Table S5: Hypothesis testing (graphical approach)

The hypotheses reflecting the primary and secondary objectives are as follows:

Let $\mu1_survodutide\ 4.8\ mg$, $\mu1_survodutide\ 3.6\ mg$, and $\mu1_placebo$ denote the true mean of percentage change in body weight from baseline to Week 52 for survodutide 4.8 mg, survodutide 3.6 mg, and placebo, respectively.

$H0_1: \mu1_survodutide\ 4.8\ mg \geq \mu1_placebo$ versus $HA_1: \mu1_survodutide\ 4.8\ mg < \mu1_placebo$

$H0_2: \mu1_survodutide\ 3.6\ mg \geq \mu1_placebo$ versus $HA_2: \mu1_survodutide\ 3.6\ mg < \mu1_placebo$

Let $OR1_survodutide\ 4.8\ mg/placebo$ and $OR1_survodutide\ 3.6\ mg/placebo$ denote the true odds ratio of achievement of body weight reduction $\geq 5\%$ from baseline to Week 52 between survodutide 4.8 mg and placebo and survodutide 3.6 mg and placebo, respectively.

$H0_3: OR1_survodutide\ 4.8\ mg/placebo \leq 1$ versus $HA_3: OR1_survodutide\ 4.8\ mg/placebo > 1$

$H0_4: OR1_survodutide\ 3.6\ mg/placebo \leq 1$ versus $HA_4: OR1_survodutide\ 3.6\ mg/placebo > 1$

Let $OR2_survodutide\ 4.8\ mg/placebo$ and $OR2_survodutide\ 3.6\ mg/placebo$ denote the true odds ratio of achievement of body weight reduction $\geq 10\%$ from baseline to Week 52 between survodutide 4.8 mg and placebo and survodutide 3.6 mg and placebo, respectively.

$H0_5: OR2_survodutide\ 4.8\ mg/placebo \leq 1$ versus $HA_5: OR2_survodutide\ 4.8\ mg/placebo > 1$

$H0_6: OR2_survodutide\ 3.6\ mg/placebo \leq 1$ versus $HA_6: OR2_survodutide\ 3.6\ mg/placebo > 1$

Let $OR3_survodutide\ 4.8\ mg/placebo$ and $OR3_survodutide\ 3.6\ mg/placebo$ denote the true odds ratio of achievement of body weight reduction $\geq 15\%$ from baseline to Week 52 between survodutide 4.8 mg and placebo and survodutide 3.6 mg and placebo, respectively.

$H0_7: OR3_survodutide\ 4.8\ mg/placebo \leq 1$ versus $HA_7: OR3_survodutide\ 4.8\ mg/placebo > 1$

$H0_8: OR3_survodutide\ 3.6\ mg/placebo \leq 1$ versus $HA_8: OR3_survodutide\ 3.6\ mg/placebo > 1$

Let $\mu2_survodutide\ 4.8\ mg$, $\mu2_survodutide\ 3.6\ mg$, and $\mu2_placebo$ denote the true mean of absolute change in waist circumference (cm) from baseline to Week 52 for survodutide 4.8 mg, survodutide 3.6 mg, and placebo, respectively.

$H0_9: \mu2_survodutide\ 4.8\ mg \geq \mu2_placebo$ versus $HA_9: \mu2_survodutide\ 4.8\ mg < \mu2_placebo$

$H0_{10}: \mu2_survodutide\ 3.6\ mg \geq \mu2_placebo$ versus $HA_{10}: \mu2_survodutide\ 3.6\ mg < \mu2_placebo$

The multiple testing procedure for all pairs of hypotheses $H_i = (H0_i, HA_i)$, $i=1, \dots, 10$, will be implemented in terms of the graphical approach, see Figure S1, which controls the Familywise error rate (FWER) at the overall two-sided significance level α of 5% in the strong sense. The 2 doses survodutide 4.8 mg and survodutide 3.6 mg are considered equally relevant; therefore, the overall two-sided significance level $\alpha=5\%$ will be equally split among the dose-control comparisons for survodutide 4.8 mg and survodutide 3.6 mg.

For each pair of hypotheses, H_i , $i=1, \dots, 10$, superiority will be claimed if its two-sided p-

value (corresponding to the test of statistical significance of the assumption of there being no treatment effect between survodutide 3.6 mg/survodutide 4.8 mg and placebo) is less than its respective “updated” local significance level α_i of the graphical approach (Figure S1) and the estimated treatment difference/ratio favours survodutide 3.6 mg/survodutide 4.8 mg. Two-sided p-values will be reported.

The trial will be considered positive if based on the treatment-regimen estimand both hypotheses H_{01} and H_{03} or both hypotheses H_{02} and H_{04} are rejected.

Abbreviations: FWER, familywise error rate; OR, odds ratio. Symbols: α , overall two-sided significance level; α_i , updated local significance level for hypothesis i in the graphical testing procedure; H_0 , null hypothesis; H_A , alternative hypothesis; H_i , pair of hypotheses consisting of H_{0i} and H_{Ai} ; μ , true mean.

Table S6: SPIRIT 2025 checklist

Section / Topic	No	SPIRIT 2025 checklist item description	Reported on page no.
Administrative information			
Title and structured summary	1a	Title stating the trial design, population, and interventions, with identification as a protocol	1
	1b	Structured summary of trial design and methods, including items from the World Health Organization Trial Registration Data Set	2
Protocol version	2	Version date and identifier	NA
Roles and responsibilities	3a	Names, affiliations, and roles of protocol contributors	1,21
	3b	Name and contact information for the trial sponsor	21
	3c	Role of trial sponsor and funders in design, conduct, analysis, and reporting of trial; including any authority over these activities	22
	3d	Composition, roles, and responsibilities of the coordinating site, steering committee, endpoint adjudication committee, data management team, and other individuals or groups overseeing the trial, if applicable	10
Open science			
Trial registration	4	Name of trial registry, identifying number (with URL), and date of registration. If not yet registered, name of intended registry	2
Protocol and statistical analysis plan	5	Where the trial protocol and statistical analysis plan can be accessed	21,22
Data sharing	6	Where and how the individual de-identified participant data (including data dictionary), statistical code, and any other materials will be accessible	21,22
Funding and conflicts of interest	7a	Sources of funding and other support (e.g., supply of drugs)	21
	7b	Financial and other conflicts of interest for principal investigators and steering committee members	22
Dissemination policy	8	Plans to communicate trial results to participants, healthcare professionals, the public, and other relevant groups (e.g., reporting in trial registry, plain language summary, publication)	2,13,21, 22
Introduction			
Background and rationale	9a	Scientific background and rationale, including summary of relevant studies (published and unpublished) examining benefits and harms for each intervention	3-6

	9 b	Explanation for choice of comparator	NA
Objectives	1 0	Specific objectives related to benefits and harms	6
Methods: Patient and public involvement, trial design			
Patient and public involvement	1 1	Details of, or plans for, patient or public involvement in the design, conduct, and reporting of the trial	NA
Trial design	1 2	Description of trial design including type of trial (e.g., parallel group, crossover), allocation ratio, and framework (e.g., superiority, equivalence, non-inferiority, exploratory)	6,7
Methods: Participants, interventions, and outcomes			
Trial setting	1 3	Settings (e.g., community, hospital) and locations (e.g., countries, sites) where the trial will be conducted	6
Eligibility criteria	1 4 a	Eligibility criteria for participants	7
	1 4 b	If applicable, eligibility criteria for sites and for individuals who will deliver the interventions (e.g., surgeons, physiotherapists)	NA
Intervention and comparator	1 5 a	Intervention and comparator with sufficient details to allow replication including how, when, and by whom they will be administered. If relevant, where additional materials describing the intervention and comparator (e.g., intervention manual) can be accessed	7,8
	1 5 b	Criteria for discontinuing or modifying allocated intervention/comparator for a trial participant (e.g., drug dose change in response to harms, participant request, or improving/worsening disease)	8
	1 5 c	Strategies to improve adherence to intervention/comparator protocols, if applicable, and any procedures for monitoring adherence (e.g., drug tablet return, sessions attended)	8
	1 5 d	Concomitant care that is permitted or prohibited during the trial	7,28,29
Outcomes	1 6	Primary and secondary outcomes, including the specific measurement variable (e.g., systolic blood pressure), analysis metric (e.g., change from baseline, final value, time to event), method of aggregation (e.g., median, proportion), and time point for each outcome	9
Harms	1 7	How harms are defined and will be assessed (e.g., systematically, non-systematically)	10
Participant timeline	1 8	Time schedule of enrollment, interventions (including any run-ins and washouts), assessments, and visits for participants. A schematic diagram is highly recommended (see Figure)	7,8

Sample size	1 9	How sample size was determined, including all assumptions supporting the sample size calculation	11
Recruitment	2 0	Strategies for achieving adequate participant enrollment to reach target sample size	11
Methods: Assignment of interventions			
Randomization:			
Sequence generation	2 1 a	Who will generate the random allocation sequence and the method used	7
	2 1 b	Type of randomization (simple or restricted) and details of any factors for stratification. To reduce predictability of a random sequence, other details of any planned restriction (e.g., blocking) should be provided in a separate document that is unavailable to those who enroll participants or assign interventions	7,8
Allocation concealment mechanism	2 2	Mechanism used to implement the random allocation sequence (e.g., central computer/telephone; sequentially numbered, opaque, sealed containers), describing any steps to conceal the sequence until interventions are assigned	NA
Implementation	2 3	Whether the personnel who will enroll and those who will assign participants to the interventions will have access to the random allocation sequence	7,8
Blinding	2 4 a	Who will be blinded after assignment to interventions (e.g., participants, care providers, outcome assessors, data analysts)	7,8
	2 4 b	If blinded, how blinding will be achieved and description of the similarity of interventions	NA
	2 4 c	If blinded, circumstances under which unblinding is permissible, and procedure for revealing a participant's allocated intervention during the trial	NA
Methods: Data collection, management, and analysis			
Data collection methods	2 5 a	Plans for assessment and collection of trial data, including any related processes to promote data quality (e.g., duplicate measurements, training of assessors) and a description of trial instruments (e.g., questionnaires, laboratory tests) along with their reliability and validity, if known. Reference to where data collection forms can be accessed, if not in the protocol	NA
	2 5 b	Plans to promote participant retention and complete follow-up, including list of any outcome data to be collected for participants who discontinue or deviate from intervention protocols	12
Data management	2 6	Plans for data entry, coding, security, and storage, including any related processes to promote data quality (e.g., double data entry; range checks	NA

		for data values). Reference to where details of data management procedures can be accessed, if not in the protocol	
Statistical methods	2 7 a	Statistical methods used to compare groups for primary and secondary outcomes, including harms	13,14
	2 7 b	Definition of who will be included in each analysis (e.g., all randomized participants), and in which group	11
	2 7 c	How missing data will be handled in the analysis	13,14
	2 7 d	Methods for any additional analyses (e.g., subgroup and sensitivity analyses)	9
Methods: Monitoring			
Data monitoring committee	2 8 a	Composition of data monitoring committee (DMC); summary of its role and reporting structure; statement of whether it is independent from the sponsor and funder; conflicts of interest and reference to where further details about its charter can be found, if not in the protocol. Alternatively, an explanation of why a DMC is not needed	10
	2 8 b	Explanation of any interim analyses and stopping guidelines, including who will have access to these interim results and make the final decision to terminate the trial	10
Trial monitoring	2 9	Frequency and procedures for monitoring trial conduct. If there is no monitoring, give explanation	10
Ethics			
Research ethics approval	3 0	Plans for seeking research ethics committee/institutional review board approval	6,7,22
Protocol amendments	3 1	Plans for communicating important protocol modifications to relevant parties	NA
Consent or assent	3 2 a	Who will obtain informed consent or assent from potential trial participants or authorized proxies, and how	7
	3 2 b	Additional consent provisions for collection and use of participant data and biological specimens in ancillary studies, if applicable	NA
Confidentiality	3 3	How personal information about potential and enrolled participants will be collected, shared, and maintained in order to protect confidentiality before, during, and after the trial	21,22
Ancillary and post-trial care	3 4	Provisions, if any, for ancillary and post-trial care, and for compensation to those who suffer harm from trial participation	NA

Abbreviations: DMC, data monitoring committee; NA, not applicable; No., number; SPIRIT, Standard Protocol Items: Recommendations for Interventional Trials; URL, uniform resource locator.

Fig. S1: Trial visit schedule of the SYNCHRONIZE™-CN trial

	Screening and randomisation		Dose escalation								Maintenance								FU	
	Screening (in-clinic)	Randomisation (in-clinic)	Remote	In-clinic	Remote	In-clinic	In-clinic	In-clinic	In-clinic	In-clinic	Remote	In-clinic	Remote	In-clinic	In-clinic	Remote	In-clinic	Remote	In-clinic (EOY) ¹⁾	In-clinic ¹⁾
Visit ²⁾	V1	V2	V3	V4	V5	V6	V7	V8	V9	V10	V11	V12	V13	V14	V15	V16	V17	V18	V19	FU/EOS
Timing of visits (weeks)	-4	0	2	4	6	8	12	16	20	24	30	36	42	48	52	58	64	70	76	79
Timing of visits (days)	-28	1	15	29	43	57	85	113	141	169	211	253	295	337	365	407	449	491	533	554
Visit window (days)		+/-0	+/-3	+/-3	+/-3	+/-3	+/-3	+/-3	+/-3	+/-3	+/-7	+/-7	+/-7	+/-7	+/-7	+/-7	+/-7	+/-7	+/-3	+7
Screening assessments and randomisation																				
Informed consent ³⁾	X																			
Review of inclusion/exclusion criteria	X	X																		
Demographics	X																			
Medical and weight history, baseline conditions ⁴⁾	X																			
Substance usage ⁵⁾	X																		X	
Height	X																			
Weight ⁶⁾	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X ¹⁾	X
Waist and hip circumference	X	X				X	X	X	X	X		X		X	X		X		X	
Physical examination ⁷⁾	X	X ²⁾																		
Eye examination ⁸⁾	X	X								X										X
Vital signs(SBP,DBP,pulse) ⁹⁾	X	X		X		X	X	X	X	X		X		X	X		X			
12-lead ECG ¹⁰⁾	X	X		X		X	X	X	X	X		X		X	X		X			
Concomitant therapy ¹¹⁾	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X
Assessment of obesity staging	X																			
Evaluation of lipid-lowering treatment ¹²⁾		X		X		X	X	X	X	X		X		X	X		X		X	X
Evaluation of anti- α 0002 hypercholesteric treatment ¹³⁾		X		X		X	X	X	X	X		X		X	X		X		X	X
Evaluation of anti- α 0002 hyperphasic treatment ¹⁴⁾		X		X		X	X	X	X	X		X		X	X		X		X	X
All AEs/SAEs/AESs and check criteria for discontinuation	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X
Randomisation		X																		
Check for injection site reaction		X		X		X	X	X	X	X		X		X	X		X		X	
MRI for body composition and MRI-PDFF for liver fat content (optional, sub-population of trial participants) ¹⁵⁾		X													X				X ¹⁾	
Laboratory tests ¹⁶⁾																				
Safety laboratory tests ¹⁷⁾	X	X		X		X	X	X	X	X		X		X	X		X		X	X
HBV, HCV, HIV	X																			
HbA _{1c} , FPG, FPG, fasting C-peptide	X ¹⁸⁾	X					X		X			X		X	X		X		X	
Lipids: total cholesterol, HDL, LDL, VLDL, triglycerides, free fatty acids	X	X					X		X			X		X	X		X		X	
Urinalysis ¹⁹⁾	X	X		X			X		X			X		X	X		X		X	
Sampling for PK, ADA, and NAb ²⁰⁾		X	X	X		X	X		X		X	X	X	X	X		X		X	X
FSH ²¹⁾	X																			
Pregnancy testing ²²⁾	X	X		X		X	X	X	X	X		X		X	X		X		X	X
Questionnaires ²³⁾																				
Eating Behavior PRO		X		X				X		X		X			X				X	
EQOL-4Lr CT Version		X										X			X				X	
PRO-9	X	X					X		X			X		X	X		X		X	
C-SSRS	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X
Other assessments																				
Training in/observer profiled syringe administration ²⁴⁾		X	X	X	X							X								
Hand out IFU		X																		
IBT call and dispense DMP ²⁵⁾	X ²⁷⁾	X		X		X	X	X	X	X		X		X	X		X		X	
eDiary review (DMP administration, injection site reactions and compliance checks)			X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	
Review of paper food, exercise and weight diary or local app, diet and physical activity		X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	
Diet and physical activity counselling ²⁸⁾		X		X		X	X	X	X	X		X		X	X		X		X	
Hand out weight scale, glucose monitoring device, and participant materials ²⁹⁾		X ³⁰⁾	X																	
Hyper-hyperphasic episode review(eDiary)			X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X
Vital status																				X

Note: For in-clinic visits after randomisation and review of inclusion/exclusion criteria, the suggested order of assessments is described. If remote visits are completed as in-clinic visits, only procedures designed for the remote visit should be completed in the clinic. EOT is 7 days after last dose and FU is 28 days after last dose (21 days after EOT).

Footnote:

- 1) If the DMP administration is scheduled on the day of the visit, trial participants have to be informed to come to the study site prior to the DMP administration so that the PK, ADA and NAb sample is obtained prior to DMP administration.
- 2) In addition to the most informed consent, a separate informed consent is required for participating in determination of body composition assessed by MRI and liver fat content assessed by MRI proton density fat fraction (PDFF).
- 3) Medical history includes assessment of pre-existing conditions (special attention to past or medical conditions reported by in-clinic criteria and other important medical conditions, e.g. history of gallbladder disease, CVD, history of psychiatric disorder, MTC, and history of any cancer other than MTC). In addition, if a mammogram or colonoscopy was performed within 2 years prior to screening or part of routine clinical practice, data should be recorded in the eCRF. Substance usage such as smoking, alcohol, and drugs will be captured as indicated.
- 4) Weight measurements should be obtained per the instructions. Body weight must be measured in fasting state (except at the screening visit). If the trial participant is not fasted, the participant should be called for a new visit within the visit window. Weight scales for home measurement will be provided at Visit 2. On days of in-clinic visits, participants are asked to measure and record their body weight at home before coming to the visit.
- 5) The physical examination should be repeated if the baseline visit (Visit 2) is performed more than 2 weeks after the screening visit.
- 6) For participants with T2DM at screening, the eye examination has to be performed in the period between screening and randomisation if not performed within the period 1 month before screening to verify uncontrolled and potentially unstable diabetic retinopathy, or maculopathy. The eye examination at Visit 9 can be performed within a time window of ± 1 month of the visit and on the EOT Visit within a time window of 2 months of the visit. Unless the eye examination for Visit 9 was performed within 1 month before the EOT Visit, the EOT eye examination must be performed on the EOT Visit with a time window of 2 months of the visit.
- 7) Vital sign measurements must be taken before obtaining an ECG tracing and before collection of blood samples for laboratory testing per the instructions.
- 8) ECG at screening will be done to replace ECG measurements should be obtained per the instructions. ECGs should be collected prior to collection of blood samples for laboratory testing, including PK samples.
- 9) Special attention has to be paid if medication with a narrow therapeutic index (NTI) is used.
- 10) Change of the medication including dose in anti-hypercholesteric, lipid-lowering, and anti-hypercholesteric medications have to be assessed for increase decrease to change and exposure in the eCRF.
- 11) Trial participants permanently discontinuing DMP will have an EOT Visit 7 days after the last dose or as soon as possible thereafter.
- 12) If a trial participant declines to come to the site for the Week 12 and Week 16 EOT Visit, collection at Week 12 and Week 16 data by a medically qualified and protocol trained person using site-supplied equipment should be attempted.
- 13) The last regular visit is the follow-up (FU) end of study (EOS) Visit. For trial participants who complete the planned treatment schedule (Week 76 Visit 19), the EOT Visit and Visit 19 should be combined in one visit (no duplicate assessments to be performed).
- 14) After the EOT visit (i.e., the individual trial participant's EOS), the investigator should only report an occurrence of cancer or new baseline, DMP-related SAE, and DMP-related AEs of which the investigator may become aware of.
- 15) MRI for body composition and MRI-PDFF for liver fat assessment to be scheduled prior to Visit 2 (randomisation visit) only for trial participants who have met all inclusion criteria and none of the exclusion criteria.
- 16) The participant should come to all in-clinic visits in a fasting state (except for screening). From Visit 2 onwards, trial participants should be instructed to come after at least 8 h without food or liquid intake, except water, and without administering anti-hypercholesteric medications, which will be taken in the clinic. The DMP dose administration (if scheduled within the day of visit) should be withheld in the morning of the clinic visit and blood sampling has been performed. If a lab parameter measured at screening is non-fasting state is out of normal range and thus prevent the participant from inclusion into the trial or per eligibility criteria, measurement can be repeated in fasting state within the screening period window. If a trial participant has come to the in-clinic visit in non-fasting state, procedures that require fasting (blood sampling for ADA, PK, FPG, fasting C-peptide, lipids) should be performed on another day within the visit window.
- 17) All safety laboratory parameters will be assessed. All laboratory assessments will be performed by a central laboratory. Instructions regarding sample collection, sample handling/processing, and sample shipment will be provided in the respective laboratory manuals.
- 18) At the screening visit, only FPG and HbA_{1c} will be assessed.
- 19) A trial participant who is part of the sub-population undergoing MRI assessment at Week 12 and Week 16. A participant from this population who permanently discontinues the DMP should be encouraged to undergo the second MRI assessment at Week 12, and a third at Week 76, if the participant is willing to return to the study site. MRI should not be acquired at the EOT Visit.
- 20) Urine sample should be collected in the clinic from the second morning (void preferably) and if not possible, from spot urine.
- 21) DMP administration prior to PK sampling should be documented in trial participant's eDiary. Sampling for PK, ADA, and NAb will be done prior to DMP administration. If the DMP administration is scheduled during the day of the visit, then the trial participant will come to the study site prior to DMP administration. Once a participant discontinues the DMP permanently, PK sample should be collected at EOT (7 days after last DMP administration) and FU (28 days after last DMP administration), but not at any further scheduled on-site visit. ADA and NAb samples should be collected at EOT, FU, and any further scheduled on-site visits.
- 22) For women between age 16 and 75 years with a negative result for 12 months, perform FSH test to confirm if they are postmenopausal. If the participant is on HRT, HRT must be withheld immediately to allow confirmation of menopausal status via FSH testing before treatment. If pausing HRT for this purpose is not possible or not accepted by the participant, the participant will have to use nonestrogen hormonal highly effective contraception methods compatible with MRI. FSH testing is not required for women who are perimenopausal, menarche, or for women 12 months without alternative medical cause other than being postmenopausal.
- 23) For WPCMP only: A urine pregnancy test will be done during screening. If it is positive, the participant will be discontinued a screen failure. If it is negative, a serum pregnancy test will be done. Urine pregnancy tests will be performed at all other in-clinic visits. If the urine pregnancy test is positive, DMP should be paused, and a serum pregnancy test will be done. If the serum pregnancy test is positive, the participant result is discontinued from DMP treatment. Pregnancy tests can be done more frequently if requested by local regulations. Once a female participant discontinues the DMP permanently, pregnancy testing will only be required during EOT and FU visit.
- 24) Completion of questionnaires should be performed prior to or after assessment scheduled for the in-clinic visit and in the following order: 1) Eating Behaviour PRO.
- 25) EQOL-4L-CF version, PRO-9, C-SSRS, PRO-9 and C-SSRS criteria requiring discontinuation and safety measures to be followed.
- 26) Each trial participant will receive training in the administration of the prefilled syring. Site staff will observe the trial participant administering the prefilled syringe in the clinic at Visit 2. The remote visits (if allowed per local regulations) are to be performed as video phone calls. DMP administration may be observed by site staff during Visits 4, 6, 8, and 10. Site staff and the trial participant might plan to schedule Visits 2, 4, 6, 8, and 10 in the day of planned DMP administration to allow site staff to observe administration at those visits if needed.
- 27) Trial participants will receive enough DMP to cover the time period until the next scheduled visit. The investigator should explain the storage temperature conditions for the DMP and instruct the trial participants about the DMP storage temperature requirements. Trial participants should be instructed about the necessity to return all DMP related packaging used and unused.
- 28) At the screening visit, no DMP will be dispensed.
- 29) The counselling on diet and physical activity should be performed by a dietitian or equivalent qualified delegate. It should include the calculation of the individualised energy requirement, TEE, and methods to change the dietary composition and amount of physical activity. The counselling on diet and physical activity may be performed on a (within 3 days) after randomisation. Visit 2) The study personnel should provide reinforcement and encouragement for lifestyle modifications. The counselling includes the review of diet and exercise goals.
- 30) Trial participant materials include: 1) Instructions and eDiary to record during information and hyper-hypercholesteric episodes. 2) Trial participant ID card. 3) Instructions and eDiary for control of sickness, recognition and handling of hyper-hypercholesteric and hyperglycemia. 4) Dietary materials and a paper food, exercise, and weight diary to record body weight measurements, physical activity, and dietary compliance, and 5) The weight scale. 6) The blood glucose monitoring device including IFU. Weekly testing is recommended. Additional measurements should be taken in case of hyper- or hyper-hypercholesteric events.
- 31) At screening, only the paper food, exercise, weight diary, and trial participant card will be given to the trial participants.

Fig. S2: Graphical visualisation of the multiple testing procedure for evaluating primary and confirmatory secondary objectives

