A Phase 2 Randomized Trial of Survodutide in MASH and Fibrosis

A Phase 2 Randomized Trial of Survodutide in MASH and Fibrosis

Arun J. Sanyal, M.D., Pierre Bedossa, M.D., Ph.D., Mandy Fraessdorf, Ph.D., Guy W. Neff, M.D., Eric Lawitz, M.D., Elisabetta Bugianesi, M.D., Quentin M. Anstee, Ph.D., F.R.C.P., Samina Ajaz Hussain, M.D., Philip N. Newsome, M.B., Ch.B., Ph.D., Vlad Ratziu, M.D., Azadeh Hosseini-Tabatabaei, Pharm.D., Ph.D., Jörn M. Schattenberg, M.D., Mazen Noureddin, M.D., M.H.Sc., Naim Alkhouri, M.D., and Ramy Younes, M.D., Ph.D., for the 1404-0043 Trial Investigators

The authors' affiliations are as follows: the Stravitz–Sanyal Institute for Liver Disease and Metabolic Health, Virginia Commonwealth University School of Medicine, Richmond (A.J.S.); Liverpat and University of Paris (P.B.), and Sorbonne Université, Institute for Cardiometabolism and Nutrition, Assistance Publique–Hôpitaux de Paris, INSERM Unité Mixte de Recherche Scientifique 1138, Centre de Recherche des Cordeliers (V.R.) — all in Paris; Boehringer Ingelheim, Ingelheim am Rhein (M.F., S.A.H and R.Y.), Saarland University Medical Center, Homburg (J.M.S.), and University of the Saarland, Saarbrücken (J.M.S.) — all in Germany; Covenant Metabolic Specialists, Sarasota, FL (G.W.N.); Houston Methodist Hospital and Houston Research Institute, Houston (M.N.), and the Texas Liver Institute, University of Texas Health San Antonio, San Antonio (E.L. and N.A.) — all in Texas; the University of Turin, Turin, Italy (E.B.); the Translational and Clinical Research Institute, Faculty of Medical Sciences, Newcastle University, and Newcastle National Institute for Health and Care Research Biomedical Research Centre, Newcastle upon Tyne Hospitals National Health Service (NHS) Foundation Trust, Newcastle upon Tyne (Q.M.A.), the University Hospitals Birmingham NHS Foundation Trust and the University of Birmingham, Birmingham (P.N.N.), and the Institute of Hepatology, Faculty of Life Sciences and Medicine, King's College London and King's College Hospital, London (P.N.N.) — all in the United Kingdom; Boehringer Ingelheim Pharmaceuticals, Ridgefield, CT (A.H.-T.); and Arizona Liver Health, Chandler (N.A.).

Dr. Sanyal can be contacted at arun.sanyal@vcuhealth.org or at Virginia Commonwealth University, MCV Box 980341, Department of Internal Medicine, Division of Gastroenterology, Hepatology, and Nutrition, 1200 E. Marshall St., Richmond, VA 23298.

ABSTRACT

Background

Dual agonism of glucagon receptor and glucagon-like peptide-1 (GLP-1) receptor may be more effective than GLP-1 receptor agonism alone for treating metabolic dysfunction–associated steatohepatitis (MASH). The efficacy and safety of survodutide (a dual agonist of glucagon receptor and GLP-1 receptor) in persons with MASH and liver fibrosis are unclear.

Methods

In this 48-week, phase 2 trial, we randomly assigned adults with biopsy-confirmed MASH and fibrosis stage F1 through F3 in a 1:1:1:1 ratio to receive once-weekly subcutaneous injections of survodutide at a dose of 2.4, 4.8, or 6.0 mg or placebo. The trial had two phases: a 24-week rapid-dose-escalation phase, followed by a 24-week maintenance phase. The primary end point was histologic improvement (reduction) in MASH with no worsening of fibrosis. Secondary end points included a

decrease in liver fat content by at least 30% and biopsy-assessed improvement (reduction) in fibrosis by at least one stage.

Results
A total of 293 randomly assigned participants received at least one dose of survodutide or placebo. Improvement in MASH with no worsening of fibrosis occurred in 47% of the participants in the survodutide 2.4-mg group, 62% of those in the 4.8-mg group, and 43% of those in the 6.0-mg group, as compared with 14% of those in the placebo group (P<0.001 for the quadratic dose–response curve as best-fitting model). A decrease in liver fat content by at least 30% occurred in 63% of the participants in the survodutide 2.4-mg group, 67% of those in the 4.8-mg group, 57% of those in the 6.0-mg group, and 14% of those in the placebo group; improvement in fibrosis by at least one stage occurred in 34%, 36%, 34%, and 22%, respectively. Adverse events that were more frequent with survodutide than with placebo included nausea (66% vs. 23%), diarrhea (49% vs. 23%), and vomiting (41% vs. 4%); serious adverse events occurred in 8% with survodutide and 7% with placebo.

Conclusions
Survodutide was superior to placebo with respect to improvement in MASH without worsening of fibrosis, warranting further investigation in phase 3 trials. (Funded by Boehringer Ingelheim; ClinicalTrials.gov number, NCT04771273; EudraCT number, 2020-002723-11.)

Metabolic dysfunction–associated steatohepatitis (MASH; previously called nonalcoholic steatohepatitis [NASH])[1] is associated with increased morbidity and mortality.[2] Its prevalence is predicted to increase worldwide, highlighting the increasing burden of the disease.[3,4]
In March 2024, the selective thyroid hormone receptor beta agonist resmetirom gained conditional approval from the Food and Drug Administration as the first pharmacotherapy for MASH with moderate-to-advanced liver fibrosis.[5] In a phase 3 trial, resmetirom was superior to placebo in MASH resolution and improvement in fibrosis; however, the difference in the percentage of patients who had an improvement in fibrosis as compared with placebo was only 10.2 to 11.8 percentage points.[6]
Compounds in development for MASH include glucagon-like peptide-1 (GLP-1) receptor agonists.[7] This receptor is a plausible therapeutic target, given that obesity is a risk factor for MASH and a coexisting condition in many persons with MASH[8]; however, hepatocytes lack GLP-1 receptor.[9] Dual agonism of glucagon receptor and GLP-1 receptor may be more effective than GLP-1 receptor monoagonism for treating MASH, because the extrahepatic benefits of GLP-1 receptor agonism (glucose control, reduced appetite, and weight loss) are combined with direct hepatic effects (increased energy expenditure, lipolysis, and mobilization of hepatic fat) associated with glucagon receptor agonism.[10-16]
Survodutide (BI 456906) is a dual agonist of glucagon receptor and GLP-1 receptor that is derived from glucagon and administered once weekly.[17] In a phase 2 trial involving persons living with obesity or overweight, survodutide treatment led to significant dose-dependent weight loss as compared with placebo.[18] In a mouse model, dual glucagon receptor–GLP-1 receptor agonism ameliorated MASH by reducing inflammation, steatosis, apoptosis, and oxidative stress and increased mitochondrial biogenesis and liver regeneration.[19] Here, we report results from a phase 2 dose-finding trial investigating the efficacy, safety, and side-effect profile of multiple subcutaneous doses of survodutide in participants with MASH and liver fibrosis.

METHODS

Trial Design and Oversight

This multicenter, randomized, double-blind, dose-finding, placebo-controlled, parallel-group trial was conducted at 155 sites in 25 countries. The protocol was approved by the institutional review board and independent ethics committee at each participating site. All the participants provided written informed consent. The trial was conducted in accordance with Good Clinical Practice, the Declaration of Helsinki, and applicable regulatory requirements.

Participants

Eligible participants were aged 18 (or of legal age) to 80 years with biopsy-confirmed MASH and a fibrosis stage of F1 through F3. Diagnosis of MASH required a nonalcoholic fatty liver disease (NAFLD) activity score[20] of at least 4, with at least 1 point each for lobular inflammation and hepatocellular ballooning. The NAFLD activity score (ranging from 0 to 8) represents the sum of subscores for steatosis (scale of 0 to 3), lobular inflammation (scale of 0 to 3), and hepatocellular ballooning (scale of 0 to 2), with higher scores indicating more severe disease.[20] The total score for fibrosis stage ranges from 0 to 4. Additional key inclusion criteria included stable body weight (<5% participant-reported change between historical biopsy and randomization), a liver fat content of at least 8% as measured by magnetic resonance imaging proton density fat fraction (MRI-PDFF), and liver stiffness of more than 6.0 kPa as measured by vibration-controlled transient elastography (FibroScan) at screening.

Among the key exclusion criteria were current or previous clinically significant alcohol consumption (>210 g per week in men and >140 g per week in women for >3 months); the use of medications associated with liver injury, hepatic steatosis, or steatohepatitis within 12 weeks before screening; and a history of other forms of chronic liver disease.

Procedures

Eligible participants were randomly assigned in a 1:1:1:1 ratio to receive once-weekly subcutaneous injections of survodutide at a dose of 2.4, 4.8, or 6.0 mg or placebo. Participants, investigators, central reviewers, and personnel involved in trial conduct or analysis (with some exceptions; see the protocol) were unaware of the trial-group assignments until after the main database lock. Randomization lists were generated with the use of a pseudorandom number generator; participants were stratified according to status with respect to type 2 diabetes (with vs. without). The trial had two phases: a 24-week rapid-dose-escalation phase (with escalations every 2 weeks until the target dose was reached), followed by a 24-week maintenance phase (Figs. S1 and S2 in the Supplementary Appendix). Dose adjustment was allowed twice (see the Supplementary Appendix). Lifestyle counseling and management of coexisting conditions were conducted according to guidelines.[21-23] A screening or historical biopsy performed within 6 months before randomization was used as a baseline for histologic variables. Baseline and end-of-treatment values were derived from one central pathologist (see the Supplementary Appendix). The MRI-PDFF was assessed at screening, week 28, and the end of treatment.

End Points

The primary end point was improvement in histologic findings on liver biopsy after 48 weeks of treatment, defined as a composite of improvement in MASH (≥2-point decrease in the NAFLD activity score with ≥1-point decrease in either lobular inflammation or hepatocellular ballooning) with no worsening of fibrosis (absence of any increase in fibrosis stage). Secondary efficacy end points included a decrease in liver fat content (as measured by the MRI-PDFF) by at least 30%, absolute change (not reported here) and percentage change in liver fat content (as measured by the MRI-PDFF), and biopsy-assessed improvement in fibrosis (≥1-stage decrease) and absolute change in the NAFLD activity score, all from baseline after 48 weeks of treatment. Further end points included

improvement in fibrosis (≥1-stage decrease) with no worsening of MASH (no increase in any of the NAFLD activity subscores), and resolution of MASH (absence of ballooning [score of 0], no or mild inflammation [score of 0 or 1], and possible steatosis [score of 0 to 3]) with no worsening of fibrosis, both from baseline after 48 weeks of treatment as assessed by liver biopsy. There were no predefined specific safety end points; safety assessment was based on the overall safety results. Table S1 shows all trial end points.

Statistical Analysis

The sample-size calculation was performed with the use of simulations in R software, version 3.6.1 (R Project for Statistical Computing). One aim was to show a significant nonflat dose–response curve across the different survodutide doses and placebo. At least one modeled dose within the considered dose range should show a benefit of a minimum clinically relevant effect with respect to the incidence of response (primary end point) as compared with placebo. The sample-size calculation assumed a maximum difference in the incidence of response (survodutide vs. placebo) of 25 percentage points, under the assumption of an incidence of response of 20% in the placebo group. With the use of a total sample of 240 evaluable participants (60 per group), the probability of a successful trial, under a minimum clinically relevant effect of 20 percentage points (i.e., nonflat curve achieved and ≥1 survodutide dose showing a difference vs. placebo of ≥20 percentage points), was approximately 76% under the assumption of a linear dose–response curve. Participants who dropped out would not have had an end-of-treatment biopsy; thus, this subpopulation is indirectly considered by the lower assumption of the incidence of response. An overall significance level of 5% (one-sided) for the contrast test of the null hypothesis of a flat dose–response was assumed.

The primary end point was analyzed in the modified intention-to-treat population, defined as all randomly assigned participants who had received at least one dose of survodutide or placebo (treated population), and was based on the maintenance dose assigned at randomization (planned treatment). Owing to the potential for dose adjustment, the preplanned primary analysis according to the protocol was based on the actual dose that participants received during the maintenance phase (actual treatment; see the Supplementary Appendix). Table S2 shows the shift between the randomized treatment group and actual maintenance treatment group. The primary analysis used all the data, with missing data imputed as nonresponse. A sensitivity analysis was based on participants with paired biopsy and MRI results at baseline and at the end of treatment.

The primary end point as well as the secondary end point of a decrease in liver fat content by at least 30% were analyzed with the use of multiple comparison and modeling techniques that allowed simultaneous evaluation of potential dose–response patterns, while protecting the overall probability of type I error (one-sided 5%).[24] Participants who met the end-point criteria were defined as having a response; participants without end-of-treatment data were imputed as having a nonresponse. Further details are provided in the Supplementary Appendix.

For continuous secondary end points, a mixed model with repeated measures analysis was performed and used to obtain covariate adjusted mean estimates of differences between survodutide doses and placebo at week 48. For binary secondary and further end points, a logistic-regression analysis was performed and used to obtain covariate-adjusted odds ratios between survodutide dose and placebo. Adverse events were analyzed in the treated population. There was no plan to adjust for multiple comparisons. A two-sided P value is reported for the analysis of the primary end point for the assessment of the dose response. All other results are reported with 95% confidence intervals and have not been adjusted for multiple comparisons; therefore, they should not be used to infer definitive treatment effects.

The sponsor (Boehringer Ingelheim) designed the trial and collected and analyzed the data. All the authors had access to the data. The authors vouch for the accuracy and completeness of the data and for the fidelity of the trial to the protocol. The manuscript was drafted with the assistance of medical writers (funded by the sponsor), under the guidance of the authors. Survodutide is licensed to the sponsor from Zealand Pharma.

Results

Participants

Participants were recruited starting on April 27, 2021, and the last participant completed the trial on December 21, 2023. A total of 1153 participants were screened for eligibility, and 295 participants were randomly assigned to receive survodutide once weekly at a dose of 2.4 mg (73 participants), 4.8 mg (73 participants), or 6.0 mg (75 participants) or to receive placebo (74 participants) (Fig. S3). The treated population included 293 participants. Overall, 281 of 293 participants (95.9%) completed the trial, of whom 219 had paired biopsy samples.

The demographic and clinical characteristics of the participants at baseline were similar across the trial groups (Table 1 and Tables S3 and S4). Baseline biopsies indicated that 70% of the participants had an NAFLD activity score of 5 or more, 16% had F1B fibrosis, 41% had F2 fibrosis, and 35% had F3 fibrosis. Table S5 shows the representativeness of the trial population.

Efficacy

In the modified intention-to-treat analysis (omitting two participants who underwent randomization but did not receive a dose of survodutide or placebo), a benefit of survodutide with respect to the primary end point of improvement in MASH with no worsening of fibrosis at 48 weeks was shown by a nonflat dose–response curve ($P<0.001$ for the quadratic dose–response curve as best-fitting model). Improvement in MASH with no worsening of fibrosis occurred in 47% (95% confidence interval [CI], 36 to 58) of the participants in the survodutide 2.4-mg group, 62% (95% CI, 51 to 73) of those in the 4.8-mg group, and 43% (95% CI, 33 to 55) of those in the 6.0-mg group, as compared with 14% (95% CI, 8 to 23) of those in the placebo group (Figure 1). Similar results were observed in the analysis of participants with paired biopsy results (Fig. S4A).

The secondary end point of improvement in fibrosis was met by 34% of the participants in the survodutide 2.4-mg group, 36% of those in the 4.8-mg group, and 34% of those in the 6.0-mg group, as compared with 22% of those in the placebo group (Fig. S5A). The absolute change from baseline in the NAFLD activity score after 48 weeks was −3.3 in the survodutide 6.0-mg group, as compared with −0.2 in the placebo group (Fig. S5B).

For the end points assessed by MRI-PDFF, a decrease in liver fat content by at least 30% occurred in 63% of the participants in the survodutide 2.4-mg group, 67% of those in the 4.8-mg group, and 57% of those in the 6.0-mg group, as compared with 14% of those in the placebo group (Fig. S5C; results for the actual-treatment analysis are shown in Fig. S10C and S10F). The percentage change from baseline in liver fat content after 48 weeks was −62.0% in the survodutide 6.0-mg group, as compared with −5.7% in the placebo group (Fig. S5D; results for the actual-treatment analysis are shown in Fig. S10D).

Improvement in fibrosis with no worsening of MASH was observed in 32% of the participants in the survodutide 6.0-mg group, as compared with 18% of those in the placebo group (Fig. S6A). Resolution of MASH was observed in 49% of the participants in the survodutide 6.0-mg group, as compared with 11% of those in the placebo group (Fig. S6B). MASH resolution with a decrease of at least 2 points in the NAFLD activity score (decrease of ≥1 point in the hepatocellular ballooning subscore) and with no worsening of fibrosis was observed in 39% of the participants in the survodutide 6.0-mg group, as compared with 5% of those in the placebo group (Fig. S6C). Results of post hoc analysis of improvement in fibrosis with no worsening of MASH and resolution of MASH with no worsening of fibrosis in participants with fibrosis stage F2 or F3 are shown in Fig. S7. Planned-treatment data for participants with paired biopsy and MRI results are shown in Figures S4, S6, and S7.

Survodutide was associated with an absolute change at week 48 of up to −38.5 U per liter in the alanine aminotransferase (ALT) level and −32.2 U per liter in the aspartate aminotransferase (AST)

level, as compared with a change of −5.7 U per liter and −2.4 U per liter, respectively, with placebo (Figure 2 and Fig. S8). Results for other clinical end points are included in Table S6.
Data from the primary analysis (actual treatment) for participants with paired biopsy samples indicated that improvement in MASH with no worsening of fibrosis occurred in up to 83% with survodutide and 18% with placebo (Fig. S9), improvement in fibrosis in up to 52% with survodutide and 26% with placebo (Fig. S10), improvement in fibrosis with no worsening of MASH in up to 50% with survodutide and 21% with placebo, and resolution of MASH in up to 75% with survodutide and 15% with placebo (Fig. S11). Complete results from the actual-treatment analysis are provided in Figures S9 through S14.

Safety

Overall, 95% of the participants receiving survodutide and 92% of those receiving placebo reported an adverse event (Table 2). The most common adverse events were gastrointestinal disorders, including nausea, diarrhea, and vomiting, all of which occurred more frequently with survodutide than with placebo. Trial discontinuation due to adverse events occurred in 20% of the participants across all survodutide doses (with 16% due to gastrointestinal events, mostly occurring in the rapid-dose-escalation phase), as compared with 3% with placebo (Table S7). Participants receiving survodutide had a higher frequency of fatigue (Table 2) and asymptomatic pancreatic hyperenzymemia (on the basis of adjudication; defined as an amylase or lipase level of ≥3 times the upper limit of the normal range not accompanied by clinical symptoms) than those receiving placebo. Hypoglycemia (grade 1 or 2) was reported in 5% of the participants receiving survodutide and 3% of those receiving placebo. All the participants with hypoglycemia had either type 2 diabetes or hyperinsulinemia at baseline and received antihyperglycemia medications. Table S8 shows adverse events according to actual treatment. The mean increase in heart rate at 48 weeks ranged from 2.4 to 4.2 bpm in participants receiving survodutide, as compared with 1.6 bpm in those receiving placebo (Fig. S15). One participant receiving placebo reported a change from baseline in the QT interval corrected for heart rate according to Fridericia's formula (QTcF) of more than 60 msec. There were no safety signals that suggested an increased risk of arrhythmia or QTcF prolongation.

Discussion

In this phase 2 trial, survodutide was associated with significant improvement in MASH with no worsening of fibrosis ($P<0.001$). Results also suggest a possibility of clinical benefit with respect to improvement in fibrosis (34% of the participants in the survodutide 6.0-mg group vs. 22% of those in the placebo group).
Dual agonism of glucagon receptor and GLP-1 receptor may confer clinical advantages over GLP-1 receptor monoagonist pharmacotherapies for MASH, mediated by a direct hepatic effect through glucagon receptor agonism[19] combined with extrahepatic effects through GLP-1 receptor agonism.[10–13,19,25] In a phase 2 trial, treatment with the GLP-1 receptor monoagonist semaglutide resulted in a significantly higher percentage of patients with MASH resolution than placebo but not in a significantly higher percentage of patients with improvement in fibrosis stage.[26] The benefit of survodutide with respect to fibrosis will need to be examined in future studies.
Cotadutide, a once-daily glucagon receptor–GLP-1 receptor dual agonist with a receptor ratio of 1:5,[27] improved the NAFLD fibrosis score and levels of ALT, AST, and propeptide of type III collagen in patients living with overweight or obesity and type 2 diabetes.[28] A phase 2 trial of SAR425899, a glucagon receptor–GLP-1 receptor dual agonist with a receptor ratio of 1:5, was halted owing to a high incidence of gastrointestinal adverse events.[12,29] Similarly, clinical development of NNC9204-1177, a glucagon receptor–GLP-1 receptor dual agonist with a receptor ratio of 1:3, was stopped owing to a dose-dependent increase in heart rate, a decrease in the reticulocyte count, and increased markers of inflammation.[30] Survodutide shows dual agonism of the glucagon receptor and

GLP-1 receptor at a ratio of approximately 1:8.[17] Our findings suggest that an appropriate ratio of glucagon receptor to GLP-1 receptor activation may achieve a beneficial effect of glucagon receptor–GLP-1 receptor dual agonism in patients with MASH, with a potentially acceptable adverse-event profile.

The adverse-event profile of survodutide was similar to that in a previous phase 2 trial involving participants living with obesity, in which the most common adverse events were nausea, vomiting, and diarrhea.[18] In our trial, the discontinuation of survodutide and placebo because of adverse events occurred in 20% and 3% of the participants, respectively. Discontinuation of survodutide mainly occurred during the rapid-dose-escalation phase of the trial and may be mitigated by a slower dose-escalation approach. Furthermore, no unexpected safety issues were identified. A limitation of this trial was that most participants were White, which may restrict the generalizability of the findings.

The results of this phase 2 trial support the potential for survodutide as a treatment for patients with MASH and liver fibrosis. These results warrant further investigation of this compound in phase 3 trials.

REFERENCES

1. Rinella ME, Lazarus JV, Ratziu V, et al. A multisociety Delphi consensus statement on new fatty liver disease nomenclature. Hepatology 2023;78:1966-86.
2. Long MT, Noureddin M, Lim JK. AGA clinical practice update: diagnosis and management of nonalcoholic fatty liver disease in lean individuals: expert review. Gastroenterology 2022;163(3):764-774.e1.
3. Le MH, Le DM, Baez TC, et al. Global incidence of non-alcoholic fatty liver disease: a systematic review and meta-analysis of 63 studies and 1,201,807 persons. J Hepatol 2023;79:287-95.
4. Wong VW-S, Ekstedt M, Wong GL-H, Hagström H. Changing epidemiology, global trends and implications for outcomes of NAFLD. J Hepatol 2023;79:842-52.
5. FDA approves first treatment for patients with liver scarring due to fatty liver disease. Food and Drug Administration, March 14, 2024 (https://www.fda.gov/news -events/press-announcements/fda-approves -first-treatment-patients-liver-scarring -due-fatty-liver-disease).
6. Harrison SA, Bedossa P, Guy CD, et al. A phase 3, randomized, controlled trial of resmetirom in NASH with liver fibrosis. N Engl J Med 2024;390:497-509.
7. Harrison SA, Loomba R, Dubourg J, Ratziu V, Noureddin M. Clinical trial landscape in NASH. Clin Gastroenterol Hepatol 2023;21:2001-14.
8. Povsic M, Wong OY, Perry R, Bottomley J. A structured literature review of the epidemiology and disease burden of nonalcoholic steatohepatitis (NASH). Adv Ther 2019;36:1574-94.
9. Uhlén M, Fagerberg L, Hallström BM, et al. Proteomics: tissue-based map of the human proteome. Science 2015;347: 1260419.
10. Cegla J, Troke RC, Jones B, et al. Coinfusion of low-dose GLP-1 and glucagon in man results in a reduction in food intake. Diabetes 2014;63:3711-20.
11. Day JW, Ottaway N, Patterson JT, et al. A new glucagon and GLP-1 co-agonist eliminates obesity in rodents. Nat Chem Biol 2009;5:749-57.
12. Eriksson O, Haack T, Hijazi Y, et al. Receptor occupancy of dual glucagonlike peptide 1/glucagon receptor agonist SAR425899 in individuals with type 2 diabetes. Sci Rep 2020;10:16758.
13. Tan TM, Field BCT, McCullough KA, et al. Coadministration of glucagon-like peptide-1 during glucagon infusion in humans results in increased energy expenditure and amelioration of hyperglycemia. Diabetes 2013;62:1131-8.
14. Sánchez-Garrido MA, Brandt SJ, Clemmensen C, Müller TD, DiMarchi RD, Tschöp MH. GLP-1/glucagon receptor coagonism for treatment of obesity. Diabetologia 2017;60:1851-61.

15. Seghieri M, Christensen AS, Andersen A, Solini A, Knop FK, Vilsbøll T. Future perspectives on GLP-1 receptor agonists and GLP-1/glucagon Receptor co-agonists in the treatment of NAFLD. Front Endocrinol (Lausanne) 2018;9:649.
16. Spezani R, Mandarim-de-Lacerda CA. The current significance and prospects for the use of dual receptor agonism GLP-1/ glucagon. Life Sci 2022;288:120188.
17. Zimmermann T, Thomas L, BaaderPagler T, et al. BI 456906: discovery and preclinical pharmacology of a novel GCGR/ GLP-1R dual agonist with robust antiobesity efficacy. Mol Metab 2022;66:101633.
18. le Roux CW, Steen O, Lucas KJ, Startseva E, Unseld A, Hennige AM. Glucagon and GLP-1 receptor dual agonist survodutide for obesity: a randomised, double-blind, placebo-controlled, dosefinding phase 2 trial. Lancet Diabetes Endocrinol 2024;12:162-73.
19. Valdecantos MP, Pardo V, Ruiz L, et al. A novel glucagon-like peptide 1/glucagon receptor dual agonist improves steatohepatitis and liver regeneration in mice. Hepatology 2017;65:950-68.
20. Kleiner DE, Brunt EM, Van Natta M, et al. Design and validation of a histological scoring system for nonalcoholic fatty liver disease. Hepatology 2005;41:1313-21.
21. Glass O, Filozof C, Noureddin M, et al. Standardisation of diet and exercise in clinical trials of NAFLD-NASH: recommendations from the Liver Forum. J Hepatol 2020;73:680-93.
22. Loomba R, Sanyal AJ, Kowdley KV, et al. Randomized, controlled trial of the FGF21 analogue pegozafermin in NASH. N Engl J Med 2023;389:998-1008.
23. Pais R, Cariou B, Noureddin M, et al. A proposal from the liver forum for the management of comorbidities in non-alcoholic steatohepatitis therapeutic trials. J Hepatol 2023;79:829-41.
24. Pinheiro J, Bornkamp B, Bretz F. Design and analysis of dose-finding studies combining multiple comparisons and modeling procedures. J Biopharm Stat 2006;16:639-56.
25. Pocai A, Carrington PE, Adams JR, et al. Glucagon-like peptide 1/glucagon receptor dual agonism reverses obesity in mice. Diabetes 2009;58:2258-66.
26. Newsome PN, Buchholtz K, Cusi K, et al. A placebo-controlled trial of subcutaneous semaglutide in nonalcoholic steatohepatitis. N Engl J Med 2021;384: 1113-24.
27. Henderson SJ, Konkar A, Hornigold DC, et al. Robust anti-obesity and metabolic effects of a dual GLP-1/glucagon receptor peptide agonist in rodents and nonhuman primates. Diabetes Obes Metab 2016;18:1176-90.
28. Nahra R, Wang T, Gadde KM, et al. Effects of cotadutide on metabolic and hepatic parameters in adults with overweight or obesity and type 2 diabetes: a 54-week randomized phase 2b study. Diabetes Care 2021;44:1433-42.
29. Adams B. GI toxicity hits midstage Sanofi GLP-1 drug as patients drop out. Fierce Biotech, April 27, 2018 (https:// www.fiercebiotech.com/biotech/gi -toxicity-hits-midstage-poc-sanofi-glp-1 -drug-as-patients-drop-out).
30. Friedrichsen MH, Endahl L, Kreiner FF, et al. Results from three phase 1 trials of NNC9204-1177, a glucagon/GLP-1 receptor co-agonist: effects on weight loss and safety in adults with overweight or obesity. Mol Metab 2023;78:101801.

Table 1
Demographic and Clinical Characteristics of the Participants at Baseline.

Characteristic	Survodutide, 2.4 mg (N=73)	Survodutide, 4.8 mg (N=72)	Survodutide, 6.0 mg (N=74)	Placebo (N=74)	Total (N=293)
Age — yr	49.6±13.7	50.2±12.9	50.4±13.1	53.0±11.5	50.8±12.8
Female sex — no. (%)	36 (49)	34 (47)	41 (55)	44 (59)	155 (53)
Body weight — kg	101.44±18.20	99.95±26.12	103.87±23.70	98.09±20.78	100.84±22.37
Waist circumference — cm	113.10±11.37	112.09±14.87	116.99±14.62	113.02±14.23	113.81±13.91
Body-mass index†	35.30±5.05	35.00±6.97	37.42±6.84	35.49±6.44	35.81±6.41
Type 2 diabetes					
Participants with condition — no. (%)	28 (38)	26 (36)	30 (41)	29 (39)	113 (39)
Glycated hemoglobin — %	6.90±1.12	6.90±1.06	6.92±0.91	7.08±0.87	6.96±0.96
Systolic blood pressure — mm Hg	128.8±14.8	132.4±14.1	127.0±14.8	129.4±12.5	129.4±14.1
Diastolic blood pressure — mm Hg	80.4±8.2	81.8±9.4	79.4±8.1	81.2±8.4	80.7±8.5
Liver-enzyme levels — U/liter					
Alanine aminotransferase	59.4±50.3	59.6±40.0	54.9±39.9	57.3±36.6	57.8±41.8
Aspartate aminotransferase	47.4±37.5	44.8±27.5	45.6±39.0	51.3±40.9	47.3±36.5
Total NAFLD activity score‡	5.2±1.0	5.3±1.0	5.1±1.0	5.2±1.1	5.2±1.0
Subscore for steatosis — no. (%)‡					
0	0	0	0	0	0
1	6 (8)	0	1 (1)	3 (4)	10 (3)
2	38 (52)	38 (53)	49 (66)	43 (58)	168 (57)
3	29 (40)	34 (47)	24 (32)	28 (38)	115 (39)
Liver fibrosis stage — no. (%)					
F1A	0	3 (4)	3 (4)	2 (3)	8 (3)
F1B	17 (23)	7 (10)	14 (19)	9 (12)	47 (16)
F1C	3 (4)	3 (4)	6 (8)	3 (4)	15 (5)
F2	30 (41)	36 (50)	24 (32)	30 (41)	120 (41)
F3	23 (32)	23 (32)	27 (36)	30 (41)	103 (35)
MRI-PDFF — %	19.75±7.56	21.09±8.26	17.85±6.34	19.62±7.59	19.57±7.51

*Plus–minus values are means ±SD. Subcutaneous doses were administered once weekly. Percentages may not total 100 because of rounding. MRI-PDFF denotes magnetic resonance imaging proton density fat fraction.
†The body-mass index is the weight in kilograms divided by the square of the height in meters.
‡The nonalcoholic fatty liver disease (NAFLD) activity score (ranging from 0 to 8) represents the sum of subscores for steatosis (scale of 0 to 3), lobular inflammation (scale of 0 to 3), and hepatocellular ballooning (scale of 0 to 2), with higher scores indicating more severe disease.

Table 2.
Summary of Adverse Events.

Event	Survodutide, 2.4 mg (N=73)	Survodutide, 4.8 mg (N=72)	Survodutide, 6.0 mg (N=74)	Survodutide, Total (N=219)	Placebo (N=74)
	number of participants (percent)				
Any adverse event	71 (97)	67 (93)	70 (95)	208 (95)	68 (92)
Adverse events from any system organ class†					
Nausea	46 (63)	49 (68)	49 (66)	144 (66)	17 (23)
Diarrhea	30 (41)	40 (56)	37 (50)	107 (49)	17 (23)
Vomiting	27 (37)	33 (46)	29 (39)	89 (41)	3 (4)
Constipation	15 (21)	12 (17)	19 (26)	46 (21)	11 (15)
Covid-19	18 (25)	16 (22)	7 (9)	41 (19)	14 (19)
Headache	13 (18)	16 (22)	11 (15)	40 (18)	12 (16)
Decreased appetite	16 (22)	9 (12)	13 (18)	38 (17)	7 (9)
Fatigue	15 (21)	11 (15)	11 (15)	37 (17)	6 (8)
Dyspepsia	7 (10)	9 (12)	15 (20)	31 (14)	3 (4)
Adverse event considered by the investigator to be related to survodutide or placebo	60 (82)	59 (82)	60 (81)	179 (82)	36 (49)
Adverse event leading to discontinuation of survodutide or placebo	12 (16)	15 (21)	17 (23)	44 (20)	2 (3)
Serious adverse event	4 (5)	7 (10)	6 (8)	17 (8)	5 (7)
Resulting in death	0	0	0	0	0
Life threatening	0	0	0	0	0
Persistent or clinically significant disability or incapacity	0	0	0	0	0
Resulting in or prolonging hospitalization	3 (4)	5 (7)	5 (7)	13 (6)	2 (3)
Congenital anomaly or birth defect	0	0	0	0	0
Other medically important serious adverse event	3 (4)	3 (4)	3 (4)	9 (4)	3 (4)
Serious adverse event considered by the investigator to be related to survodutide or placebo	1 (1)	0	0	1 (<1)	0

*All adverse events occurred during the on-treatment observation period for planned treatment. Additional information on adverse events is provided in Tables S7 and S8. Covid-19 denotes coronavirus disease 2019.
†Shown are adverse events with an incidence of at least 20% in any trial group, according to the preferred term in the *Medical Dictionary for Regulatory Activities*.

Figure 1.
Primary End Point after 48 Weeks of Planned Treatment. Subcutaneous doses were administered once weekly. The primary end point was histologic improvement (reduction) in metabolic dysfunction– associated steatohepatitis (MASH) with no worsening of fibrosis at week 48. Improvement in MASH was defined as a decrease in the nonalcoholic fatty liver disease activity score (range, 0 to 8, with higher scores indicating more severe disease) of at least 2 points with a decrease in either the lobu- lar inflammation subscore (range, 0 to 3) or hepatocellular ballooning sub- score (range, 0 to 2) of at least 1 point. No worsening of fibrosis was de- fined as the absence of any increase in the fibrosis stage. Participants who did not undergo endoftreatment biopsy were considered to have a nonre- sponse. Error bars represent 95% confidence intervals and have not been adjusted for multiplicity, so they should not be used for hypothesis testing.

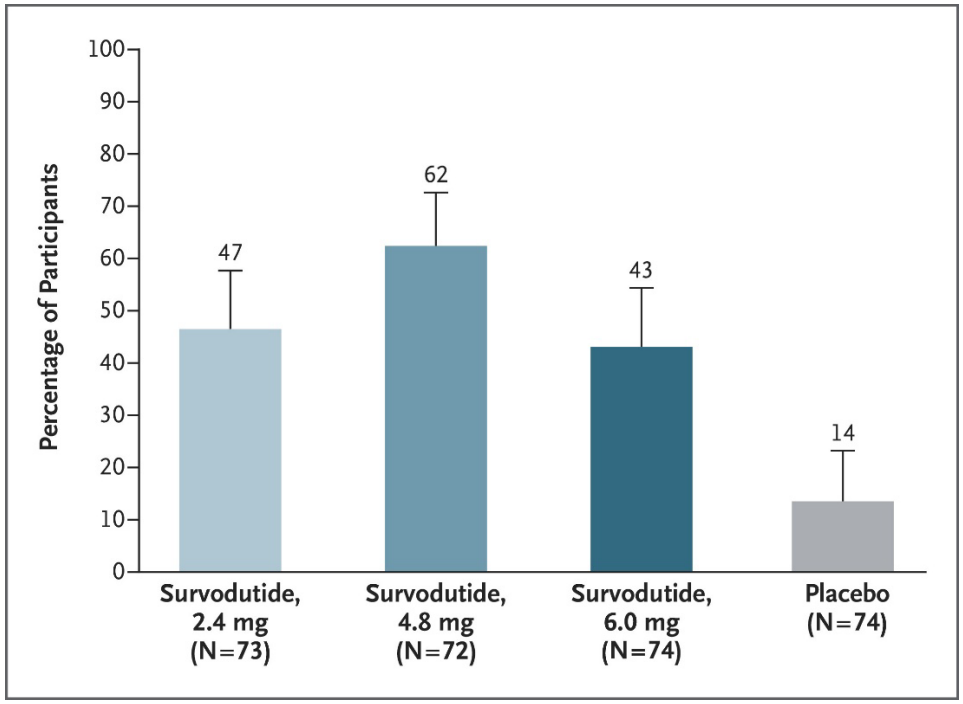

Figure 2.
Change in Liver-Enzyme Levels over Time. Shown are the mean absolute changes from baseline in the alanine aminotransferase level (Panel A) and aspartate aminotransferase level (Panel B) from the plannedtreatment analysis. I bars represent standard deviations.