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Tirzepatide for Metabolic Dysfunction–Associated Steatohepatitis with Liver Fibrosis

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ABSTRACT

BACKGROUND

Metabolic dysfunction–associated steatohepatitis (MASH) is a progressive liver disease associated with liver-related complications and death. The efficacy and safety of tirzepatide, an agonist of the glucose-dependent insulinotropic polypeptide and glucagon-like peptide-1 receptors, in patients with MASH and moderate or severe fibrosis is unclear.

METHODS

We conducted a phase 2, dose-finding, multicenter, double-blind, randomized, placebo-controlled trial involving participants with biopsy-confirmed MASH and stage F2 or F3 (moderate or severe) fibrosis. Participants were randomly assigned to receive once-weekly subcutaneous tirzepatide (5 mg, 10 mg, or 15 mg) or placebo for 52 weeks. The primary end point was resolution of MASH without worsening of fibrosis at 52 weeks. A key secondary end point was an improvement (decrease) of at least one fibrosis stage without worsening of MASH.

RESULTS

Among 190 participants who had undergone randomization, 157 had liver-biopsy results at week 52 that could be evaluated, with missing values imputed under the assumption that they would follow the pattern of results in the placebo group. The percentage of participants who met the criteria for resolution of MASH without worsening of fibrosis was 10% in the placebo group, 44% in the 5-mg tirzepatide group (difference vs. placebo, 34 percentage points; 95% confidence interval [CI], 17 to 50), 56% in the 10-mg tirzepatide group (difference, 46 percentage points; 95% CI, 29 to 62), and 62% in the 15-mg tirzepatide group (difference, 53 percentage points; 95% CI, 37 to 69) ($P<0.001$ for all three comparisons). The percentage of participants who had an improvement of at least one fibrosis stage without worsening of MASH was 30% in the placebo group, 55% in the 5-mg tirzepatide group (difference vs. placebo, 25 percentage points; 95% CI, 5 to 46), 51% in the 10-mg tirzepatide group (difference, 22 percentage points; 95% CI, 1 to 42), and 51% in the 15-mg tirzepatide group (difference, 21 percentage points; 95% CI, 1 to 42). The most common adverse events in the tirzepatide groups were gastrointestinal events, and most were mild or moderate in severity.

CONCLUSIONS

In this phase 2 trial involving participants with MASH and moderate or severe fibrosis, treatment with tirzepatide for 52 weeks was more effective than placebo with respect to resolution of MASH without worsening of fibrosis. Larger and longer trials are needed to further assess the efficacy and safety of tirzepatide for the treatment of MASH. (Funded by Eli Lilly; SYNERGY-NASH ClinicalTrials.gov number, NCT04166773.)

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*A complete list of the investigators in this trial is provided in the Supplementary Appendix, available at NEJM.org.

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CME

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Metabolic dysfunction–associated steatohepatitis (MASH), formerly known as nonalcoholic steatohepatitis (NASH), is a progressive liver disease that is characterized by excess fat accumulation in the liver, hepatic inflammation, and hepatocyte injury (histologically confirmed by the presence of ballooning), with or without fibrosis.[1,2] MASH is associated with an increased risk of cardiovascular disease, and in patients who also have clinically significant liver fibrosis, it conveys a higher risk of liver-related complications and death.[2-4] The prevalence of MASH is increasing globally in parallel with obesity and type 2 diabetes mellitus.[2,5] In 2019, MASH was the second most common indication for liver transplantation and the most rapidly increasing indication.[6]

The beneficial effects of weight reduction on MASH are well documented.[2,7,8] Higher incidences of resolution of MASH and regression of liver fibrosis have been observed with achievement of a weight reduction of 10% or more by means of lifestyle modification or with bariatric metabolic surgery.[8,9] In phase 2 trials with 48-week and 72-week treatment periods, glucagon-like peptide-1 (GLP-1) receptor agonists have been shown to be efficacious for the resolution of MASH but not for regression of fibrosis.[10,11] Tirzepatide, a once-weekly glucose-dependent insulinotropic polypeptide (GIP) and GLP-1 receptor agonist,[12] has been shown to induce substantial weight reduction in placebo-controlled trials involving persons with type 2 diabetes mellitus, obesity, or both.[13-15] In patients with type 2 diabetes mellitus, treatment with tirzepatide resulted in a reduction in liver fat and improvement in biomarkers of MASH and fibrosis.[16,17] Here we report the results of the SYNERGY-NASH trial, in which the efficacy and safety of tirzepatide was investigated in patients with biopsy-confirmed MASH and moderate or severe fibrosis.

Methods

Trial Design and Oversight

The SYNERGY-NASH trial was a phase 2, multicenter, double-blind, randomized, placebo-controlled trial that was conducted at 130 sites in 10 countries (see the Supplementary Appendix, available with the full text of this article at NEJM.org). The protocol (available at NEJM.org) was approved by the ethical review board at each site. The trial was conducted in accordance with the principles of the Declaration of Helsinki, the International Council for Harmonisation Good Clinical Practice guidelines, and applicable laws and regulations. All the participants provided written informed consent. The trial was designed by the sponsor (Eli Lilly) in collaboration with two academic authors; site monitoring, data collation, and data analysis were performed by the sponsor. The first draft of the manuscript was written by the first and second authors. All the authors participated in the interpretation of the data, provided critical review of the manuscript, and vouch for the accuracy and completeness of the data and for the fidelity of the trial to the protocol.

Participants

Eligible participants were 18 to 80 years of age and had a body-mass index (the weight in kilograms divided by the square of the height in meters) between 27 and 50, with or without type 2 diabetes mellitus. Histologically confirmed inclusion criteria were a diagnosis of MASH with stage 2 (F2) or 3 (F3) fibrosis (on a scale of 0 [no fibrosis] to 4 [cirrhosis]) and a nonalcoholic fatty liver disease (NAFLD) activity score of 4 or higher (on a scale of 0 to 8, with higher scores indicating more severe disease), with a score of 1 or higher for each subcomponent (steatosis [on a scale of 0 to 3], hepatocellular ballooning [on a scale of 0 to 2], and lobular inflammation [on a scale of 0 to 3]). These criteria were evaluated by two central pathologists (academic authors) with the use of the NASH Clinical Research Network scoring system[18] and on the basis of a liver biopsy that was performed at screening or no more than 6 months before screening. Key exclusion criteria were chronic liver disease other than MASH, cirrhosis, evidence of hepatic decompensation, excessive alcohol consumption (defined as >14 standard drinks per week for women and >21 standard drinks per week for men), uncontrolled type 2 diabetes mellitus (as defined by a glycated hemoglobin level of >9.5%) and the use of confounding concomitant medication (including GLP-1 receptor agonists or medications that are intended to promote weight reduction). Full eligibility criteria are listed in the protocol.

PROCEDURES

Participants were randomly assigned in a 1:1:1:1 ratio to receive maintenance treatment with tirzepatide at doses of 5 mg, 10 mg, or 15 mg or to receive placebo; all the doses were administered subcutaneously once weekly for 52 weeks. Randomization was performed with the use of an interactive Web-response system (IWRS) and was stratified according to type 2 diabetes mellitus status (present vs. absent) and geographic region (Japan vs. United States or Mexico vs. Europe or Israel). The starting dose of tirzepatide or placebo was 2.5 mg and was increased by 2.5 mg every 4 weeks, in a blinded manner with the use of the IWRS, until the target maintenance dose was attained. If dose escalation resulted in adverse events, the investigators could reduce the dose to the next lower maintenance dose. Throughout the trial, all the participants received counseling regarding nutrition and physical activity in accordance with site programs.

A liver biopsy was planned to be performed at the end of the 52-week treatment period, and the results were evaluated by the central pathologists, who were unaware of the trial-group assignments and the clinical characteristics of the participants. In some cases, the biopsy was performed before or after week 52 owing to early withdrawal from the trial, participant availability, or delays in scheduling, particularly during the coronavirus disease 2019 pandemic. Further details regarding the liver histologic evaluations are provided in the Supplementary Appendix.

END POINTS AND ASSESSMENTS

The primary end point was resolution of MASH without worsening of fibrosis (defined as no increase in the fibrosis stage) at week 52. MASH resolution was defined as no steatotic liver disease (steatosis score of 0) or simple steatosis (a steatosis score of 1, 2, or 3) without steatohepatitis and an inflammation score of 0 or 1 and a ballooning score of 0. Secondary end points, all of which were assessed at week 52, were a decrease of at least one fibrosis stage without worsening of MASH (defined as no increase in the NAFLD activity score), an increase of at least one fibrosis stage, a decrease of at least 2 points in the NAFLD activity score with a reduction of at least 1 point in at least two NAFLD activity score components (steatosis, hepatocellular ballooning, and lobular inflammation), and changes in liver fat content (as assessed by means of the magnetic resonance imaging proton density fat fraction [MRI-PDFF]) and body weight. Images from MRI were transmitted to a reader at a central facility (Perspectum) for evaluation.

A list of the exploratory end points is provided in the Supplementary Appendix. These end points include change in extracellular hepatic water content (which provides an indication of hepatic fibroinflammation[19]) as assessed by means of iron-corrected T1-weighted MRI, change in liver stiffness as measured by means of vibration-controlled transient elastography (FibroScan), changes in liver-enzyme levels, and changes in serum biomarkers of steatohepatitis and fibrosis, including the cytokeratin 18 and N-terminal type III collagen propeptide (Pro-C3) levels, the scores on the Enhanced Liver Fibrosis test and the Fibrosis-4 index, and the result of a noninvasive diagnostic blood test known as NIS4.

Safety assessments included adverse events, vital signs, clinical laboratory assessments, and electrocardiograms. Selected clinical events were adjudicated by an independent, external adjudication committee whose members were unaware of the trial-group assignments. Additional details of the trial design and procedures have been described previously.[20]

STATISTICAL ANALYSIS

We estimated that a sample of 196 participants would provide the trial with at least 80% power to show the superiority of each tirzepatide dose level to placebo with respect to resolution of MASH without worsening of fibrosis (the primary end point) at a two-sided significance level of 0.05. The sample size was based on the assumption that 42.5% of the participants in the tirzepatide groups and 12.5% of those in the placebo group would have a response and that 20% of the participants would withdraw from the trial.

The efficacy end points were analyzed with the use of a treatment-regimen estimand that included data from all the participants who had undergone randomization; multiple imputation was used to handle missing data (see the Supplementary Appendix). A prespecified analysis of the primary end point was performed in which data from all the randomly assigned participants

were included except for data obtained after permanent discontinuation of tirzepatide or placebo. The safety analyses included data obtained from all the randomly assigned participants during the 52-week treatment period and a 4-week safety follow-up period.

Logistic regression was used to analyze all the binary end points. Comparisons among the trial groups for continuous variables that were assessed over time were analyzed with the use of either an analysis of covariance model or a mixed model for repeated measures. Analyses were adjusted for the stratification factors (type 2 diabetes mellitus status and geographic region). All statistical analyses were performed with the use of SAS software, version 9.4 (SAS Institute), or R software, version 4.2.2 (R Foundation for Statistical Computing). No prespecified plan was made to adjust for multiple comparisons. The P values reported for the primary end point reflect a post hoc adjustment to accommodate three dose comparisons against placebo; all the other end points are reported with the use of point estimates and 95% confidence intervals. The confidence intervals have not been adjusted for multiple comparisons and should not be used to infer definitive treatment effects. An interim analysis for futility was performed, and on the basis of the results, the trial was continued without modification (see the Supplementary Appendix). Further details are provided in the statistical analysis plan, available with the protocol.

RESULTS

PARTICIPANTS

Between January 24, 2020, and January 10, 2023, a total of 190 participants underwent randomization. Overall, 165 participants (87%) completed the trial, 161 (85%) completed the trial regimen, and 157 (83%) had end-of-treatment liver-biopsy results that could be evaluated (Fig. S1 in the Supplementary Appendix). The percentage of participants who ultimately received the randomly assigned dose with dose escalation was 96%, 96%, and 85% in the 5-mg, 10-mg, and 15-mg tirzepatide groups, respectively; after the target dose was reached, the dose was reduced in 0, 9 (20%), and 3 (7%) of these participants. The demographic and clinical characteristics of the participants at baseline were generally similar across the trial groups, except for the mean γ-glutamyltransferase (GGT) level, which was higher in the placebo group than in the tirzepatide groups (Table 1 and Table S2). Most of the participants were White (86%) or Asian (12%), with 36% identifying as Hispanic or Latino. The mean age was 54.4 years, and the mean body-mass index was 36.1; a total of 57% were women, and 58% had type 2 diabetes mellitus. Overall, 57% had stage F3 fibrosis; the incidence was higher in the placebo and 5-mg tirzepatide groups than in the other groups. Table S1 describes the representativeness of the trial population.

EFFICACY

The percentage of participants who met the criteria for resolution of MASH without worsening of fibrosis (the primary end point) was significantly higher in all three tirzepatide groups than in the placebo group (10%), with an incidence of 44% in the 5-mg tirzepatide group (difference vs. placebo, 34 percentage points; 95% confidence interval [CI], 17 to 50), 56% in the 10-mg tirzepatide group (difference, 46 percentage points; 95% CI, 29 to 62), and 62% in the 15-mg tirzepatide group (difference, 53 percentage points; 95% CI, 36 to 69) ($P<0.001$ for all three comparisons) (Fig. 1A). The results of the analysis of the primary end point in which data from all the participants who had undergone randomization were included except for data obtained after permanent discontinuation of tirzepatide or placebo are provided in Figure S2.

The percentage of participants who had an improvement (decrease) of at least one fibrosis stage without worsening of MASH (a key secondary end point) was 30% in the placebo group, 55% in the 5-mg tirzepatide group (difference vs. placebo, 25 percentage points; 95% CI, 5 to 46), 51% in the 10-mg tirzepatide group (difference, 22 percentage points; 95% CI, 1 to 42), and 51% in the 15-mg tirzepatide group (difference, 21 percentage points; 95% CI, 1 to 42) (Fig. 1B). Reduction in fibrosis was more apparent among participants with stage F3 fibrosis than among those with stage F2 fibrosis, possibly owing to a lower placebo response (Fig. S3). Tirzepatide treatment did not have an apparent effect on the percentage of participants who had a decrease of at least two fibrosis stages without worsening of MASH, an increase of at least one fibrosis stage,

or an absence of fibrosis at week 52 (Fig. S4 and Table S3).

A decrease of at least 2 points in the NAFLD activity score with a reduction of at least 1 point in at least two NAFLD activity score components at week 52 occurred in 72 to 78% of the participants across the three tirzepatide groups and in 37% of those in the placebo group (Fig. S5). Changes in the three components of the NAFLD activity score at week 52 were evaluated as an exploratory end point. In this analysis, 1-point improvements in the steatosis score occurred in 62 to 75% of the participants in the tirzepatide groups and in 32% of those in the placebo group; 1-point improvements in the lobular inflammation score occurred in 61 to 62% of those in the tirzepatide groups and in 36% of those in the placebo group; and 1-point improvements in the hepatocellular ballooning score occurred in 77 to 82% of those in the tirzepatide groups and in 54% of those in the placebo group (Table S4).

Figure S6 shows changes in body weight after 52 weeks in the overall trial population and in the subgroups of participants with or without type 2 diabetes mellitus. In the overall trial population, the mean percentage change in body weight was −10.7%, −13.3%, and −15.6% in the 5-mg, 10-mg, and 15-mg tirzepatide groups, respectively, as compared with −0.8% in the placebo group. There appeared to be an association between greater degrees of weight reduction and higher incidences of MASH resolution without worsening of fibrosis, but the relationship with weight reduction was less apparent for reduction in fibrosis without worsening of MASH (Fig. S7). Changes in serum lipid levels and glycated hemoglobin levels are shown in Table S5.

Across the three doses of tirzepatide, reductions at week 52 were observed for serum levels of alanine aminotransferase (ALT) (mean percentage decreases, 51.6 to 56.7%), aspartate aminotransferase (AST) (42.1 to 47.7%), and GGT (39.3 to 49.0%) (Table 2 and Fig. 2 and Table S6 and Fig. S8). In a post hoc analysis, ALT levels had normalized (defined as a level of ≤30 U per liter at week 52 in participants with a baseline level of >30 U per liter) in 47%, 64%, and 75% of the participants in the 5-mg, 10-mg, and 15-mg tirzepatide groups, respectively, and in 12% of those in the placebo group (Fig. S9). Changes in liver fat content (as assessed by MRI-PDFF), extracellular hepatic water content (as assessed by iron-corrected T1-weighted MRI), liver stiffness, NIS4 test results, the score on the Enhanced Liver Fibrosis test, the Pro-C3 level, the cytokeratin 18 level, and the score on the Fibrosis-4 index are shown in Table 2 and Table S6.

SAFETY

Overall, adverse events were reported in 92% of the participants in the tirzepatide groups and in 83% of those in the placebo group (Table 3). The most common adverse events reported with tirzepatide were gastrointestinal events, and most (96%) were mild or moderate in severity. Discontinuation of tirzepatide or placebo because of an adverse event occurred in 4% of the participants in the tirzepatide groups and also in 4% of those in the placebo group. Serious adverse events were reported in nine participants (6%) in the tirzepatide groups and in three participants (6%) in the placebo group. A list of serious adverse events is provided in Table S7.

Adjudicated cases of progression to cirrhosis occurred in four participants (3%) in the tirzepatide groups and in two participants (4%) in the placebo group (Table 3). There was no evidence of drug-induced liver injury (Fig. S10). One adjudicated major adverse cardiovascular event (a transient ischemic attack) occurred in the 5-mg tirzepatide group. Gallbladder-related adverse events were reported in four participants (3%) in the tirzepatide groups and in one participant (2%) in the placebo group. No cases of acute pancreatitis were reported.

DISCUSSION

At 52 weeks, all three doses of tirzepatide — a once-weekly GIP and GLP-1 receptor agonist — were superior to placebo with respect to resolution of MASH without worsening of fibrosis, the primary end point. Tirzepatide treatment was associated with changes in fibrosis, the NAFLD activity score, and the subscores for the individual components of the NAFLD activity score, including steatosis, lobular inflammation, and hepatocellular ballooning. In addition, changes were observed in body weight; in blood markers of liver injury, including serum levels of ALT, AST, GGT, and cytokeratin 18; and in biomarkers of liver fat, inflammation, and fibrosis such as liver fat content (as assessed by MRI-PDFF), extracellular hepatic water content (as assessed

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

Characteristic	Tirzepatide, 5 mg (N=47)	Tirzepatide, 10 mg (N=47)	Tirzepatide, 15 mg (N=48)	Placebo (N=48)	Total (N=190)
Age — yr	55.0±11.6	54.3±12.1	54.9±10.0	53.5±11.6	54.4±11.3
Female sex — no. (%)	27 (57)	26 (55)	29 (60)	27 (56)	109 (57)
Race or ethnic group — no. (%)†					
American Indian or Alaska Native	1 (2)	1 (2)	1 (2)	0	3 (2)
Asian	5 (11)	6 (13)	6 (12)	5 (10)	22 (12)
Black	0	1 (2)	0	0	1 (<1)
White	41 (87)	39 (83)	41 (85)	43 (90)	164 (86)
Hispanic or Latino ethnic group — no. (%)†	19 (40)	15 (32)	17 (35)	18 (38)	69 (36)
Body weight — kg	100.7±22.2	102.6±23.8	100.0±18.1	96.0±21.6	99.8±21.5
Body-mass index‡	36.1±6.0	36.6±6.3	35.9±5.7	36.0±6.7	36.1±6.1
Type 2 diabetes — no. (%)	26 (55)	27 (57)	29 (60)	29 (60)	111 (58)
Liver fibrosis stage — no. (%)§					
F2	17 (36)	25 (53)	22 (46)	17 (35)	81 (43)
F3	30 (64)	22 (47)	26 (54)	31 (65)	109 (57)
NAFLD activity score¶	5.4±1.0	5.3±0.9	5.0±0.9	5.3±1.0	5.3±0.9
Alanine aminotransferase (U/liter)	67.9±39.9	61.2±35.9	58.7±25.4	59.7±30.3	61.8±33.2
Aspartate aminotransferase (U/liter)	55.5±28.2	47.0±23.8	47.5±20.7	52.3±21.3	50.6±23.7
Glycated hemoglobin — %	6.6±1.3	6.4±1.1	6.4±0.9	6.8±1.2	6.5±1.1
Liver fat content — %‖	19.0±6.9	17.6±7.5	18.8±8.3	18.2±6.8	18.4±7.3
Extracellular hepatic water content — msec**	920.5±120.5	894.1±88.5	923.3±88.1	917.7±92.0	913.0±97.5
Liver stiffness — kPa††	12.6±5.9	11.1±4.3	11.4±5.7	12.0±5.1	11.8±5.3
Fibrosis-4 index score‡‡	1.8±1.1	1.5±0.7	1.5±0.6	1.6±0.7	1.6±0.8
NIS4 test score§§	0.8±0.2	0.7±0.2	0.8±0.2	0.8±0.2	0.8±0.2
Enhanced Liver Fibrosis test score¶¶	9.9±1.0	9.8±0.8	9.7±0.6	9.9±0.8	9.8±0.8
Pro-C3 — μg/liter‖‖	145.3±103.2	127.9±76.8	115.6±49.7	127.4±57.9	128.9±74.6

* Plus–minus values are means ±SD. Percentages may not total 100 because of rounding.
† Race and ethnic group were reported by the participants. Participants could be recorded as both White and Hispanic or Latino.
‡ The body-mass index is the weight in kilograms divided by the square of the height in meters.
§ The fibrosis stages according to the nonalcoholic steatohepatitis (NASH) Clinical Research Network are as follows: F0 indicates no fibrosis, F1 mild (perisinusoidal or periportal) fibrosis, F2 moderate (perisinusoidal and portal or periportal) fibrosis, F3 severe (bridging) fibrosis, and F4 cirrhosis.[18]
¶ The nonalcoholic fatty liver disease (NAFLD) activity score is the unweighted sum of scores for steatosis (on a scale of 0 to 3), lobular inflammation (on a scale of 0 to 3), and hepatocellular ballooning (on a scale of 0 to 2) and ranges from 0 to 8 on the basis of the NASH Clinical Research Network scoring system.[18] Higher scores indicate more severe disease.
‖ Liver fat content was assessed by means of the magnetic resonance imaging proton density fat fraction (MRI-PDFF); values of 5% or higher are consistent with hepatic steatosis.[2]
** Extracellular hepatic water content, which is a measure of hepatic fibroinflammation, was assessed by means of iron-corrected T1-weighted MRI. Values of 875 msec or higher have a high specificity for metabolic dysfunction–associated steatohepatitis (MASH) with an NAFLD activity score of 4 or higher and a fibrosis stage of F2 or higher.[19]
†† Liver stiffness was assessed by means of vibration-controlled transient elastography (FibroScan). Higher values indicate more severe fibrosis. Advanced fibrosis is considered to be unlikely if the value is below 8 kPa and to be likely if the value is 12 kPa or higher.[2]
‡‡ The score on the Fibrosis-4 index is derived from platelet count, alanine aminotransferase and aspartate aminotransferase levels, and age. Advanced fibrosis is considered to be unlikely if the score is below 1.3 and to be likely if the score is 2.67 or higher.[2]
§§ The NIS4 test consists of a panel of four serum biomarkers, including microRNA-34a, α-2 macroglobulin, YKL-40, and glycated hemoglobin. The presence of MASH with an NAFLD activity score of 4 or higher and a fibrosis stage of F2 or higher is considered to be unlikely if the value is below 0.36 and to be likely if the value is 0.63 or higher.[21]
¶¶ The Enhanced Liver Fibrosis test consists of a panel of three serum biomarkers associated with matrix turnover: hyaluronic acid, tissue inhibitor of metalloproteinase 1, and procollagen type III N-terminal peptide. Advanced fibrosis is considered to be unlikely if the value is below 7.7 and to be likely if the value is 9.8 or higher. A score of 9.8 or higher indicates an increased risk of progression to cirrhosis and liver-related clinical events.[2]
‖‖ N-terminal type III collagen propeptide (Pro-C3) is a serum biomarker that detects the formation of type III collagen. On the basis of the first-generation assay, a level of higher than 13.45 μg per liter was indicative of advanced fibrosis.[22] The results shown here were measured with the use of the second generation assay; to compare these results with published data that were measured with the first-generation assay, multiply by 0.152.

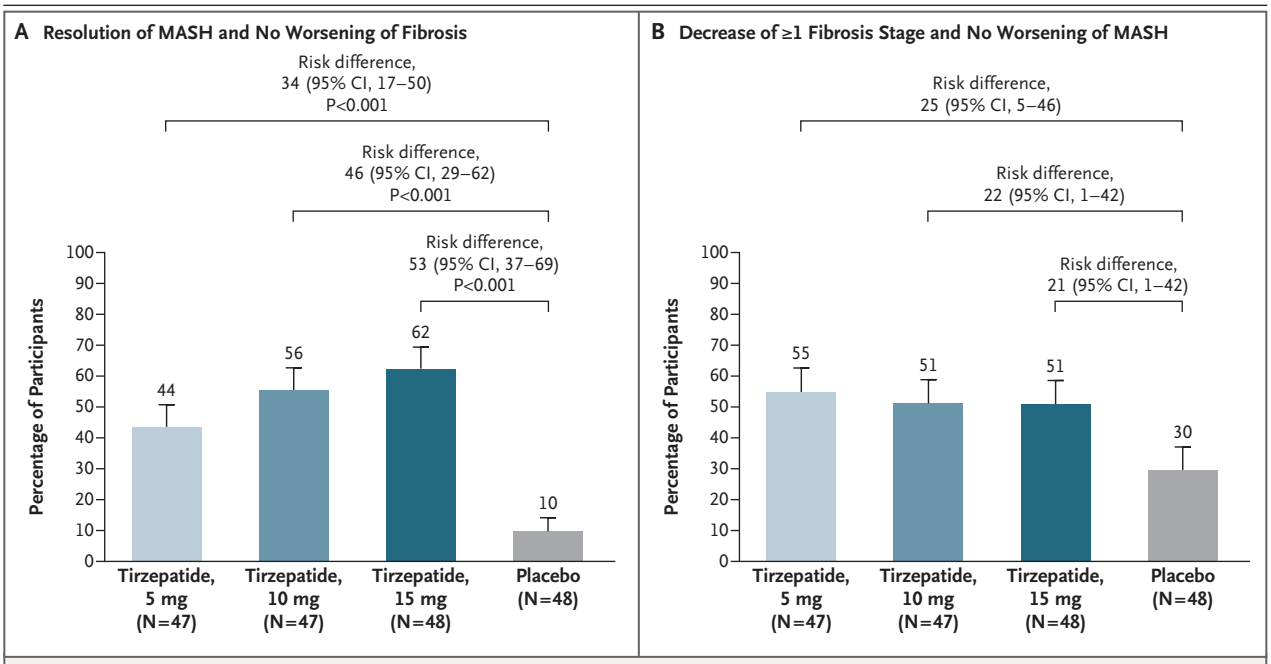


Figure 1. Primary and Key Secondary End Points.

Panel A shows the percentage of participants with resolution of metabolic dysfunction–associated steatohepatitis (MASH) and no worsening of fibrosis (defined as no increase in the fibrosis stage) at week 52 (primary end point). MASH resolution was defined as no steatotic liver disease (steatosis score of 0 [on a scale of 0 to 3]) or simple steatosis (a steatosis score of 1, 2, or 3) without steatohepatitis and an inflammation score of 0 or 1 (on a scale of 0 to 2) and a hepatocellular ballooning score of 0 (on a scale of 0 to 2); higher scores indicate more severe disease. Panel B shows the percentage of participants with an improvement (decrease) of at least one fibrosis stage and no worsening of MASH (defined as no increase in the nonalcoholic fatty liver disease activity score) at week 52 (key secondary end point). Risk differences indicate percentage-point differences between the groups. The confidence intervals have not been adjusted for multiple comparisons and should not be used to infer definitive effects of tirzepatide. The percentage estimates and risk differences were calculated with the use of a logistic-regression model.[23] I bars indicate standard errors.

by iron-corrected T1-weighted MRI), liver stiffness, the Pro-C3 level, the score on the Enhanced Liver Fibrosis test, and NIS4 test results.

Weight reduction induced by lifestyle interventions, bariatric metabolic surgery, and the use of GLP-1 receptor agonists has a beneficial effect on MASH.[7-9] Whereas previous trials have shown substantial reductions in body weight and liver fat with tirzepatide therapy,[13-16] this trial included the use of histologic assessments to also show that treatment with tirzepatide led to a higher incidence of MASH resolution than placebo without worsening of fibrosis. The addition of GIP receptor agonism to GLP-1 receptor agonism not only increases the degree of weight reduction observed[24] but also has direct effects on white adipose tissue that may benefit patients with MASH. In subcutaneous white adipose tissue, GIP receptor activation increases blood flow in adipose tissue, augments postprandial triglyceride uptake, and improves insulin sensitivity.[25,26] In preclinical models, the insulin-sensitizing effects of GIP receptor agonism have been found to be independent of changes in body weight,[27] and in clinical trials, tirzepatide treatment yielded greater improvements in insulin sensitivity than GLP-1 receptor agonists.[28,29] Improved lipid storage in white adipose tissue may reduce ectopic fat deposition in the liver.[30] In addition to its effects on adipose tissue, tirzepatide increases fat oxidation during weight reduction.[31]

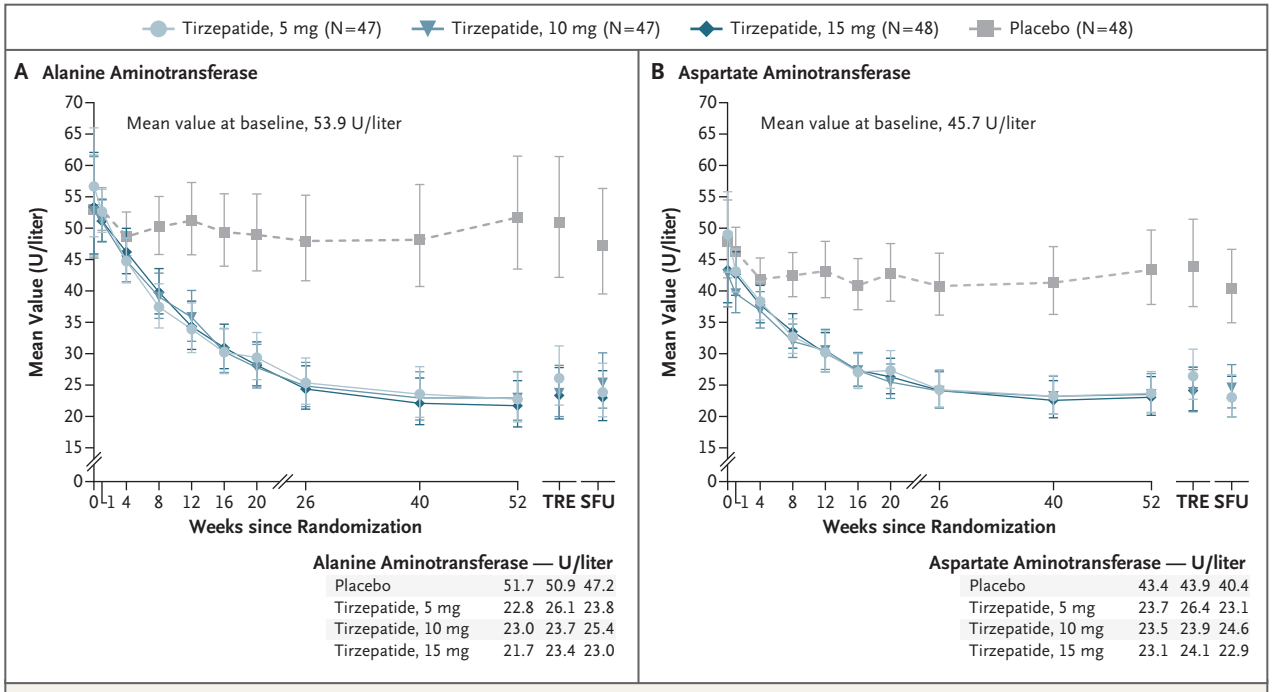
MASH resolution has been hypothesized to result in fibrosis regression and a reduction in major adverse liver outcomes (also known as MALO).[4] In a natural history study, a decrease in disease activity was associated with an improvement in fibrosis, and an increase in disease activity was associated with fibrosis progression.[32] In an observational study, weight reduction induced by bariatric metabolic surgery was shown to reduce major adverse liver outcomes.[33] However, MASH resolution after surgery occurs more

Table 2. Changes from Baseline to Week 52 in Selected Liver End Points.*

End Point	Tirzepatide, 5 mg (N=47)	Tirzepatide, 10 mg (N=47)	Tirzepatide, 15 mg (N=48)	Placebo (N=48)
Alanine aminotransferase				
Percentage change	−51.6±4.4	−56.0±3.8	−56.7±3.9	−5.6±9.1
LS mean difference between tirzepatide and placebo (95% CI) — percentage points	−48.7 (−60.2 to −33.9)	−53.4 (−63.8 to −40.0)	−54.1 (−64.3 to −41.0)	—
Aspartate aminotransferase				
Percentage change	−42.1±4.4	−47.7±3.7	−47.1±3.9	−3.8±7.7
LS mean difference between tirzepatide and placebo (95% CI) — percentage points	−39.8 (−51.4 to −25.5)	−45.7 (−55.9 to −33.0)	−45.1 (−55.3 to −32.4)	—
Liver fat content				
Percentage change	−45.7±8.0	−41.3±7.7	−57.0±8.1	−9.8±8.2
LS mean difference between tirzepatide and placebo (95% CI) — percentage points	−35.9 (−57.9 to −13.9)	−31.4 (−53.4 to −9.5)	−47.2 (−69.4 to −25.0)	—
Extracellular hepatic water content — msec				
Absolute change	−70.7±15.5	−87.2±13.3	−107.2±13.5	−16.7±14.2
LS mean difference between tirzepatide and placebo (95% CI)	−54.0 (−93.3 to −14.8)	−70.5 (−107.2 to −33.8)	−90.5 (−128.2 to −52.9)	—
Liver stiffness — kPa				
Absolute change	−3.1±0.7	−3.3±0.6	−3.5±0.6	−0.02±0.7
LS mean difference between tirzepatide and placebo (95% CI)	−3.1 (−5.0 to −1.2)	−3.3 (−5.1 to −1.5)	−3.5 (−5.3 to −1.7)	—
NIS4 test score				
Absolute change	−0.29±0.04	−0.36±0.04	−0.39±0.04	−0.02±0.04
LS mean difference between tirzepatide and placebo (95% CI)	−0.27 (−0.39 to −0.15)	−0.34 (−0.45 to −0.22)	−0.36 (−0.48 to −0.24)	—
Enhanced Liver Fibrosis test score				
Absolute change	−0.50±0.12	−0.47±0.11	−0.45±0.11	0.16±0.12
LS mean difference between tirzepatide and placebo (95% CI)	−0.66 (−0.98 to −0.33)	−0.63 (−0.94 to −0.31)	−0.61 (−0.93 to −0.29)	—
Pro-C3 — μg/liter				
Absolute change	−40.1±6.9	−45.7±6.2	−44.0±6.5	5.2±6.8
LS mean difference between tirzepatide and placebo (95% CI)	−45.3 (−64.4 to −26.1)	−50.9 (−69.0 to −32.7)	−49.1 (−67.4 to −30.9)	—

* Plus–minus values are estimates ±SE. The confidence intervals have not been adjusted for multiple comparisons and should not be used to infer definitive treatment effects. The number of participants with test results at baseline varied by test. Alanine aminotransferase and aspartate aminotransferase data were analyzed with the use of log transformation. LS denotes least-squares.

rapidly than regression of fibrosis. A longitudinal study showed that a higher percentage of patients had an improvement of at least one fibrosis stage at 5 years after surgery than at 1 year.[34] Thus, treatment periods of longer than 52 to 72 weeks may be needed to show substantial treatment effects on fibrosis with pharmacologic agents that induce weight reduction. The relatively short duration of the SYNERGY-NASH trial (52 weeks) may account for the similar incidence of improvement in fibrosis (51 to 55%) across the three doses of tirzepatide. Alternatively, fibrosis regression of approximately 50% may be the ceiling effect with weight reduction. In a recent trial, the incidence of MASH resolution after bariatric metabolic surgery did not increase further above a weight-reduction threshold of 20%.[9] The use of tirzepatide in combination with other agents



Alanine Aminotransferase — U/liter

Placebo	51.7	50.9	47.2
Tirzepatide, 5 mg	22.8	26.1	23.8
Tirzepatide, 10 mg	23.0	23.7	25.4
Tirzepatide, 15 mg	21.7	23.4	23.0

Aspartate Aminotransferase — U/liter

Placebo	43.4	43.9	40.4
Tirzepatide, 5 mg	23.7	26.4	23.1
Tirzepatide, 10 mg	23.5	23.9	24.6
Tirzepatide, 15 mg	23.1	24.1	22.9

Figure 2. Mean Liver-Enzyme Levels over Time.

Shown are the mean alanine aminotransferase and aspartate aminotransferase levels from baseline through week 52 and during the subsequent 4-week safety follow-up period (SFU). Values were estimated with the use of a mixed model for repeated measures with log transformation, and the analysis included data for all the participants who had undergone randomization. Week 52 estimates for the treatment-regimen estimand (TRE) are also shown (see the Supplementary Appendix for details). The TRE included data obtained during the treatment period for all the randomly assigned participants who received at least one dose of tirzepatide or placebo, regardless of adherence to the trial drug. The mean values at baseline (top left of each graph) are geometric means from actual measurements at baseline. I bars indicate 95% confidence intervals.

may lead to a higher incidence of fibrosis reduction; such agents may include fibroblast growth factor 21 analogues,[35] pan-PPAR (peroxisome proliferator–activated receptor) agonists,[36] or thyroid hormone receptor beta–selective agonists.[37]

The safety profile of tirzepatide in this trial involving persons with MASH was consistent with that observed in previous phase 3 clinical trials involving persons with type 2 diabetes mellitus, obesity, or both.[13-16] Gastrointestinal events (nausea, diarrhea, and constipation) were the most commonly reported adverse events and were mostly mild or moderate in severity. The incidence of nausea and diarrhea was higher in both the placebo group and the tirzepatide groups of the current trial than in the corresponding groups of the SURPASS-1 trial (a phase 3 trial involving patients with type 2 diabetes mellitus)[13] and the SURMOUNT-1 trial (a phase 3 trial involving patients with obesity but without type 2 diabetes mellitus)[14] (Fig. S11), but the incidence of adverse events leading to discontinuation of tirzepatide or placebo was similar (Fig. S12). There were no reports of drug-induced liver injury or pancreatitis. No new safety signals were identified.

The strengths of this trial include its multicenter, international, double-blind, randomized, placebo-controlled design. Liver-biopsy results were evaluated in a blinded manner by two expert liver pathologists. The histologic inclusion criteria and end points have been endorsed by both the Food and Drug Administration and the European Medicines Agency. The trial included adequate numbers of persons with and persons without type 2 diabetes mellitus.

The key limitations of the trial were the sample size, which did not provide adequate statistical power to evaluate the effect of tirzepatide on fibrosis while controlling for multiple comparisons, and the trial duration, which was too short to assess the effect of tirzepatide on major adverse liver outcomes. This trial did not

Table 3. Adverse Events.*

Variable	Tirzepatide, 5 mg (N=47)	Tirzepatide, 10 mg (N=47)	Tirzepatide, 15 mg (N=48)	Placebo (N=48)	Total (N=190)
			number (percent)		
Any adverse event	43 (91)	44 (94)	44 (92)	40 (83)	171 (90)
Any serious adverse event	5 (11)	4 (9)	0	3 (6)	12 (6)
Adverse event leading to the discontinuation of tirzepatide or placebo	2 (4)	0	4 (8)	2 (4)	8 (4)
Gastrointestinal disorder leading to the discontinuation of tirzepatide or placebo	2 (4)	0	2 (4)	1 (2)	5 (3)
Adverse event from any system organ class, according to preferred term	43 (91)	44 (94)	44 (92)	40 (83)	171 (90)
Nausea	17 (36)	16 (34)	21 (44)	6 (12)	60 (32)
Diarrhea	15 (32)	17 (36)	13 (27)	11 (23)	56 (29)
Decreased appetite	9 (19)	10 (21)	11 (23)	1 (2)	31 (16)
Constipation	11 (23)	9 (19)	7 (15)	3 (6)	30 (16)
Covid-19	5 (11)	6 (13)	9 (19)	4 (8)	24 (13)
Headache	3 (6)	6 (13)	3 (6)	5 (10)	17 (9)
Abdominal distention	3 (6)	3 (6)	6 (12)	4 (8)	16 (8)
Abdominal pain	6 (13)	3 (6)	4 (8)	3 (6)	16 (8)
Fatigue	4 (9)	4 (9)	5 (10)	3 (6)	16 (8)
Dizziness	2 (4)	6 (13)	4 (8)	2 (4)	14 (7)
Dyspepsia	2 (4)	8 (17)	2 (4)	2 (4)	14 (7)
Vomiting	3 (6)	3 (6)	7 (15)	1 (2)	14 (7)
Weight decreased	5 (11)	3 (6)	4 (8)	0	12 (6)
Urinary tract infection	2 (4)	3 (6)	2 (4)	4 (8)	11 (6)
Abdominal pain, upper	6 (13)	2 (4)	0	2 (4)	10 (5)
Arthralgia	5 (11)	2 (4)	2 (4)	1 (2)	10 (5)
Adjudicated major adverse cardiovascular event†	1 (2)	0	0	0	1 (<1)
Adjudicated MASH-related clinical events, all with progression to cirrhosis‡	2 (4)	2 (4)	0	2 (4)	6 (3)

* Covid-19 denotes coronavirus disease 2019.

† The adjudicated major adverse cardiovascular event that occurred in one participant was a transient ischemic attack. Major adverse cardiovascular events were defined as myocardial infarction, hospitalization for unstable angina, hospitalization for heart failure, coronary interventions such as coronary-artery bypass graft and percutaneous coronary intervention, and cerebrovascular events including cerebrovascular accident (stroke) and transient ischemic attack.

‡ One additional participant in the 5-mg tirzepatide group had fibrosis that progressed from stage F3 to stage F4 on the basis of the central pathologist's assessment, but this result was adjudicated as "no event" on the basis of information obtained from the investigator and the local pathologist who performed a side-by-side comparison of the biopsy results at baseline with those at the end of treatment.

assess the safety and efficacy of tirzepatide in patients with MASH that had progressed to cirrhosis. No adjustment for multiplicity was made in the calculation of the sample size and confidence intervals. Although the trial had good representation of Asian and Hispanic persons, persons of African and Indian descent were underrepresented.

In this trial, treatment with tirzepatide, a GIP and GLP-1 receptor agonist, was more effective

than placebo with respect to resolution of MASH without worsening of fibrosis in patients with MASH and moderate or severe fibrosis. Larger and longer trials are needed to further assess the efficacy and safety of tirzepatide for the treatment of MASH with liver fibrosis and to determine whether tirzepatide treatment could reduce the risk of major adverse liver outcomes.

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APPENDIX

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