**Supplemental Table 1.** Principal phase 2 multicenter, double-blind, randomized placebo-controlled trials (with a follow-up ≥48 weeks) assessing the efficacy and safety of incretin-based pharmacotherapies, i.e., single, dual or triple incretin receptor agonists, for the treatment of MASLD or MASH.

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| --- | --- | --- | --- | --- | --- |
| Author, Year (Ref.) | Study design, and Participant characteristics | Drug tested, Participants included, and Trial duration | Major hepatic effects | Major metabolic effects | Major adverse effects |
| GLP-1 receptor agonists |
| Newsome PN et al., 2021 (1) | Phase 2b randomized, double-blind, placebo-controlled trial involving 320 patients with biopsy-confirmed MASH and liver fibrosis (stage F1 to F3); ~77% White, 60% female, mean age 55 years, BMI 35.5 kg/m2, 62% with type 2 diabetes | Subcutaneous semaglutide 0.1 mg/day (n=80 pts), 0.2 mg/day (n=78 pts), 0.4 mg/day (n=82 pts) or placebo (n=80 pts) for 72 weeks | The percentageof patients in whom MASH resolution was achieved with no worsening of fibrosis (primary endpoint)was 40% in the 0.1-mg group, 36% in the 0.2-mg group, 59% in the 0.4-mg group,and 17% in the placebo group (P<0.001 for semaglutide 0.4 mg vs. placebo). Improvement in liver fibrosis by at least one stage with no worsening of MASH occurred in 49% of the patients in the 0.1-mg group, 32% of the patients in the 0.2-mg group, 43% of the patients in the 0.4-mg group and in 33% of the patients in the placebo group (P=0.48 vs. placebo) | Treatment with semaglutide resulted in dose-dependent significant reductions in body weight, HbA1c levels and plasma lipid profile (triglycerides, VLDL, HDL cholesterol) at week 72. The mean percent changes in body weight were −5% in the semaglutide 0.1-mggroup, −9% in the 0.2-mg group, −13% in the0.4-mg group, and −1% in the placebo group. The mean estimated glomerular filtration rate (eGFR) declined slightly across all treatment groups, including the placebo group, from baseline to week 72 | Rates of nausea, constipation, and vomiting were significantly higher in the 0.4-mg group than in the placebo group (nausea, 42% vs. 11%; constipation, 22% vs. 12%; and vomiting,15% vs. 2%). The percentage of patients who discontinuedtreatment because of adverse events was 7% with semaglutide (for all doses) and 5% with placebo |
| Loomba R et al., 2023 (2) | Phase 2b randomized, double-blind, placebo-controlled trial involving 71 patients with biopsy-confirmed MASH-related compensated cirrhosis (stage F4); ~87% White, 69% female, mean age 59.5 years, BMI 35 kg/m2, 75% with type 2 diabetes | Subcutaneous semaglutide 2.4 mg/week (n=47 pts) or placebo (n=24 pts) for 48 weeks | There was no significant difference between the two groups neither in the proportion of patients with an improvement in liver fibrosis of one stage or more without worsening of NASH (five [11%] of 47 patients in the semaglutide group vs. seven [29%] of 24 in the placebo group (p=0.087) nor in the proportion of patients who achieved NASH resolution (p=0.29). Compared to placebo, semaglutide led to significant reductions in serum liver enzymes, liver fat content (but not liver stiffness), and levels of the exploratory hepatic collagen biomarker pro-collagen 3 peptide | Patients treated with semaglutide lost more body weight, had lower serum triglycerides and VLDL cholesterol concentrations, and those with type 2 diabetes also had significant reductions in HbA1c levels, compared with placebo | Similar proportions of patients in each group reported adverse events (42 [89%] patients in the semaglutide group vs. 19 [79%] in the placebo group) and serious adverse events (six [13%] vs. two [8%]). The most common adverse events were nausea (21 [45%] vs. four [17%]), diarrhea (nine [19%] vs. two [8%]), and vomiting (eight [17%] vs. none) |
| Dual GLP-1/glucagon receptor agonists |
| Sanyal AJ et al., 2024 (3) | Phase 2b randomized, double-blind, placebo-controlled trial involving 293 patients with biopsy-confirmed MASH and liver fibrosis (stage F1 to F3); ~70% White, 53% female, mean age 51 years, BMI 35.8 kg/m2, 39% with type 2 diabetes | Subcutaneous survodutide 2.4 mg/week (n=73 pts), 4.6 mg/week (n=72 pts), 6.0 mg/week (n=74 pts) or placebo (n=74 pts) for 48 weeks (including a dose escalation phase of 24 weeks) | Improvement (reduction)\* in MASH with no worsening of fibrosis (primary endpoint) occurredin 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 dose-response curve). A decrease in liver fat content (on MRI-PDFF) 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 liver fibrosis by at least one stage with no worsening of MASH occurred in 34%, 36%, 32%, and 18%, respectively (P-value for between-group differences not tested)§ | Patients treated with survodutide lost more body weight, had significantly lower concentrations of triglycerides and HbA1c, and lower blood pressure compared to placebo. Survodutide increased heart rate compared to placebo | Adverse events that were more frequent with survodutide than placebo included nausea (66% vs. 23%), diarrhea (49% vs. 23%), and vomiting (41% vs. 4%); serious adverse events occurred in 8% with survodutide vs. 7% with placebo. Discontinuation of survodutide and placebo because ofadverse events occurred in 20% and 3% of participants, respectively |
| Dual GLP-1/GIP receptor agonists |
| Loomba R et al., 2024 (4) | Phase 2b randomized, double-blind, placebo-controlled trial involving 190 patients with biopsy-confirmed MASH and moderate or severe liver fibrosis (stage F2 and F3); ~85% White, 57% female, mean age 54.4 years, BMI 36.1 kg/m2, 58% with type 2 diabetes | Subcutaneous tirzepatide 5 mg/week (n=47 pts), 10 mg/week (n=47 pts), 15 mg/week (n=48 pts) or placebo (n=48 pts) for 52 weeks  | The percentage of participants who met the criteria for MASH resolution withoutworsening of fibrosis (primary endpoint) 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 percentagepoints; 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 tirzepatidegroup (difference vs. placebo, 25 percentage points; 95% CI 5 to 46), 51% in the10-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) (P-value for between-group differences not tested)§ | In the overall trialpopulation, the mean percentage change in body weight was −11%, −13%, and −16% in the 5-mg, 10-mg, and 15-mg tirzepatide groups, respectively. Tirzepatide also decreased significantly plasma lipids and HbA1c levels compared to placebo | The most common adverse events reported with tirzepatide were gastrointestinal events, and most (96%) were mild or moderate in severity. Serious adverse events were reported in nine participants (6%) in the tirzepatide groups and in three participants (6%) in the placebo group. Discontinuation of tirzepatide or placebo because of an adverse event occurred in 4% of the participants in the tirzepatide groups and in 4% of thosein the placebo group |
| Triple GLP-1/GIP/glucagon receptor agonists |
| Sanyal AJ et al., 2024 (5) | Phase 2a randomized, double-blind, placebo-controlled trial involving 98 patients with imaging-defined MASLD (measured by MRI-PDFF >10%); ~98% White, 47% female, mean age 46.6 years, BMI 38.4 kg/m2, no type 2 diabetics included | Subcutaneous retatrutide 1 mg/week (n=20 pts), 4 mg/week (n=19 pts), 8 mg/week (n=22 pts), 12 mg/week (n=18 pts) or placebo (n=19 pts) for 48 weeks | Most of the reduction in liver fat occurred within the first 24 weeks. The mean relative changefrom baseline in liver fat content (LFC on MRI-PDFF) at 24 weeks was −43% (1 mg), −57% (4 mg), −81% (8 mg), −82% (12 mg) and +0.3% (placebo) (all P<0.001 versus placebo).At 24 weeks, normal LFC (<5%) was achieved by 27% (1 mg), 52% (4 mg), 79% (8 mg), 86% (12 mg) and 0% (placebo) of participants. The mean relative changefrom baseline in liver fat content (LFC on MRI-PDFF) at 48 weeks was −51% (1 mg), −59% (4 mg), −82% (8 mg), −86% (12 mg) and -4.6% (placebo) (all P<0.001 versus placebo) | Retatrutide induced significant reductions in body weight, abdominal adiposity and improvements in insulin sensitivity, lipid metabolism (triglycerides, very low-density lipoprotein cholesterol andnon-high-density lipoprotein cholesterol) and adipocyte hormones (including adiponectin, leptin and FGF-21) | Transient andgenerally mild-to-moderate gastrointestinal events were the mostfrequently reported adverse events in MASLD. The frequency of these adverse events was higher in the 8 mg and 12 mg dose groups. Two participantstreated with retatrutide (2.5%) experienced a total of three seriousadverse events |

NB: The phase 2 placebo-controlled RCTs included in the table became available after publication of our 2021 meta-analysis examining the efficacy of different GLP-1RAs for the treatment of MASLD or MASH (Mantovani A et al. Metabolites 2021; 11(2): 73. doi: 10.3390/metabo11020073).

\*Histologic improvement in MASH was defined as reduction of at least two points in NAFLD activity score (NAS) with at least one point decrease in NAS subscore of either lobular inflammation or ballooning.

§Risk differences indicate percentage-point differences between the groups; since the confidence intervals have not been adjusted for multiple comparisons (using the Bonferroni or other multiple comparison tests) and should not be used to infer definitive treatment effects of tirzepatide or survodutide on liver fibrosis improvement with no worsening of MASH.

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