Peer review file

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Review Comments:

Comment 1: Page 6, lines 17-25 (weight loss): Here the authors missed two seminal papers: (1) Vilar-Gomez et al, Gastroenterology 2015, DOI: 10.1053/j.gastro.2015.04.005, showing in a prospective study in nearly 300 patients with biopsy-proven NASH that weight loss is associated with NASH resolution (90% at >10% weight loss) and even fibrosis regression. (2) Lassailly et al, Gastroenterology 2015, doi 10.1053/j.gastro.2015.04.014, showing that weight loss after bariatric surgery is associated with NASH resolution.
Reply 1: We have included these two papers as suggested
Changes in the text: We have added the following data: " In a study of 109 severely or morbidly obese patients, 85.4% had resolution of NASH on biopsy 1 year after undergoing bariatric surgery. NASH resolution was higher among patient with mild disease compared to moderate to severe NASH (94.2% vs. 70%, p=0.007). A prospective study of 293 patients evaluated the effects of varying degrees of weight loss on NASH-related histological parameters. Of the subjects who achieved ≥10% weight loss, 90% experienced NASH resolution and 45% had fibrosis regression on biopsy." (see Page 6, Line 16-19 and line 22-25)

Comment 2: Page 10, line 23: Semaglutide (not semeglutide)
Reply 2: We have corrected the spelling
Changes in the text: "A phase 2 randomized controlled trial of 320 NASH patients evaluated the efficacy and safety of three doses of subcutaneous semaglutide for 72 weeks (45). " See page 11 line 5

Comment 3: Page 11, first paragraph – please mention that co-agonists of GLP1R and the glucagon receptor (e.g., cotadutide, Ambery et al, Lancet 2018, doi: 10.1016/S0140-6736(18)30726-8; Boland et al, Nat Metab 2020, doi 10.1038/s42255-020-0209-6) or the GLP1R and GIPR (e.g., tirzepatide: Frias et al, Lancet 2018, doi 10.1016/S0140-6736(18)32260-8; Hartman et al, Diabetes Care 2020, 10.2337/dc19-1892) have clinically demonstrated strong weight loss and reduction in NASH biomarkers. A study in a pre-clinical model of NASH investigating the effect of combined GLP1R, GIPR and glucagon receptor agonism has also recently been published (Kannt et al, Diab Obes Metab 2020, doi 10.1111/dom.14035)
Reply 3: We have added the following text to include the suggested information as below
Changes in the text: We have added the following data: "Based on the positive outcomes observed with GLP-1 agonists, several new combination agents affecting this pathway are currently under investigation. The dual GLP-1 and glucagon receptor (GCGR) agonist, cotadutide, has been shown to decrease body weight and liver fat

content (46). Similarly, treatment with tirzepatide, a dual glucose-dependent insulinotropic polypeptide (GIPR) and GLP-1 agonist, resulted in significant weight loss and decreased NASH-related biomarkers at doses ≥ 10 mg/week (47, 48). The triple combination of GLP-1/GCGR/GIPR agonism was studied in mice with biopsy-proven NASH. This triple incretin combination treatment led to significant reductions in body weight, hepatic steatosis, and NAS scores (49). Although these novel dual/triple therapies still require additional testing within the NASH population, the initial results are promising. (See page 11 and line 11-21)

Comment 4: Page 12f., saroglitazar: Here, the authors primarily cite conference abstracts. Have any of the studies been published in peer-reviewed journals? Please mention in the first paragraph that the approval from March 2020 is for NASH.
Reply 4: Unfortunately there are no full studies published on saroglitazar. There are only abstracts presented at conference proceedings as cited in our article. We have modified the text to reflect that the approval from March 2020 is for NASH.
Changes in the text: We have the modified this statement in the text. "Saroglitazar magnesium, a first in class dual PPARα/γ agonist approved by the Drug Controller General of India for the treatment of NASH in March 2020, improves dyslipidemia and insulin sensitivity. " (See Page 13 and line 13)
"The complete results of both EVIDENCES trials have not yet been published." (See Page 14 and line 8-9)

Comment 5: Page 15, line 4: Please remove the sentence "This trial provided conclusive evidence that Ezetimibe has no role in the treatment of NASH." While Ezetimibe did not provide benefit in the MOZART trial, it cannot be ruled out that it may show efficacy in other settings with different patient populations.
Reply 5: We have removed this sentence and added another statement in its place as below.
Changes in the text: Although ezetimibe did reduce liver fat from baseline (as measured by magnetic resonance imaging-derived proton density-fat fraction [MRI-PDFF]), it was not better than placebo. In addition, ezetimibe did not improve histological features. Further studies should be conducted to determine if ezetimibe has any role in the treatment of NAFLD. (See Page 15 and line 22-24)

Comment 6: Page 16, OCA: Please add that the FDA has issued a complete response letter not supporting the use of OCA for the treatment of fibrosis due to NASH (https://ir.interceptpharma.com/node/13671/pdf).
Reply 6: We have modified the text to reflect this change and added the following text as below.
Changes in the text: " OCA currently has a black box warning for hepatic decompensation and failure when dosed incorrectly in patients with primary biliary cholangitis (PBC) and Child-Pugh Class B or C or decompensated cirrhosis. A recently published report of 8 patients with PBC or primary sclerosing cholangitis highlighted the risk of hepatoxicity with OCA (86). All patients in this case series developed cholestatic liver injury with modest increases in aminotransferase levels. The onset of injury ranged from 87 to 379 days after the initiation of OCA and half of the patients progressed to liver failure requiring transplantation. Only one patient within this cohort

was initiated on an inappropriate dose of OCA based on Child-Pugh score. The FDA recently recommended additional safety analysis from the ongoing REGENERATE study in support of its potential approval for NASH (87). Additional long-term data from this trial is highly anticipated to further assess the potential role of OCA in this patient population." (See Page 18 and line 7-19)

Comment 7: Page 21, elafibranor: Please move it up to the Lipid-lowering agents section. Please add that elafibranor did not meet the primary endpoint in RESOLVE-IT (https://ir.genfit.com/news-releases/news-release-details/genfit-announces-results-interim-analysis-resolve-it-phase-3)

Reply 7: We have moved elafibranor up to the lipid-lowering agents section as suggested. We added the statement that elafibranor did not meet the primary endpoint in RESOLVE-IT. We have added the following text as below

Changes in the text: " Elafibranor (GFT505) is a dual PPAR-α and -δ agonist that has proven to be hepatoprotective in animal models (76). An important distinction between elafibranor and other agents targeting PPARs in NASH is that it does not possess any PPARγ activity; therefore it is devoid of the unwanted side effects commonly associated with PPARγ activation such as weight gain, edema, and fluid retention. This newly developed drug underwent studies for the treatment of NASH and to assess for improvements in cardiometabolic risk profiles. The GOLDEN-505 trial was a randomized, international phase 2b trial comparing elafibranor 80 mg and 120 mg to placebo in 274 NASH subjects (77). After 52 weeks of therapy, significantly more patients in the elafibranor 120 mg group achieved resolution of NASH without worsening fibrosis (19% vs. 12% placebo, P=0.045). Resolution of NASH was defined as the disappearance of ballooning and disappearance or persistence of mild lobular inflammation. The RESOLVE-IT phase 3 trial evaluating long-term outcomes of elafibranor 120 mg in patients with NASH and fibrosis is currently underway (78). The primary endpoints of this study are: reversal of NASH without worsening of fibrosis at week 72 and a composite of all-cause mortality, cirrhosis, and liver-related outcomes after 4 years of therapy. Unfortunately, an interim analysis showed no difference in NASH resolution without worsening fibrosis between groups (19.2% elafibranor vs. 14.7% placebo) (79). Additional analyses will be conducted to further determine the utility of elafibranor in the treatment of NASH. "

(See page 16 and line 14-25 and page 17 and line 1-8)

Comment 8: Page 22, selonsertib: Results from both Stellar 3 and 4 have been published: SA Harrison et al, J Hepatol 2020, doi 10.1016/j.jhep.2020.02.027. In both trials, selonsertib failed to reach primary efficacy endpoints.

Reply 8: We have added results from these 2 studies as suggested and added the following information to the text as below

Changes in the text: The planned treatment duration was 240 weeks in both studies; however, both studies were terminated early due to lack of efficacy at the 48-week analysis. (See page 24 and line 10-12)

Comment 9: Page 23, ACC inhibitor GS-0976: Please mention the reduction in hepatic steatosis came at the expense of an increase in serum triglycerides.

Reply 9: We have added the following information to the text as below

Changes in the text: " However, more patients receiving GS-0976 experienced on-treatment hypertriglyceridemia (+14 mg/dl from baseline in the GS-0976 20 mg group vs -6 mg/dl from baseline in placebo group) which responded to treatment with fibrates or fish oil. A multivariate analysis determined that subjects with a baseline triglyceride level ≥250 mg/ml were more likely to develop hypertriglyceridemia on GS-0976. " (See page 25 and line 7-12)

Comment 10: Page 26: VK2809 -> Please introduce a Section "Thyroid-hormone receptor beta agonists" in the "Lipid-lowering agents" part. Include resmetirom (MGL-3196) in addition to VK2809, see, e.g., AM Harrison et al, Lancet 2019, doi: 10.1016/S0140-6736(19)32517-6

Reply 10: We have added a section on thyroid-hormone receptor beta-agonists. We have also added a section on Resmetirom and added the following information to the text as below. However, since we have divided our paper into approved drugs for NASH in the top section and drugs in ongoing clinical trials in a separate section, we would like to keep resmetirom in the section under ongoing clinical trials.

Changes in the text: "Another liver-selective thyroid hormone receptor beta agonist, resmetirom (MGL-3196) was studied in a multi-center, randomized, placebo-controlled trial in 125 patients with biopsy-proven NASH (130). Among the 116 patients with MRI-PDFF assessment at week 12, there was a significant reduction in relative hepatic fat fraction in the resmetirom arm vs. placebo (-32.9% vs. 10.4%, respectively). Based on these results, a phase 3 clinical trial is being conducted to further evaluate the efficacy and safety of resmetirom in patients with NASH and fibrosis with a planned enrollment of 2000 patients. The primary outcomes are NASH resolution at week 52 in patients with stage 2 or 3 fibrosis and a composite end-point of all-cause mortality, cirrhosis, and other significant liver-related events. (See page 28 and line 9-18)

Comment 11: If possible, the authors should include primary outcomes for the treatment in table 1.

Reply 11: We have added a new column in table 1 with primary outcomes

Changes in the text: Please see Table 1 for the added text

Comment 12: FDA recently declined to approve Intercept's OCA as chronic liver disease/NASH therapy. It would be great to include some comments on it.

Reply 12: We have modified the text to reflect this change and added the following text as below.

Changes in the text: " OCA currently has a black box warning for hepatic decompensation and failure when dosed incorrectly in patients with primary biliary cholangitis (PBC) and Child-Pugh Class B or C or decompensated cirrhosis. A recently published report of 8 patients with PBC or primary sclerosing cholangitis highlighted the risk of hepatoxicity with OCA (86). All patients in this case series developed cholestatic liver injury with modest increases in aminotransferase levels. The onset of injury ranged from 87 to 379 days after the initiation of OCA and half of the patients progressed to liver failure requiring transplantation. Only one patient within this cohort was initiated on an inappropriate dose of OCA based on Child-Pugh score. The FDA recently recommended additional safety analysis from the ongoing REGENERATE study in support of its potential approval for NASH (87). Additional long-term data

from this trial is highly anticipated to further assess the potential role of OCA in this patient population. ” (See Page 18 and line 7-19)