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OPINION REVIEW

Semaglutide might be a key for breaking the vicious cycle of metabolically associated fatty liver disease spectrum?

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Abstract

Metabolically associated fatty liver disease (MAFLD) is a liver manifestation of metabolic syndrome potentially related to unfavorable hepatic and extrahepatic outcomes and progression to cirrhosis. Up to date, there are no approved pharmacotherapies for the treatment of MAFLD, so management focused on lifestyle interventions to encourage weight loss, and treatment of coexisting conditions is the only available option. Unfortunately, the aforementioned is often not potent enough to offer reversal or slow down hepatic inflammation and fibrosis. Glucagon-like peptide-1 receptor agonists have a favorable effect on glycemic management and weight loss of patients with type 2 diabetes mellitus and recently published data suggest their potential in MAFLD treatment. In addition, some of the agents have proven cardiovascular and renal benefits in dedicated cardiovascular outcome trials, making them an interesting therapeutic option. In this opinion review, we discuss the role of semaglutide in MAFLD.

Key Words: Semaglutide; Non-alcoholic fatty liver disease; Glucagon-like peptide-1 receptor agonists; Metabolically associated fatty liver disease

Core Tip: The pathogenesis of metabolically associated fatty liver disease (MAFLD) is closely interrelated to type 2 diabetes mellitus (T2DM), with insulin resistance and hyperinsulinemia as key characteristics. Glucagon-like peptide-1 receptor agonists have a favorable effect on glycemic management and weight loss in T2DM patients. Semaglutide is an especially interesting agent with favorable metabolic actions in patients sharing T2DM and MAFLD (but also sole MAFLD) phenotype, available in injectable and oral formulation, thus more attractive for a broader spectrum of patients.

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INTRODUCTION

Metabolically associated fatty liver disease: The trigger of the vicious cycle ending in cardiovascular disease, cirrhosis, and liver cancer. What to offer to our patients?

Non-alcoholic fatty liver disease (NAFLD) is a chronic liver disease that includes a broad spectrum of clinical and histopathological conditions, from simple steatosis (non-alcoholic fatty liver) to liver inflammation and injury with or without fibrosis [non-alcoholic steatohepatitis (NASH)] that can further progress to cirrhosis and hepatocellular carcinoma (HCC)[1]. Exclusion of patients with alcohol intake, or other chronic liver diseases is mandatory for the diagnosis. Nowadays, NAFLD is the leading cause of liver disease worldwide. Its prevalence is rising, becoming a major cause of liver disease-related deaths and liver transplantation[2,3]. Additionally, it carries an increased risk for cardiovascular disease (CVD) morbidity and mortality[4]. The condition is strongly associated with obesity and type 2 diabetes mellitus (T2DM) and is considered a liver manifestation of metabolic syndrome. The definition of NAFLD is relatively narrow and based on exclusion. Thus, in recent years, a new concept has emerged, better represented by the term metabolically associated fatty liver disease (MAFLD). The diagnosis of MAFLD is based on the presence of hepatic fat (diagnosed by histology, imaging, or blood biomarkers) along with at least one of these three metabolic conditions: overweight/obesity, T2DM, or evidence of metabolic dysregulation[5]. The latter is defined by at least two criteria in patients with normal body mass index (BMI): enlarged waist circumference; hypertension or anti-hypertensive treatment; increased triglycerides or treatment with hypolipemic drugs; low high-density lipoprotein cholesterol; prediabetes; high Homeostatic Model Assessment of Insulin Resistance score; and high-sensitivity C-reactive protein[6]. In addition, MAFLD diagnosis does not exclude excessive alcohol consumption and other causes of liver disease.

The pathogenesis of MAFLD is multifactorial and closely interrelated to the pathogenesis of T2DM, with insulin resistance (IR) and hyperinsulinemia as key shared characteristics of both conditions. Moreover, individuals with MAFLD are more insulin resistant than those without MAFLD, irrespective of glucose tolerance and BMI[7]. IR acts on adipose tissue, worsens adipocyte dysfunction, induces lipolysis, and releases adipokines and proinflammatory cytokines. IR increases de novo lipogenesis in the liver, resulting in elevated free fatty acids and lipid accumulation within hepatocytes, predisposing to liver injury and inflammation[8]. Proinflammatory environment further contributes to CVD[9].

The relationship between T2DM and NAFLD/MAFLD is bidirectional; T2DM is a risk factor for the progression of NAFLD/MAFLD to fibrosis[10,11], as well as HCC[12], and conversely, NAFLD/MAFLD increases the risk of developing T2DM[13]. In addition, patients with NAFLD are known to have high cardiovascular (CV) risk and CVD is the leading cause of death in NAFLD patients[4]. Furthermore, given its broader definition, it should be expected that MAFLD is associated with higher CVD morbidity and mortality compared to NAFLD. However, the data comparing the two are inconclusive and scarce. In consideration that MAFLD is inclusive of patients with alcohol consumption and other liver disease, and it is relatively new concept additional studies are needed to define group of patients that are especially at risk of CVD morbidity and mortality[14].

Nevertheless, a treatment that addresses all of the above conditions would be strongly recommended.

Currently, no specific therapies alter the natural history of MAFLD and its progression to more severe forms of steatohepatitis ending in liver cirrhosis and/or liver cancer. Lifestyle modification remains the cornerstone of treatment[15,16].

Considering that IR is the pathogenetic factor involved in MAFLD, antihyperglycemic agents, especially insulin sensitizers, emerged as the potential therapeutic option. Pioglitazone is currently the only pharmacological agent recommended in patients with biopsy-proven NASH as it improves liver histology, both in patients with and without T2DM[15-17].

In recent years, newer antihyperglycemic agents, glucagon-like peptide-1 receptor agonists (GLP-1RAs), have exhibited beneficial direct and indirect effects on metabolism and weight loss, raising the interest as a new drug class with potential in MAFLD prevention and treatment. Moreover, some of these agents showed CV protection in dedicated CV outcome trials, placing them in the spotlight for broader use in additional indications, particularly suitable for patients sharing diabetes and MAFLD phenotype (Figure 1).

GLP-1RAs: LIGHT AT THE BEGINNING, MIDDLE OR AT THE END OF THE TUNNEL?

GLP-1RAs are agents available to treat T2DM patients, especially those with atherosclerotic CVD and obesity. Either daily (liraglutide, lixisenatide, exenatide) or weekly injectable GLP1-RA preparations (dulaglutide, semaglutide, exenatide once weekly) have been available, and recently, a daily oral formulation (semaglutide) was approved[18]. GLP-1RAs have many beneficial effects, including stimulating glucose-dependent insulin secretion, inhibition of glucagon secretion and stimulation of β-cell proliferation, delay of gastric emptying, and increasing satiety *via* central nervous system pathways [18]. In dedicated randomized control trials (RCTs), including T2DM patients all over the diabetes spectrum, GLP-1RAs have proven glucose-lowering and significant weight-lowering effects alongside their cardio- and renoprotective properties[19,20]. Also, GLP-1RAs can improve serum transaminase levels in patients with MAFLD[21]. Additionally, patients with MAFLD have exhibited a decrease in endogenous GLP-1 secretion, highlighting GLP-1RAs as a potential treatment[22]. Given their multifactorial effects and targeting many pathways involved in MAFLD, including IR, inflammation, obesity, and offering cardiovascular protection, GLP-1 RAs are emerging as a promising treatment for MAFLD patients.

PREVENTION/SLOWING DOWN THE PROGRESSION TO NASH

The hepatic effects of GLP-1 RAs are mostly evident indirectly by reducing body weight, IR and improving fatty acid metabolism. Obese patients with NAFLD are insulin resistant at the level of adipose tissue, liver, and skeletal muscle. They exhibit a progressive deterioration in metabolic parameters, hepatic IR, and liver fibrosis as adipose tissue IR worsens[23]. The liver acts as a metabolic sensor of dysfunctional adipose tissue, and insulin resistant adipose tissue is closely connected to intrahepatic triglyceride accumulation[24]. By acting favorably on body weight, GLP1-RAs decrease adipose tissue (primarily visceral) and indirectly reduce intrahepatic fat content and lead to MAFLD prevention/amelioration. Additionally, GLP-1RAs show a beneficial effect on lipoprotein metabolism, modulating reverse cholesterol transport, reducing triglyceride production rate from the liver and intrahepatic triglyceride content, and consequently reducing fasting and postprandial concentration of triglycerides[25].

But what about their direct effects on the liver? We know that GLP-1RAs exert their effects by binding to receptors found in islet cells and other extrapancreatic tissues (lung, kidney, brain, nervous system, gastrointestinal system, *etc*.). Gupta *et al*[26] found GLP-1 receptors on human hepatocytes in vitro, showing a direct role in improving hepatic steatosis by modulating insulin signaling pathways and decreasing hepatic IR and fatty acid synthesis. Furthermore, GLP-1 RAs improved hepatocyte survival and reduced hepatic steatosis by inhibiting endoplasmic reticulum stress response and reducing fatty acid accumulation by inducing autophagy[27,28]. Still, the direct effects of GLP-1 RAs on the liver remain not fully understood, and large-scale RCTs are needed to investigate the efficacy and safety of GLP-1-based therapies in treating patients with MAFLD.

REVERSAL/IMPROVEMENT OF NASH

In recent years, several studies have examined the efficacy of GLP-1 RAs in managing MAFLD in patients with and without T2DM. These studies mainly evaluated exenatide and liraglutide in the treatment of MAFLD/NASH, primarily in patients with concomitant T2DM. Liraglutide was the most widely studied among GLP-1 RAs and, until recently, the only one that showed improvement in liver histology for patients with biopsy-proven NASH. The LEAN study (liraglutide safety and efficacy in patients with non-alcoholic steatohepatitis)[29] included patients with and without T2DM and showed the histological resolution of NASH in patients treated with liraglutide. In addition to improvements in histological steatosis and hepatocyte ballooning, fewer patients had fibrosis progression. Other trials with liraglutide were not conducted in biopsy-proven NASH. Few studies compared liraglutide to other antihyperglycemic agents in NAFLD and T2DM. Ohki *et al*[30] conducted a retrospective study evaluating the efficacy of liraglutide *vs* sitagliptin and pioglitazone. A significant decrease in serum aminotransferase levels for all groups was reported, while the aspartate aminotransferase (AST)-to-

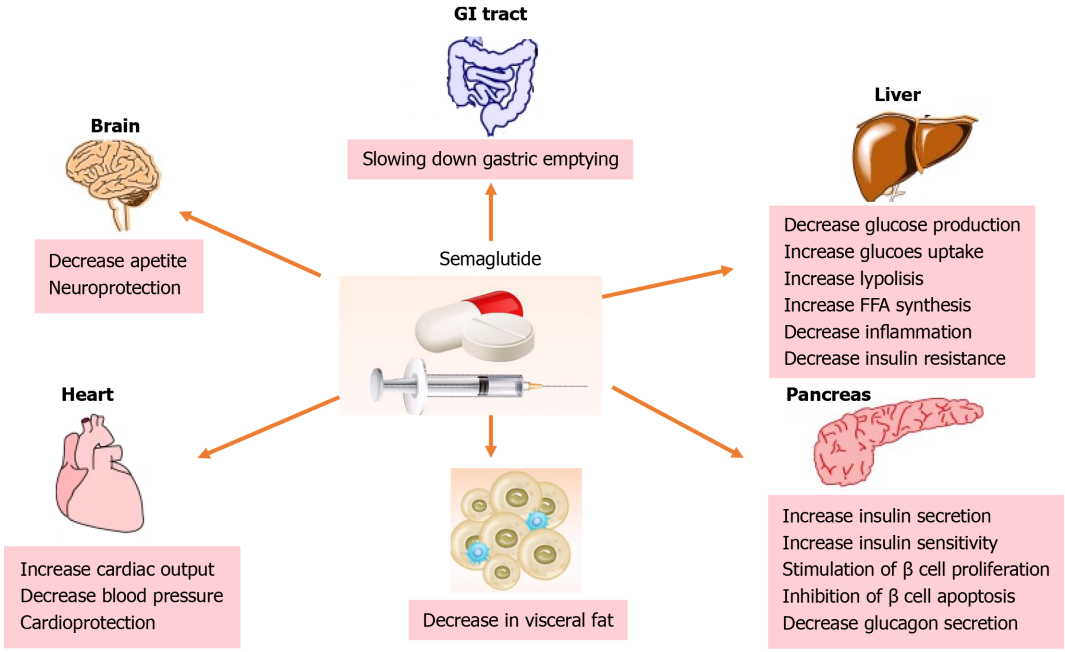

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Figure 1 Semaglutide-mechanisms of action with potential benefits for metabolically associated fatty liver disease/non-alcoholic fatty liver disease patients with increased hepatic and extrahepatic (cardiovascular) risk. FFA: Free fatty acids.

platelet counts ratio index was significantly reduced only for the liraglutide and pioglitazone groups [30]. Another trial by Feng *et al*[31] randomized T2DM patients with NAFLD to receive liraglutide, metformin, or gliclazide. The liraglutide group showed the greatest reduction in intrahepatic steatosis and liver enzymes[31]. Few trials compared exenatide to other hypoglycaemic agents in NAFLD patients with T2DM. Shao *et al*[32] compared exenatide plus insulin glargine U-100 (exenatide group) with insulin glargine U-100 plus insulin aspart (intensive insulin group). The liver enzymes were significantly lower, and the reversal rate of liver steatosis was higher in the exenatide group than in the intensive insulin group[32]. Another RCT compared the efficacy of exenatide *vs* metformin in patients with NAFLD and T2DM, concluding that exenatide was more effective than metformin in reducing body weight and improving liver enzymes[33]. Exenatide has not been studied in RCTs with liver histology outcomes in NASH patients. Nevertheless, a recent meta-analysis of eight studies with exenatide and liraglutide in patients with T2DM and MAFLD found significant improvements in hepatic fat content, liver biochemistry, body composition, metabolic parameters (glucose parameters, lipid parameters, insulin sensitivity), and inflammatory markers following GLP-1 RAs treatment. Moreover, GLP-1RAs also improved fibrosis markers without statistical significance[34]. The mentioned meta-analysis did not include studies that examined liver histology. The data regarding dulaglutide and NAFLD are limited and primarily based on retrospective studies[35]. Only one RCT evaluated the effect of dulaglutide on liver fat in patients with type 2 diabetes and NAFLD (D-LIFT trial). This study compared patients receiving dulaglutide (add-on to usual care) *vs* the usual care. The dulaglutide group showed a significant reduction in liver fat content and gamma-glutamyl transferase levels in participants with NAFLD. The dulaglutide group showed non-significant reductions in pancreatic fat content, liver stiffness, serum AST, and serum alanine aminotransferase (ALT) levels[36]. Lastly, an updated meta-analysis included eleven placebo-controlled or active-controlled phase-2 RCTs that used liraglutide (n = 6 RCTs), exenatide (n = 3 RCTs), dulaglutide (n = 1 RCT) or semaglutide (n = 1 RCT) to specifically treat NAFLD or NASH, detected by liver biopsy (n = 2 RCTs) or imaging techniques (n = 9 RCTs). Compared to placebo or reference therapy, treatment with GLP-1 RAs was associated with significant reductions in liver fat content on magnetic resonance-based techniques and serum aminotransferase levels, as well as with the greater histological resolution of NASH without worsening of liver fibrosis (for liraglutide and semaglutide only)[37].

WHY SEMAGLUTIDE?

Semaglutide is a novel GLP-1 receptor agonist that has been recently approved for the treatment of T2DM and obesity. Two formulations are currently available, once-weekly subcutaneous semaglutide and once-daily oral semaglutide, the subcutaneous form in different dose ranges depending on the indication (for T2DM subcutaneous semaglutide up to 1 mg weekly and oral semaglutide up to 14 mg

Table 1 Completed studies with subcutaneous semaglutide in type 2 diabetes mellitus and their main conclusions

Study	Ref.	Main conclusion
SUSTAIN 1	Sorli *et al*[38], 2017	Semaglutide significantly improved HbA1c and bodyweight in T2DM patients compared to placebo
SUSTAIN 2	Ahren *et al*[39], 2017	Semaglutide is superior to sitagliptin at improving glycemia and bodyweight when added to metformin+/- pioglitazon
SUSTAIN 3	Ahmann *et al*[40], 2018	Semaglutide is superior to exenatide ER in glycemic control and body weight reduction
SUSTAIN 4	Aroda *et al*[41], 2017	semaglutide is superior to insulin glargine U100 in glycemic control and bodyweight reduction
SUSTAIN 5	Rodbar *et al*[42], 2018	Semaglutide, added to basal insulin, significantly reduced HbA1c and body weight in patients with uncontrolled T2D *vs* placebo
SUSTAIN 6[1]	Marso *et al*[43], 2016	In T2DM patients at high cardiovascular risk, semaglutide was significantly better compared to placebo in reduction of 3 point MACE
SUSTAIN 7	Pratley *et al*[44], 2018	At low and high doses, semaglutide was superior to dulaglutide in improving glycaemic control and reducing body weight of T2DM patients
SUSTAIN 8	Lingway *et al*[45], 2019	Once-weekly semaglutide 1.0 mg was superior to daily canagliflozin 300 mg in reducing HbA1c and bodyweight in patients with type 2 diabetes uncontrolled on metformin therapy
SUSTAIN 8 substudy	McCrimmon *et al* [46], 2019	In individuals with uncontrolled T2DM on stable-dose metformin, the changes in body composition with semaglutide and canagliflozin were not significantly different
SUSTAIN 9	Zinman *et al*[47], 2019	Adding semaglutide to SGLT-2 inhibitor therapy significantly improves glycaemic control and reduces bodyweight in patients with inadequately controlled T2DM
SUSTAIN 10	Capehorn *et al*[48], 2020	Semaglutide was superior to liraglutide in reducing HbA1c and body weight
SUSTAIN (Japan)	Kaku *et al*[49], 2018	Semaglutide treatment significantly reduced HbA1c and body weight *vs* additional OAD treatment in Japanese people with T2D
SUSTAIN Forte	Frias *et al*[50], 2021	Semaglutide 2.0 mg was superior to 1.0 mg in reducing HbA1c, with additional body weight loss and a similar safety profile in poorly controlled T2DM
SUSTAIN China MRCT	Ji *et al*[51], 2020	Once-weekly semaglutide was superior to sitagliptin in improving glycaemic control and reducing body weight in Chinese T2DM patients inadequately controlled on metformin

[1]Cardiovascular safety study. CV: Cardiovascular; T2DM: Type 2 diabetes mellitus; HbA1c: Hemoglobin A1c.

daily; for obesity subcutaneous semaglutide 2.4 mg weekly). Currently completed studies with subcutaneous in T2DM[38-56] and oral semaglutide[57-67] are presented in Table 1, Table 2, and Table 3.

Across the SUSTAIN program, once-weekly subcutaneous semaglutide showed more pronounced metabolic effects than active comparators (including liraglutide, a widely used GLP-1RA)[68]. Semaglutide was associated with reduced CV risk among patients with T2DM at high CV risk[43]. Recently published data from STEP RCTs, on patients receiving subcutaneous semaglutide in dose 2.4 mg once weekly for treatment of obesity suggest its favorable and prolonged effect on weight reduction (twice as many patients reduced more than 5% of initial weight compared to placebo, with a range of weight loss of 10% to 20% in the majority of patients on semaglutide), which is associated with clinically meaningful improvements in cardiovascular and metabolic risk factors and more pronounced when compared to reduction achieved on liraglutide 3.0 mg sc daily[69]. In addition, a new oral formulation is available, with similar efficacy and safety profile to the subcutaneous formulation, confirmed across the PIONEER program. Furthermore, oral semaglutide offers an alternative for patients with concerns regarding injectable treatment and creates an opportunity to expand the utilization of GLP-1 RAs[68].

Semaglutide has been shown to significantly reduce ALT and markers of inflammation[70]. Recently, a RCT comparing subcutaneous semaglutide *vs* placebo in subjects with NAFLD assessed by MRI was conducted. The trial investigated the effects of subcutaneous semaglutide on liver stiffness, a marker of fibrosis, and liver steatosis in subjects with NAFLD, using non-invasive MRI methods after 24, 48, and 72 wk of treatment. Significant improvement in liver steatosis was found, accompanied by improvements in liver enzymes and metabolic parameters. In addition, more participants receiving semaglutide achieved > 15% reduction in liver stiffness compared to placebo, although the difference was not significant[71].

For now, only two RCTs were conducted with GLP-1 RAs in patients with biopsy-proven NASH, the already mentioned liraglutide[29] and semaglutide. A 72-wk phase 2 trial evaluated the effect of semaglutide on the histologic resolution of NASH in patients with biopsy-proven NASH and fibrosis. Patients were randomized to receive 0.1 mg, 0.2 mg, or 0.4 mg once daily semaglutide or placebo. The semaglutide 0.4 mg was superior to placebo regarding NASH resolution without worsening liver

Table 2 Completed studies with subcutaneous semaglutide in obesity and their main conclusions

Study	Ref.	Main conclusion
Step 1	Wilding *et al* [52], 2021	In participants with overweight or obesity, 2.4 mg of semaglutide once weekly plus lifestyle intervention was associated with sustained, clinically relevant reduction in body weight
Step 2	Davies *et al*[53], 2021	In adults with overweight or obesity, and type 2 diabetes, semaglutide 2.4 mg once a week achieved a superior and clinically meaningful decrease in body weight compared with placebo
Step 3	Wadden *et al* [54], 2021	Among adults with overweight or obesity, once-weekly subcutaneous semaglutide compared with placebo, used as an adjunct to intensive behavioral therapy and initial low-calorie diet, resulted in significantly greater weight loss during 68 wk
Step 4	Rubino *et al*[55], 2022	Among adults with overweight or obesity without diabetes, once-weekly subcutaneous semaglutide compared with once-daily subcutaneous liraglutide, added to counseling for diet and physical activity, resulted in significantly greater weight loss during 68 wk
Step 6	Kadowaki *et al* [56], 2022	Adults from east Asia with obesity, with or without type 2 diabetes, given semaglutide 2.4 mg once a week had superior and clinically meaningful reductions in body weight, and greater reductions in abdominal visceral fat area compared with placebo

Step 5: Completed, not published.

Table 3 Completed studies with oral semaglutide and their main conclusions

Study	Ref.	Main conclusion
PIONEER 1	Aroda *et al*[57], 2019	Oral semaglutide monotherapy demonstrated superior and clinically relevant improvements in HbA1c (all doses) and body weight loss (14 mg dose) versus placebo
PIONEER 2	Rodbard *et al* [58], 2019	Oral semaglutide was superior to empagliflozin in reducing HbA1c but not body weight at 26 wk in T2DM patients uncontrolled on metformin. At week 52, HbA1c and body weight (trial product estimand) were significantly reduced versus empagliflozin
PIONEER 3	Rosenstock *et al* [59], 2019	Oral semaglutide, 7 mg/d and 14 mg/d, compared with sitagliptin, resulted in significantly greater reductions in HbA1c over 26 wk
PIONEER 4	Pratley *et al*[60], 2019	Oral semaglutide was non-inferior to subcutaneous liraglutide and superior to placebo in decreasing HbA1c, and superior in decreasing body weight compared with both liraglutide and placebo at week 26
PIONEER 5	Mosenzon *et al* [61], 2019	Oral semaglutide was effective in patients with type 2 diabetes and moderate renal impairment
PIONEER 6[1]	Husain *et al*[62], 2019	The cardiovascular risk profile of oral semaglutide was not inferior to that of placebo in high CV risk T2DM patients
PIONEER 7	Pieber *et al*[63], 2019	Superior glycemic control and weight loss with once-daily oral semaglutide with flexible dose adjustment versus sitagliptin 100 mg in type 2 diabetes
PIONEER 7 EXTENSION	Buse *et al*[64], 2020	Switching from sitagliptin to flexibly dosed oral semaglutide maintained HbA1c reductions, helped more patients achieve HbA1c targets with less use of additional glucose-lowering medication, and offers the potential for additional reductions in body weight
PIONEER 8	Zinman *et al* [65], 2019	Oral semaglutide was superior to placebo in reducing HbA1c and body weight when added to insulin with or without metformin in patients with T2DM
PIONEER 9	Yamada *et al* [66], 2020	Oral semaglutide provides significant reductions in HbA1c compared with placebo in a dose-dependent manner in Japanese patients with T2DM
PIONEER 10	Yabe *et al*[67], 2020	Once-daily oral semaglutide reduced HbA1c and bodyweight *vs* weekly dulaglutide 0.75 μg in Japanese T2DM patients

[1]Cardiovascular safety study. CV: Cardiovascular; T2DM: Type 2 diabetes mellitus; HbA1c: Hemoglobin A1c.

fibrosis. However, a significant between-group difference in improving at least one fibrosis stage was not shown[70]. A much longer duration may be required for improvements in the fibrosis stage to become apparent, especially since most patients in the current study had advanced fibrosis. The most reported adverse events were gastroenterological disorders (nausea, constipation, decreased appetite, vomiting, and abdominal pain), which are already known from RCTs and real-world data. They were dose-dependent and mainly occurred during the dose-escalation period in the first 20 wk of the trial.

Semaglutide is a promising treatment for patients with NASH. Additional studies are needed to evaluate the optimal dosage and formulation for MAFLD treatment. The approved doses of injectable semaglutide for treatment of T2DM are 0.5 mg and 1.0 mg once weekly and for obesity 2.4 mg once weekly, which is different from the once daily 0.1 mg, 0.2 mg, and 0.4 mg doses used in the previously mentioned study. Future dedicated trials enrolling MAFLD patients to receive subcutaneous semaglutide 2.4 mg and development of oral semaglutide for treatment of obesity, almost an

inseparable condition from MAFLD, is holding promise as a new therapeutic option.

CONCLUSION

Semaglutide efficacy in the treatment of NASH was undoubtedly confirmed in the recent RCT in patients with and without T2DM. Even though improvement in the fibrosis stage was not shown in this study, a longer duration of treatment may be needed, especially for advanced-stage fibrosis. Furthermore, semaglutide is currently the only GLP-1RA available in an injectable and oral formulation. Thus, the dosage and formulation of semaglutide in NASH treatment need to be further established. Given its definite potency, it is a promising drug for the treatment of NASH, offering the benefit of the choice of the formulation to best suit individual patients' preferences.

FOOTNOTES

Author contributions: Cigrovski Berkovic M made contribution to the conception and design of the study, drafted, and revised the manuscript critically; Rezic T, Bilic-Curcic I, and Mrzljak A collected the data, drafted, and wrote the manuscript; all authors read and approved the final manuscript.

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REFERENCES

1 **Vernon G**, Baranova A, Younossi ZM. Systematic review: the epidemiology and natural history of non-alcoholic fatty liver disease and non-alcoholic steatohepatitis in adults. *Aliment Pharmacol Ther* 2011; **34**: 274-285 [PMID: 21623852 DOI: 10.1111/j.1365-2036.2011.04724.x]
2 **Younossi ZM**, Koenig AB, Abdelatif D, Fazel Y, Henry L, Wymer M. Global epidemiology of nonalcoholic fatty liver disease-Meta-analytic assessment of prevalence, incidence, and outcomes. *Hepatology* 2016; **64**: 73-84 [PMID: 26707365 DOI: 10.1002/hep.28431]
3 **Younossi ZM**, Marchesini G, Pinto-Cortez H, Petta S. Epidemiology of Nonalcoholic Fatty Liver Disease and Nonalcoholic Steatohepatitis: Implications for Liver Transplantation. *Transplantation* 2019; **103**: 22-27 [PMID: 30335697 DOI: 10.1097/TP.0000000000002484]
4 **Targher G**, Byrne CD, Tilg H. NAFLD and increased risk of cardiovascular disease: clinical associations, pathophysiological mechanisms and pharmacological implications. *Gut* 2020; **69**: 1691-1705 [PMID: 32321858 DOI: 10.1136/gutjnl-2020-320622]
5 **Eslam M**, Sanyal AJ, George J; International Consensus Panel. MAFLD: A Consensus-Driven Proposed Nomenclature for Metabolic Associated Fatty Liver Disease. *Gastroenterology* 2020; **158**: 1999-2014.e1 [PMID: 32044314 DOI: 10.1053/j.gastro.2019.11.312]
6 **Eslam M**, Newsome PN, Sarin SK, Anstee QM, Targher G, Romero-Gomez M, Zelber-Sagi S, Wai-Sun Wong V, Dufour JF, Schattenberg JM, Kawaguchi T, Arrese M, Valenti L, Shiha G, Tiribelli C, Yki-Järvinen H, Fan JG, Grønbæk H, Yilmaz Y, Cortez-Pinto H, Oliveira CP, Bedossa P, Adams LA, Zheng MH, Fouad Y, Chan WK, Mendez-Sanchez N, Ahn SH, Castera L, Bugianesi E, Ratziu V, George J. A new definition for metabolic dysfunction-associated fatty liver disease: An international expert consensus statement. *J Hepatol* 2020; **73**: 202-209 [PMID: 32278004 DOI: 10.1016/j.jhep.2020.03.039]
7 **Marchesini G**, Brizi M, Morselli-Labate AM, Bianchi G, Bugianesi E, McCullough AJ, Forlani G, Melchionda N. Association of nonalcoholic fatty liver disease with insulin resistance. *Am J Med* 1999; **107**: 450-455 [PMID: 10569299 DOI: 10.1016/s0002-9343(99)00271-5]
8 **Buzzetti E**, Pinzani M, Tsochatzis EA. The multiple-hit pathogenesis of non-alcoholic fatty liver disease (NAFLD). *Metabolism* 2016; **65**: 1038-1048 [PMID: 26823198 DOI: 10.1016/j.metabol.2015.12.012]

9 **Adams LA**, Anstee QM, Tilg H, Targher G. Non-alcoholic fatty liver disease and its relationship with cardiovascular disease and other extrahepatic diseases. *Gut* 2017; **66**: 1138-1153 [PMID: 28314735 DOI: 10.1136/gutjnl-2017-313884]

10 **Adams LA**, Sanderson S, Lindor KD, Angulo P. The histological course of nonalcoholic fatty liver disease: a longitudinal study of 103 patients with sequential liver biopsies. *J Hepatol* 2005; **42**: 132-138 [PMID: 15629518 DOI: 10.1016/j.jhep.2004.09.012]

11 **McPherson S**, Hardy T, Henderson E, Burt AD, Day CP, Anstee QM. Evidence of NAFLD progression from steatosis to fibrosing-steatohepatitis using paired biopsies: implications for prognosis and clinical management. *J Hepatol* 2015; **62**: 1148-1155 [PMID: 25477264 DOI: 10.1016/j.jhep.2014.11.034]

12 **Reeves HL**, Zaki MY, Day CP. Hepatocellular Carcinoma in Obesity, Type 2 Diabetes, and NAFLD. *Dig Dis Sci* 2016; **61**: 1234-1245 [PMID: 26921078 DOI: 10.1007/s10620-016-4085-6]

13 **Anstee QM**, Targher G, Day CP. Progression of NAFLD to diabetes mellitus, cardiovascular disease or cirrhosis. *Nat Rev Gastroenterol Hepatol* 2013; **10**: 330-344 [PMID: 23507799 DOI: 10.1038/nrgastro.2013.41]

14 **Nguyen VH**, Le MH, Cheung RC, Nguyen MH. Differential Clinical Characteristics and Mortality Outcomes in Persons With NAFLD and/or MAFLD. *Clin Gastroenterol Hepatol* 2021; **19**: 2172-2181.e6 [PMID: 34033923 DOI: 10.1016/j.cgh.2021.05.029]

15 **Chalasani N**, Younossi Z, Lavine JE, Charlton M, Cusi K, Rinella M, Harrison SA, Brunt EM, Sanyal AJ. The diagnosis and management of nonalcoholic fatty liver disease: Practice guidance from the American Association for the Study of Liver Diseases. *Hepatology* 2018; **67**: 328-357 [PMID: 28714183 DOI: 10.1002/hep.29367]

16 **European Association for the Study of the Liver (EASL)**; European Association for the Study of Diabetes (EASD); European Association for the Study of Obesity (EASO). EASL-EASD-EASO Clinical Practice Guidelines for the management of non-alcoholic fatty liver disease. *J Hepatol* 2016; **64**: 1388-1402 [PMID: 27062661 DOI: 10.1016/j.jhep.2015.11.004]

17 **Sanyal AJ**, Chalasani N, Kowdley KV, McCullough A, Diehl AM, Bass NM, Neuschwander-Tetri BA, Lavine JE, Tonascia J, Unalp A, Van Natta M, Clark J, Brunt EM, Kleiner DE, Hoofnagle JH, Robuck PR; NASH CRN. Pioglitazone, vitamin E, or placebo for nonalcoholic steatohepatitis. *N Engl J Med* 2010; **362**: 1675-1685 [PMID: 20427778 DOI: 10.1056/NEJMoa0907929]

18 **Brunton SA**, Wysham CH. GLP-1 receptor agonists in the treatment of type 2 diabetes: role and clinical experience to date. *Postgrad Med* 2020; **132**: 3-14 [PMID: 32815454 DOI: 10.1080/00325481.2020.1798099]

19 **Nauck MA**, Quast DR, Wefers J, Meier JJ. GLP-1 receptor agonists in the treatment of type 2 diabetes - state-of-the-art. *Mol Metab* 2021; **46**: 101102 [PMID: 33068776 DOI: 10.1016/j.molmet.2020.101102]

20 **Sachinidis A**, Nikolic D, Stoian AP, Papanas N, Tarar O, Rizvi AA, Rizzo M. Cardiovascular outcomes trials with incretin-based medications: a critical review of data available on GLP-1 receptor agonists and DPP-4 inhibitors. *Metabolism* 2020; **111**: 154343 [PMID: 32810485 DOI: 10.1016/j.metabol.2020.154343]

21 **Dhir G**, Cusi K. Glucagon like peptide-1 receptor agonists for the management of obesity and non-alcoholic fatty liver disease: a novel therapeutic option. *J Investig Med* 2018; **66**: 7-10 [PMID: 28918389 DOI: 10.1136/jim-2017-000554]

22 **Bernsmeier C**, Meyer-Gerspach AC, Blaser LS, Jeker L, Steinert RE, Heim MH, Beglinger C. Glucose-induced glucagon-like Peptide 1 secretion is deficient in patients with non-alcoholic fatty liver disease. *PLoS One* 2014; **9**: e87488 [PMID: 24489924 DOI: 10.1371/journal.pone.0087488]

23 **Lomonaco R**, Ortiz-Lopez C, Orsak B, Webb A, Hardies J, Darland C, Finch J, Gastaldelli A, Harrison S, Tio F, Cusi K. Effect of adipose tissue insulin resistance on metabolic parameters and liver histology in obese patients with nonalcoholic fatty liver disease. *Hepatology* 2012; **55**: 1389-1397 [PMID: 22183689 DOI: 10.1002/hep.25539]

24 **Cusi K**. Role of obesity and lipotoxicity in the development of nonalcoholic steatohepatitis: pathophysiology and clinical implications. *Gastroenterology* 2012; **142**: 711-725.e6 [PMID: 22326434 DOI: 10.1053/j.gastro.2012.02.003]

25 **Patel VJ**, Joharapurkar AA, Shah GB, Jain MR. Effect of GLP-1 based therapies on diabetic dyslipidemia. *Curr Diabetes Rev* 2014; **10**: 238-250 [PMID: 24998439 DOI: 10.2174/1573399810666140707092506]

26 **Gupta NA**, Mells J, Dunham RM, Grakoui A, Handy J, Saxena NK, Anania FA. Glucagon-like peptide-1 receptor is present on human hepatocytes and has a direct role in decreasing hepatic steatosis *in vitro* by modulating elements of the insulin signaling pathway. *Hepatology* 2010; **51**: 1584-1592 [PMID: 20225248 DOI: 10.1002/hep.23569]

27 **Wang XC**, Gusdon AM, Liu H, Qu S. Effects of glucagon-like peptide-1 receptor agonists on non-alcoholic fatty liver disease and inflammation. *World J Gastroenterol* 2014; **20**: 14821-14830 [PMID: 25356042 DOI: 10.3748/wjg.v20.i40.14821]

28 **Sharma S**, Mells JE, Fu PP, Saxena NK, Anania FA. GLP-1 analogs reduce hepatocyte steatosis and improve survival by enhancing the unfolded protein response and promoting macroautophagy. *PLoS One* 2011; **6**: e25269 [PMID: 21957486 DOI: 10.1371/journal.pone.0025269]

29 **Armstrong MJ**, Gaunt P, Aithal GP, Barton D, Hull D, Parker R, Hazlehurst JM, Guo K; LEAN trial team, Abouda G, Aldersley MA, Stocken D, Gough SC, Tomlinson JW, Brown RM, Hübscher SG, Newsome PN. Liraglutide safety and efficacy in patients with non-alcoholic steatohepatitis (LEAN): a multicentre, double-blind, randomised, placebo-controlled phase 2 study. *Lancet* 2016; **387**: 679-690 [PMID: 26608256 DOI: 10.1016/S0140-6736(15)00803-X]

30 **Ohki T**, Isogawa A, Iwamoto M, Ohsugi M, Yoshida H, Toda N, Tagawa K, Omata M, Koike K. The effectiveness of liraglutide in nonalcoholic fatty liver disease patients with type 2 diabetes mellitus compared to sitagliptin and pioglitazone. *ScientificWorldJournal* 2012; **2012**: 496453 [PMID: 22927782 DOI: 10.1100/2012/496453]

31 **Feng W**, Gao C, Bi Y, Wu M, Li P, Shen S, Chen W, Yin T, Zhu D. Randomized trial comparing the effects of gliclazide, liraglutide, and metformin on diabetes with non-alcoholic fatty liver disease. *J Diabetes* 2017; **9**: 800-809 [PMID: 28332301 DOI: 10.1111/1753-0407.12555]

32 **Shao N**, Kuang HY, Hao M, Gao XY, Lin WJ, Zou W. Benefits of exenatide on obesity and non-alcoholic fatty liver disease with elevated liver enzymes in patients with type 2 diabetes. *Diabetes Metab Res Rev* 2014; **30**: 521-529 [PMID: 24823873 DOI: 10.1002/dmrr.2561]

33 **Fan H**, Pan Q, Xu Y, Yang X. Exenatide improves type 2 diabetes concomitant with non-alcoholic fatty liver disease. *Arq Bras Endocrinol Metabol* 2013; **57**: 702-708 [PMID: 24402015 DOI: 10.1590/s0004-27302013000900005]

34 **Wong C**, Lee MH, Yaow CYL, Chin YH, Goh XL, Ng CH, Lim AYL, Muthiah MD, Khoo CM. Glucagon-Like Peptide-1 Receptor Agonists for Non-Alcoholic Fatty Liver Disease in Type 2 Diabetes: A Meta-Analysis. *Front Endocrinol (Lausanne)* 2021; **12**: 609110 [PMID: 33897616 DOI: 10.3389/fendo.2021.609110]

35 **Sofogianni A**, Filippidis A, Chrysavgis L, Tziomalos K, Cholongitas E. Glucagon-like peptide-1 receptor agonists in non-alcoholic fatty liver disease: An update. *World J Hepatol* 2020; **12**: 493-505 [PMID: 32952876 DOI: 10.4254/wjh.v12.i8.493]

36 **Kuchay MS**, Krishan S, Mishra SK, Choudhary NS, Singh MK, Wasir JS, Kaur P, Gill HK, Bano T, Farooqui KJ, Mithal A. Effect of dulaglutide on liver fat in patients with type 2 diabetes and NAFLD: randomised controlled trial (D-LIFT trial). *Diabetologia* 2020; **63**: 2434-2445 [PMID: 32865597 DOI: 10.1007/s00125-020-05265-7]

37 **Mantovani A**, Petracca G, Beatrice G, Csermely A, Lonardo A, Targher G. Glucagon-Like Peptide-1 Receptor Agonists for Treatment of Nonalcoholic Fatty Liver Disease and Nonalcoholic Steatohepatitis: An Updated Meta-Analysis of Randomized Controlled Trials. *Metabolites* 2021; **11** [PMID: 33513761 DOI: 10.3390/metabo11020073]

38 **Sorli C**, Harashima SI, Tsoukas GM, Unger J, Karsbøl JD, Hansen T, Bain SC. Efficacy and safety of once-weekly semaglutide monotherapy versus placebo in patients with type 2 diabetes (SUSTAIN 1): a double-blind, randomised, placebo-controlled, parallel-group, multinational, multicentre phase 3a trial. *Lancet Diabetes Endocrinol* 2017; **5**: 251-260 [PMID: 28110911 DOI: 10.1016/S2213-8587(17)30013-X]

39 **Ahrén B**, Masmiquel L, Kumar H, Sargin M, Karsbøl JD, Jacobsen SH, Chow F. Efficacy and safety of once-weekly semaglutide versus once-daily sitagliptin as an add-on to metformin, thiazolidinediones, or both, in patients with type 2 diabetes (SUSTAIN 2): a 56-week, double-blind, phase 3a, randomised trial. *Lancet Diabetes Endocrinol* 2017; **5**: 341-354 [PMID: 28385659 DOI: 10.1016/S2213-8587(17)30092-X]

40 **Ahmann AJ**, Capehorn M, Charpentier G, Dotta F, Henkel E, Lingvay I, Holst AG, Annett MP, Aroda VR. Efficacy and Safety of Once-Weekly Semaglutide Versus Exenatide ER in Subjects With Type 2 Diabetes (SUSTAIN 3): A 56-Week, Open-Label, Randomized Clinical Trial. *Diabetes Care* 2018; **41**: 258-266 [PMID: 29246950 DOI: 10.2337/dc17-0417]

41 **Aroda VR**, Bain SC, Cariou B, Piletič M, Rose L, Axelsen M, Rowe E, DeVries JH. Efficacy and safety of once-weekly semaglutide versus once-daily insulin glargine as add-on to metformin (with or without sulfonylureas) in insulin-naive patients with type 2 diabetes (SUSTAIN 4): a randomised, open-label, parallel-group, multicentre, multinational, phase 3a trial. *Lancet Diabetes Endocrinol* 2017; **5**: 355-366 [PMID: 28344112 DOI: 10.1016/S2213-8587(17)30085-2]

42 **Rodbard HW**, Lingvay I, Reed J, de la Rosa R, Rose L, Sugimoto D, Araki E, Chu PL, Wijayasinghe N, Norwood P. Semaglutide Added to Basal Insulin in Type 2 Diabetes (SUSTAIN 5): A Randomized, Controlled Trial. *J Clin Endocrinol Metab* 2018; **103**: 2291-2301 [PMID: 29688502 DOI: 10.1210/jc.2018-00070]

43 **Marso SP**, Bain SC, Consoli A, Eliaschewitz FG, Jódar E, Leiter LA, Lingvay I, Rosenstock J, Seufert J, Warren ML, Woo V, Hansen O, Holst AG, Pettersson J, Vilsbøll T; SUSTAIN-6 Investigators. Semaglutide and Cardiovascular Outcomes in Patients with Type 2 Diabetes. *N Engl J Med* 2016; **375**: 1834-1844 [PMID: 27633186 DOI: 10.1056/NEJMoa1607141]

44 **Pratley RE**, Aroda VR, Lingvay I, Lüdemann J, Andreassen C, Navarria A, Viljoen A; SUSTAIN 7 investigators. Semaglutide versus dulaglutide once weekly in patients with type 2 diabetes (SUSTAIN 7): a randomised, open-label, phase 3b trial. *Lancet Diabetes Endocrinol* 2018; **6**: 275-286 [PMID: 29397376 DOI: 10.1016/S2213-8587(18)30024-X]

45 **Lingvay I**, Catarig AM, Frias JP, Kumar H, Lausvig NL, le Roux CW, Thielke D, Viljoen A, McCrimmon RJ. Efficacy and safety of once-weekly semaglutide versus daily canagliflozin as add-on to metformin in patients with type 2 diabetes (SUSTAIN 8): a double-blind, phase 3b, randomised controlled trial. *Lancet Diabetes Endocrinol* 2019; **7**: 834-844 [PMID: 31540867 DOI: 10.1016/S2213-8587(19)30311-0]

46 **McCrimmon RJ**, Catarig AM, Frias JP, Lausvig NL, le Roux CW, Thielke D, Lingvay I. Effects of once-weekly semaglutide *vs* once-daily canagliflozin on body composition in type 2 diabetes: a substudy of the SUSTAIN 8 randomised controlled clinical trial. *Diabetologia* 2020; **63**: 473-485 [PMID: 31897524 DOI: 10.1007/s00125-019-05065-8]

47 **Zinman B**, Bhosekar V, Busch R, Holst I, Ludvik B, Thielke D, Thrasher J, Woo V, Philis-Tsimikas A. Semaglutide once weekly as add-on to SGLT-2 inhibitor therapy in type 2 diabetes (SUSTAIN 9): a randomised, placebo-controlled trial. *Lancet Diabetes Endocrinol* 2019; **7**: 356-367 [PMID: 30833170 DOI: 10.1016/S2213-8587(19)30066-X]

48 **Capehorn MS**, Catarig AM, Furberg JK, Janez A, Price HC, Tadayon S, Vergès B, Marre M. Efficacy and safety of once-weekly semaglutide 1.0mg *vs* once-daily liraglutide 1.2mg as add-on to 1-3 oral antidiabetic drugs in subjects with type 2 diabetes (SUSTAIN 10). *Diabetes Metab* 2020; **46**: 100-109 [PMID: 31539622 DOI: 10.1016/j.diabet.2019.101117]

49 **Kaku K**, Yamada Y, Watada H, Abiko A, Nishida T, Zacho J, Kiyosue A. Safety and efficacy of once-weekly semaglutide *vs* additional oral antidiabetic drugs in Japanese people with inadequately controlled type 2 diabetes: A randomized trial. *Diabetes Obes Metab* 2018; **20**: 1202-1212 [PMID: 29322610 DOI: 10.1111/dom.13218]

50 **Frías JP**, Auerbach P, Bajaj HS, Fukushima Y, Lingvay I, Macura S, Søndergaard AL, Tankova TI, Tentolouris N, Buse JB. Efficacy and safety of once-weekly semaglutide 2·0 mg versus 1·0 mg in patients with type 2 diabetes (SUSTAIN FORTE): a double-blind, randomised, phase 3B trial. *Lancet Diabetes Endocrinol* 2021; **9**: 563-574 [PMID: 34293304 DOI: 10.1016/S2213-8587(21)00174-1]

51 **Ji L**, Dong X, Li Y, Lim S, Liu M, Ning Z, Rasmussen S, Skjøth TV, Yuan G, Eliaschewitz FG. Efficacy and safety of once-weekly semaglutide versus once-daily sitagliptin as add-on to metformin in patients with type 2 diabetes in SUSTAIN China: A 30-week, double-blind, phase 3a, randomized trial. *Diabetes Obes Metab* 2021; **23**: 404-414 [PMID: 33074557 DOI: 10.1111/dom.14232]

52 **Wilding JPH**, Batterham RL, Calanna S, Davies M, Van Gaal LF, Lingvay I, McGowan BM, Rosenstock J, Tran MTD, Wadden TA, Wharton S, Yokote K, Zeuthen N, Kushner RF; STEP 1 Study Group. Once-Weekly Semaglutide in Adults with Overweight or Obesity. *N Engl J Med* 2021; **384**: 989 [PMID: 33567185 DOI: 10.1056/NEJMoa2032183]

53 **Davies M**, Færch L, Jeppesen OK, Pakseresht A, Pedersen SD, Perreault L, Rosenstock J, Shimomura I, Viljoen A, Wadden TA, Lingvay I; STEP 2 Study Group. Semaglutide 2·4 mg once a week in adults with overweight or obesity, and type 2 diabetes (STEP 2): a randomised, double-blind, double-dummy, placebo-controlled, phase 3 trial. *Lancet* 2021; **397**: 971-984 [PMID: 33667417 DOI: 10.1016/S0140-6736(21)00213-0]

54 **Wadden TA**, Bailey TS, Billings LK, Davies M, Frias JP, Koroleva A, Lingvay I, O'Neil PM, Rubino DM, Skovgaard D, Wallenstein SOR, Garvey WT; STEP 3 Investigators. Effect of Subcutaneous Semaglutide *vs* Placebo as an Adjunct to

Intensive Behavioral Therapy on Body Weight in Adults With Overweight or Obesity: The STEP 3 Randomized Clinical Trial. *JAMA* 2021; **325**: 1403-1413 [PMID: 33625476 DOI: 10.1001/jama.2021.1831]

55 **Rubino D**, Abrahamsson N, Davies M, Hesse D, Greenway FL, Jensen C, Lingvay I, Mosenzon O, Rosenstock J, Rubio MA, Rudofsky G, Tadayon S, Wadden TA, Dicker D; STEP 4 Investigators. Effect of Continued Weekly Subcutaneous Semaglutide *vs* Placebo on Weight Loss Maintenance in Adults With Overweight or Obesity: The STEP 4 Randomized Clinical Trial. *JAMA* 2021; **325**: 1414-1425 [PMID: 33755728 DOI: 10.1001/jama.2021.3224]

56 **Kadowaki T**, Isendahl J, Khalid U, Lee SY, Nishida T, Ogawa W, Tobe K, Yamauchi T, Lim S; STEP 6 investigators. Semaglutide once a week in adults with overweight or obesity, with or without type 2 diabetes in an east Asian population (STEP 6): a randomised, double-blind, double-dummy, placebo-controlled, phase 3a trial. *Lancet Diabetes Endocrinol* 2022; **10**: 193-206 [PMID: 35131037 DOI: 10.1016/S2213-8587(22)00008-0]

57 **Aroda VR**, Rosenstock J, Terauchi Y, Altuntas Y, Lalic NM, Morales Villegas EC, Jeppesen OK, Christiansen E, Hertz CL, Haluzík M; PIONEER 1 Investigators. PIONEER 1: Randomized Clinical Trial of the Efficacy and Safety of Oral Semaglutide Monotherapy in Comparison With Placebo in Patients With Type 2 Diabetes. *Diabetes Care* 2019; **42**: 1724-1732 [PMID: 31186300 DOI: 10.2337/dc19-0749]

58 **Rodbard HW**, Rosenstock J, Canani LH, Deerochanawong C, Gumprecht J, Lindberg SØ, Lingvay I, Søndergaard AL, Treppendahl MB, Montanya E; PIONEER 2 Investigators. Oral Semaglutide Versus Empagliflozin in Patients With Type 2 Diabetes Uncontrolled on Metformin: The PIONEER 2 Trial. *Diabetes Care* 2019; **42**: 2272-2281 [PMID: 31530666 DOI: 10.2337/dc19-0883]

59 **Rosenstock J**, Allison D, Birkenfeld AL, Blicher TM, Deenadayalan S, Jacobsen JB, Serusclat P, Violante R, Watada H, Davies M; PIONEER 3 Investigators. Effect of Additional Oral Semaglutide *vs* Sitagliptin on Glycated Hemoglobin in Adults With Type 2 Diabetes Uncontrolled With Metformin Alone or With Sulfonylurea: The PIONEER 3 Randomized Clinical Trial. *JAMA* 2019; **321**: 1466-1480 [PMID: 30903796 DOI: 10.1001/jama.2019.2942]

60 **Pratley R**, Amod A, Hoff ST, Kadowaki T, Lingvay I, Nauck M, Pedersen KB, Saugstrup T, Meier JJ; PIONEER 4 investigators. Oral semaglutide versus subcutaneous liraglutide and placebo in type 2 diabetes (PIONEER 4): a randomised, double-blind, phase 3a trial. *Lancet* 2019; **394**: 39-50 [PMID: 31186120 DOI: 10.1016/S0140-6736(19)31271-1]

61 **Mosenzon O**, Blicher TM, Rosenlund S, Eriksson JW, Heller S, Hels OH, Pratley R, Sathyapalan T, Desouza C; PIONEER 5 Investigators. Efficacy and safety of oral semaglutide in patients with type 2 diabetes and moderate renal impairment (PIONEER 5): a placebo-controlled, randomised, phase 3a trial. *Lancet Diabetes Endocrinol* 2019; **7**: 515-527 [PMID: 31189517 DOI: 10.1016/S2213-8587(19)30192-5]

62 **Husain M**, Birkenfeld AL, Donsmark M, Dungan K, Eliaschewitz FG, Franco DR, Jeppesen OK, Lingvay I, Mosenzon O, Pedersen SD, Tack CJ, Thomsen M, Vilsbøll T, Warren ML, Bain SC; PIONEER 6 Investigators. Oral Semaglutide and Cardiovascular Outcomes in Patients with Type 2 Diabetes. *N Engl J Med* 2019; **381**: 841-851 [PMID: 31185157 DOI: 10.1056/NEJMoa1901118]

63 **Pieber TR**, Bode B, Mertens A, Cho YM, Christiansen E, Hertz CL, Wallenstein SOR, Buse JB; PIONEER 7 investigators. Efficacy and safety of oral semaglutide with flexible dose adjustment versus sitagliptin in type 2 diabetes (PIONEER 7): a multicentre, open-label, randomised, phase 3a trial. *Lancet Diabetes Endocrinol* 2019; **7**: 528-539 [PMID: 31189520 DOI: 10.1016/S2213-8587(19)30194-9]

64 **Buse JB**, Bode BW, Mertens A, Cho YM, Christiansen E, Hertz CL, Nielsen MA, Pieber TR; PIONEER 7 investigators. Long-term efficacy and safety of oral semaglutide and the effect of switching from sitagliptin to oral semaglutide in patients with type 2 diabetes: a 52-week, randomized, open-label extension of the PIONEER 7 trial. *BMJ Open Diabetes Res Care* 2020; **8** [PMID: 33318068 DOI: 10.1136/bmjdrc-2020-001649]

65 **Zinman B**, Aroda VR, Buse JB, Cariou B, Harris SB, Hoff ST, Pedersen KB, Tarp-Johansen MJ, Araki E; PIONEER 8 Investigators. Efficacy, Safety, and Tolerability of Oral Semaglutide Versus Placebo Added to Insulin With or Without Metformin in Patients With Type 2 Diabetes: The PIONEER 8 Trial. *Diabetes Care* 2019; **42**: 2262-2271 [PMID: 31530667 DOI: 10.2337/dc19-0898]

66 **Yamada Y**, Katagiri H, Hamamoto Y, Deenadayalan S, Navarria A, Nishijima K, Seino Y; PIONEER 9 investigators. Dose-response, efficacy, and safety of oral semaglutide monotherapy in Japanese patients with type 2 diabetes (PIONEER 9): a 52-week, phase 2/3a, randomised, controlled trial. *Lancet Diabetes Endocrinol* 2020; **8**: 377-391 [PMID: 32333875 DOI: 10.1016/S2213-8587(20)30075-9]

67 **Yabe D**, Nakamura J, Kaneto H, Deenadayalan S, Navarria A, Gislum M, Inagaki N; PIONEER 10 Investigators. Safety and efficacy of oral semaglutide versus dulaglutide in Japanese patients with type 2 diabetes (PIONEER 10): an open-label, randomised, active-controlled, phase 3a trial. *Lancet Diabetes Endocrinol* 2020; **8**: 392-406 [PMID: 32333876 DOI: 10.1016/S2213-8587(20)30074-7]

68 **Meier JJ**. Efficacy of Semaglutide in a Subcutaneous and an Oral Formulation. *Front Endocrinol (Lausanne)* 2021; **12**: 645617 [PMID: 34248838 DOI: 10.3389/fendo.2021.645617]

69 **Kushner RF**, Calanna S, Davies M, Dicker D, Garvey WT, Goldman B, Lingvay I, Thomsen M, Wadden TA, Wharton S, Wilding JPH, Rubino D. Semaglutide 2.4 mg for the Treatment of Obesity: Key Elements of the STEP Trials 1 to 5. *Obesity (Silver Spring)* 2020; **28**: 1050-1061 [PMID: 32441473 DOI: 10.1002/oby.22794]

70 **Newsome PN**, Buchholtz K, Cusi K, Linder M, Okanoue T, Ratziu V, Sanyal AJ, Sejling AS, Harrison SA; NN9931-4296 Investigators. A Placebo-Controlled Trial of Subcutaneous Semaglutide in Nonalcoholic Steatohepatitis. *N Engl J Med* 2021; **384**: 1113-1124 [PMID: 33185364 DOI: 10.1056/NEJMoa2028395]

71 **Flint A**, Andersen G, Hockings P, Johansson L, Morsing A, Sundby Palle M, Vogl T, Loomba R, Plum-Mörschel L. Randomised clinical trial: semaglutide versus placebo reduced liver steatosis but not liver stiffness in subjects with non-alcoholic fatty liver disease assessed by magnetic resonance imaging. *Aliment Pharmacol Ther* 2021; **54**: 1150-1161 [PMID: 34570916 DOI: 10.1111/apt.16608]