

Emerging Treatments for Non-alcoholic Fatty Liver Disease and Non-alcoholic Steatohepatitis

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Disclosures:

Dr. Gawrieh has ongoing participations in safety committees for TREAT (NIH-sponsored Translational Research and Emerging Therapies for Alcoholic Hepatitis) and Transmedics. These roles are in the alcoholic hepatitis and liver transplantation areas, respectively. These activities have been disclosed to his institutional authorities.

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Dr. Chalasani has ongoing consulting activities (or had in the preceding 12 months) with NuSirt, Abbvie, Eli Lilly, Afimmune (DS Biopharma), Tobira (Allergan), Madrigal, Shire, Cempra, Ardelyx, Gen Fit and Amarin. These consulting activities are generally in the areas of nonalcoholic fatty liver disease and drug hepatotoxicity. Dr. Chalasani receives research grant support from Intercept, Lilly, Gilead, Galectin Therapeutics and Cumberland where his institution receives the funding. Over the last decade, Dr. Chalasani has served as a paid consultant to more than 30 pharmaceutical companies and these outside activities have regularly been disclosed to his institutional authorities.

Abstract:

The field of NASH therapeutics has recently witnessed a dramatic increase in clinical trials. In this review, we discuss emerging promising compounds that have demonstrated positive effects on NASH histology in completed phase II randomized controlled trials (RCT). These compounds include obeticholic acid (OCA), Elafibranor, and liraglutide. OCA and Elafibranor have now moved to be tested in ongoing large phase III RCTs. These RCTs are slated to provide the largest efficacy and safety data in NASH therapeutic trials to date and will also collect hard clinical outcomes. The data from the completed Cenicrivorc phase II RCT is expected in the next year, which may provide impetus for yet another large phase III RCT. Based on promising results from a small phase II study, there are now two ongoing large phase III trials are assessing the efficacy of Selonsertib in NASH patients with bridging fibrosis or cirrhosis. Ultimately, demonstration of long term efficacy, tolerability and safety will be essential for these and other agents in the pipeline.

Keywords: NAFLD, NASH, Obeticholic acid, Elafibranor, Liraglutide, Cenicriviroc , Selonsertib.

Key points:

- There is a dramatic increase in the number of clinical trial testing various compounds that target different important molecules and pathways in NASH pathogenies
- Obeticholic acid, Elafibranor, and liraglutide have demonstrated variable beneficial effects on NASH histology in phase II randomized controlled trials.
- The 1 year, mid-study interim analysis of Cenicrivorc's phase IIb study showed an encouraging improvement in hepatic fibrosis. Completed results after an addition 1 year of therapy are expected later this year.
- Exciting results from phase II study of Selonsertib provided impetus for two large ongoing phase III trials to assess the efficacy of Selonsertib in NASH patients with bridging fibrosis or cirrhosis
- Cysteamine Bitartrate and Long-chain polyunsaturated fatty acids did not achieve the primary endpoint of histological improvement in high quality phase II randomized controlled trials.

Synopsis:

This review will discuss completed phase II randomized clinical trials with high quality published results for compounds that demonstrate effects on NASH histology (Obeticholic acid, Elafibranor and Liraglutide). We will also review the available preliminary data on Cenicrivorc, and Selonsertib-with or without Simtuzumab's phase II studies. Finally, we will briefly discuss compounds that have been tested but did not achieve the primary endpoint of histological improvement and appeared in high quality published papers (Cysteamine Bitartrate and Long-chain polyunsaturated fatty acids).

Introduction

The public health burden of NAFLD is now widely recognized. NAFLD is the most common liver disease in children and adults in the US [1-3]. End stage liver disease and hepatocellular carcinoma secondary to NAFLD are now the second leading indications for liver transplantation in the US, an alarming trend that is expected to culminate in NAFLD replacing hepatitis C as the most common indication for liver transplantation in the next decade [4-6].

The rise of prevalence and importance has been paralleled by better understanding of NAFLD pathophysiology (reviewed in details in Chapter 7 in this issue). Numerous molecules and pathways driving the progression of NAFLD are currently the targets of emerging therapies. The intense interest in finding treatments for NAFLD and NASH is best highlighted by the dramatic increase in registered phase II and III clinical trials for NAFLD and NASH over the past 10 years (Figure. 1).

Goals of NAFLD and NASH therapy include improving or stabilizing liver histological injury and fibrosis, prevention of liver-related poor outcomes and death, and improving or not worsening associated cardio-metabolic comorbidities. With the many pathways and molecules involved in NAFLD-NASH pathogenesis, it is likely that a combination of drugs targeting different molecules and pathways may be used in the future to achieve these goals. Because therapy for NAFLD and NASH is probably going to be chronic, drugs used will not only need to be efficacious, but also have a favorable profile on safety, tolerance and cardio-metabolic comorbidities.

Current treatments of NAFLD and NASH are discussed in details in Chapter.13. In this chapter, we will review completed phase II randomized controlled trials (RCTs) with high quality published positive results (Table. 1). We will also review the available preliminary data on Cenicrivorc and Selonsertib-with or without Simtuzumab's phase II studies which have

histological end points (Table.2). Finally, we will touch on compounds that have been tested and failed to meet the primary endpoint of histological improvement and had high quality published papers.

I. Promising emerging drugs from completed phase II RCTs

Obeticholic acid (OCA)

As an agonist of the bile acid nuclear receptor farnesoid X receptor (FXR), OCA regulates of bile acids synthesis and transport and modulates lipid and glucose homeostasis and hepatic inflammation [7, 8].

The efficacy of OCA in treating NASH was tested in FLINT (Farnesoid X Receptor Ligand Obeticholic acid In NASH Treatment) [9]. In this trial, 283 subjects with histologically confirmed NASH but without cirrhosis were randomized to receive OCA 25 mg orally daily or matching placebo for 72 weeks. Type 2 diabetes was present in 53% of the OCA and 52% of the control groups. The primary outcome was a decrease in NAFLD fibrosis score (NAS) by at least 2 points without worsening of fibrosis from baseline to the end of treatment. A planned interim analysis showed significant improvement in liver histology in subjects receiving OCA which led to modifying the study protocol and not pursuing end of treatment liver biopsy on the last 64 subjects. In an intention to treat analysis, 45% of subjects in the OCA group versus 21% in the placebo group achieved the study primary outcome (relative risk 1.9, 95% CI 1.3 to 2.8; $p=0.0002$). OCA was also associated with significant improvement in fibrosis (35% vs 19%, $p=0.004$), hepatocyte ballooning (46% vs 31%, $p=0.03$), steatosis (61% vs 38%, $p=0.001$), and lobular inflammation (53% vs 35%, $p=0.006$). There was no significant difference in the frequency of NASH resolution with OCA vs placebo (22% vs 13%, $p=0.08$).

OCA was associated with significant reduction in ALT (-38 vs -18 U/L, $p < 0.0001$), AST (-27 vs -10 U/L, $p = 0.0001$), GGT (-37 vs -6, $p < 0.0001$) and bilirubin (-1.0 vs 0.6 $\mu\text{mol/L}$, $p = 0.002$) but increase in alkaline phosphatase (12 vs -6, $p < 0.0001$). These changes resolved 24 weeks after study drug cessation, at which point, no significant difference in liver biochemistries were noted between those on OCA vs placebo.

Subjects on OCA experienced significant weight loss compared to placebo (-2.3 vs 0.0 kg, $p = 0.008$), higher insulin (29 vs 10 pmol/L, $p = 0.02$) and HOMA-IR (15 vs 4, $p = 0.01$). Significant changes in serum lipoproteins were also observed with OCA vs placebo: increase in total cholesterol (0.16 vs -0.19 mmol/L, $p = 0.0009$), LDL (0.22 vs -0.22 mmol/L, $p < 0.0001$) and a decrease in HDL (-0.02 vs 0.03 mmol/L, $p = 0.01$). These changes attenuated while on drug but were not sustained after completion of the study.

OCA therapy was associated with pruritus in 23% of subjects vs 6% of those on placebo. Pruritus was also more severe with OCA and led to stopping OCA in one subject and using antipruritic therapies and holding OCA briefly in other subjects.

There were 5 severe or life-threatening adverse events that were thought to be related to OCA. These include severe pruritus ($n = 3$), hyperglycemia ($n = 1$), and possible cerebral ischemia ($n = 1$). This compared to 4 severe or life-threatening adverse events in subjects on placebo (abdominal pain, headache, weakness, vertigo with nausea and vomiting). Two deaths occurred during the study duration; one from congestive heart failure and sepsis and one from myocardial ischemia or infarction both in subjects receiving OCA but were deemed not to be related to OCA.

Subsequently, a large phase III RCT of OCA has been launched (NCT02548351). A target of 2000 subjects with biopsy proven NASH will be randomized to OCA 10 mg daily, OCA 25 mg daily, or matching placebo for 18 months. The primary endpoints are 1) reduction in fibrosis without worsening of NASH, 2) resolution of NASH and 3) all-cause mortality and liver-related clinical outcomes spanning 6 years from the start of the study. This study is currently recruiting in centers around the world.

Elafibranor

Elafibranor (GFT505) is a dual agonist of the nuclear peroxisome proliferator activated receptors (PPAR)- α and δ . It has been shown to improve insulin sensitivity, lipid handling and inflammation [10, 11]. Elafibranor improved liver histology in different animal models of NASH [11-13].

In a large phase II RCT, 276 subjects with biopsy proven NASH without cirrhosis were randomized to receive Elafibranor 80 mg vs Elafibranor 120 mg vs placebo for 52 weeks. In the intention to treat group, 40% had type 2 diabetes. NASH resolution without worsening of fibrosis was the primary end point. This was not achieved as there was no significant difference in the primary end point between the three study groups. There was no significant effect for either dose of Elafibranor on steatosis, lobular inflammation or hepatocyte ballooning in the primary analysis. A post-hoc analysis was then performed looking at patients with NASH and NAS ≥ 4 , which showed that in this subgroup, Elafibranor 120 mg resulted in higher proportion of NASH resolution vs placebo (20% vs 11%; odds ratio=3.16; 95% confidence interval: 1.22-8.13; $p=0.018$), in addition to improving steatosis, ballooning, lobular inflammation, and NAS by 2 points. There was no effect for Elfibranor on fibrosis in the primary analysis. In the post-hoc analysis, those with NAS ≥ 4 who received the 120 mg dose and had NASH resolution showed

significant improvement in fibrosis as well as other histological features compared to those on the same dose without NASH resolution.

Patients receiving either dose of Elafibranor had significant improvement in liver enzymes, lipoproteins, triglycerides and circulating markers of inflammation (haptoglobin and fibrinogen). There was significant improvement in HOMA-IR fasting glucose level and hemoglobin A1c only in diabetic subjects in the Elafibranor 120 mg arm.

No cardiovascular events or deaths occurred in subjects receiving Elafibranor. There was no effect on body weight. Mild increase in serum creatinine was noted in the Elafibranor arms in 7 subjects (6 in the 120 mg arm) who had elevated creatinine and decreased glomerular filtration rate at baseline which led to discontinuation of the drug with subsequent improvement in creatinine in most but not all subjects. Serious adverse events occurred in 15 (16.1%), patients in the 80-mg, and 14 (15.8%) patients in the 120-mg and 11 (12%) patients in the placebo arms. There were 8 treatment-related serious adverse events: 2 in the 80-mg Elafibranor group (spontaneous abortion, ataxia, fasciculation, and tremor), in 2 in the Elafibranor 120 mg group (acute pancreatitis, Parkinson disease), and in 4 patients from the placebo arm (renal cancer, breast cancer, bladder cancer, and pancreatic cancer): In addition, one bladder cancer occurred in the elafibranor 80-mg arm. All cancers were assessed to be unlikely related to study drug.

There is currently an ongoing phase III RCT of Elafibranor (NCT02704403) in patients with biopsy proven NASH without cirrhosis. The target enrollment is 2000 subjects who will be randomized to Elafibranor 120 mg vs placebo for 72 weeks. Resolution of NASH without worsening of fibrosis as well as clinical outcomes (all cause death and liver related events over 4 year period) will be the primary outcome measures.

Liraglutide

Liraglutide is a glucagon-like peptide-1 (GLP-1) analogue that is used for glycemic control in patients with type 2 diabetes. GLP-1 has many biological effects that make it an attractive option to treat NASH. It reduces glucagon secretion, increases insulin secretion, suppresses hepatic de novo lipogenesis, increases fatty acid oxidation and delays gastric emptying. These effects result in insulin sensitivity and weight loss [14]. Preliminary human data suggested the GLP-1 analogues may improve liver histology in patients with NASH [15, 16].

More recently, a phase II RCT examined the effects of Liraglutide on biopsy proven NASH [17]. The LEAN trial (Liraglutide Efficacy and Action in Non-alcoholic steatohepatitis) randomized 52 patients with histologically proven NASH to receive either 1.8 mg/day of Liraglutide subcutaneously or placebo for 48 weeks. Subjects with type 2 diabetes and compensated cirrhosis were not excluded from the study. Similar proportion of patients with type 2 diabetes were included in the Liraglutide group vs placebo (35% vs 32%), but lower proportion of subjects on Liraglutide had advanced hepatic fibrosis (Kleiner stage 3 and 4) (46% vs 58%) and cirrhosis (8% vs 15%) compared to placebo. The primary endpoint of this trial was resolution of NASH with no worsening of fibrosis at the end of the study. More subjects receiving Liraglutide achieved the primary end point compared to placebo (39% vs 9% relative risk 4.3 [95% CI 1.0–17.7]; $p=0.019$). Improvement of steatosis was more common on Liraglutide (83% vs 45%, $p=0.009$) and worsening of fibrosis was less frequent on Liraglutide (9% vs 36%, $p=0.04$) (Figure.2). No significant differences were noted in the frequency of improvement in NAS or lobular inflammation but the improvement of hepatocyte ballooning showed a trend towards significance on Liraglutide (61% vs 32%, $p=0.05$).

There was significant improvement in hemoglobin A1c and HDL on Liraglutide. There was a numeric but non-statistically significant improvement in ALT, AST, and keratin-18 on Liraglutide. Importantly, there was more weight loss in subject on Liraglutide vs placebo (-5.5 kg vs -0.6 kg, $p=0.003$).

Gastrointestinal side effects (e.g. nausea, diarrhea, abdominal pain, loss of appetite, etc...) were most common in both study arms (81% in Liraglutide arm vs 65% in placebo arm) and more common in the Liraglutide arm than controls. Constipation occurred in 27% of subjects on Liraglutide but in none of the subjects on placebo. There were 2 severe adverse events (tuberculosis and migraine) in the Liraglutide arm that were deemed not related to study drug. The drug withdrawal rate was similar between the 2 groups (19%).

To our knowledge, there is no registered phase III RCT for Liraglutide in NASH.

II. Drugs in phase II studies with biopsy end points

Cenicriviroc

The chemokines CCL2 and CCL5 play an important role in macrophage recruitment and migration to the liver and are overexpressed in livers of obese patients with NASH [18]. Cenicriviroc is an oral antagonist of C-C chemokine receptors (CCR) 2 and 5. In animal models of different liver diseases, Cenicriviroc exhibited anti-inflammatory and anti-fibrotic effects [19].

The preliminary 1 year results of a phase IIb RCT (CENTAUR) were recently presented at the 2016 liver meeting [20]. In this trial, 289 subjects with biopsy proven NASH were randomized to receive Cenicriviroc 150 mg daily vs placebo for 2 years. In total, 52% had type 2 diabetes, 72% metabolic syndrome and 67% stage 2-3 fibrosis. The primary outcome is ≥ 2 points

improvement in NAS and secondary endpoints include complete resolution of steatohepatitis without worsening of fibrosis, and improvement in hepatic fibrosis by ≥ 1 stage. In this mid-study interim analysis, the proportion of subjects achieving the primary end point was not different between the two groups (16% vs 19% for Cenicriviroc vs placebo, $p=0.5$), however, 20% of subjects on Cenicriviroc achieved improvement in fibrosis by ≥ 1 stage without worsening of steatohepatitis compared to 10% of those on placebo ($p=0.023$) (Table.2). Treatment emergent adverse events of Grade ≥ 2 severity at a frequency $\geq 2\%$ included fatigue (2.8%) and diarrhea (2.1%) for Cenicriviroc, and headache (3.5%) for placebo.

These are exciting results and the final effects of Cenicriviroc on liver histology at the end of the trial (an additional 1 year of therapy), are awaited.

Selonsertib and Simtuzumab

Inhibition of Apoptosis Signal-Regulating Kinase (ASK1) in mice and monkeys with diet induced NAFLD results in improvement in hepatic fibrosis, inflammation, steatosis, and insulin sensitivity [21, 22]. Selonsertib (GS-4997) is a selective oral inhibitor of ASK1. In a recent randomized phase II clinical trial, Selonsertib's safety and efficacy in human NASH were tested in combination with Simtuzumab, an injectable humanized monoclonal antibody to LOX like-2 which exhibits anti-fibrotic effects [23, 24].

In this study, 72 subjects with histologically proven NASH with NAS ≥ 5 and stage 2-3 fibrosis were randomized to receive Selonsertib 6 mg or 18 mg orally once daily, with or without Simtuzumab 125 mg subcutaneously once weekly, or just Simtuzumab 125 mg subcutaneously once weekly for 24 weeks. Diabetes was present in 70.8% of all subjects. All subjects had a repeat biopsy at the end of study. In addition, fibrosis and fat were assessed by MR-elastography (MRE) and proton density fat fraction (MR-PDFF) at baseline, 12 weeks and end

of study. Fibrosis improvement by ≥ 1 stage and progression to cirrhosis were the primary histological efficacy end points, whereas $\geq 15\%$ reduction in MRE measured liver stiffness and $\geq 30\%$ reduction in MR=PDFF measured hepatic fat were the MR-based efficacy end points. Fibrosis improvement by ≥ 1 stage without worsening of steatohepatitis was observed in 37%, 30%, and 20% whereas progression to cirrhosis was observed in 3%, 7%, and 20%, in the Selonsertib 18 mg (\pm Simtuzumab), Selonsertib 6 mg (\pm Simtuzumab), vs Simtuzumab alone groups, respectively (Table 2). MRE-stiffness reduction $\geq 15\%$ was noted in 20%, 32% and 0% whereas MR-PDFF fat reduction $\geq 30\%$ was noted in 26%, 13%, and 10% in the Selonsertib 18 mg (\pm Simtuzumab), Selonsertib 6 mg (\pm Simtuzumab), vs Simtuzumab alone groups, respectively. Stability or improvement in NAS and lobular inflammation, and reduction of fibrosis as measured by morphometric hepatic collagen per 1% decrease and MRE stiffness per 1-kPa decrease, were associated with improvement in pathologist's assessment of fibrosis. No deaths occurred during the study. Five serious adverse events were reported in the Selonsertib \pm Simtuzumab groups vs none in the Simtuzumab group, with only 1 serious adverse event deemed related to study drug. Treatment was discontinued to adverse events in 3 subjects (4.8%) Selonsertib \pm Simtuzumab groups vs none in the Simtuzumab group.

The safety and efficacy of Selonsertib vs placebo is currently being tested in two phase III RCTs in adults with bridging fibrosis (STELLAR 3, NCT03053050) or compensated cirrhosis (STELLAR 4, NCT03053063) due to NASH. Each study plans to recruit 800 subjects and study duration will be 240 weeks. Two phase II clinical trials in patients with NASH and bridging fibrosis (NCT01672866) or cirrhosis (NCT01672879) evaluating intravenous simtuzumab's efficacy and safety have been terminated.

III. Drugs that have been tested in phase II trials without achieving primary histological end point

Cysteamine Bitartrate

As a precursor to glutathione, Cysteamine has the advantage of crossing of cellular membranes more efficiently than glutathione. Its efficacy at protecting against acetaminophen-induced liver injury has been demonstrated in prior studies in humans [25, 26].

A recent RCT in 169 children with NAFLD activity scores ≥ 4 (CyNCh; Cysteamine bitartrate delayed-release for the treatment of Nonalcoholic fatty liver disease in Children) randomized subjects to receive weight-based Cysteamine or placebo twice daily for 52 weeks [27]. A decrease in NAS ≥ 2 points without worsening fibrosis was the primary outcome. Despite a significant improvement in liver enzymes (ALT -53 ± 88 U/L vs -8 ± 77 U/L; $p = 0.02$, AST -31 ± 52 vs -4 ± 36 U/L; $p = 0.008$), and lobular inflammation (36% vs 21%; $p = 0.03$) on Cysteamine compared to placebo, the primary end point was not achieved. In subgroup analyses, children younger than 13 years showed histological improvement with Cysteamine [43% (16/37) vs 21% (8/39), relative risk, 2.3; 95% CI, 1.0–5.2; $p=0.04$]. Children weighing ≤ 65 kg also showed histologic improvement and achieved the primary outcome on cysteamine vs placebo [observed in 50% (12/24) vs 13%(3/23); relative risk, 4.0; 95% CI, 1.3-12.3; $p=0.005$], which was due to improvement in lobular inflammation (54% vs 22%, relative risk, 2.6; 95% CI, (1.1–6.0); $p=0.02$) and hepatocyte ballooning (33% vs 4%, relative risk, 8.3; 95% CI, 1.0–71.3; $p=0.01$).

Validation of the effects of Cysteamine on NASH histology per age and weight will require adequately powered RCT to measure any potential effect. To our knowledge, there is currently no registered future clinical trial for Cysteamine.

Long-chain polyunsaturated fatty acids (LC-PUFAs)

LC-PUFAs are abundant in fish and fish oil supplements and exhibit beneficial metabolic and anti-inflammatory effects, including improvement in insulin sensitivity and reduction in serum triglycerides, endothelial dysfunction and adipose tissue inflammation [28-30].

Earlier reports of favorable effects on liver enzymes and hepatic steatosis with LC-PUFAs were not substantiated by larger phase II RCTs [31-34]. One RCT randomized 103 subjects with NAFLD to receive docosahexaenoic acid (DHA) and eicosapentaenoic acid (EPA) (4 gm/day) for 15-18 months [35]. There was no significant change in hepatic steatosis or non-invasive markers of fibrosis at the end of the study. The largest RCT of LC-PUFAs randomized 243 subjects with histologically confirmed NASH to receive EPA 1800 mg/day, EPA 2700 mg/day, or placebo for 12 months [36]. Subjects on EPA showed no significant change in liver enzymes, markers of fibrosis, insulin resistance or liver histology compared to those on placebo. This data suggests that LC-PUFAs are not an effective therapy for NASH.

Conclusions

The intense interest in NASH therapeutics has translated in a significant increase in clinical trials. Of the emerging promising compounds, OCA, Elafibranor, and liraglutide have evidence from phase II RCT of variable beneficial effects on NASH histology. Exciting preliminary results from a small phase II study, have led to the launch of two large phase III trials to assessing the efficacy of Selonsertib in NASH patients with bridging fibrosis or cirrhosis. OCA and Elafibranor have now moved to be tested in ongoing large phase III RCTs. These RCTs are slated to provide the largest efficacy and safety data in NASH therapeutic trials to date and will also collect hard clinical outcomes. The data from the completed Cenicrivorc phase II RCT is

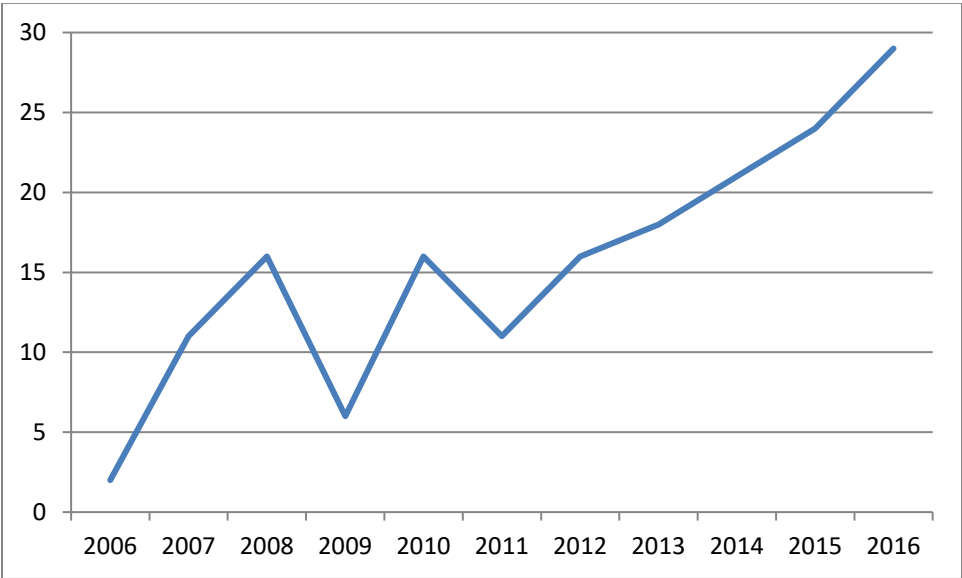
expected in the next year, which may provide impetus for yet another large phase III RCT. For all these promising compounds and others in different stages of development, establishment of long term safety, efficacy and tolerability will be key for their approvals as therapies for patients with NASH.

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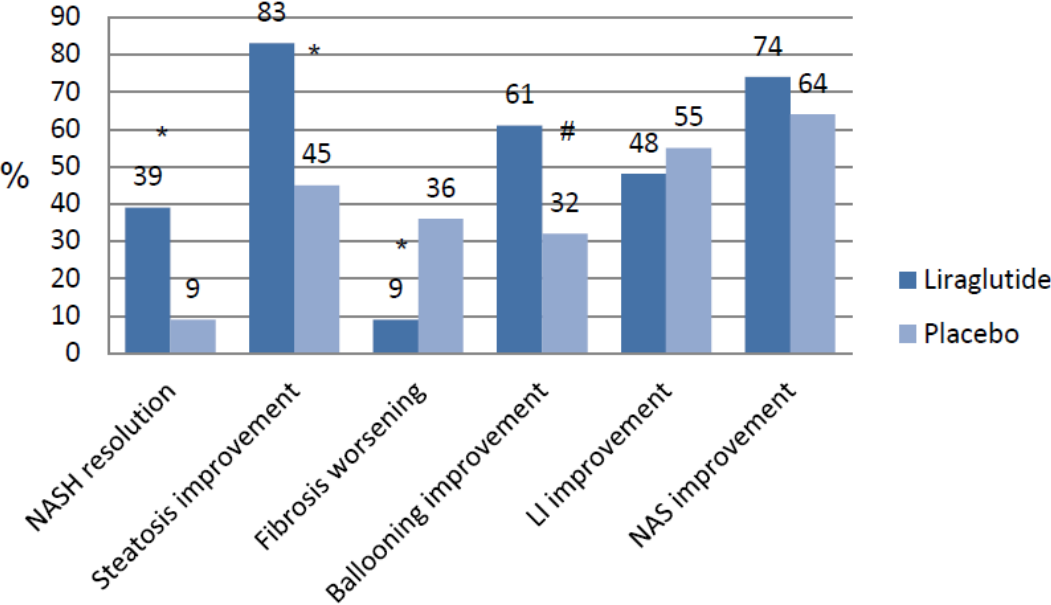
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Figure 1. Registered phase II and III clinical trials for NAFLD-NASH from 2006-2016*.



* Search of clinicaltrials.gov as of 2/8/17 for NAFLD | Interventional Studies | Phase II, III |
Studies received from 01/01/2006 to 01/01/2017.

Figure.2. Results of the LEAN trial.



* : $p < 0.05$, #: $p = 0.05$, remaining comparisons $p > 0.05$.

LI: Lobular inflammation, NAS: NAFLD Activity Score.

Table.1 Summary of drugs with published phase II trials with evidence of effect on NASH histology.

Drug	Mechanism	Study size (n)	Route of administration	Effect on histology	Common side effects
Obeticholic acid	FXR agonist	283	Oral	Improvement in NAS, steatosis, ballooning, lobular inflammation and fibrosis	Pruritus Weight loss Temporary increase in alkaline phosphatase Temporary changes in lipoprotein profile
Elafibranor	PPAR- α and δ agonist	276	Oral	In subjects with NAS \geq 4, Elafibranor 120 mg resulted in higher proportion of NASH resolution, improved ballooning, lobular inflammation, and NAS by 2 points. No significant effect on steatosis or fibrosis.	Mild increase in serum creatinine in 7.1% of subjects on Elafibranor 120 mg.
Liraglutide	GLP-1 analogue	52	Subcutaneous	Resolution of NASH with no worsening of fibrosis. Improved steatosis	Gastrointestinal symptoms Weight loss

Table. 2 Summary of preliminary studies of anti-fibrotic agents, Cenicrivoric and Selonsertib-Simtuzumab

	Cenicrivoric	Selonsertib 18 mg (\pm Simtuzumab), Selonsertib 6 mg (\pm Simtuzumab), Simtuzumab alone
Mechanism	Antagonist of C-C chemokine receptors 2 and 5	Inhibitor of ASK1 (Selonsertib) Humanized monoclonal antibody to LOX like 2 (Simtuzumab)
Route of administration	Oral	Oral (Selonsertib) Subcutaneous (Simtuzumab)
Size of initial study	289	72
Diabetics included	Yes	Yes
% Improvement in fibrosis \geq 1 stage without worsening of steatohepatitis	20	37, 30, 20
Interval Histological effect observed	1 year	6 months
Ongoing clinical trials	Current IIb with 289 subjects for 2 years	2 ongoing phase III trials Selonsertib vs placebo (NASH with bridging fibrosis or cirrhosis), each with 800 subjects for 240 weeks

*Note these are separate studies with preliminary results, not head to head comparisons between the agents.