

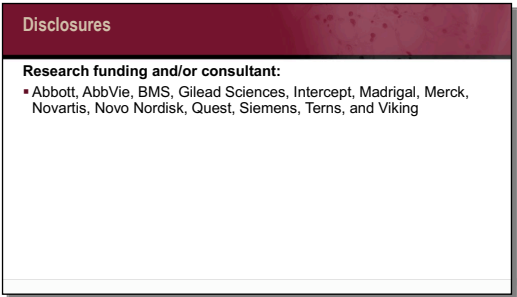


**TARGETING METABOLIC DYSREGULATION IN NASH: EXPLORING NOVEL STRATEGIES TO MITIGATE HEPATIC AND CARDIOVASCULAR DISEASE**

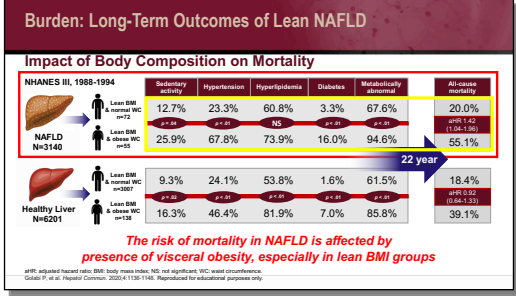
*Emerging Targeted Strategies to Mitigate Disease Progression in NAFLD/NASH*

<p>1</p>		<p>Hello, I'm Zobair Younossi. I'm the president of Inova Medicine. It's my pleasure to welcome you to this symposium on targeting metabolic dysregulation in NASH. I will be focusing on exploring novel strategies to medicate hepatic disease and non-alcoholic steatohepatitis. And you're also welcome to join the presentation by Dr. Kathleen Corey, who's going to cover strategies to mitigate cardiovascular diseases in patients with NASH.</p>
<p>2</p>		<p>My task over the next 40 minutes or so will be to talk about emerging targeted strategies to mitigate disease progression in non-alcoholic fatty liver diseases in NASH. As I mentioned, I'm at the Inova Health System in Falls Church, Virginia.</p>
<p>3</p>		<p>These are my disclosures.</p>



# TARGETING METABOLIC DYSREGULATION IN NASH: EXPLORING NOVEL STRATEGIES TO MITIGATE HEPATIC AND CARDIOVASCULAR DISEASE

## Emerging Targeted Strategies to Mitigate Disease Progression in NAFLD/NASH

		<p>much lower. You have to pay attention to this, but the rate is lower, so you don't have to actually screen these patients for HCC.</p> <p>The second peculiarity of this disease has to do with progression and regression that happens over a period of time. This is a non-linear progression of liver disease. There are times that these patients progress. There are times that they remain stable. And there are times that they actually will regress. That makes this disease relatively complicated.</p> <p>And actually a placebo rate of 10 to 20% can be seen in patients with NASH in clinical trials, and that can be explained by this sort of uneven or non-linear progression.</p> <p>It is important to also remember that although cirrhosis is a common cause of liver mortality, the number one cause of mortality in patients with NAFLD is cardiovascular mortality. And this is why Dr. Corey's presentation will be important.</p>																																																								
5	 <p><b>Burden: Long-Term Outcomes of Lean NAFLD</b></p> <p><b>Impact of Body Composition on Mortality</b></p> <table border="1"> <thead> <tr> <th></th> <th>Dietary Intake</th> <th>Hypertension</th> <th>Hyperlipidemia</th> <th>Diabetes</th> <th>Metabolically Abnormal</th> <th>Alcoholic Obesity</th> </tr> </thead> <tbody> <tr> <td><b>NHANES III, 1988-1994</b></td> <td></td> <td></td> <td></td> <td></td> <td></td> <td></td> </tr> <tr> <td>Lean BMI &amp; normal WC (n=72)</td> <td>12.7%</td> <td>23.3%</td> <td>60.8%</td> <td>3.3%</td> <td>67.6%</td> <td>20.0%</td> </tr> <tr> <td>Lean BMI &amp; obese WC (n=68)</td> <td>25.9%</td> <td>67.8%</td> <td>73.9%</td> <td>16.0%</td> <td>94.6%</td> <td>55.1%</td> </tr> <tr> <td><b>NAFLD N=5140</b></td> <td></td> <td></td> <td></td> <td></td> <td></td> <td></td> </tr> <tr> <td>Lean BMI &amp; normal WC (n=201)</td> <td>9.3%</td> <td>24.1%</td> <td>53.8%</td> <td>1.6%</td> <td>61.5%</td> <td>18.4%</td> </tr> <tr> <td>Lean BMI &amp; obese WC (n=124)</td> <td>16.3%</td> <td>46.4%</td> <td>81.9%</td> <td>7.0%</td> <td>85.8%</td> <td>39.1%</td> </tr> <tr> <td><b>Healthy Liver N=6201</b></td> <td></td> <td></td> <td></td> <td></td> <td></td> <td></td> </tr> </tbody> </table> <p><i>The risk of mortality in NAFLD is affected by presence of visceral obesity, especially in lean BMI groups</i></p> <p><small>HR, adjusted hazard ratio; BMI, body mass index; NS, not significant; WC, waist circumference. Glaser T, et al. Hepatology. 2020;61:1136-1146. Reproduced for educational purposes only.</small></p>		Dietary Intake	Hypertension	Hyperlipidemia	Diabetes	Metabolically Abnormal	Alcoholic Obesity	<b>NHANES III, 1988-1994</b>							Lean BMI & normal WC (n=72)	12.7%	23.3%	60.8%	3.3%	67.6%	20.0%	Lean BMI & obese WC (n=68)	25.9%	67.8%	73.9%	16.0%	94.6%	55.1%	<b>NAFLD N=5140</b>							Lean BMI & normal WC (n=201)	9.3%	24.1%	53.8%	1.6%	61.5%	18.4%	Lean BMI & obese WC (n=124)	16.3%	46.4%	81.9%	7.0%	85.8%	39.1%	<b>Healthy Liver N=6201</b>							<p>The most common cause of death is cardiovascular mortality. In fact, non-liver cancer mortality and then liver mortality would be the other causes.</p> <p>Now, in the context of metabolic components, which are risk factors for non-alcoholic fatty liver disease in NASH, it really is important to remember that it's the body composition that impacts mortality.</p> <p>And that's actually determined not just by body mass index, but actually by waist circumference. The more components of metabolic syndrome you have, obviously, the more increased rate of mortality that you'll have.</p> <p>On the other hand, when you look at lean patients that are determined by body mass index and they have also normal waist circumference, and you look at lean patients who are by BMI lean, but</p>
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		<p>they're obese by waist circumference, you'll see that the mortality is significantly higher in those patients that have central obesity as determined by increased waist circumference.</p> <p>It's really the visceral obesity that drives mortality of these patients.</p>
<p>6</p>	<p><b>Burden: Extrahepatic Outcomes</b></p> <p><b>Associations With Extrahepatic Disease</b></p> <p>NAFLD is associated with:</p> <ul style="list-style-type: none"> <li>Gallstone disease</li> <li>Chronic kidney disease</li> <li>Osteoarthritis</li> <li>Cardiac disease</li> <li>Cerebrovascular Disease</li> <li>Sarcopenia</li> <li>Diabetes</li> <li>Obstructive sleep apnea</li> <li>Polycystic ovary syndrome</li> <li>Malignancy: Stomach 3.0, Pancreas 2.7, Lung 2.0</li> </ul> <p><small>Park SH, et al. Hepatol Commun. 2015;3:1430-1471. Galati F, et al. Medicine (Baltimore). 2018;97:e2114. Dulai PS, et al. Hepatology. 2017;65:1557-1565. Younossi ZM, et al. Hepatology. 2011;53:1074-1082. Younossi ZM, et al. Hepatology. 2011;53:1725-1730. Evans C, et al. Hepatology. 2016;62:121-123. Younossi ZM, et al. Clin Gastroenterol Hepatol. 2016;14(10):1625-1632.e1. Younossi Z, et al. Clin Gastroenterol Hepatol. 2011;9:667. Younossi ZM, et al. Clin Gastroenterol Hepatol. 2011;9:667. Younossi ZM, et al. Clin Gastroenterol Hepatol. 2011;9:667. Younossi ZM, et al. Clin Gastroenterol Hepatol. 2011;9:667. Younossi ZM, et al. Clin Gastroenterol Hepatol. 2011;9:667.</small></p>	<p>Let's now look at the other component of this metabolic complication that has to do with non-hepatic.</p> <p>As I mentioned, cardiovascular and cerebrovascular disease are very common in these patients. Non-hepatic malignancy, gastric cancer, pancreatic cancer, and lung cancer are common.</p> <p>Probably one of the ones that's probably least emphasized is sarcopenia, which is also common in patients with non-alcoholic fatty liver disease.</p>
<p>7</p>	<p><b>Interactive Question</b></p> <p><b>For every 1-kPa increase in liver stiffness, how much more likely are patients with cirrhosis NASH likely to develop decompensation and/or die in 5 years?</b></p> <p>A. 8%          B. 21%          C. 32%          D. 46%</p>	<p>Let me actually ask you a question about assessment of outcomes in these patients.</p> <p>If you look at patients that have fatty liver disease or NASH, especially those that have NASH with cirrhosis, and you do an MRE, which is MR elastography, for every one kilopascal increase in liver stiffness, how much more likely do you think these patients are to develop decompensation or die in five years?</p> <p>Is it 8%, 21%, 32%, or 46%?</p>

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<p>8</p>	<p><b>Transient Elastography and MRE: Threshold and Outcomes</b></p> <ul style="list-style-type: none"> <li>Cumulative probability of death correlates with TE</li> <li>For each 1-kPa increase in liver stiffness by MRE:             <ul style="list-style-type: none"> <li>Patients with non-cirrhotic NAFLD are 3x more likely to develop cirrhosis in the future</li> <li>Patients with NASH cirrhosis are <b>32% more likely</b> to develop decompensation and/or die in 5 years</li> </ul> </li> </ul> <p><small>EVB: esophageal variceal bleeding; HE: hepatic encephalopathy; MRE: magnetic resonance elastography; CR: cutoff ratio; TE: transient elastography. Sauerbrun T, et al. J Hepatol. 2016;63(2):279. Younossi ZM, et al. Gastroenterology. 2015;148(5):953-961. Han MK, et al. Liver Int. 2009;6(2):221. Gohar T, et al. Clin Gastroenterol Hepatol. 2011;9:1935-1944.e6.</small></p>	<p>Now let's look at elastography, which is a way to assess stiffness of the liver, which is a surrogate of fibrosis, which by itself is a predictor of mortality.</p> <p>This is a study that was published in the past year or so looking at MRE and looking at different increases in the MRE over time.</p> <p>And as you can see in the graph on the right, when you go from cirrhosis to development of hepatic decompensation, you really see almost a two-point jump in the liver stiffness by kilopascal – from 4.39 to 6.48 when you have ascites as a part of decompensation.</p> <p>Liver transplant, you get into about 10 kilopascal in the MRE.</p> <p>When you look at non-cirrhotic NAFLD patients, for every one kilopascal increase in MRE, they are three times more likely to develop cirrhosis in the future.</p> <p>On the other hand, when you look at patients who have cirrhosis from NASH, and for each kilopascal increase in MRE, they're about 32% more likely to develop decompensation or die in five years.</p> <p>The correct answer to the previous question was 32%.</p>
<p>9</p>	<p><b>Goals of Treatment for NAFLD and NASH</b></p> <ul style="list-style-type: none"> <li>Improve metabolic abnormalities</li> <li>Prevent/arrest/reverse liver fibrosis</li> <li>Prevent advanced liver disease, liver failure, liver cancer, and non-liver-related outcomes</li> <li>Improve PROs</li> <li>Improve long-term outcomes (eventually)</li> <li>Improve economic burden</li> <li>Acceptable AE profile</li> </ul> <p><small>AE: adverse events; PRO: patient-reported outcomes. Park JH, et al. Hepatol Commun. 2015;1(4):1471. Gohar T, et al. Medicine (Baltimore). 2013;92(14):e214. Dale PR, et al. Hepatology. 2017;65:1557-1565. Younossi ZM, et al. Hepatology. 2015;61(4):1284-1291. Younossi ZM, et al. Hepatology. 2015;61(2):773-779. Elias C, et al. Hepatology. 2016;62:127-133. Younossi ZM, et al. Clin Gastroenterol Hepatol. 2016. Younossi Z, et al. Clin Gastroenterol Hepatol. 2011;9(7). Younossi ZM, et al. Gut. 2005;54(5):654-658. Park J, et al. SOJ 2016. Abstract 017. Younossi ZM, et al. AASLD 2016.</small></p>	<p>Now, let's look at goals of treatment for non-alcoholic fatty liver disease. Now, obviously, one of the most important goals would be to improve metabolic abnormality because these metabolic abnormalities drive this disease and also these metabolic abnormalities drive mortality in non-alcoholic fatty liver disease.</p> <p>Second is to prevent, arrest or reverse liver fibrosis to prevent advanced liver disease. But also, from a patient perspective, it's important to improve their experience, as indicated by measures of patient-reported outcomes. And of course, eventually and</p>

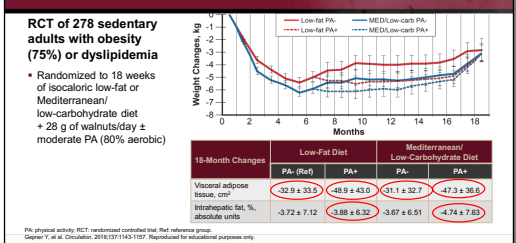
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		<p>ultimately, you have to improve long-term outcomes.</p> <p>And you have to do this in a way that it is economical, that the economic burden of NAFLD is going to improve.</p> <p>Since I believe that NAFLD is going to be treated like diabetes or other components of metabolic syndrome, you're going to have to treat patients for a very long time. In that context, it's important to have drugs that have an acceptable adverse event profile.</p>																				
10	<p><b>Interactive Question</b></p> <p><b>What do you feel is the biggest challenge that you face in managing patients with NAFLD/NASH?</b></p> <p>A. Few approved pharmacologic treatments          B. Patients adhering to diet recommendations          C. Patients adhering to exercise recommendations          D. Managing comorbidities</p>	<p>Let's actually look at another question that may be important for your practice:</p> <p>What do you feel is the biggest challenge that you face in managing patients with NAFLD and NASH?</p> <p>Few approved pharmacologic treatments?          Patients adhering to diet recommendations?          Patients adhering to exercise recommendations?          Managing comorbidities?</p> <p>Let's actually look at some of the data that we have.</p>																				
11	<p><b>Old Regimens: Weight Loss—Diet and Exercise</b></p> <p><b>Probability of Improvement Based on Weight Loss</b></p> <p>52 weeks of lifestyle intervention          • Caloric intake reduction • No heavy alcohol          • Exercise • &gt;2 cups of coffee</p> <table border="1"> <thead> <tr> <th></th> <th>5%</th> <th>7%</th> <th>10%</th> </tr> </thead> <tbody> <tr> <td>NASH Resolution</td> <td>10%</td> <td>26%</td> <td>64%</td> </tr> <tr> <td>Fibrosis Regression</td> <td>49%</td> <td>38%</td> <td>50%</td> </tr> <tr> <td>Steatosis Improvement</td> <td>35%</td> <td>65%</td> <td>76%</td> </tr> <tr> <td>% Patients Achieving WL</td> <td>70%</td> <td>12%</td> <td>9%</td> </tr> </tbody> </table> <p><small>Romero-Gomez M, et al. J Hepatol. 2017;67:529-540. Reproduced for educational purposes only.</small></p>		5%	7%	10%	NASH Resolution	10%	26%	64%	Fibrosis Regression	49%	38%	50%	Steatosis Improvement	35%	65%	76%	% Patients Achieving WL	70%	12%	9%	<p>When you look at the weight loss with diet and exercise – this is an important study by Romero-Gomez that was published in 2017: 52 weeks of lifestyle intervention with caloric intake reduction and exercise – you'll see that if you lose about 50% of the baseline weight, about 70% of patients can achieve this. But only 10% of patients resolve their NASH, and about 50% of patients have fibrosis regression.</p> <p>Now, in order to actually get significant number of patients to actually improve both NASH resolution and also experience fibrosis regression, you have to lose 10% or more.</p>
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		<p>Unfortunately, that happens in about 10% of patients.</p> <p>It's important to remember that significant weight loss that will lead to improvement of fibrosis will be hard to achieve.</p>																			
<p>12</p>	<p><b>Old Regimens: Weight Loss—Diet and Exercise (cont)</b></p>  <p><b>RCT of 278 sedentary adults with obesity (75%) or dyslipidemia</b></p> <ul style="list-style-type: none"> <li>Randomized to 18 weeks of isocaloric low-fat or Mediterranean/low-carbohydrate diet + 28 g of walnuts/day ± moderate PA (80% aerobic)</li> </ul> <table border="1"> <thead> <tr> <th rowspan="2">18-Month Changes</th> <th colspan="2">Low-Fat Diet</th> <th colspan="2">Mediterranean/ Low-Carbohydrate Diet</th> </tr> <tr> <th>PA- (Ref)</th> <th>PA+</th> <th>PA-</th> <th>PA+</th> </tr> </thead> <tbody> <tr> <td>Visceral adipose tissue, cm<sup>3</sup></td> <td>-32.9 ± 33.5</td> <td>-48.9 ± 43.0</td> <td>-51.1 ± 32.7</td> <td>-47.3 ± 36.6</td> </tr> <tr> <td>Intrahepatic fat, %, absolute units</td> <td>-3.72 ± 7.12</td> <td>-3.88 ± 6.32</td> <td>-3.67 ± 6.51</td> <td>-4.74 ± 7.65</td> </tr> </tbody> </table>	18-Month Changes	Low-Fat Diet		Mediterranean/ Low-Carbohydrate Diet		PA- (Ref)	PA+	PA-	PA+	Visceral adipose tissue, cm <sup>3</sup>	-32.9 ± 33.5	-48.9 ± 43.0	-51.1 ± 32.7	-47.3 ± 36.6	Intrahepatic fat, %, absolute units	-3.72 ± 7.12	-3.88 ± 6.32	-3.67 ± 6.51	-4.74 ± 7.65	<p>Another study looked at sedentary adult patients with obesity or dyslipidemia who were randomized to 18 weeks of isocaloric low-fat diet, or a Mediterranean diet with moderate physical activity.</p> <p>And look at the line graph. As you can see, both of these two types of lifestyle intervention led to significant weight loss. However, if you look at the table below, you'll see that it's the Mediterranean diet that improved not only the weight loss with physical activity, but also improved visceral adiposity and also intrahepatic fat.</p> <p>The best regimen that we recommend, at least in the United States, is to combine moderate physical activity with a Mediterranean diet.</p>
18-Month Changes	Low-Fat Diet		Mediterranean/ Low-Carbohydrate Diet																		
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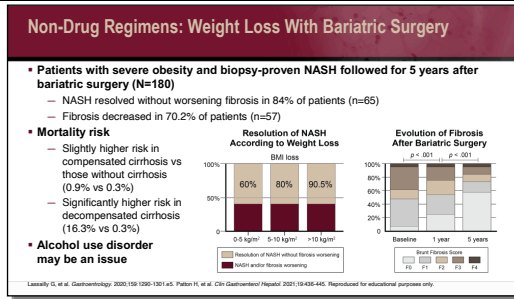
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<p>13</p>	<p><b>Old Regimens: The Impact of Diet on NAFLD</b></p> <ul style="list-style-type: none"> <li>• Open-label RCT in 74 subjects with NAFLD</li> <li>• Study groups             <ul style="list-style-type: none"> <li>– Standard of care (SoC)</li> <li>– Intermittent caloric restriction 5:2</li> <li>– Low-carbohydrate high fat (LCHF)</li> </ul> </li> <li>• Primary outcome measure: MRS</li> </ul> <p>MRS: magnetic resonance spectroscopy. Heller M, et al. JHEP Rep. 2021;3:10026. Reproduced for educational purposes only.</p>	<p>The final data that I'm going to show you has been very recently published and actually presented or written. And this was an open-label, randomized clinical trial of 74 subjects with NAFLD. And they were randomized to either standard of care, intermittent caloric restriction, or so-called fasting diet, or low-carb/high-fat diet</p> <p>And primary outcome here was to look at hepatic fat with MRS.</p> <p>You can see that the diet composition really in terms of the fat intake and carbohydrate intake is depicted over here, but most importantly when you look at the liver fat fraction, this happened, of course, in both types of diet – the intermittent diet and also the low-carb/high-fat diet, as compared to standard of care.</p>
<p>14</p>	<p><b>Old Regimens: The Impact of Diet on NAFLD (cont)</b></p> <ul style="list-style-type: none"> <li>• 5:2 and LCHF diets were superior to SoC on short-term reduction of steatosis, weight, and insulin resistance</li> <li>• 5:2 and LCHF have similar short-term efficacy</li> <li>• Weight reduction is more important than composition of macronutrients</li> <li>• Close monitoring and support was crucial for a successful diet treatment</li> <li>• Sustainability and impact on long-term outcomes are unknown</li> </ul> <p>Heller M, et al. JHEP Rep. 2021;3:10026.</p>	<p>The conclusion of these authors was that both diets were superior to standard of care on short-term reduction of steatosis, weight and insulin resistance. And they both had at least similar short-term efficacy.</p> <p>On the other hand, the weight reduction was more important than really composition of the macronutrients in the diet.</p> <p>Also, this study, of course, close monitoring and support was implemented, and this was crucial for successful diet treatment.</p> <p>And finally, it's important to remember that sustainability of the weight loss and the impact of long-term outcomes of these interventions are really unknown at this point.</p>



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And let me also show you the extreme weight loss approach. And this is with bariatric surgery. This is patients with severe obesity and biopsy-proven NASH who were followed for five years. This is a French cohort five years after bariatric surgery. NASH resolved without worsening fibrosis in 84% of these patients. And in fact, fibrosis decreased in about 70% of patients.

And you can see this actually in the slide according to both different BMI losses, but also according to the resolution of NASH without fibrosis in sort of beige and NASH or fibrosis worsening in burgundy. And as you can see, the beige numbers are bigger. Same thing with fibrosis.

Now, a couple of things about bariatric surgery that you need to remember is that there is a slightly higher risk in compensated cirrhosis patients. So this risk needs to be considered.

And second, of course, is that alcohol-use disorder may be an issue.

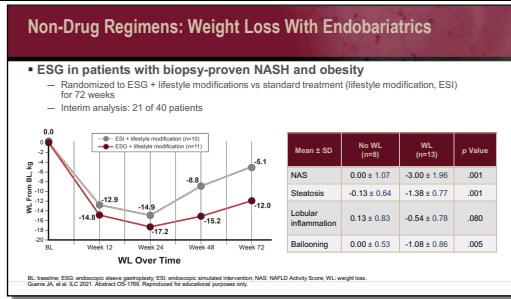
And not only actually the risk is higher in compensated cirrhotics, from .9 to .3%, but for those who have decompensated cirrhosis, then the risk is really substantial.

You need to take into consideration the stage of liver disease of these patients before you recommend bariatric surgery.

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Finally, instead of bariatric surgery, of course, there is a lot of attempts to use endobariatrics to manage the weight loss.

Here is a study that was presented in our liver meeting, in ILC 2021. And here, the patients were basically either randomized to an endoscopic treatment, which is endoscopic sleeve gastroplasty, versus a sham intervention, or endoscopic simulated intervention.

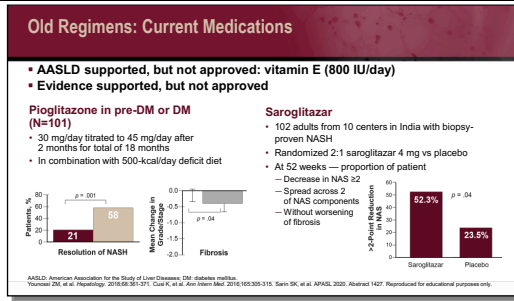
And as you can see, in both of these two, there is actually a weight loss that happens by week 12 that is similar. And of course, this may be in terms of lifestyle modification because both groups received lifestyle modification.

As you move patients over time, by week 72 you'll see that those who had bariatric endoscopy, they actually maintained their weight loss than those patients that basically received simulation.

And when you look at the components of fatty liver that were here, whether it's NAFLD activity score, or steatosis, lobular inflammation and ballooning, those who achieved weight loss actually had significant improvement of the histologic progress.

Of course, this is a small number of patients and relatively short study. This was an interim analysis. We need to get better data here.

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Other types of treatment that have been available for non-alcoholic fatty liver disease, these are really the old regimens and they have been a part of the American Association for the Study of Liver Disease guidance document that was published in 2018.

There are lots of drugs that have actually been tested in patients with NASH. One of them is vitamin E. Vitamin E actually was used in the PIVENS trial, and it was supposed to be a second placebo, but to the surprise of the investigators, vitamin E at 800 international units for non-diabetics without cirrhosis was actually better than placebo. So this is for non-cirrhotics, non-diabetics with NASH, vitamin E as an option.

Pioglitazone initially in the PIVENS study did not actually meet its outcome criteria that was established. But subsequently, there has been a number of studies showing pioglitazone in pre-diabetic or diabetic can actually improve histology in terms of resolution of NASH. And there are some studies suggesting improvement of fibrosis.

Saroglitazar, which is another PPAR agonist, has been tested in India. It's not been available in the United States. This is the study that led to the approval of this drug in India. And more studies need to be done for us to be able to utilize this drug.

# TARGETING METABOLIC DYSREGULATION IN NASH: EXPLORING NOVEL STRATEGIES TO MITIGATE HEPATIC AND CARDIOVASCULAR DISEASE

## Emerging Targeted Strategies to Mitigate Disease Progression in NAFLD/NASH

<p>18</p>	<p><b>Old Regimens: Current Medications (cont)</b></p> <p>▪ <b>Not supported</b></p> <ul style="list-style-type: none"> <li>– Caspase inhibitors</li> <li>– Ursodeoxycholic acid</li> <li>– Anti-obesity medications</li> <li>– Betaine</li> <li>– N-acetyl-cysteine</li> <li>– Silymarin</li> <li>– Beta-carotene</li> <li>– Omega 3 fatty acid (PUFA, "fish oil")</li> <li>– Anti-TNF agents (pentoxifylline)</li> <li>– ACE inhibitors/ARBs</li> <li>– Probiotics (VSL#3)</li> <li>– Lipid-lowering agents (statins)</li> </ul> <p><small>ACE, angiotensin-converting enzyme; ARB, angiotensin receptor blocker; PUFA, polyunsaturated fatty acid; TNF, tumor necrosis factor. Younossi ZM, et al. Hepatology. 2015;61:301-311; Cusi K, et al. Ann Intern Med. 2010;152:305-315.</small></p>	<p>Drugs that have been used and have not had any significant efficacy are listed to the left: ursodeoxycholic acid; NAC; silymarin; omega-3 fatty acid; ACE inhibitors.</p> <p>Probiotics are interesting because of course there is a pathogenic reason to use probiotics, and that has to do with the fact that dysbiosis is common in patients with NAFLD. But at least the regimens that have been used have not shown efficacy.</p> <p>Lipid-lowering agents with statins would be important because a lot of our patients need statins. I can tell you that statins are safe and effective in terms of lowering lipids, but in terms of using it solely to treat NASH, efficacy is not there. But I have no problem using statins in our patients with NASH.</p>
<p>19</p>	<p><b>Future Treatment Regimens: Drugs in Phase 2 and 3</b></p> <p><small>ACE, angiotensin-converting enzyme; ARB, angiotensin receptor blocker; PUFA, polyunsaturated fatty acid; TNF, tumor necrosis factor; Younossi ZM, et al. Hepatology. 2015;61:301-311; Cusi K, et al. Ann Intern Med. 2010;152:305-315.</small></p>	<p>These are some of the future treatments that are listed here. And we will review a few of them.</p> <p>And you can see that some of them are related to SCD1 inhibitor.</p> <p>Some of these are related to bacterial products – dysbiosis. FXR agonist is part of them.</p> <p>PPAR agonists, I just reviewed those with you; lanifibranor is one of them, and I'll mention that.</p> <p>Thyroid hormone receptors. And there are a number of other drug mechanisms.</p> <p>GLP-1 agonists are probably the ones that are really promising, and I will review that as well.</p>

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20	<p><b>New Regimens: Drugs in Phase 3</b></p> <table border="1"> <thead> <tr> <th>AGENT</th> <th>MECHANISM</th> <th>STUDY</th> <th>OUTCOME</th> </tr> </thead> <tbody> <tr> <td><b>Elafibranor</b></td> <td>Lipotoxicity/oxidative stress (PPAR<math>\alpha</math>/<math>\delta</math> agonist)</td> <td><b>GOLDEN-505</b> (n=276, F0-F3)</td> <td>—Reversal of NASH without worsening the fibrosis</td> </tr> <tr> <td><b>Cenicriviroc</b></td> <td>Inflammation/immune activation (CCR2/5 antagonist)</td> <td><b>CENTAURO</b> (n=288, F1-F3)</td> <td>—Improvement in NAS by <math>\geq 2</math> points and <math>\geq 1</math>-point decrease in lobular inflammation or hepatocellular ballooning without worsening of fibrosis at year 1</td> </tr> <tr> <td><b>Selonsertib</b></td> <td>Apoptosis/hepatocellular (ASK1 inhibitor)</td> <td><b>STELLAR-4</b> (n=183, compensated cirrhosis)</td> <td>—Fibrosis improvement <math>\geq 1</math> stage without NASH worsening —Event-free survival</td> </tr> <tr> <td></td> <td></td> <td><b>STELLAR-3</b> (n=188, F3)</td> <td>—Fibrosis improvement <math>\geq 1</math> stage without NASH worsening —Event-free survival</td> </tr> <tr> <td><b>Semaglutide</b></td> <td>GLP-1</td> <td><b>Phase 3 SEMA</b> (n=1200, F2-F3)</td> <td>—Improvement of fibrosis without worsening NASH —Reversal of NASH without worsening of fibrosis</td> </tr> <tr> <td><b>Resmetirom (MGL-3196)</b></td> <td>Lipotoxicity (FXR agonist)</td> <td><b>MAESTRO-NASH</b> (n=2000, F2-F3)</td> <td>—NASH resolution with <math>\geq 2</math>-point improvement in NAS without worsening of fibrosis</td> </tr> <tr> <td><b>Obeticholic acid</b></td> <td>Lipotoxicity/oxidative stress (FXR agonist)</td> <td><b>REGENERATE</b> (n=2370, F1-F3)</td> <td>—Fibrosis improvement <math>\geq 1</math> stage without NASH worsening</td> </tr> </tbody> </table> <p><small>ClinicalTrials.gov: NCT01948486, NCT02114475, NCT02803052, NCT04622191, NCT02803052, NCT02846851</small></p>	AGENT	MECHANISM	STUDY	OUTCOME	<b>Elafibranor</b>	Lipotoxicity/oxidative stress (PPAR $\alpha$ / $\delta$ agonist)	<b>GOLDEN-505</b> (n=276, F0-F3)	—Reversal of NASH without worsening the fibrosis	<b>Cenicriviroc</b>	Inflammation/immune activation (CCR2/5 antagonist)	<b>CENTAURO</b> (n=288, F1-F3)	—Improvement in NAS by $\geq 2$ points and $\geq 1$ -point decrease in lobular inflammation or hepatocellular ballooning without worsening of fibrosis at year 1	<b>Selonsertib</b>	Apoptosis/hepatocellular (ASK1 inhibitor)	<b>STELLAR-4</b> (n=183, compensated cirrhosis)	—Fibrosis improvement $\geq 1$ stage without NASH worsening —Event-free survival			<b>STELLAR-3</b> (n=188, F3)	—Fibrosis improvement $\geq 1$ stage without NASH worsening —Event-free survival	<b>Semaglutide</b>	GLP-1	<b>Phase 3 SEMA</b> (n=1200, F2-F3)	—Improvement of fibrosis without worsening NASH —Reversal of NASH without worsening of fibrosis	<b>Resmetirom (MGL-3196)</b>	Lipotoxicity (FXR agonist)	<b>MAESTRO-NASH</b> (n=2000, F2-F3)	—NASH resolution with $\geq 2$ -point improvement in NAS without worsening of fibrosis	<b>Obeticholic acid</b>	Lipotoxicity/oxidative stress (FXR agonist)	<b>REGENERATE</b> (n=2370, F1-F3)	—Fibrosis improvement $\geq 1$ stage without NASH worsening	<p>The drugs that have not actually shown efficacy in Phase 3 clinical trials are listed at the top. The first one is elafibranor, which was a dual-PPR agonist. And the clinical trial of GOLDEN-505 that was actually a potential for efficacy, but subsequently did not show efficacy.</p> <p>Cenicriviroc, which basically targeted inflammation/immune activation. It was a CCR2 and CCR5 antagonist. Unfortunately, the Phase 3 clinical trial did not show efficacy.</p> <p>Selonsertib, which was an ASK1 inhibitor, in Phase 3 clinical trial, STELLAR-3 and STELLAR-4, did not show efficacy.</p> <p>Semaglutide, resmetirom, and obeticholic acid I will review for you in the next few minutes.</p>
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21	<p><b>REGENERATE: Obeticholic Acid in NASH</b></p> <ul style="list-style-type: none"> <li>• <b>Global phase 3 study</b></li> <li>• <b>Patients with biopsy-confirmed NASH and F2-F3</b></li> <li>• <b>Randomized 1:1:1</b> <ul style="list-style-type: none"> <li>— OCA 10 mg, OCA 25 mg, vs placebo</li> </ul> </li> <li>• <b>End of study analyses</b> <ul style="list-style-type: none"> <li>— Progression to cirrhosis</li> <li>— Complications secondary to cirrhosis</li> <li>— Liver transplant</li> <li>— All-cause mortality</li> </ul> </li> <li>• <b><math>\approx 7.5</math> years in total study duration</b> <ul style="list-style-type: none"> <li>— Minimum 4 years of follow-up</li> </ul> </li> </ul> <p><small>Younossi ZM, et al. Lancet. 2019;394:2184-2196.</small></p>	<p>Let's actually start with obeticholic acid, which is an FXR agonist. The study that I presented, and was subsequently published in <i>Lancet</i>, was a global Phase 3 clinical trial for patients with biopsy-proven NASH with stage two and three fibrosis.</p> <p>These patients were randomized to 10-milligram, 25-milligram or placebo.</p> <p>End of the study was progression to cirrhosis and a number of other sort of outcomes, but remember this is an outcomes study. And the interim analysis that was published had to look at two histologic endpoints – one was resolution of NASH without worsening of fibrosis; or improvement of fibrosis by one stage without worsening of NASH.</p>																																

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<p>22</p>	<p><b>REGENERATE: Obeticholic Acid Improves Fibrosis in NASH</b></p> <p><b>Primary Endpoint (ITT): Fibrosis Improvement by ≥1 Stage With No Worsening of NASH</b></p> <table border="1"> <thead> <tr> <th>Group</th> <th>% Patients</th> </tr> </thead> <tbody> <tr> <td>Placebo (n=311)</td> <td>11.9%</td> </tr> <tr> <td>OCA 10 mg (n=312)</td> <td>17.6%</td> </tr> <tr> <td>OCA 25 mg (n=308)</td> <td>23.1%</td> </tr> </tbody> </table> <p><b>Primary Endpoint (ITT): NASH Resolution With No Worsening of Fibrosis</b></p> <table border="1"> <thead> <tr> <th>Group</th> <th>% Patients</th> </tr> </thead> <tbody> <tr> <td>Placebo (n=311)</td> <td>8.0%</td> </tr> <tr> <td>OCA 10 mg (n=312)</td> <td>11.2%</td> </tr> <tr> <td>OCA 25 mg (n=308)</td> <td>11.7%</td> </tr> </tbody> </table> <p><small>ITT: intent-to-treat. Younossi ZM, et al. Lancet. 2019;394:2184-2196. Sayin A, et al. AASLD 2019. Abstract 34. Reproduced for educational purposes only.</small></p>	Group	% Patients	Placebo (n=311)	11.9%	OCA 10 mg (n=312)	17.6%	OCA 25 mg (n=308)	23.1%	Group	% Patients	Placebo (n=311)	8.0%	OCA 10 mg (n=312)	11.2%	OCA 25 mg (n=308)	11.7%	<p>This is the interim analysis. ITT is on the left. When you look at fibrosis improvement, as you can see here, the 25-milligram arm of OCA actually met the endpoint. And least with this improvement, at least this drug is considered to be approvable, although there were other issues that are a concern.</p> <p>Unfortunately, in the ITT, NASH resolution without worsening of fibrosis, the 25-milligram arm did not meet the criteria.</p>
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<p>23</p>	<p><b>REGENERATE: Safety of Obeticholic Acid</b></p> <ul style="list-style-type: none"> <li>▪ SAEs similar across groups (11%-14%)</li> <li>▪ Pruritus was the most frequent AE (19% placebo, 28% OCA 10 mg, 51% OCA 25 mg)</li> <li>▪ In patients receiving OCA, LDL-C increased by month 1 and decreased thereafter, approaching baseline by month 18</li> <li>▪ Statin therapy was initiated in 10% of placebo patients and 24% of patients in each OCA treatment arm</li> <li>▪ Among patients receiving OCA who initiated statins, LDL-C increases reversed and fell to below baseline levels by month 6</li> </ul> <p><small>LDL-C: low-density lipoprotein cholesterol; SAE: serious adverse event. Younossi ZM, et al. Lancet. 2019;394:2184-2196.</small></p>	<p>And the subsequent analysis, which was a larger group that included stage one with some risk factor, NASH improvement also, resolution also happened.</p> <p>There were a number of safety issues that need to be discussed. First of all, serious adverse events were similar across the three groups. Pruritus was more frequent in the 25-milligram arm than the placebo group. And it was mostly mild and easy to manage.</p> <p>Of course, dyslipidemia, especially an LDL increase was observed in patients treated with OCA.</p> <p>But statin therapy was very effective in these patients. In fact, when you saw patients on statin, the LDL increases were reversed, and returned to baseline or below baseline by month six.</p>																

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<p>24</p>	<p><b>Resmetirom: A Thyroid Receptor <math>\beta</math> Agonist</b></p> <p>Phase 2 placebo-controlled study (N=125) lasting 36 weeks          Randomized 2:1 resmetirom 80 mg <math>\pm</math> 20-mg dose adjustment at week 4</p> <p><b>≥30 Fat Reduction (%)</b></p> <table border="1"> <thead> <tr> <th>Week</th> <th>Placebo</th> <th>MGL-3196 (40)</th> <th>MGL-3196 (High exp)</th> </tr> </thead> <tbody> <tr> <td>12</td> <td>18</td> <td>60</td> <td>75</td> </tr> <tr> <td>36</td> <td>30</td> <td>68</td> <td>77</td> </tr> </tbody> </table> <p><b>F2/F3</b></p> <table border="1"> <thead> <tr> <th>Week</th> <th>Placebo</th> <th>MGL-3196 (40)</th> <th>MGL-3196 (High exp)</th> </tr> </thead> <tbody> <tr> <td>12</td> <td>11</td> <td>22</td> <td>61</td> </tr> <tr> <td>36</td> <td>22</td> <td>68</td> <td>68</td> </tr> </tbody> </table> <p><b>Histologic Response</b></p> <table border="1"> <thead> <tr> <th>Response</th> <th>Placebo</th> <th>Resmetirom</th> </tr> </thead> <tbody> <tr> <td>Fibrosis resolution</td> <td>~10%</td> <td>~25%</td> </tr> <tr> <td>NASH resolution</td> <td>~10%</td> <td>~25%</td> </tr> </tbody> </table> <p><small>Harrison SA, et al. Lancet. 2019;394:2012-2024; Harrison SA, et al. Hepatology. 2018;66(1):suppl(SA). Reproduced for educational purposes only.</small></p>	Week	Placebo	MGL-3196 (40)	MGL-3196 (High exp)	12	18	60	75	36	30	68	77	Week	Placebo	MGL-3196 (40)	MGL-3196 (High exp)	12	11	22	61	36	22	68	68	Response	Placebo	Resmetirom	Fibrosis resolution	~10%	~25%	NASH resolution	~10%	~25%	<p>Another family of drugs is resmetirom, which is a thyroid receptor-beta agonist. The mechanism is very different than the FXR agonists that I've reviewed. This is the data on Phase 2 placebo-controlled trial for 36 weeks.</p> <p>And as you can here, there was actually evidence of fat reduction, more than 30% fat reduction in patients who received the active drug versus placebo.</p> <p>Some of these patients also had liver biopsies. And also there was significant improvement of fibrosis response as well as NASH resolution.</p>
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<p>25</p>	<p><b>MAESTRO-NAFLD-1: Resmetirom in NASH</b></p> <p>Phase 3 MAESTRO-NAFLD-1 Study Design (F1-F3)</p> <p><b>INCLUSION:</b></p> <ol style="list-style-type: none"> <li>≥3 metabolic risk factors</li> <li>FibroScan kPa <math>\geq</math>F1; CAP <math>\geq</math>280</li> <li>MRI-PDFF <math>\geq</math>8%</li> </ol> <p><small>MRI: magnetic resonance imaging; PDFF: proton density fat fraction; D1SD: alanine aminotransferase; LDL-C: low-density lipoprotein cholesterol. Harrison SA, et al. AASLD 15MO 2020, Abstract 1107. Reproduced for educational purposes only.</small></p>	<p>This drug went on to a Phase 3 clinical trial called MAESTRO-NAFLD-1 study. And there is some preliminary data that these non-invasive tests, such as MRE, MR elastography, MRI-PDFF, will also improve with this regimen.</p>																																	

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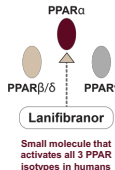
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<p>26</p>	<p><b>MAESTRO-NAFLD-1: Resmetirom in NASH (cont)</b></p> <p>Week 16 MRI-PDFF (%) and MRE (kPa) Changes From BL</p> <table border="1"> <thead> <tr> <th colspan="3"></th> <th colspan="6">Hepatic and Inflammatory Biomarker Effects</th> </tr> <tr> <th></th> <th>All</th> <th>SHBG (High)</th> <th>Biomarker</th> <th>BL</th> <th>SD</th> <th>PostBL*</th> <th>SD</th> <th>CFB</th> <th>p Value</th> </tr> </thead> <tbody> <tr> <td>MRI-PDFF, %</td> <td>17.6</td> <td>17.9</td> <td>ALT (BL &gt;34 U/L)</td> <td>58.3</td> <td>47.4</td> <td>38.9</td> <td>16.1</td> <td>-17.7</td> <td>&lt; .0001</td> </tr> <tr> <td>BL, %</td> <td>17.6</td> <td>17.9</td> <td>AST (BL &gt;26 U/L)</td> <td>39.3</td> <td>12.2</td> <td>31.8</td> <td>11.3</td> <td>-6.9</td> <td>.0060</td> </tr> <tr> <td>Relative % change</td> <td>-53%</td> <td>-62%</td> <td>GGT (BL &gt;38 U/L)</td> <td>70.2</td> <td>58.3</td> <td>54.6</td> <td>47.8</td> <td>-16.2</td> <td>.0015</td> </tr> <tr> <td>p value</td> <td>&lt; .0001</td> <td>&lt; .0001</td> <td>Adiponectin, µg/mL</td> <td>5.0</td> <td>3.5</td> <td>5.9</td> <td>1.6</td> <td>0.9</td> <td>&lt; .0001</td> </tr> <tr> <td>MRE</td> <td></td> <td></td> <td>Reverse T3, ng/dL</td> <td>17.7</td> <td>5.4</td> <td>12.4</td> <td>4.8</td> <td>-5.3</td> <td>&lt; .0001</td> </tr> <tr> <td>BL (&lt;2.5, P1-F3)</td> <td>3.5</td> <td>3.5</td> <td>PRO-C3 (BL ≥14), ng/L</td> <td>19.2</td> <td>4.9</td> <td>16.0</td> <td>3.5</td> <td>-3.4</td> <td>.019</td> </tr> <tr> <td>Relative % change</td> <td>-0.34</td> <td>-0.46</td> <td>hs-CRP, mg/L</td> <td>4.9</td> <td>(1.9-8.4)</td> <td>3.3</td> <td>(1.5-6.2)</td> <td>-1.1</td> <td>.027</td> </tr> <tr> <td>p value</td> <td>.003</td> <td>.003</td> <td></td> <td></td> <td></td> <td></td> <td></td> <td></td> <td></td> </tr> </tbody> </table> <p><small>*Biomarkers were assessed at weeks 12 or 24. CFB, conditional factor; BL, baseline; CRP, high-sensitivity C-reactive protein; DMG, de novo homone binding globulin; T3, triiodothyronine. Harrison S, et al. AASLD TLMAX 2020. Abstract 1707. Reproduced for educational purposes only.</small></p>				Hepatic and Inflammatory Biomarker Effects							All	SHBG (High)	Biomarker	BL	SD	PostBL*	SD	CFB	p Value	MRI-PDFF, %	17.6	17.9	ALT (BL >34 U/L)	58.3	47.4	38.9	16.1	-17.7	< .0001	BL, %	17.6	17.9	AST (BL >26 U/L)	39.3	12.2	31.8	11.3	-6.9	.0060	Relative % change	-53%	-62%	GGT (BL >38 U/L)	70.2	58.3	54.6	47.8	-16.2	.0015	p value	< .0001	< .0001	Adiponectin, µg/mL	5.0	3.5	5.9	1.6	0.9	< .0001	MRE			Reverse T3, ng/dL	17.7	5.4	12.4	4.8	-5.3	< .0001	BL (<2.5, P1-F3)	3.5	3.5	PRO-C3 (BL ≥14), ng/L	19.2	4.9	16.0	3.5	-3.4	.019	Relative % change	-0.34	-0.46	hs-CRP, mg/L	4.9	(1.9-8.4)	3.3	(1.5-6.2)	-1.1	.027	p value	.003	.003								<p>And this is the data that I just reviewed for you. As you can see, the MRI-PDFF actually improved in these patients who received the higher dose of resmetirom. And when you look at some of the non-invasive tests, such as liver enzymes, adiponectin, PRO-C3, which is a fibrosis marker, a number of these drugs showed favorable response patterns.</p>
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<p>27</p>	<p><b>VK2809 (Thyroid Receptor Agonist) in NAFLD</b></p> <p>Multi-arm, dose-ranging, 12-week phase 2a trial</p> <ul style="list-style-type: none"> <li>Primary endpoint: change in LDL-C vs placebo</li> <li>Secondary endpoint: change in liver fat by MRI-PDFF</li> <li>Exploratory endpoints: changes in atherogenic proteins</li> </ul> <p><small>QD, every day; QOD, every other day. Loomis R, et al. SASL, ILC 2020. Abstract A0071. Reproduced for educational purposes only.</small></p>	<p>Now, another thyroid receptor agonist in NAFLD is this drug called VK2809 by a company called Viking. This was presented in 2020 at the multi-arm, dose-ranging, 12-week Phase 2a trial.</p>																																																																																																			
<p>28</p>	<p><b>VK2809 (Thyroid Receptor Agonist) in NAFLD (cont)</b></p> <table border="1"> <caption>Patients With ≥30% Relative Reduction in Liver Fat at 12 Weeks</caption> <thead> <tr> <th>Group</th> <th>n</th> <th>Response (%)</th> </tr> </thead> <tbody> <tr> <td>Placebo</td> <td>12</td> <td>16.7</td> </tr> <tr> <td>VK2809 5 mg QD</td> <td>9</td> <td>100</td> </tr> <tr> <td>VK2809 10 mg QD</td> <td>15</td> <td>76.9</td> </tr> <tr> <td>VK2809 10 mg QD combined</td> <td>11</td> <td>90.0</td> </tr> <tr> <td>VK2809 10 mg QD combined</td> <td>13</td> <td>87.9</td> </tr> </tbody> </table> <table border="1"> <caption>Patients With ≥30% Relative Reduction in Liver Fat at 16 Weeks (4 Weeks Post-Treatment)</caption> <thead> <tr> <th>Group</th> <th>n</th> <th>Response (%)</th> </tr> </thead> <tbody> <tr> <td>Placebo</td> <td>9</td> <td>22.2</td> </tr> <tr> <td>VK2809 5 mg QD</td> <td>8</td> <td>100</td> </tr> <tr> <td>VK2809 10 mg QD</td> <td>8</td> <td>62.5</td> </tr> <tr> <td>VK2809 10 mg QD combined</td> <td>11</td> <td>54.5</td> </tr> <tr> <td>VK2809 10 mg QD combined</td> <td>27</td> <td>70.4</td> </tr> </tbody> </table> <p>Encouraging safety and tolerability, no dose-related trends</p> <p><small>Loomis R, et al. SASL, ILC 2020. Abstract A0071. Reproduced for educational purposes only.</small></p>	Group	n	Response (%)	Placebo	12	16.7	VK2809 5 mg QD	9	100	VK2809 10 mg QD	15	76.9	VK2809 10 mg QD combined	11	90.0	VK2809 10 mg QD combined	13	87.9	Group	n	Response (%)	Placebo	9	22.2	VK2809 5 mg QD	8	100	VK2809 10 mg QD	8	62.5	VK2809 10 mg QD combined	11	54.5	VK2809 10 mg QD combined	27	70.4	<p>And again, this is the design of the study. And the bottom line is that you'll see that at the higher dose, this new drug also had significant improvement of fat content or relative reduction of fat by 30% or more after 12 weeks.</p> <p>And some of this improvement actually continued 12 weeks post-treatment, and those were treated with active regimen.</p>																																																															
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# TARGETING METABOLIC DYSREGULATION IN NASH: EXPLORING NOVEL STRATEGIES TO MITIGATE HEPATIC AND CARDIOVASCULAR DISEASE

## Emerging Targeted Strategies to Mitigate Disease Progression in NAFLD/NASH

<p>29</p>	<h3>Elafibranor in NASH: RESOLVE-IT</h3> <ul style="list-style-type: none"> <li>Elafibranor: a dual PPAR<math>\alpha</math>/PPAR<math>\delta</math> agonist</li> <li>Phase 3 study: randomized 2:1 elafibranor 120 mg vs placebo             <ul style="list-style-type: none"> <li>Initial 72-week treatment period + extension</li> </ul> </li> <li>Results             <ul style="list-style-type: none"> <li>Surrogate Efficacy Results (ITT Set): Histological Endpoints</li> </ul> <table border="1"> <thead> <tr> <th rowspan="2">Histological endpoints</th> <th colspan="2">Elafibranor (n=717)</th> <th colspan="2">Placebo (n=353)</th> <th rowspan="2">Raw p Value</th> </tr> <tr> <th>n</th> <th>%</th> <th>n</th> <th>%</th> </tr> </thead> <tbody> <tr> <td>Primary endpoint</td> <td>138/717</td> <td>19.2</td> <td>52/353</td> <td>14.7</td> <td>.0509</td> </tr> <tr> <td>Key secondary endpoint</td> <td>176/717</td> <td>24.5</td> <td>79/353</td> <td>22.4</td> <td>.4457</td> </tr> </tbody> </table> <ul style="list-style-type: none"> <li>No differences in treatment-emergent AEs compared with placebo</li> <li>Significantly reduced non-HDL cholesterol, TG, ALT, and GGT, suggesting target engagement</li> <li>Improvement in some surrogate markers (YKL-40, A2M, FibroTest)             <ul style="list-style-type: none"> <li>No improvement in others (FIB-4, ELF, NFS, CK18, FibroMeter)</li> </ul> </li> <li><b>Development discontinued due to lack of efficacy of surrogate endpoints</b></li> </ul> <small>             NASH: liver histology (NASH resolution); ALT: serum alanine aminotransferase; TG: triglyceride; HDL-C: high-density lipoprotein cholesterol; NFS: NAFLD fibrosis score; FibroTest: FibroScan elastography; YKL-40: YKL-40; A2M: alpha-2-macroglobulin; FIB-4: FIB-4; ELF: ELF; CK18: CK18; FibroMeter: FibroMeter.           </small> </li></ul>	Histological endpoints	Elafibranor (n=717)		Placebo (n=353)		Raw p Value	n	%	n	%	Primary endpoint	138/717	19.2	52/353	14.7	.0509	Key secondary endpoint	176/717	24.5	79/353	22.4	.4457	<p>Elafibranor was another drug, which was a dual PPAR agonist, and a Phase 3 clinical trial, as I mentioned. Unfortunately, the primary endpoint of this study wasn't met, as well as the key secondary endpoint. And because of that, the development of elafibranor was discontinued.</p>
Histological endpoints	Elafibranor (n=717)		Placebo (n=353)		Raw p Value																			
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Primary endpoint	138/717	19.2	52/353	14.7	.0509																			
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<p>30</p>	<h3>Lanifibranor in NASH: NATIVE</h3> <p>PANPPAR (PPAR<math>\alpha</math>/<math>\delta</math>/<math>\gamma</math>) agonist</p> <ul style="list-style-type: none"> <li>Phase 2b study of 247 patients, randomization 1:1:1</li> <li>24 weeks treatment + 4 weeks of follow-up</li> <li>Stratification on T2D</li> <li>Once-daily oral administration</li> <li><b>Main inclusion criteria:</b> patients with biopsy-proven NASH confirmed by central reader having SAF scores of 1-3 for steatosis, 3-4 for activity, and &lt;4 for fibrosis</li> </ul>  <p>Small molecule that activates all 3 PPAR isotypes in humans</p> <small>             By using SAF Activity score 3 as inclusion criterion rather than NASH 3, NATIVE selected a higher percentage of patients with severely active steatophagocytosis associated with advanced fibrosis (although no a priori steatophagocytosis criterion was set). SAF: Steatosis, Activity and Fibrosis; T2D: type 2 diabetes.           </small>	<p>Lanifibranor is another triple PPAR agonist. And now there is data from a Phase 2b study of 247 patients. It's a once-daily oral administration.</p>																						
<p>31</p>	<h3>Lanifibranor in NASH: NATIVE (cont)</h3> <ul style="list-style-type: none"> <li>Statistically significant decrease of ALT, AST, and GGT in both lanifibranor groups by week 4</li> <li>Statistically significant increase in HDL-C at week 4</li> <li>Statistically significant decrease in triglycerides at week 14</li> <li>No change in LDL-C</li> <li>Statistically significant decrease of HbA<sub>1c</sub></li> <li>Beneficial metabolic profile and well tolerated</li> </ul> <p>Full analysis set — F2-F3 patients</p> <table border="1"> <thead> <tr> <th>Endpoint</th> <th>Placebo (n=82)</th> <th>Lanifibranor 600 mg (n=83)</th> <th>Lanifibranor 1200 mg (n=69)</th> </tr> </thead> <tbody> <tr> <td>Resolution of NASH and no worsening of fibrosis</td> <td>9%</td> <td>34% (p &lt; .001)</td> <td>44% (p &lt; .001)</td> </tr> <tr> <td>Improvement of fibrosis by <math>\geq 1</math> stage and no worsening of NASH</td> <td>30%</td> <td>32% (p = .738)</td> <td>48% (p &lt; .048)</td> </tr> <tr> <td>Resolution of NASH and improvement of fibrosis</td> <td>7%</td> <td>24% (p = .012)</td> <td>33% (p &lt; .001)</td> </tr> </tbody> </table> <small>             Data are mean <math>\pm</math> SD or n (%). By using SAF Activity score 3 as inclusion criterion rather than NASH 3, NATIVE selected a higher percentage of patients with severely active steatophagocytosis associated with advanced fibrosis (although no a priori steatophagocytosis criterion was set). HDL-C: high-density lipoprotein cholesterol; HbA<sub>1c</sub>: glycosylated hemoglobin; FibroTest: FibroScan elastography; YKL-40: YKL-40; A2M: alpha-2-macroglobulin; FIB-4: FIB-4; ELF: ELF; CK18: CK18; FibroMeter: FibroMeter.           </small>	Endpoint	Placebo (n=82)	Lanifibranor 600 mg (n=83)	Lanifibranor 1200 mg (n=69)	Resolution of NASH and no worsening of fibrosis	9%	34% (p < .001)	44% (p < .001)	Improvement of fibrosis by $\geq 1$ stage and no worsening of NASH	30%	32% (p = .738)	48% (p < .048)	Resolution of NASH and improvement of fibrosis	7%	24% (p = .012)	33% (p < .001)	<p>And as you can see here, you see that with histology, there was significant improvement of histology in terms of resolution of NASH without worsening of fibrosis; improvement of fibrosis by one stage; or resolution of NASH and improvement of fibrosis, that you can see a higher dose of lanifibranor, just 1200 milligrams per day.</p> <p>There is some potential future of real opportunity for this drug to be developed. And there was also a beneficial metabolic profile for this drug, which was also well tolerated.</p>						
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## Emerging Targeted Strategies to Mitigate Disease Progression in NAFLD/NASH

<p>32</p>	<p><b>Phase 2b NATIVE Study</b></p> <p><b>Subanalysis: Effects of Lanifibranor in F2-F3 NASH</b> Subgroup analysis: 188 patients F2-F3</p> <table border="1"> <thead> <tr> <th>Mean ± SE (vs. Placebo)</th> <th>Lanifibranor 800 mg</th> <th>Lanifibranor 1200 mg</th> <th>Lanifibranor Pooled</th> <th>Placebo</th> </tr> </thead> <tbody> <tr> <td>ApoB/ApoA1</td> <td>-0.09 ± 0.02 (.001)</td> <td>-0.07 ± 0.02 (.01)</td> <td>-0.08 ± 0.01 (.001)</td> <td>0.01 ± 0.02</td> </tr> <tr> <td>hs-CRP, mg/L</td> <td>-2.01 ± 0.50 (.02)</td> <td>-1.00 ± 0.52 (.31)</td> <td>-1.53 ± 0.38 (.053)</td> <td>-0.23 ± 0.55</td> </tr> <tr> <td>TM6CK-3</td> <td>-0.32 ± 0.03 (&lt;.001)</td> <td>-0.28 ± 0.03 (&lt;.001)</td> <td>-0.30 ± 0.02 (&lt;.001)</td> <td>-0.01 ± 0.03</td> </tr> <tr> <td>TM6-MMP-2</td> <td>-0.79 ± 0.10 (&lt;.001)</td> <td>-0.88 ± 0.10 (&lt;.001)</td> <td>-0.83 ± 0.07 (&lt;.001)</td> <td>-0.07 ± 0.11</td> </tr> </tbody> </table> <p><small>*From mixed-effects model for repeated measures including absolute change from BL as endpoint. BL, baseline; time, treatment; SE, standard error; interaction treatment*time and BL value as fixed effects; time repeated effect with each subject. Key endpoints: TM6CK-3, concentration of transmembrane matrix assessment; hs-CRP, AST, and CRP; MMP-2, matrix metalloproteinase-2; TM6P, serum inhibitor of metalloproteinase-1. Papanicolaou, et al. EASL 2021. Abstract GS-104. Reproduced for educational purpose only.</small></p>	Mean ± SE (vs. Placebo)	Lanifibranor 800 mg	Lanifibranor 1200 mg	Lanifibranor Pooled	Placebo	ApoB/ApoA1	-0.09 ± 0.02 (.001)	-0.07 ± 0.02 (.01)	-0.08 ± 0.01 (.001)	0.01 ± 0.02	hs-CRP, mg/L	-2.01 ± 0.50 (.02)	-1.00 ± 0.52 (.31)	-1.53 ± 0.38 (.053)	-0.23 ± 0.55	TM6CK-3	-0.32 ± 0.03 (<.001)	-0.28 ± 0.03 (<.001)	-0.30 ± 0.02 (<.001)	-0.01 ± 0.03	TM6-MMP-2	-0.79 ± 0.10 (<.001)	-0.88 ± 0.10 (<.001)	-0.83 ± 0.07 (<.001)	-0.07 ± 0.11	<p>Another subanalysis of the same drug for a subgroup that was just presented a few weeks ago, this is looking at patients with F2 and F3. And looking now at fibrosis markers, these are serum markers of fibrosis, and some metabolic parameters, ApoB and ApoA1. And as you can see, lanifibranor had significant improvement of these metabolic and fibrosis profiles as compared to placebo.</p>
Mean ± SE (vs. Placebo)	Lanifibranor 800 mg	Lanifibranor 1200 mg	Lanifibranor Pooled	Placebo																							
ApoB/ApoA1	-0.09 ± 0.02 (.001)	-0.07 ± 0.02 (.01)	-0.08 ± 0.01 (.001)	0.01 ± 0.02																							
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<p>33</p>	<p><b>Aldafermin (NGM282) in NASH</b></p> <ul style="list-style-type: none"> <li>Aldafermin – FGF19 analog</li> <li>78 patients randomized 2:1 aldafermin 1 mg subcutaneous daily vs placebo</li> <li>1-mg aldafermin for 24 weeks led to significant reduction in LFC vs placebo</li> <li>Clinically significant improvements in histologic endpoints were noted</li> </ul> <p><small>LFC liver fat content. Papanicolaou, et al. Gastroenterology 2021;150:219-221.e1. Reproduced for educational purpose only.</small></p>	<p>Another family of drugs is this aldafermin, which is an FGF19 analog. This is the study, patients with NASH; 78 patients were randomized, two-to-one aldafermin one-milligram subcutaneous daily versus placebo. And one-milligram for 24 weeks led to significant reduction of liver fat content.</p> <p>And as you can see here, this is the placebo and of course here is the 66% in the active drugs. And for a subgroup of these patients, also there was some improvement of fibrosis and resolution of NASH.</p>																									
<p>34</p>	<p><b>Aldafermin (NGM282) in NASH (cont)</b></p> <p><small>*p &lt; .05, †p &lt; .01, ‡p &lt; .001 vs placebo</small></p> <p><b>Safety:</b></p> <ul style="list-style-type: none"> <li>No increase in GI AEs</li> <li>No increase in pruritus (4% aldafermin vs 8% placebo)</li> <li>Generally well tolerated and appears to be safe up to 24 weeks</li> </ul> <p><small>GI, gastrointestinal. Papanicolaou, et al. NASLD TLMX 2020. Abstract T2. Reproduced for educational purpose only.</small></p>	<p>Liver enzymes also improved, as well as PRO-C3, which is a fibrosis marker, with aldafermin regimen. There was no increase in GI adverse events. There was not a significant increase in the pruritus. So generally well tolerated, up to 24 weeks for this regimen.</p>																									

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<p>35</p>		<p>Finally, let me remind you of the GLP-1 drug mechanism here. There are a number of different mechanisms that have to do with a decreased appetite, increased satiety, which is probably more sensory-driven. It also affects adipose tissue in terms of improvement of insulin-resistant lipolysis. It probably has impact on liver in terms of, de novo lipogenesis is decreased. And also, GI tract, which is a decrease in gastric emptying, dietary fat, et cetera.</p> <p>There are a multitude of mechanisms GLP-1 agonists can actually affect.</p>
<p>36</p>		<p>This is the data from semaglutide. This is a Phase 2 clinical trial. This data was published in <i>New England Journal of Medicine</i> earlier this year. And there are three different doses of semaglutide versus placebo.</p> <p>And as you can see, some of the highest resolution of NASH, data resolution of NASH occurred in semaglutide 0.4 milligram dose as compared to only 17% in patients who were receiving placebo.</p> <p>Now, unfortunately, when you look at the improvement of liver fibrosis, it was a very high placebo rate of 33%. So although the semaglutide arms had pretty good fibrosis improvement, but since the placebo rate was very high, this was not statistically significant.</p> <p>Now this drug is also going into Phase 3 clinical trial.</p>

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<p>37</p>	<p><b>New Regimens: Monotherapy Landscape in NASH</b></p> <ul style="list-style-type: none"> <li>▪ Resolution of NASH without worsening fibrosis</li> <li>▪ ≥1-stage improvements in fibrosis without worsening NASH             <ul style="list-style-type: none"> <li>— Efruxifermin</li> <li>— Lanifibranor</li> <li>— Aldafermin</li> <li>— Resmetrom</li> <li>— Seladelpar</li> <li>— Semaglutide</li> <li>— Obeticholic acid</li> </ul> </li> </ul>	<p>Now, when you look at the monotherapy landscape in NASH, now remember the two important outcomes that we are talking about – resolution of NASH without worsening of fibrosis; or one stage or higher improvement of fibrosis without worsening of NASH. These are some of the drugs that are listed here that are now being considered for treatment of NASH.</p>								
<p>38</p>	<p><b>Targeting Lipid Carbohydrate Metabolism</b></p> <p>ACC inhibitors</p> <p>Targeting lipid carbohydrate metabolism</p> <p>Citrate → Acetyl-CoA → Malonyl-CoA → Fatty acyl-CoA → TG</p> <p>Enzymes: ACC, FASN, SCD, DGAT2, MGAT2</p> <p>Targets: ACC inhibitors, SCD1 inhibitor, FGF variant, FXR agonist</p> <p><small>ACC: acetyl-CoA synthetase; FASN: fatty acid synthase; SCD: stearoyl-CoA desaturase; DGAT2: diacylglycerol acyltransferase 2; MGAT2: monoacylglycerol acyltransferase 2</small></p>	<p>Now, there are other regimens that target carbohydrate and lipid metabolism, and we will review some of these in the next few slides. One of them, of course, is ACC inhibitors. And part of the challenge we have is because of the complexity of the pathogenesis of the disease is to see if you can combine multiple different regimens.</p>								
<p>39</p>	<p><b>New Regimens: Combinations in NASH</b></p> <p>Regimens With Cilofexor (FXR), Firsocostat (ACCI), and Semaglutide (GLP-1a)</p> <p>Primary: ≥1-Stage Improvement in Fibrosis Without Worsening NASH</p> <p>Patients (%)</p> <table border="1"> <tr> <th>Regimen</th> <th>Percentage</th> </tr> <tr> <td>Placebo</td> <td>11%</td> </tr> <tr> <td>FIR 20 mg QD</td> <td>12%</td> </tr> <tr> <td>Combination (FIR 20 mg QD, SEL 18 mg QD, SEM 1.0 mg QD)</td> <td>21%</td> </tr> </table> <p> <ul style="list-style-type: none"> <li>• Most common AE: pruritus, majority of cases mild in severity</li> <li>• GI AE more common in FIR-containing groups, majority mild in severity</li> <li>• Increased TGs in FIR-containing arms; no significant increases in LDL</li> </ul> </p> <p><small>ACC: acetyl-CoA synthetase inhibitor; CLO: cilofexor; FIR: firsocostat; LS: liver stiffness; SEL: selonsynib; VCTE: vibration-controlled transient elastography</small></p>	Regimen	Percentage	Placebo	11%	FIR 20 mg QD	12%	Combination (FIR 20 mg QD, SEL 18 mg QD, SEM 1.0 mg QD)	21%	<p>This is another combination regimen that was a collaboration between Gilead Sciences and Novo Nordisk. The regimen included an FXR agonist, which is cilofexor, and an ACC inhibitor, which is firsocostat, and also a GLP-1 agonist, which is semaglutide.</p> <p>This is a Phase 2 clinical trial. As you can see, there is actually the regimen on the left, the design of the study. And when you look at the primary outcome of the study, one stage improvement in fibrosis without worsening of NASH, you will see that the number of these regimens, and especially those that have firsocostat ACC inhibitor showed</p>
Regimen	Percentage									
Placebo	11%									
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		<p>probably the best efficacy here, when you combine it specifically with cilo.</p> <p>But of course, none of these are significant, and this study has to be replicated in Phase 3, and there is an ongoing study Phase 3 clinical trial.</p>																								
<p>40</p>		<p>There is a subgroup analysis of the same study that will be subsequently presented.</p>																								
<p>41</p>	<table border="1"> <thead> <tr> <th>Group</th> <th>n</th> <th>Mean</th> <th>95% CI</th> </tr> </thead> <tbody> <tr> <td>SEMA</td> <td>22 (80)</td> <td>-5.6</td> <td>-8.1 to -3.1</td> </tr> <tr> <td>SEMA + FIR</td> <td>22 (87)</td> <td>-11.6</td> <td>-14.1 to -9.1</td> </tr> <tr> <td>SEMA + CILO 30 mg</td> <td>22 (84)</td> <td>-10.6</td> <td>-13.1 to -8.1</td> </tr> <tr> <td>SEMA + CILO 100 mg</td> <td>22 (85)</td> <td>-9.6</td> <td>-12.1 to -7.1</td> </tr> <tr> <td>SEMA + FIR + CILO 30 mg</td> <td>21 (82)</td> <td>-12.6</td> <td>-15.1 to -10.1</td> </tr> </tbody> </table>	Group	n	Mean	95% CI	SEMA	22 (80)	-5.6	-8.1 to -3.1	SEMA + FIR	22 (87)	-11.6	-14.1 to -9.1	SEMA + CILO 30 mg	22 (84)	-10.6	-13.1 to -8.1	SEMA + CILO 100 mg	22 (85)	-9.6	-12.1 to -7.1	SEMA + FIR + CILO 30 mg	21 (82)	-12.6	-15.1 to -10.1	<p>And you can look at now at the regimen to the left here, you have liver stiffness, and liver stiffness changes over time. And you can see, again, that there was significant improvement of liver stiffness from baseline in some of these regimens.</p> <p>The greatest reduction in MRI-PDFF occurred in the firsocostat group. And also a similar finding was observed in those that showed changes in CAP, which is from FibroScan or from MR elastography. This is controlled attenuation parameter.</p>
Group	n	Mean	95% CI																							
SEMA	22 (80)	-5.6	-8.1 to -3.1																							
SEMA + FIR	22 (87)	-11.6	-14.1 to -9.1																							
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SEMA + CILO 100 mg	22 (85)	-9.6	-12.1 to -7.1																							
SEMA + FIR + CILO 30 mg	21 (82)	-12.6	-15.1 to -10.1																							

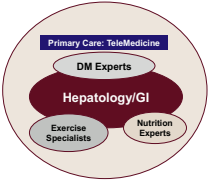
# TARGETING METABOLIC DYSREGULATION IN NASH: EXPLORING NOVEL STRATEGIES TO MITIGATE HEPATIC AND CARDIOVASCULAR DISEASE

## Emerging Targeted Strategies to Mitigate Disease Progression in NAFLD/NASH

<p>42</p>	<p><b>New Regimens: Combinations in NASH (cont)</b></p> <p><b>ACCi ± DGAT2 inhibitor</b></p> <p><b>ACCi ± DGAT2 inhibitor</b></p> <ul style="list-style-type: none"> <li>• 2 studies in patients with NASH             <ul style="list-style-type: none"> <li>– PF-05221304 (ACCi, clesacostat) daily dose escalation (2-50 mg) vs placebo for 16 weeks</li> <li>– PF-05221304 (ACCi, clesacostat) 15 mg twice daily + PF-06865571 (DGAT2 inhibitor, ervogastat) vs placebo for 6 weeks</li> <li>– Primary endpoint % change in liver fat</li> </ul> </li> </ul> <p><small>DGAT2: ervegastat (ervogastat) Calle RA, et al. Nat Med 2021;27:1556-1565.</small></p>	<p>Another regimen here is an ACC inhibitor and DGAT2 inhibitor. These are the two drugs that are being developed by Pfizer. And one of them was for 16 weeks of monotherapy of an ACC inhibitor versus placebo. And the other one is a combination of an ACC inhibitor with DGAT2 for six weeks. Primary endpoint was change in liver fat.</p>
<p>43</p>	<p><b>New Regimens: Combinations in NASH (cont)</b></p> <p><b>ACCi Without DGAT2i</b></p> <p>PF-05221304 ≥10 mg 50%-65% dose-dependent reductions in liver fat</p> <p><small>AE: 8% experienced dose-dependent elevations in serum TG; 4% of patient withdrew from treatment (n=305) Calle RA, et al. Nat Med 2021;27:1556-1565. Reproduced for educational purposes only.</small></p>	<p>Let's look at the first slide which is the ACC inhibitor without DGAT2. And this was liver stiffness measurement on the left, and you can see that there is a decrease, especially with the higher dose of 50-milligram.</p> <p>And when you look at liver fat improvement by 30% or more, again, the higher doses of the active drug was significantly better than placebo.</p>
<p>44</p>	<p><b>New Regimens: Combinations in NASH (cont)</b></p> <p><b>ACCi With DGAT2i</b></p> <p>PF-05221304 + PF-06865571 reduced liver fat by 45%</p> <p><small>AE: No discontinuation due (n=28) Calle RA, et al. Nat Med 2021;27:1556-1565. Reproduced for educational purposes only.</small></p>	<p>Now, when you look at ACC inhibitor with DGAT2 combination, and you can look at liver stiffness measurement on the left, fat reduction in both at the right, you can see that compared to placebo, the active regimens had significantly improved efficacy.</p>

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45	<p><b>New Regimens: Combinations in NASH (cont)</b></p> <p><b>ACCi ± DGAT2</b></p> <p>DGAT2 inhibitor mitigates adverse serum TG effect due to ACCi</p> <table border="1"> <thead> <tr> <th></th> <th colspan="4">PF-05221304 (ACCi) Monotherapy Study</th> <th colspan="4">PF-05221304 (ACCi) + PF-06865571 (DGAT2) Study</th> </tr> <tr> <th>Fasting Serum TG</th> <th>Placebo (n=61)</th> <th>PF 1304 QD 10 mg (n=62)</th> <th>PF 1304 QD 25 mg (n=58)</th> <th>PF 1304 QD 50 mg (n=61)</th> <th>Placebo (n=14)</th> <th>PF 1304 BID 15 mg (n=14)</th> <th>PF 5571 BID 300 mg (n=27)</th> <th>PF 1304 + PF 5571 BID 15 mg + 300 mg (n=26)</th> </tr> </thead> <tbody> <tr> <td>≥400 mg/dL</td> <td>6 (10%)</td> <td>22 (36%)</td> <td>24 (41%)</td> <td>37 (61%)</td> <td>2 (14%)</td> <td>11 (38%)</td> <td>2 (7%)</td> <td>3 (12%)</td> </tr> <tr> <td>≥600 mg/dL</td> <td>2 (3%)</td> <td>11 (18%)</td> <td>11 (19%)</td> <td>20 (33%)</td> <td>1 (7%)</td> <td>4 (14%)</td> <td>1 (4%)</td> <td>0 (0%)</td> </tr> <tr> <td>≥800 mg/dL</td> <td>1 (2%)</td> <td>5 (8%)</td> <td>6 (10%)</td> <td>12 (20%)</td> <td>0 (0%)</td> <td>3 (10%)</td> <td>0 (0%)</td> <td>0 (0%)</td> </tr> </tbody> </table> <p><small>BID, twice daily. Calle RA, et al. Nat Med 2021;27:1836-1848. Reproduced for educational purposes only.</small></p>		PF-05221304 (ACCi) Monotherapy Study				PF-05221304 (ACCi) + PF-06865571 (DGAT2) Study				Fasting Serum TG	Placebo (n=61)	PF 1304 QD 10 mg (n=62)	PF 1304 QD 25 mg (n=58)	PF 1304 QD 50 mg (n=61)	Placebo (n=14)	PF 1304 BID 15 mg (n=14)	PF 5571 BID 300 mg (n=27)	PF 1304 + PF 5571 BID 15 mg + 300 mg (n=26)	≥400 mg/dL	6 (10%)	22 (36%)	24 (41%)	37 (61%)	2 (14%)	11 (38%)	2 (7%)	3 (12%)	≥600 mg/dL	2 (3%)	11 (18%)	11 (19%)	20 (33%)	1 (7%)	4 (14%)	1 (4%)	0 (0%)	≥800 mg/dL	1 (2%)	5 (8%)	6 (10%)	12 (20%)	0 (0%)	3 (10%)	0 (0%)	0 (0%)	<p>Of course, one thing that is important to remember, that when you look at monotherapy, you see that there's an increase in fasting serum triglyceride of over 400, 600, or 800-milligram in the monotherapy side. You will see that is resolved when you add DGAT2 in the right-arm part of this study.</p> <p>Although as monotherapy, the ACC inhibitor can have an issue with triglyceride as an adverse event, that by adding DGAT2, you will actually remedy this.</p> <p>This is the monotherapy. This is basically the combination with significant improvement. And even with the higher dose of DGAT2, you almost basically resolve the fasting serum triglyceride increases.</p>
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46	<p><b>Emerging Targeted Strategies to Mitigate Disease Progression in NAFLD/NASH</b></p> <p><b>Summary</b></p> <ul style="list-style-type: none"> <li>NASH and its global burden are growing</li> <li>NASH is a part of multisystemic disease</li> <li>Stage of fibrosis is important predictor of long-term outcomes</li> <li>Lifestyle modification should be carried out by a multidisciplinary team</li> <li>Few pharmacologic options are currently available to treat NASH</li> <li>A large number of new agents are being developed</li> </ul> 	<p>Let me actually summarize treatment of non-alcoholic steatohepatitis.</p> <p>In general, as I showed in the initial first slides that I had, NASH and its global burden are increasing, growing.</p> <p>It's important to remember that NASH is a part of multisystemic disease.</p> <p>Although I didn't show you this data, there's plenty of data to suggest that it is stage of fibrosis that's the most important predictor of long-term outcome.</p> <p>Lifestyle modification really should be recommended for everyone. It should be carried out by a multidisciplinary team. It is important to remember that it's hard to achieve weight loss and then sustain it, but it should be attempted for everyone.</p> <p>Currently, there are few pharmacologic options that are available for treatment of NASH.</p> <p>There are a large number of clinical trials that are available.</p>																																													

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*Emerging Targeted Strategies to Mitigate Disease Progression in NAFLD/NASH*

		<p>And we recommend that treatment of NASH should be in the context of care pathways. Management of patients with NASH, that they include not only a heptaologist and gastroenterologist, but primary care physician, diabetologist, exercise specialist, and nutrition specialist.</p> <p>With that, I'm going to stop here. And again, thank you for your attention.</p>
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