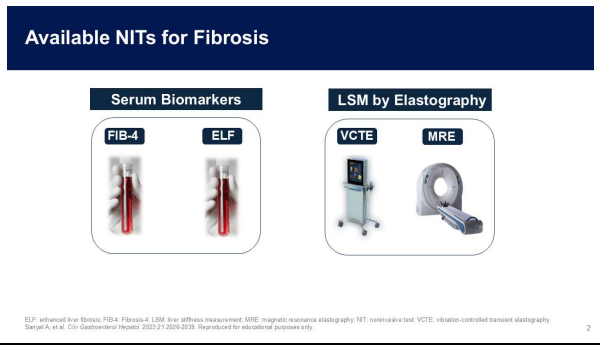
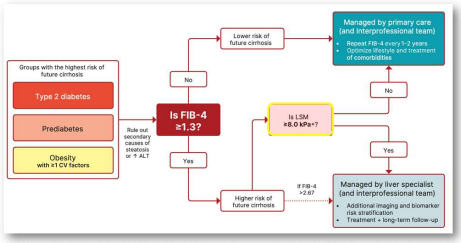
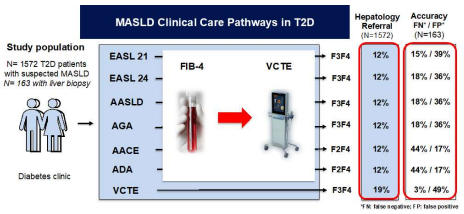
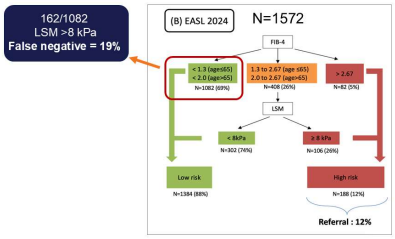
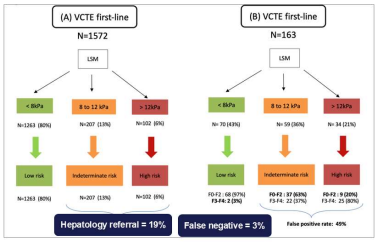
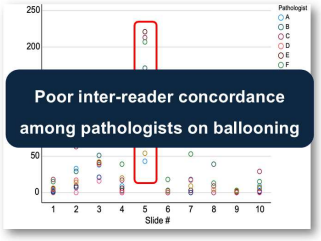
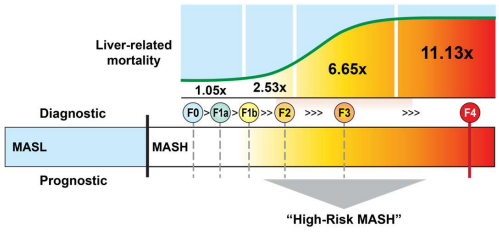
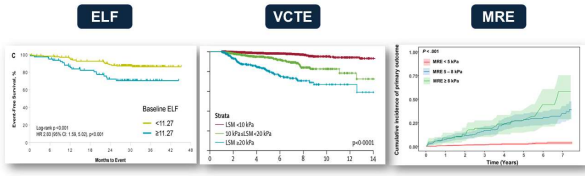
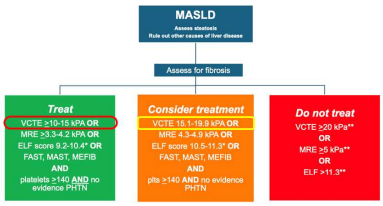
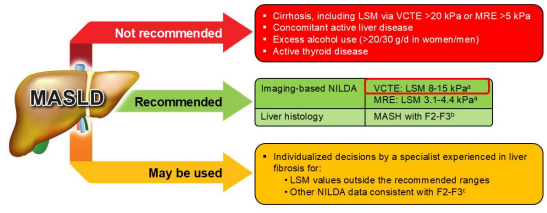
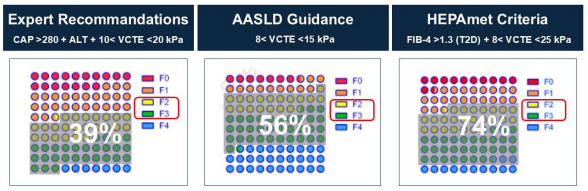
1.		**Meena Bansal, MD, FAASLD** We're glad to have you as part of this symposium, "A New Era in MASH: How Disease-Specific Therapies Are Changing the Game and Best Practices for Clinical Integration."
2.		I am joined by my good friends Laurent, a local friend, and Frank from Germany. I'm Meena Bansal, I'm at Mount Sinai in New York.
3.		I'm going to pass it on to my colleague Laurent Castera, who's going to talk to us about NITs. **Prof. Laurent Castera, MD, PhD** Good morning. Good afternoon.
4.		Thank you very much, Meena, for the kind introduction.
5.		So you're a very expert audience and you're very familiar with the available NITs for fibrosis. There are many around and this is kind of a hot topic. So I just briefly summarize the most popular and validated that there are for serum biomarker FIB-4 and ELF and for liver stiffness measurement by elastography, VCTE, better known as FibroScan, and MR elastography.

6.	**Composite Scores for At-Risk MASH** **FAST** = CAP + AST + LSM (VCTE) - Rule-in: ≥0.67 - Rule-out: ≤0.35 - Gray zone: 0.35-0.67 **MAST** = PDFF + AST + LSM (MRE) - Rule-in: >0.242 - Rule-out: <0.165 - Gray zone: 0.165-0.242 **MEFIB** = LSM (MRE) + FIB-4 - Rule-in: MRE ≥3.3 kPa + FIB-4 ≥1.6 - Rule-out: MRE <3.3 kPa + FIB-4 <1.6 - Gray zone: Neither rule-in nor rule-out	There are also composite scores for at-risk MASH because the previous ones are for measuring advanced fibrosis, the so-called FAST, the MAST that is a copy paste of the FAST using MRE instead of VCTE, and the method that is FIB-4 and MRE (MEFIB).
7.	**Outline** 1. Improving screening strategies to promote access to disease-specific therapy 2. Selecting patients who should be treated (F2/F3) 3. Excluding patients who should not be treated (F4)	So this is the outline: improving screening strategy to promote access to disease-specific therapy, selecting patients who should be treated, and excluding patients who should not be treated.
8.	**Screening for MASLD With Fibrosis in Primary Care** EASL AGA AACE/AA-SLD AASLD	So as you can see on this slide, this started actually with the EASL guideline back in 2021, so 4 years ago, with a sequential algorithm starting with simple tests like FIB-4 and a second specialized test, VCTE or ELF. And many other societies, which is a very good sign, have produced similar algorithms including the AGA, the AASLD/AACE. And last but not least, the AASLD.
9.	**Guidelines Consensus: EASL-EASD-EASO** T2D or obesity + ≥1 cardiometabolic risk factor(s) or persistently elevated liver enzymes FIB-4* VCTE or alternative test*** Intensified management of comorbidities** Hepatology referral Re-assess FIB-4 every 1-3 years FIB-4 <1.3 FIB-4 ≥1.3	These are the well known EASL-EASD-EASO guidelines that were issued now 1 year ago. And basically for the at-risk population you start with a simple test, FIB-4. If you're below 1.3, you're on the safe side and you don't need further evaluation. If you're above 1.3, there are 2 situations: either you're in between and either you repeat or you go directly to VCTE. If you're above 2.67, which in the general population is a low proportion of patients, 3% to 5%, then you can go directly to hepatology referral in the second test.
10.	**6 International Guidelines Aligned!** aga EASL 2021 2024 AASLD MASLD F3F4 AACE American Diabetes Association	So the good news is you have 6 international guidelines that align. And this just means that the field has agreed to use NIT in clinical practice.

11.	**Simplifying Screening: Single FIB-4 Cutoff Strategy** 	I think we should probably go for the sake of easiness, especially when you're talking with the GPs who are not familiar with NITs and also not that familiar like we heard this morning with MASLD, is to make it easier within single cutoff in primary care using FIB-4 and if FIB-4—so these are the ADA guidelines, latest release so far—and then if the FIB-4 is above 1.3, you may go directly to a second test. And the most popular one is VCTE.
12.	**Comparison of 6 Algorithms in Diabetology Clinics** 	I just would like to share this recent paper in press in *CGH* from our group. In a large cohort of patients with type 2 diabetes seen in the diabetes clinic, and we look and compare at the different algorithm, as you can see, with also different endpoints. And basically in this population, referral would be around 12%, in primary care will be around 5%. What we also tested in a subgroup with liver biopsy is the false-negative and the false-positive rates. And as you can see, there are more false positives than false negative whatever the algorithm you're using.
13.	**What Is the Best Strategy: Sequential Algorithm?** 	Now if we look at the EASD-EASL algorithm in the large population, what is interesting, you end up with around 20% of patients that are false negative when using only FIB-4. If you look at LSM, 20% of patients are missed, which is no surprise in this population where the pre-test probability is high.
14.	**What Is the Best Strategy: VCTE as First-Line?** 	So what we've tested as a strategy is using directly liver stiffness as first line, and you can see that you increase the referral from 12% to 19% and you decrease the rate of false-negative results at the expense of more false-positive results.
15.	**Target Population to Be Treated** Eligible Patients for MAESTRO-NASH: **CAP** ≥280 dB/m and **LSM** ≥8.5 kPa and **platelets** ≥140 k/μL **Characteristics** / **MAESTRO-NASH (N=888)** / **ESSENCE (N=800)** Age, mean (SD), y — 56 (11.5) — 56 (11.6) CAP, mean (SD), dB/m — 346 (37) — 330 (45) LSM-VCTE, mean (SD), kPa — 13.3 (6.8) — 12.9 (7.2)	Now how should we select the patients who should be treated—so they are MASH with F2, F3. Just want to remind you the target population to be treated in the 2 phase 3 studies that have been published. You can see the populations are very similar in terms of age, sex balance, BMI. So between 34% and 35%, the proportion of F3 is about two-thirds of patients. The FIB-4 is slightly higher in the ESSENCE study. The ELF is very similar and CAP and LSM, LSM is around 12 to 13 kPa. These are mean values. And

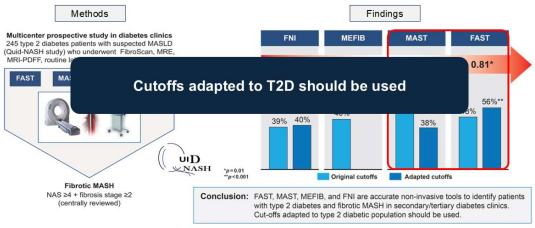
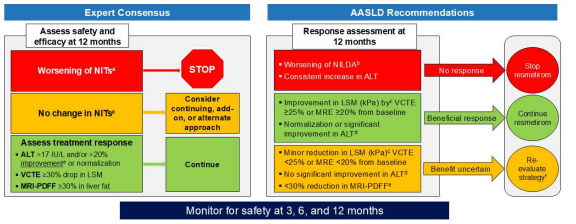
		CAP is around 330 to 350 dB/m. Let me remind you that eligible patients for the MAESTRO-NASH had to have CAP above 280 dB/m and liver stiffness, so they were already selected on liver stiffness above 8.5 kPa. And platelet count should be above 140 k/µL.
16.	**Is Diagnosing MASH Relevant?** 	One question in our clinical practice is how diagnosis of MASH is relevant. Because, as you know, in this important study, there is poor inter-observer concordance for MASH diagnoses, especially for ballooning. So now, of course ,we are off liver biopsy since the approval of resmetirom in the United States, but not sure that it would have been, let's say, easy to convince our colleague diabetologist to screen for MASH and with the liver biopsy.
17.	**Prognostic Is Not Related to MASH but to Fibrosis** 	And actually the prognosis is not related to MASH but to fibrosis. You all know very well this meta-analysis, so I'll just skip for the sake of time.
18.	**NITs Have Suboptimal Performance for MASH but High Performance for Fibrosis** [a]Unreliable.	This table summarizes the fact that emerging NITs have suboptimal performance for MASH but high performance for fibrosis. And you can see that for F2/F3/F4 and F3/F4, we have a large number of studies and patients and good AUROCs.
19.	**ELF, VCTE, and MRE Predict Liver-Related Outcomes** 	Another important point is the fact that all these tests predict liver-related outcomes. And we have now several studies including meta-analyses for each of the tests.

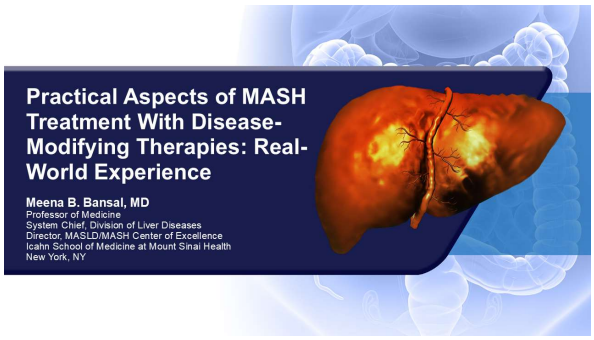
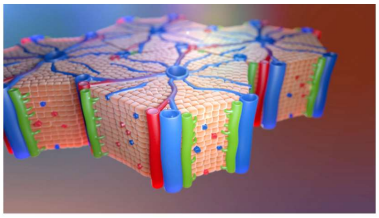
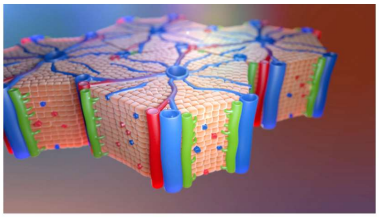
NIT	Endpoint	Studies, n	Patients, n	AUROC (95% CI)
VCTE	MASH	2	192	0.65-0.74[a]
MRE		4	224	0.83[a]
cT1		5	543	0.78
VCTE	F2F3F4	37	2763	0.85 (0.80-0.87)
MRE		7	798	0.92 (0.90-0.94)
VCTE	F3F4	44	4219	0.85 (0.83-0.87)
MRE		7	798	0.92 (0.90-0.94)

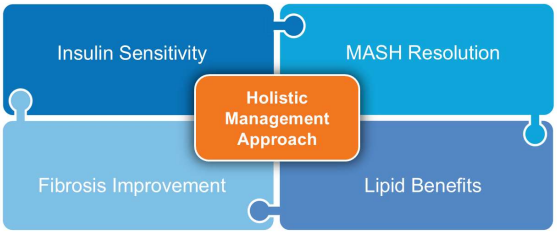
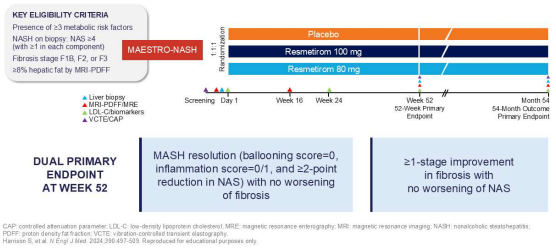
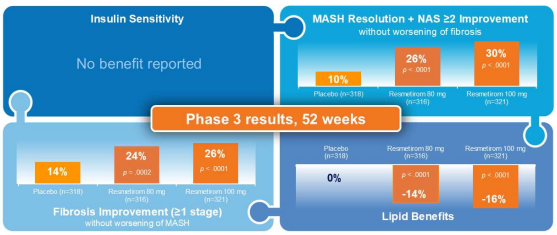
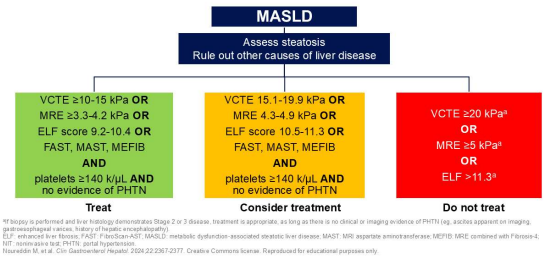
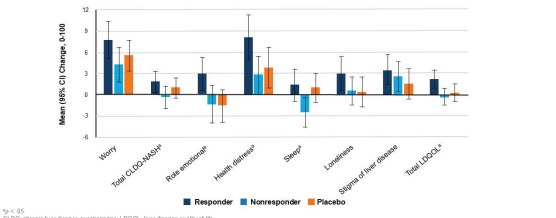
20.	**Proposed Algorithm for Selecting Patients for Treatment Using NITs: Expert Consensus**  18	So this is now the well-known slide regarding the expert consensus and the proposed algorithm for selecting patients for treatment using NIT. I guess you are all very familiar with it, so I don't want to go too much into detail. I will take more time to describe brand new data. Looking at the application in real-world practice. So the population to treat, according to the experts led by Mazen Noureddin, is liver stiffness above 10 to 15 kPa. But you might consider treatment until 20 kPa excluding cirrhosis. You can use MRE and also ELF score and also FAST.
21.	**Proposed Algorithm for Selecting Patients for Treatment Using NITs: AASLD Guidance**  19	This is the AASLD Guidance. And let me draw your attention to that in green. The cutoff is slightly different from 8 to 15 kPa. But actually you can treat until 20 kPa like has been mentioned by the expert consensus.
22.	**Application in a Real-Life Cohort** **Patients With MASLD F2/F3** Multicenter Spanish cohort: 1,281 patients with biopsy-proven MASLD; 38% with MASLD F2/F3  20	So let's now have a look at how it goes in a real-life cohort. This is a paper that is in press in *CGH*. It's been released online a couple of days ago. Interesting, because it's a large, multicenter Spanish cohort led by Manuel Romero Gomez. Almost 1300 patients with biopsy-proven MASLD, of whom 38% had MASLD with F2/F3. Be careful the endpoint is not MASH, is MASLD with F2/F3. If you go by MASH, you will lose around 10% of these patients, will go to 25%. So if you look at the expert recommendation, what I did not mention, the experts use the criteria of MAESTRO-NASH. CAP above 280 dB/m, ALT above 20 IU/L in males, and 17 IU/L in females and VCTE between 10 and 20 kPa. So, if you look at the distribution of fibrosis and how many patients you can catch up using this, you catch 40%, so less than 50% of patients that would be eligible. Now if you look at the AASLD guidance, but they took 15 and not 20 kPa, you increase to 56%. And the authors from the HEPAmet group propose to combine the FIB-4 and the presence of, not of diabetes and VCTE, but expanding. They go from 8 to 25 kPa and they end up with 74%. Don't forget this is 74% of 38%. So, at the end of the day, it's not that much. So the message is—this is interesting, but they are suboptimal.

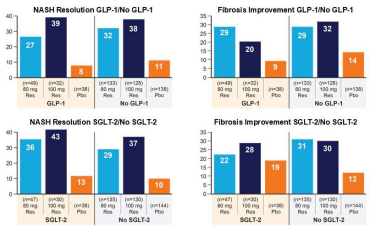
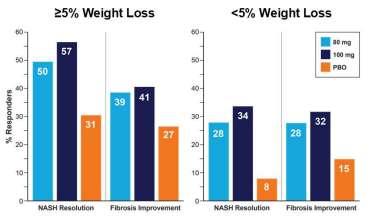
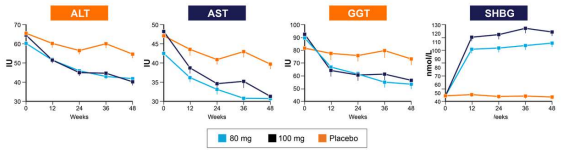
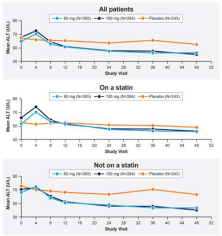
23.	**False-Positive Results With VCTE in MASLD** N=97 patients with MASLD and 2 LSMs before liver biopsy (interval = 6 months) Baseline LSM <8 kPa Baseline LSM ≥8 kPa 1/3 of patients with high baseline LSM (≥8 kPa) may have normal results on 2nd examination with no or mild fibrosis on liver biopsy, suggesting false-positive results Chow JC-L, et al. *J Gastroenterol Hepatol*. 2019;34:241-248. Reproduced for educational purposes only. 22	I also want to draw your attention to the false-positive results with VCTE in MASLD, especially when you're above 8 kPa. This is a study from the group of Vincent Wong, 100 patients with MASLD and 2 liver biopsy. And before and after liver biopsy. There was an interval of 6 months. And what you can see, those with baseline above 8 kPa, they have a decline on the second measurement. And the message is 1 set of patients with liver stiffness above 8 kPa may have normal results on second examination with no or mild fibrosis on liver biopsy, suggesting false-positive results.
24.	**False-Positive Results With VCTE in MASLD** N=97 patients with MASLD and 2 LSMs before liver biopsy (interval = 6 months) Baseline LSM <8 kPa Baseline LSM ≥8 kPa 1/3 of patients with high baseline LSM (≥8 kPa) may have normal results on 2nd examination with no or mild fibrosis on liver biopsy, suggesting false-positive results Chow JC-L, et al. *J Gastroenterol Hepatol*. 2019;34:241-248. Reproduced for educational purposes only. 22	This is an old study, but showing the magnitude of the issue, largest study ever, more than 10,000 exams. Obesity is associated with high failure and reliable rate of liver stiffness. You know that.
25.	**Risk of LRE Begins to Rise at LSM (VCTE) >10 kPa** Prospective: 1403 patients with MASLD (NASH-CRN; BL LSM 7.7 kPa); mean follow-up 4.4 y; 89 LRE (6.3%) Log-transformed HRs for LRE LSM cut-offs kPa Log (HR) 95% CI BL: baseline; LRE: liver-related event. Gawrieh S, et al. *J Hepatol*. 2024;81:600-608. Reproduced for educational purposes only. 24	Another important point regarding the cutoff is we know that 10 kPa is really the turning point for the occurrence of liver-related events.
26.	**Composite Scores for At-Risk MASH: Summary of Performance** AUC: area under the curve; CC: correctly classified; NPV: negative predictive value; PPV: positive predictive value. Stern C, Castera L. *Clin Mol Hepatol*. 2023;29(suppl):S196-S209. 25	So composite score. I will be brief. This is just a table summarizing the evidence of the initial test, and you can see that you end up with 57% to 70% of patients correctly classified using these tests.
27.	**FAST Is the Most Validated** Meta-analysis N=12 studies: 5835 patients with biopsy-proven NAFLD Rule-out FAST ≤0.35 sROC = 0.81 Sum sensitivity = 89% Sum specificity = 55% Gray zone 29.3% (12%-47%) Rule-in FAST ≥0.67 sROC = 0.73 Sum sensitivity = 46% Sum specificity = 89% sROC: summary receiver operating characteristic. Rawala F, et al. *Gut*. 2023;72:1399-1409. Reproduced for educational purposes only. 26	FAST is the most validated by far. This is a meta-analysis showing that you have a gray zone in around 30%.

Score	AUC	N	At-Risk MASH	Rule-out Cutoff	Sensi-tivity	NPV	Gray Zone	Rule-in Cutoff	Speci-ficity	PPV	CC
FAST	0.85	1026	27%	<0.35	0.89	0.94	30%	>0.67	0.49	0.69	60.3%
MAST	0.93	244	11.5%	<0.165	0.89	0.98	18%	>0.242	0.90	0.50	72.5%
MEFIB	0.77	563	31.4%	MRE <3.3 kPa and FIB-4 <1.6	0.91	0.93	25%	MRE ≥3.3 kPa and FIB-4 ≥1.6	0.78	0.55	57.4%

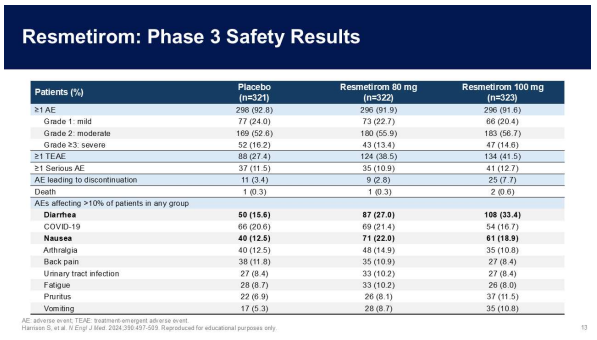
28.	**Don't Forget Comorbidities: T2D** 	And also don't forget the context of use and the comorbidity. This is in patients with type 2 diabetes from the QUID-NASH cohort. And you can see if you look at the percentage of correctly classified according to the original cutoff MAST outperformed FAST. If you're using the adapted cutoff to the populations, you end up with FAST outperforming MAST.
29.	**Cutoffs for Diagnosing Cirrhosis** NIT / Cutoff / Comments ELF / ≥11.3 / ELF ≥11.3 is associated with increased risk of hepatic decompensation among patients with cirrhosis Imaging VCTE / ≥20 kPa / LSM by VCTE ≥20 kPa is associated with cirrhosis, but for ruling out, cirrhosis optimal cut point is <8 kPa MRE / ≥5 kPa / LSM by MRE ≥5 kPa has a very good specificity (approaches 95%) for diagnosis of cirrhosis and is associated with increased risk of incident hepatic decompensation	So who should not be treated? We have cutoff well-established with ELF VCTE I mentioned already and 5 kPa for MRE, 11.3 for ELF.
30.	**Patient Follow-Up Using NITs** 	And then of course, we are going to learn in the next talks about the use in clinical practice of treatment. But if there's worsening of an NIT then you should stop treatment. Otherwise continue.
31.	**Conclusions** ▪ Staged application of available NITs helps to rule-out patients who are unlikely to have significant disease • FIB-4 followed by a second NIT (eg, FibroScan, ELF, or MRE) • 6 international guidelines aligned ▪ NITs are the new standard for selecting patients with non-cirrhotic MASLD (F2-F3) for pharmacologic therapies • VCTE is most widely available and validated NIT • Optimal lower cutoff requires further validation in real-life cohorts • Patients with VCTE >20 kPa should not be treated • Do not hesitate to repeat VCTE if the patient has a high BMI (false-positive results)	So in conclusion, staged application of available NITs helps to rule-out patients who are unlikely to have significant disease. FIB-4 followed by a second NIT, 6 international guidelines aligned. NITs are the new standard for selecting patients with non-cirrhotic MASLD for treatment. VCTE is the most widely available and validated NIT. Optimal lower cutoff requires further validation in real-life cohorts. Patients with liver stiffness by VCTE above 20 kPa should not be treated, and do not hesitate to repeat if the patient has a high BMI, which is a major factor for false-positive result. Thank you very much for your attention.

32.		**Meena Bansal, MD, FAASLD** So I'm going to be focusing on practical aspects of MASH treatment with disease-modifying therapies in real-world experience that we now have from the United States.
33.	**Current and Emerging THR-β Agonists** Drug / Study Stage / Endpoints Resmetirom — FDA conditional approval, Phase 3, Biopsy-confirmed MASH (N=966) — Dual primary endpoint at 52-week: • MASH resolution with no worsening of fibrosis • ≥1-stage improvement in fibrosis with no worsening of NAS VK2809 — Phase 2, Biopsy-confirmed MASH (N=248) — 12-week reduction of liver fat content; 52-week biopsy data presented at AASLD TERN-501 — Phase 2, Presumed MASH (N=162) — 12-week reduction of liver fat content; Results available[a] ALG-055009 — Phase 2, Presumed MASH (N=100) — 12-week reduction of liver fat content; Data presented at AASLD TLM 2024 [a]No longer in development. AASLD: American Association for the Study of Liver Diseases; FDA: US Food and Drug Administration; MASH: metabolic dysfunction-associated steatohepatitis; NAS: nonalcoholic fatty liver disease activity score; THR: thyroid hormone receptor; TLM: The Liver Meeting; Harrison S, et al. *N Engl J Med*. 2024;390:497-509; Loomba R, et al. The Liver Meeting 2024. Abstract 5016; ClinicalTrials.gov: NCT04173065; ClinicalTrials.gov: NCT05415722; ClinicalTrials.gov: NCT06342947.	So as we know, there are a number of thyroid hormone receptor-β agonists that are being studied. Resmetirom, obviously, being the first and only FDA-approved therapy. But we know that there are other agents such as Viking and Aligos, now I'll mention their data that was presented at the liver meeting last fall.
34.	**THR-β Agonists: Mechanism of Action** 	So this is just a video that gives the underlying mechanism of how thyroid hormone receptor-β agonists work.
35.	**THR-β Agonists: Mechanism of Action** 	**[Video]** Thyroid hormone receptor-β agonists, or THR-β agonists, are small molecules designed to specifically act in the liver. These agents enter the nucleus within the hepatocyte and bind to THR-β to activate target gene expression, which mediates several metabolic pathways. First, enhanced mitophagy removes damaged mitochondria while mitochondrial biogenesis generates new organelles. At the same time, reductions in reactive oxygen species or ROS limit mitochondrial damage and accumulation of toxic long-chain lipids. Finally, increases in lipophagy generate free fatty acids that are then transported to mitochondria to produce ATP via β oxidation. Overall, treatment with a THR-β agonist is effective in reducing hepatic fat content and fibrosis.

36.	**Need for a Holistic Management Approach for Patients With MASH** 	**Meena Bansal, MD, FAASLD** Great. So when we think about management of patients with MASH, we have to have a holistic approach. While as hepatologists we're very interested in MASH resolution and fibrosis improvement, we need to recognize that the number 1 cause of death in these patients is cardiovascular. So ideally you would also like to see lipid benefits and an improvement in insulin sensitivity.
37.	**Resmetirom: Phase 3 Program** 	So I think everybody is very familiar with the registrational program of resmetirom, the phase 3 study that was 52-week biopsy. Looking at the dual primary endpoint of either MASH resolution without worsening of fibrosis or improvement of fibrosis by 1 stage with no worsening of MASH.
38.	**Resmetirom[a]: THR-β, Oral, Once Daily** 	And the data reveal that there is improvement in MASH in about 38% of patients, 30% compared to 10% in placebo. About a 16% reduction in LDL. A fibrosis improvement of 26% compared with 14% in placebo, and no impact on insulin sensitivity.
39.	**Expert Consensus Algorithm for Patient Selection Using NITs** 	Laurent already showed this. This was the expert consensus. Basically, these criteria were based on the criteria of the patients who were actually in the MAESTRO-NASH study. That's where those kind of ranges came from. The median kPa was about 12 within IQR of 10 to 15.
40.	**Resmetirom: MAESTRO-NASH Health-Related Quality of Life (HRQOL)** Improved HRQOL with improvement of fibrosis or resolution of MASH with resmetirom at week 52 	So the FDA, as well as the EMA, is also interested in how patients feel. Right. How how do they feel. And this was a quality-of-life study done by Zobair's group, where they showed that essentially improvement in many parameters of quality of life increased in those who had histologic improvement, either fibrosis or MASH resolution.

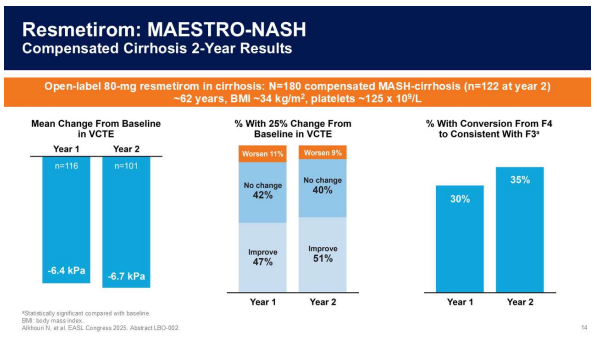
41.	**GLP-1RA and SGLT-2 Inhibitor Therapy: No Impact on Biopsy Responses to Resmetirom**  ▪ Patients with T2D on resmetirom + SGLT-2 inhibitor or GLP-1RA therapy had equivalent liver biopsy responses to patients with T2D not on these therapies ▪ There were no differences in safety or tolerability in patients with T2D treated with a combination of GLP-1RA + resmetirom	Now, in the MAESTRO-NASH study, patients were allowed to be on a GLP-1. This was the 1-mg dose, but they could not have any significant weight loss in the 6 months prior to that baseline biopsy. And this demonstrates that whether patients were on a GLP-1RA or SGLT2, there was no difference in their biopsy responses. Nor were there any difference in safety or tolerability.
42.	**Liver Biopsy Responses: Impact of Weight Loss**  ▪ Weight loss ≥5% observed in about 22% of patients on resmetirom (12% on placebo) increased the percentage of patients with fibrosis improvement (41%) and NASH resolution (57%) on liver biopsy and maintained the difference from placebo with similar weight loss	On the other hand, once patients were enrolled in the study at baseline, they had their baseline biopsy if they lost weight. And this was independent of a GLP-1, if they lost greater than 5% of their baseline weight, which was observed in about 22 patients on resmetirom, compared with 12% on placebo. There was an increased percentage of patients with fibrosis improvement now increasing to 41% and MASH resolution increasing to 57%. So kind of shows that diet and lifestyle changes when on therapy are going to have still a beneficial or additive effect.
43.	**Change From Baseline in Liver Enzymes[a] and SHBG** ▪ Significant reduction of liver enzymes relative to placebo, both percentage change and absolute reduction ▪ Associated with the biomarker SHBG that increases in proportion to resmetirom reflecting target engagement (exposure)  	In patients who had elevated ALT at baseline, you can see that those start on resmetirom had reductions in ALT, AST, and GGT, and sex hormone-binding globulin simply reflects adherence and target engagement.
44.	**Initial Transient Increases in ALT Associated With Statin Use** ▪ 49% statin use ▪ 98% in current recommended dose • Rosuvastatin 20 mg • Atorvastatin 40 mg ▪ Patients taking a statin had lower baseline ALT levels than patients not taking a statin • Transient increases to approximately 1.3x baseline in week 4 were observed in patients taking resmetirom and a statin • No significant elevations were observed in patients taking resmetirom but no statin • ALT levels improved relative to baseline over time in patients on resmetirom vs placebo, independent of statin use  	Now, about half the patients who were in the study were on a statin. They were on the recommended doses. About 98% were on the recommended doses of rosuvastatin 20 mg and atorvastatin 40 mg. And so when you look at the top graph and you look at all patients, you'll see a slight bump in liver enzymes at week 4. And then those all come down even below placebo. But when you break down whether they were on a statin or not, you can see that that blip is really only seen in patients who are on a baseline statin. And this is important because you want to advise patients ahead of time that these numbers might go up and do not prematurely think that this is anything of concern, because the numbers will come down.

45.



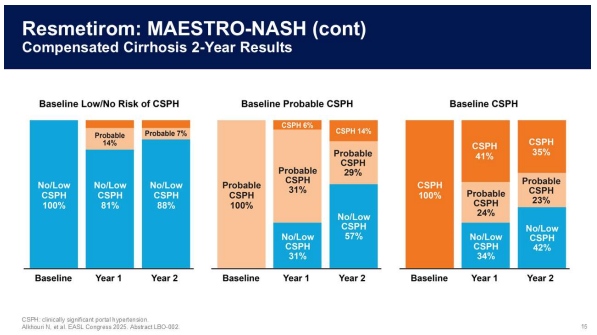
In terms of side effects, we know that diarrhea and nausea were the predominant side effects. They tend to occur within the first 4 weeks, but then are resolved by 12 weeks.

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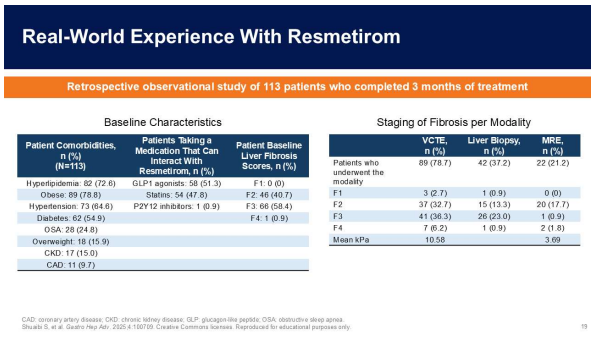
Now these were data that were presented at EASL. These were patients who have compensated cirrhosis. They were in the open-label study of 80 mg. You can see average BMI was about 34 kg/m^2 and the platelet count was about 125 k/µL. So a pretty advanced group. When you look at the mean change from baseline in VCTE, you can see there was a reduction of about 6.5 kPa. And when you look at that kind of parameter of those who have at least a 25% change from their baseline VCTE, which is what the ASLD recommendations suggest in terms of response to treatment, you can see that almost half had improvement in their baseline VCTE, meeting that threshold of 25%, and about 40% had no change. When you look at the percentage that converted from F4 to F3—now having a kPa consistent with F3, which was defined as less than 15 kPa—you can see that 30% and up to 35% of patients hit that parameter.

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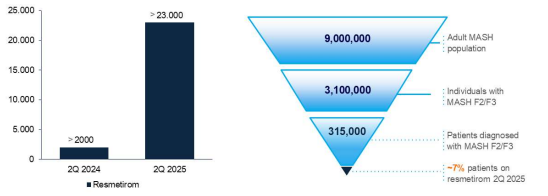
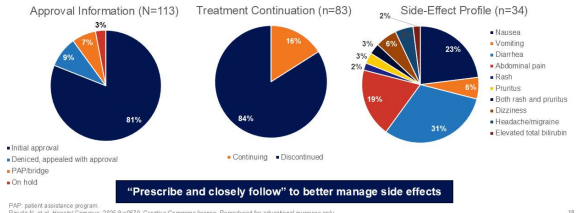
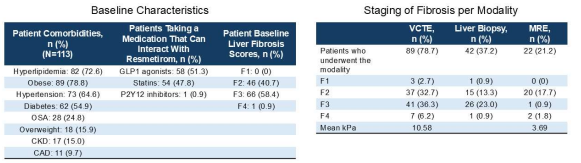
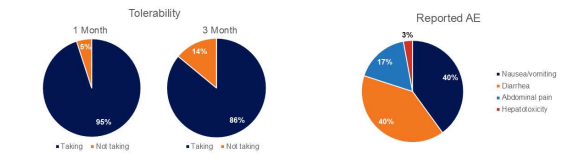


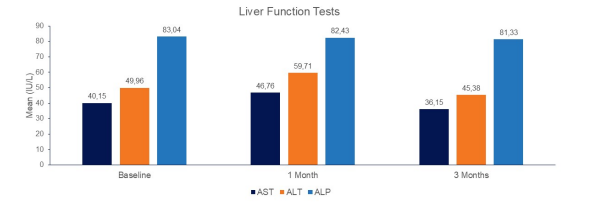
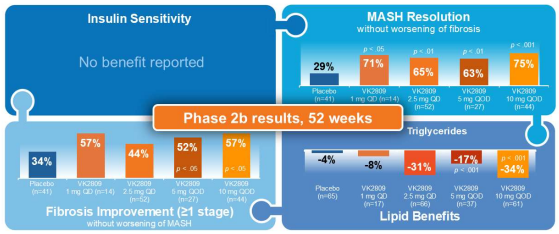
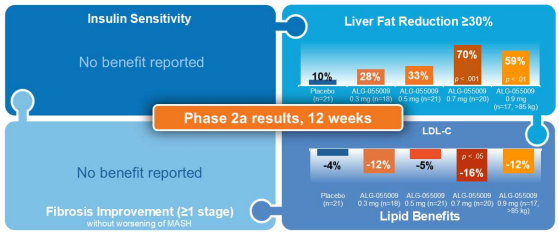
Now focusing on the right, those that had clinically significant portal hypertension based on Baveno criteria at baseline, you can see that there's a shift. So now only 41% and then 35% still have clinically significant portal hypertension, while many patients—over half now—shifted to a lower risk group. While we await the outcomes from these studies, I think that these are very encouraging data.

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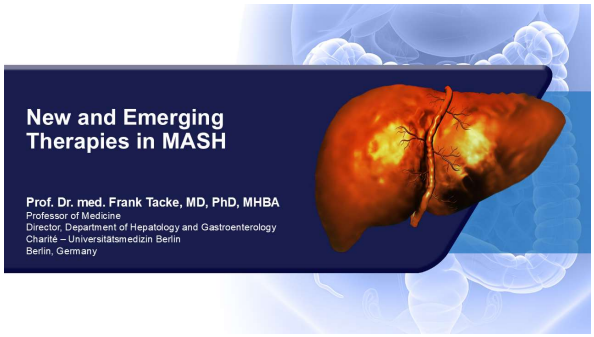
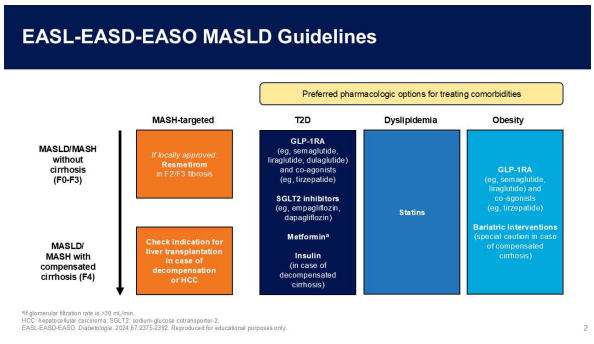
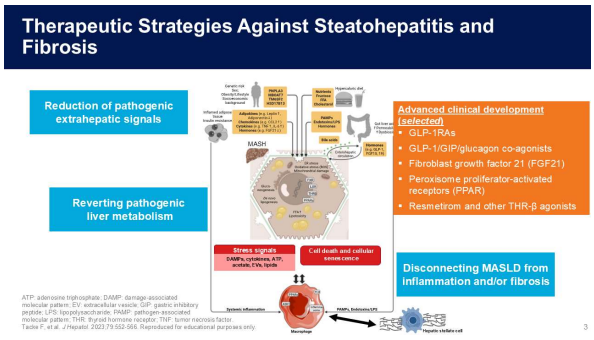


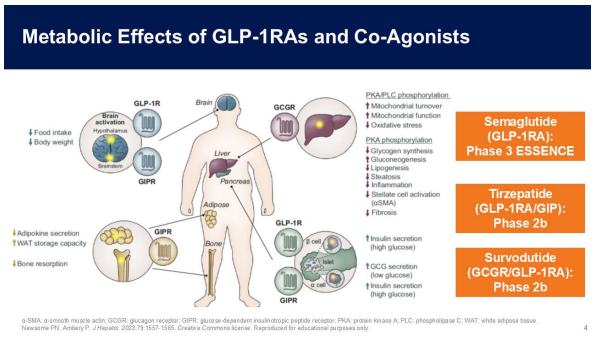
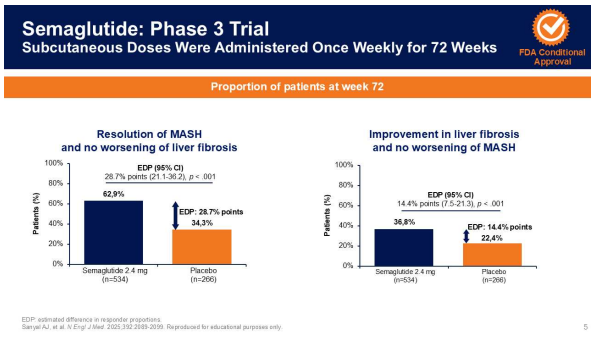
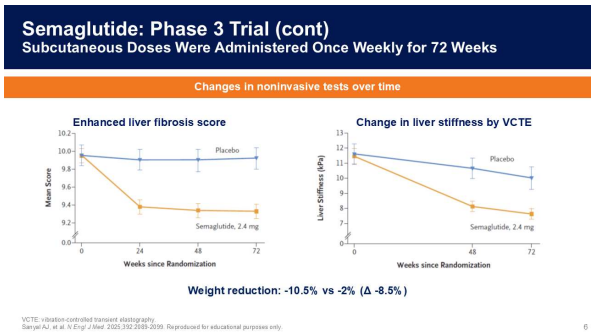
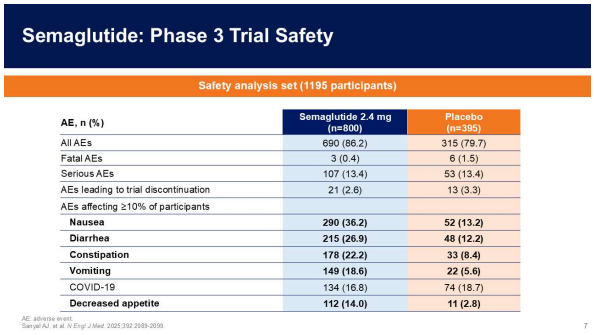
The side effects and safety profile in those with cirrhosis were really no different than what we saw in those with F2 and F3 fibrosis. Also there were no serious AEs related to study drug.

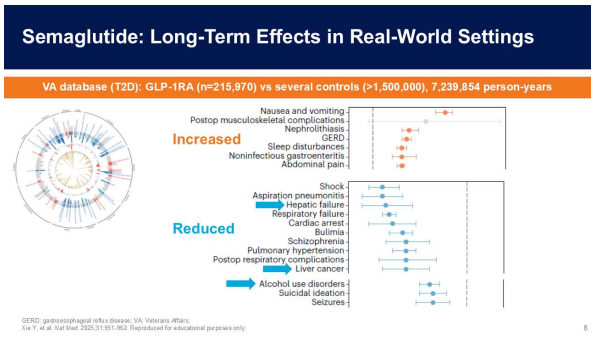
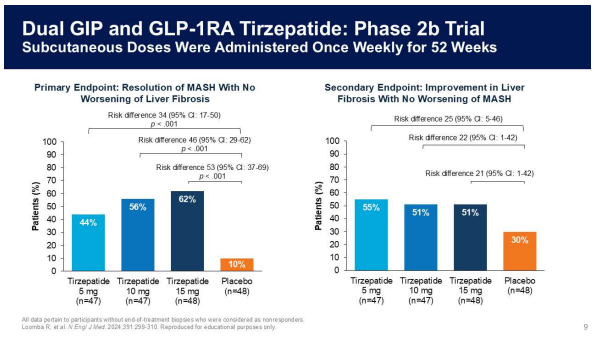
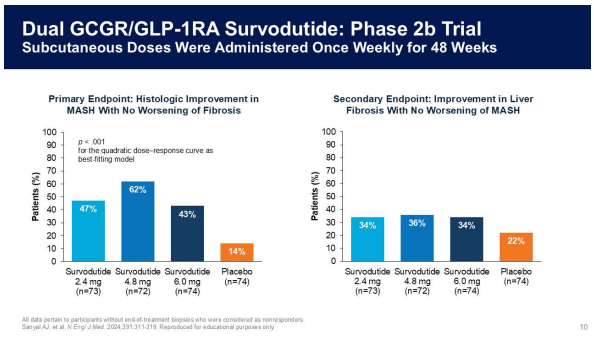
49.	**Current Utilization of Disease-Directed Therapy in the United States** ~7% of eligible patients with MASH are receiving treatment with resmetirom  Fixlan Claims Data; Clearview Analysis; figure adapted for educational purposes only from Fishman J, et al. *Adv Ther*. 2024;41:4172-4190. 17	And now what's been our experience thus far in the United States. So we know that we got the approval in quarter 2 of 2024. And now there are over 23,000 patients in the United States who are currently on therapy. When you look at the eligible patients diagnosed with MASH at about 300,000, about 7% are now on resmetirom.
50.	**Early Experience With Resmetirom** "Prescribe and forget" is associated with a high discontinuation rate due to side effects  "Prescribe and closely follow" to better manage side effects PAP: patient assistance program. Ravela N, et al. *Hepatol Commun*. 2025;9:e0070. Creative Commons license. Reproduced for educational purposes only. 18	And so how has our experience been in getting these approvals. So this is a real-world study out of the IU group where you can see that initial approval 81%, those that were then denied and then received approval about 9%. So really about 90% of patients for whom a prescription was written, they were able to get that prescription. In terms of treatment continuation at 3 months, you can see that 84% are continuing on therapy, while 16% stop therapy with the side-effect profile shown all the way on the right, mainly. Nausea, vomiting, diarrhea, and abdominal pain. Part of the thing is kind of educating the patient out of the gate to expect these side effects and to kind of push through, because we know that if we can push through and manage those symptoms, they're going to improve over time.
51.	**Real-World Experience With Resmetirom** Retrospective observational study of 113 patients who completed 3 months of treatment Baseline Characteristics Staging of Fibrosis per Modality  CAD: coronary artery disease; CKD: chronic kidney disease; GLP: glucagon-like peptide; OSA: obstructive sleep apnea. Shuaibi S, et al. *Gastro Hep Adv*. 2025;4:100709. Creative Commons licenses. Reproduced for educational purposes only. 19	This was another retrospective real-world experience study looking at 113 patients. You can see about 50% were on a GLP-1. About 50% were on a statin and they were at stage [F2-F3]. Their liver fibrosis was staged by either VCTE, liver biopsy, or MRE. And you can see the mean kPa for VCTE was about 10.5, MRE about 3.7.
52.	**Real-World Experience With Resmetirom (cont)** Retrospective observational study of 113 patients who completed 3 months of treatment  Shuaibi S, et al. *Gastro Hep Adv*. 2025;4:100709. Creative Commons licenses. Reproduced for educational purposes only. 20	Very similar to the other study, 95% were still taking the medication at 1 month and that dropped down to 86%. So that kind of 14% to 15% discontinuation rate, very similar. Again, educating the patient is the key to minimizing that. Side effects, again, were mainly GI.

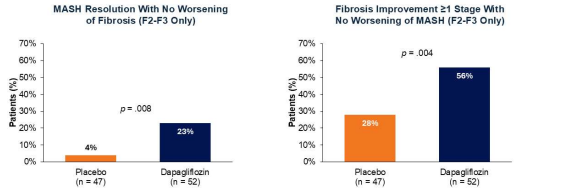
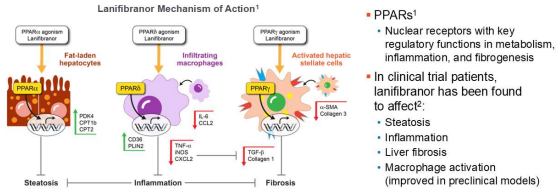
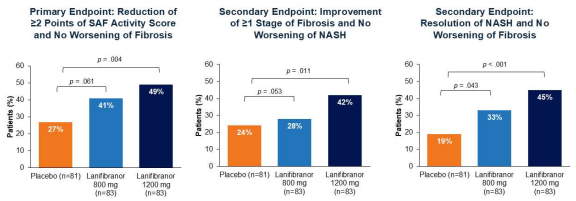
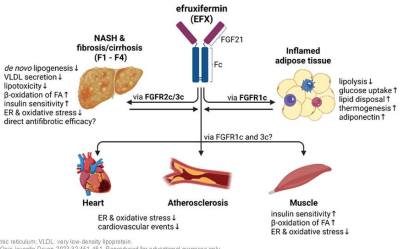
53.	**Real-World Experience With Resmetirom (cont)** Retrospective observational study of 113 patients who completed 3 months of treatment  ALP: alkaline phosphatase. Shuaibi S, et al. *Gastro Hep Adv*. 2025;4:100709. Creative Commons licenses. Reproduced for educational purposes only. 21	And when you look at liver function tests at baseline and then all the way over at 3 months you can see a reduction in AST, ALT.
54.	**VK2809: THR-β Oral, Once Daily or Once Every Other Day**  QD: once daily; QOD: once every other day. Loomba R, et al. The Liver Meeting 2024. Abstract 5016. 22	And so in terms of other thyroid hormone receptor-β agonists that are in the pike. These were Viking data that were presented at The Liver Meeting. And you can see again MASH resolution across the board, a little bit higher placebo response rate, improvement in lipid benefits, and fibrosis improvement at the 5-mg and 10-mg every-other-day doses.
55.	**ALG-055009: THR-β Oral, Once Daily**  Loomba R, et al. The Liver Meeting 2024. Abstract 3226. 23	These are just the phase 2a data, 12 weeks, where we just have liver fat reduction greater than that threshold of 30%, which is associated with histologic response improvement in lipids. And we don't yet have the data for fibrosis.
56.	**Case: 56-Year-Old Hispanic Woman** ▪ **Clinical status** • BMI 27 kg/m^2 • BP 128/95 mm Hg • HbA$_{1c}$ 37.7 mmol/mol (5.6%) • AST 58 U/L • ALT 40 U/L • Platelets 170 k/µL • LDL-C 1.55 mmol/L (60 mg/dL) • HDL-C 1.01 mmol/L (39 mg/dL) ▪ **Medications** • Metformin • Atorvastatin 80 mg ▪ **NITs** • FIB-4 3.02 • VCTE 11 kPa BP: blood pressure; FIB-4: Fibrosis-4; HbA$_{1c}$: hemoglobin A$_{1c}$; HDL-C: high-density lipoprotein cholesterol. 24	So we'll just do a really quick case to bring up a couple of points. So, this is a 56-year-old Hispanic woman, BMI of 27 kg/m^2. Well controlled hemoglobin A$_{1c}$, AST 58 IU/L, ALT 40 IU/L, platelets of 170 k/µL. LDL and HDL in good ranges. On metformin and atorvastatin 80 mg. In terms of NITs, the FIB-4 is 3.02 and the VCT is 11 kPa.
57.	**Question** Is this patient a candidate for treatment with resmetirom? A. Yes B. No C. Unsure 25	So I think you're going to have to scan a QR code or something if you join that to tell us, is this patient a candidate for treatment, whether it's better? Um, we'll discuss. We can discuss this a little bit further. I don't know how to advance this. Okay. So, you know, certainly the patient meets criteria from an F2/F3 fibrosis standpoint. Their BMI is 27 kg/m^2. So I think some you know… I, okay well everybody's already on that okay. All right. That's fine. So certainly let's assume that you just make the decision to start resmetirom…and we

		can have a discussion later about other therapies that might be important.
58.	**Question** What is the next best step for the management of this patient? A. Switch to pravastatin 80 mg once daily B. Begin dapagliflozin 5 mg once daily C. Reduce atorvastatin to 40 mg once daily D. Begin lisinopril 5 mg once daily 26	But I think the important point to make there is that the patient's current statin dose is higher than the recommended dose, so that patient is on 80 mg of atorvastatin. And so you would want to drop them down to 40 mg. Since we know resmetirom also has an LDL effect, you could then monitor to see whether or not the LDL stays in the range that you want in terms of cardiovascular risk.
59.	**Question** The patient's PCP orders laboratory testing after 4 weeks on treatment with resmetirom. The PCP notes that the patient's liver enzymes have increased: Baseline / Current AST (U/L) 58 87 ALT (U/L) 40 60 What should do you do next? A. Reduce resmetirom to 60 mg every other day B. Reassure the PCP and continue therapy C. Order a PEth test D. Repeat VCTE imaging PEth: phosphatidylethanol; PCP: primary care physician. 27	Okay, now, the patient's PCP orders laboratory testing after 4 weeks on treatment. You can see the baseline there. AST of 58 IU/L, ALT of 40 IU/L. And now their liver enzymes bump up a little bit and you get the call, "Oh my gosh. Do I need to stop therapy?" What would you do next? Right. Exactly. Reassure the PCP and continue therapy. I tell people don't check it. Like why are you checking it? But if they do, you tell them if somebody checks it and there's a slight bump in your liver enzymes, don't worry. Continue therapy and we'll recheck at 3 months. The only time you would reduce the dose of resmetirom... really, the reason is that 60-mg dose is because of a drug-drug interaction with clopidogrel. And so that's why you have it. And certainly you can dose reduce somebody if you need to. But generally that's the reason that the 60-mg dose is there. We could repeat the VCTE as we heard that there is high fluctuations there. PEth test would be reasonable. The AST is greater than ALT, so those are all reasonable choices.
60.	**Summary** ▪ Resmetirom is a THR-β agonist and the first FDA-approved MASH-specific therapy • Liver-specific mechanism of action • Increases mitochondrial capacity for β oxidation – Mitochondrial biogenesis and mitophagy • Increases lipophagy • Increases cholesterol clearance • Reduces inflammation and fibrosis ▪ Current utilization of MASH-specific therapy in the United States remains low ▪ Real-world experience with resmetirom has shown: • Patients need support to manage side effects when beginning treatment • Temporary increases in liver enzymes are common within the first months of treatment 28	Okay. So in summary we know that resmetirom is a thyroid hormone receptor-β agonist, the first FDA-approved therapy for MASH. It has a liver-directed and liver-specific mechanism of action, increases mitochondrial capacity for β-oxidation both through mitochondrial biogenesis, and motophagy also increases lipophagy. Increases cholesterol clearance, ultimately reducing inflammation and fibrosis. Current utilization in the United States remains low, but is growing. Real-world experience with resmetirom has shown that patients should have a little bit of support to manage the side effects when beginning treatment, though it's a pretty low discontinuation rate. Temporary increase in liver enzymes is common in the first month of treatment, so don't check it and monitor patients at 3, 6, and 12 months as Laurent showed. And

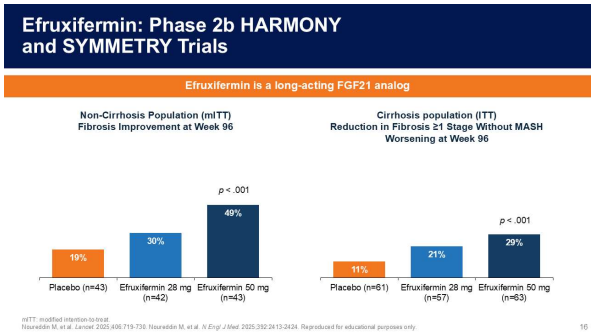
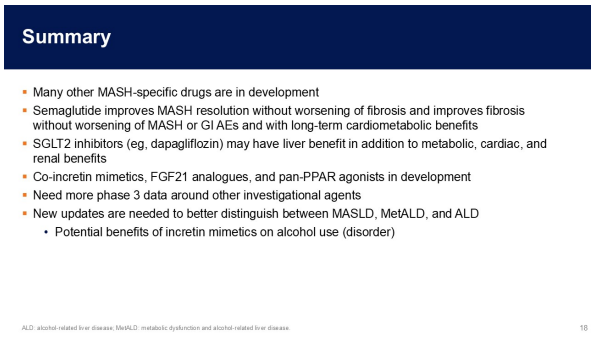
		with that, I'm going to pass it over to my colleague. Thank you.
61.		**Prof. Dr. med. Frank Tacke, MD, PhD, MHBA** Thank you very much, Meena. My name is Frank Tacke from the Charité University Hospital in Berlin, Germany. And we are very excited because on Monday, resmetirom will be available in Germany. So I now know what to do. So let's see what we can manage with it. My task is to kind of, and that is of course here quite challenging, to explain the new and emerging therapies, the topic of this conference. And so you're all very knowledgeable about it. But it's probably good if we decide on how to treat the patients knowing what's coming soon.
62.		And I guess one aspect that you already highlighted is that we need to treat the comorbidities in an optimal fashion before we start prescribing MASH-directed therapies. So that means for obesity or type 2 diabetes, choose drugs, for instance, like the GLP-1 receptor agonists that are expected to improve also MASH. As SGLT2 inhibitors were already mentioned a bit in the slide, I saw that many of you tried to add 5 mg of dapagliflozin, which is probably useful in this case, but already the EASL-EASD-EASO MASLD guidelines mentioned that resmetirom should be considered in F2/F3 fibrosis if it's locally approved and available.
63.		So what type of targets do we have in the near future? So I guess a lot of the research has focused on reducing signals that come to the liver by reducing weight, by maybe even modifying a little bit of the genetics or the probiotics. We have very few drugs that are really targeting the liver metabolism and revert some of the pathogenic mechanisms, and resmetirom I think may be the first candidate of showing that, but maybe modification of some of the incretins with adding glucagon or targeting FGF21 could be able to support this concept. And we have relatively few data supporting drugs that would disconnect the steatosis from the inflammation and fibrosis. So this is probably a bit of the harder task to achieve.

64.		Let's focus briefly on the incretin mimetics, the GLP-1 receptor agonists, and then the co-agonist. And we have learned over the years that GLP-1 does not only work on the gut and producing gut motility and food resorption, but also has an impact on the brain, on the pancreas. And if we combine the GLP-1 receptor agonist with GIP that works on the adipose tissue, or possibly also with glucagon agonists that target directly pathways in the liver, that could be beneficial. And we have a lot of studies supporting this concept. The most advanced ones are available for semaglutide. As you know, the phase 3 trial for tirzepatide, which is approved already for obesity and type 2 diabetes, and survodutide with phase 2b data targeting GLP-1 receptor agonists in glucagon.
65.		And semaglutide, has been approved in the United States for the indication of treating MASH with fibrosis, based on the phase 3 clinical trial data showing a clear difference from placebo for resolution of MASH after 1.5 years—so a bit longer than for resmetirom—and an improvement in liver fibrosis without worsening of MASH.
66.		One aspect Laurent taught us, the magic number is 10 kPa. So we have to go below 10 kPa with our treatment. And these are the data from the *New England Journal of Medicine* paper for semaglutide, showing that on average we reduce from >10 to <10 kPa. So we hope to see also long-term beneficial effects for the liver and for the ELF score. I think 9.8 is one of these magic numbers. And we reduce below 9.8. The weight reduction was a bit less than the phase 3 trial than we had seen that in the non-diabetic populations before, but nonetheless more than 10% weight reduction.
67.	 AE, n (%) / Semaglutide 2.4 mg (n=800) / Placebo (n=395) All AEs: 690 (86.2) / 315 (79.7) Fatal AEs: 3 (0.4) / 6 (1.5) Serious AEs: 107 (13.4) / 53 (13.4) AEs leading to trial discontinuation: 21 (2.6) / 13 (3.3) AEs affecting ≥10% of participants **Nausea**: 290 (36.2) / 52 (13.2) **Diarrhea**: 215 (26.9) / 48 (12.2) **Constipation**: 178 (22.2) / 33 (8.4) **Vomiting**: 149 (18.6) / 22 (5.6) COVID-19: 134 (16.8) / 74 (18.7) **Decreased appetite**: 112 (14.0) / 11 (2.8)	The side effects for semaglutide, I think is well known to everybody. Particular gastrointestinal side effects. Nausea, diarrhea, abdominal pain.

68.		How about the long-term effects? And we try to or are we accumulating data now for the long-term use of this class of drugs for type 2 diabetes? And I think one aspect from the VA database is really interesting to look at with many patients and MASH controls in the type 2 diabetes setting, and we do see an increased incidence of all the gastrointestinal side effects, as expected. And also nephrology as this for instance, is increased. What we do see also clearly reduced is all the cardiovascular outcomes in these real-world data and also our liver outcomes. Liver cancer and hepatic failure were reduced in these large databases. Another interesting aspect that we do see is some beneficial results on dependency disorders, alcohol use disorders, also suicide numbers were decreased, which makes us think that maybe the MetALD, ALD could also benefit potentially from the GLP-1 receptor agonists. And I saw that some of you clicked the PEth test for the resmetirom and the increase in transaminase. And maybe that is also something to consider. And maybe there's a place for the GLP-1 receptor agonists.
69.		For tirzepatide, the phase 2b data after 1 year of therapy—significant MASH resolution and improvement in liver fibrosis. Tirzepatide is already available to treat obesity and type 2 diabetes.
70.		Survodutide is now in a phase 3 clinical trial. The endpoint was a bit different. So it was improvement of MASH which was met. But the different doses of survodutide and the endpoint of improvement in liver fibrosis, if you look into the subsets, was also quite impressive for the F2/F3 population. These are the original data from the *New England Journal of Medicine* paper.

71.	**SGLT2 Inhibitor Dapagliflozin for the Treatment of MASH: Phase 2b Trial** RCT from China (6 centers), n=78 dapagliflozin 10 mg vs n= 76 placebo, biopsy at 48 weeks (2% F0, 33% F1, 45% F2, 19% F3, 1% F4; aged 35 years; 85% male; BMI 29 kg/m²)  BMI: body mass index; RCT: randomized controlled trial. Lin J, et al. *BMJ*. 2025; 389:e083735. Reproduced for educational purposes only. 11	I already said, some of you said, why don't we add dapagliflozin to our treatment? When you had the resmetirom case that was presented by Meena, we do have an RCT from China. A bit strange because they included also some F0/F1 fibrosis. But if we focus on the F2/F3 fibrosis population from this relatively small phase 2b trial, we can see that fibrosis improvement was actually quite impressive with the SGLT2 inhibitors. So maybe something to consider and to follow further.
72.	**Lanifibranor: Mechanism of Action** Lanifibranor is a pan-PPAR (PPAR α/δ/γ) agonist  • PPARs¹ • Nuclear receptors with key regulatory functions in metabolism, inflammation, and fibrogenesis • In clinical trial patients, lanifibranor has been found to affect²: • Steatosis • Inflammation • Liver fibrosis • Macrophage activation (improved in preclinical models) α-SMA: α-smooth muscle actin; IL: interleukin; iNOS: inducible NO synthase; PDK: pyruvate dehydrogenase kinase; PLIN2: perilipin-2; TGF: transforming growth factor. 1. Lefere S, et al. *J Hepatol*. 2020;73:757-770. 2. Francque SM, et al. *N Engl J Med*. 2021;385:1547-1558. Reproduced for educational purposes only. 12	Some of the newer drugs that we're expecting—lanifibranor data, probably next year, then from the phase 3 clinical trial. Lanifibranor, pan-PPAR agonist, that targets more than 1 isotype of the PPARs, the PPAR α, β, δ, and the γ.
73.	**Lanifibranor: Phase 2b NATIVE Trial**  NASH: nonalcoholic steatohepatitis; SAF: Steatosis, Activity, and Fibrosis. Francque SM, et al. EASL International Liver Congress 2021. Abstract OS-1044. Reproduced for educational purposes only. 13	The data from the phase 2 trial after 24 weeks of therapy, so only half a year. Quite, significant in the endpoints of MASH resolution and also on fibrosis improvement.
74.	**Lanifibranor: NATIVE Trial Safety** Francque SM, et al. *N Engl J Med*. 2021;385:1547-1558. 14	The side effects you've heard about probably a bit better tolerated from the GI side, but we did see a little bit of weight gain. So we'll need to monitor that closely.
75.	**Rationale for FGF21 Analogues**  FA: fatty acid; ER: endoplasmic reticulum; VLDL: very low-density lipoprotein. Puengel T, Tacke F. *Expert Opin Investig Drugs*. 2023;32:451-461. Reproduced for educational purposes only. 15	Of course, the probably one of the most promising emerging drugs is FGF21 analogues, which is a hormone that's produced by the liver but has also beneficial effects on other tissues in adipose tissue also the cardiovascular system. And I think what's very impressive, are the data that we have now, for instance, for efruxifermin after 2 years, and that was just released for the non-cerrhotic population on the left side in Lancet and for the cerrhotic population at EASL in the *New England Journal of Medicine*. This is the intention to treat analysis after 2 years.

Most Frequent AEs, n (%)	Lanifibranor 1200 mg (n=83)	Lanifibranor 800 mg (n=83)	Placebo (n=81)
Diarrhea	10 (12)	8 (10)	1 (1)
Fatigue	11 (13)	3 (4)	8 (10)
Nausea	7 (8)	8 (10)	3 (4)
Weight gain	7 (8)	8 (10)	0 (0)
Peripheral edema	7 (8)	5 (6)	2 (2)
Headache	7 (8)	4 (5)	4 (5)
Abdominal pain	5 (6)	4 (5)	4 (5)
Dizziness	6 (7)	2 (2)	3 (4)
Anemia	6 (7)	1 (1)	0 (0)
Constipation	5 (6)	3 (4)	6 (7)
Increase in aminotransferase levels	3 (4)	5 (6)	1 (1)

		Really, we see a much higher gap between placebo and efruxifermin regarding fibrosis improvement.
76.		And if we just look at the small subset of patients that had really biopsies available at both time points and could be read, then you see really a clear difference emerging after 2 years of therapy for a efruxifermin in the non-cirrhosis and cirrhosis population. So quite encouraging data. But maybe for this class of drug even more important to watch, also the long-term safety GI side effects were noted. Injection site erythema, which is, I think, manageable, but also a reduction in bone density, was mentioned. The risk of antidrug antibodies seems to be considerable for this class of drug.
77.		So I think we will have many Paris MASH meetings to come, because there's so much in the pipeline, emerging drugs beyond the first drug resmetirom that is now approved. Many other drugs are in development. I think very encouraging data from semaglutide, now approved in the United States also for the treatment of MASH because it improves fibrosis and MASH resolution. The SGLT2 inhibitors, for instance, dapagliflozin, may also have benefits in addition to their metabolic, cardiac, and renal benefits that are well-documented. The FGF21 analogues are very promising, pan-PPAR agonists. I think we will see these data soon. We do need, of course, more long-term data on the safety, particularly for the new classes of drugs that we're going to use. And of course, the aspect of MetALD, ALD and who benefits from what is also an emerging field. And maybe the incretin mimetics may have a place here. Thank you very much.