Resmetirom for treating moderate-to-advanced liver fibrosis (without cirrhosis) caused by metabolic dysfunction-associated steatohepatitis (MASH)

Part 1 for screen – contains redacted CON information

Technology appraisal committee B [14 May 2026]

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Resmetirom for treating moderate-to-advanced liver fibrosis (without cirrhosis) caused by metabolic dysfunction-associated steatohepatitis (MASH)

- ✓ **Background and key issues**
- ❑ Clinical effectiveness
- ❑ Modelling and cost effectiveness
- ❑ Other considerations
- ❑ Summary

NICE National Institute for Health and Care Excellence

Background on moderate-to-advanced liver fibrosis caused by MASH

MASH is chronic, progressive, and can lead to fibrosis, increasing the risk of major complications such as cirrhosis, HCC, liver transplantation and liver-related mortality

Causes and epidemiology

- MASH develops when excess fat accumulates in liver, causing inflammation
- People with MASH typically have multiple comorbidities, including obesity, metabolic syndrome, hypertriglyceridaemia and T2DM
- Prevalence of MASH in England estimated to be 26.6 per 100,000 people, but believed to be substantially underdiagnosed

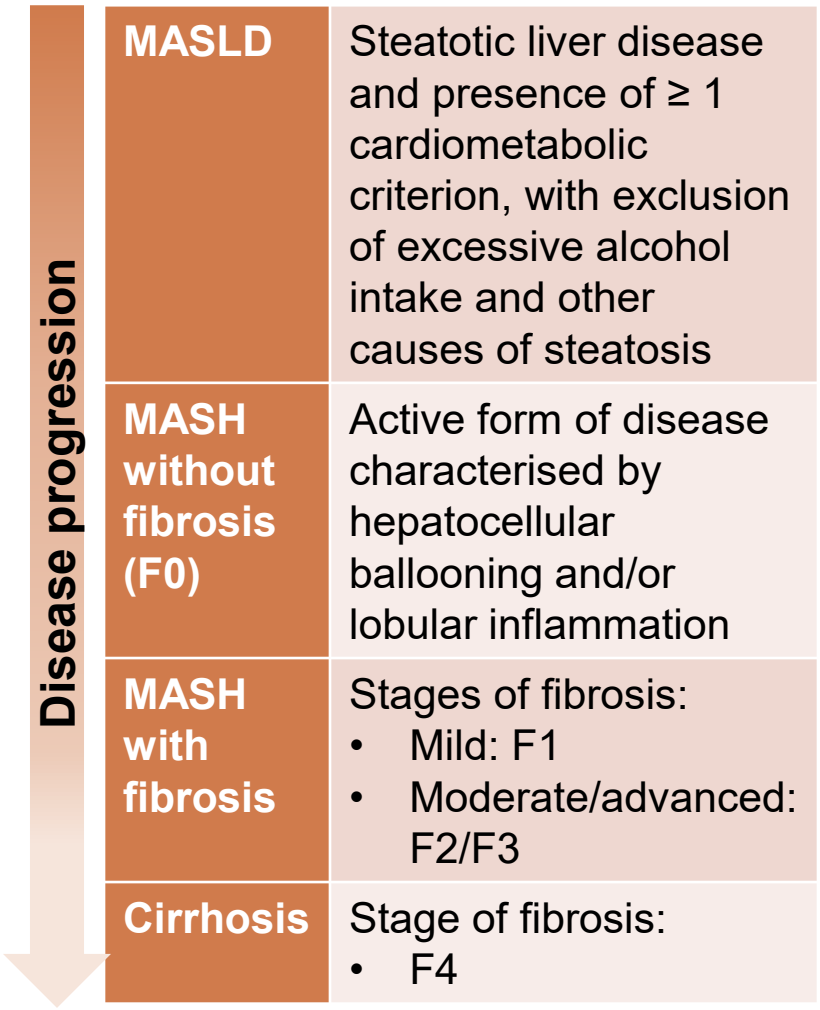
Diagnosis

- Diagnosis of MASLD usually determined by fatty liver presence on ultrasound
- Liver fibrosis usually assessed in two stages using NITs: first using FIB-4; then FibroScan VCTE or ELF as second-line tests

Prognosis

- Disease progression is highly heterogeneous and can depend on various factors such as genetics, lifestyles, comorbidities

Overview of disease classification



Abbreviations: ELF, Enhanced Liver Fibrosis Test; FIB-4, Fibrosis-4 Index; HCC, hepatocellular carcinoma; MASH, metabolic dysfunction-associated steatohepatitis; MASLD, metabolic dysfunction-associated steatotic liver disease; NIT, non-invasive test; T2DM, type 2 diabetes mellitus; VCTE, Vibration-Controlled Transient Elastography

Patient perspectives

Resmetirom would be the first pharmacological treatment available for MASH

Submissions from British Liver Trust and patient experts

- MASH is usually asymptomatic in early stages and is often diagnosed late. MASH can cause serious complications and lead to liver cancer or liver transplantation.
- As disease progresses, common symptoms include poor sleep quality, sleep apnoea, lethargy, anxiety/depression, weight gain and cognition problems
- Slowing or stopping progression to cirrhosis is important → With cirrhosis, people have fatigue, weakness, nausea and appetite issues. They may become unable to do daily tasks and experience cognitive changes.
- People must often attend many hospital appointments and family members may become caregivers.
- Managing MASH typically requires major lifestyle changes (diet, exercise, weight management), which many patients find overwhelming. Currently, there are no pharmacological treatments available for treating moderate to advanced liver fibrosis.
- This medicine could halt disease progression and reduce mortality.

"The tiredness came from nowhere and doesn't improve with sleep; I have two small children and I really struggle. I feel guilty that I'm not being a proper mum"

"The toll this illness has on families is horrendous with little to no support available"

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Abbreviations: MASH, metabolic dysfunction-associated steatohepatitis

Clinical perspectives

Resmetirom could be the first licensed treatment for MASH and may require service redesign

Submissions from The British Association for the Study of the Liver (BASL), British Hepatology Pharmacy Group, and UK Clinical Pharmacy Association

- Will be first licensed pharmacological treatment to show meaningful improvements in MASH resolution and fibrosis
- MASH resolution and fibrosis improvement accepted as surrogate outcomes. Need for long-term data on mortality and liver morbidity.
- Treatment priorities: weight loss and optimisation of cardiometabolic risk factors.
- Resmetirom could be positioned as second-line treatment after GLP-1 RAs
- Liver biopsy should not be required to determine eligibility for treatment but may be helpful in some cases. Patients are identified using risk factors and non-invasive fibrosis scores, and specialist assessment
- Likely to have significant impact on hepatology service capacity due to large patient cohort

Abbreviations: GLP-1 RA, glucagon-like peptide-1 receptor agonist; MASH, metabolic dysfunction-association steatohepatitis; MASLD, metabolic dysfunction-associated steatotic liver disease

NHS England perspective

Link to use of NITs

Substantial implementation challenges are expected if resmetirom is recommended

- There is significant geographical variation in diagnostic pathways, FibroScan and ELF test availability, and variation in test result threshold values
- There is variation in approaches taken by clinicians within many elements of the pathway, e.g.:
  - Different thresholds for referring to secondary care
  - Use of automated FIB-4 by some clinicians to identify patients for follow up
  - Some clinicians in secondary care may repeat diagnostics already taken place in primary care
- Resmetirom likely to be prescribed in secondary care until patient is stabilised, with potential shift to primary care for ongoing management. Primary care staff may not feel comfortable initiating a patient on resmetirom.
- Implementation faces major system and capacity challenges → implementation to full population within 90 days unlikely to be feasible and funding variation likely to be required
  - Access to FibroScan VCTE varies significantly and more rapid expansion needed to meet demand
  - Availability and uptake of ELF testing is limited
  - Specialist clinicians emphasise current lack of education for primary care clinicians in diagnosing MASLD and liver fibrosis

Abbreviations: ELF, enhanced liver fibrosis; MASLD, metabolic dysfunction-associated steatotic liver disease; VCTE, Vibration-Controlled Transient Elastography

Equality considerations

There are potential equality considerations related to geographical variation in clinical practice, socioeconomic status and ethnicity

The following equalities considerations have been raised by stakeholders:

- There are differences between ethnic groups in the likelihood of developing MASLD/MASH
- Liver fibrosis is linked to BMI and any criteria for diagnosing obesity through BMI should take account of ethnic differences
- Rates of premature death from MASLD are higher for people living in more deprived areas of England
- There is geographical variation in treatment pathways and diagnostic capacity, which could impact the number of patients identified and lead to potential geographical inequity in access to treatment
- Access to specialist services is unevenly distributed in England. The need to travel long distances to specialist centres could disproportionately affect older people, disabled people and socioeconomically disadvantaged people

Abbreviations: BMI, Body Mass Index; MASH, metabolic dysfunction-association steatohepatitis; MASLD, metabolic dysfunction-associated steatotic liver disease

Resmetirom (Rezdiffra, Madrigal Pharmaceuticals)

Marketing authorisation	• UK marketing authorisation not yet granted • Expected marketing authorisation wording: 'indicated in conjunction with diet and exercise for the treatment of adults with non-cirrhotic MASH with moderate-to-advanced liver fibrosis (consistent with fibrosis stages F2 to F3)'* • Currently being assessed by MHRA via International Recognition Procedure
Mechanism of action	• Works directly in the liver by stimulating thyroid hormone receptor-beta (THR-β) • This allows for the expression of genes that improve critical hepatic processes, leading to reduced inflammation in the liver
Administration	• Oral tablet taken once daily available in 60mg**, 80mg and 100mg forms: i. For people weighing <100 kg, the recommended daily dose is 80mg ii. For people weighing ≥100 kg, the recommended daily dose is 100mg
Price	• List price per day across all doses is £[redacted]*** • List price for 12 months of treatment is £[redacted] • The company has not submitted a patient access scheme

*No stopping rules. Economic model includes stopping rule for patients who regress to F0 or F1 or progress to ALD
** 60mg dose used as modification for some drug interactions
*** List price has been provisionally agreed with DHSC, but is confidential until MHRA marketing authorisation

Abbreviations: ALD, advanced liver disease; DHSC, department of health and social care; MASH, metabolic dysfunction-associated steatohepatitis; MHRA, medicines and healthcare products regulatory agency; THR-β; thyroid hormone receptor-beta

Key issues for discussion

Issue	Resolved at TE?	ICER impact
1. Current and anticipated use of GLP-1 RAs in the UK	No – for discussion	Unknown
2. Use of resmetirom in clinical practice guided by NITs	No – for discussion	Large
3. Generalisability of the clinical trial	No – for discussion	Unknown
4. Reliance on surrogate endpoints	No – for discussion	Unknown
5. Validation of the company model	Partly – for discussion	Unknown
6. NIT criteria used as proxy for fibrosis stage in the model	No – for discussion	Unknown
7. Natural history of MASH and face validity of model progression rates	No – for discussion	Large
8. Population used for transition probabilities	Partly – for discussion	Moderate
9. Repeated application of transition probabilities	No – for discussion	Moderate
10. Transition probabilities to advanced liver complications	Partly – for discussion	Moderate
11. Utility values and MASH resolution increment	Partly – for discussion	Moderate
12. Extrahepatic treatment effects	No – for discussion	Small

Note that key issue numbers and names do not match with EAG report

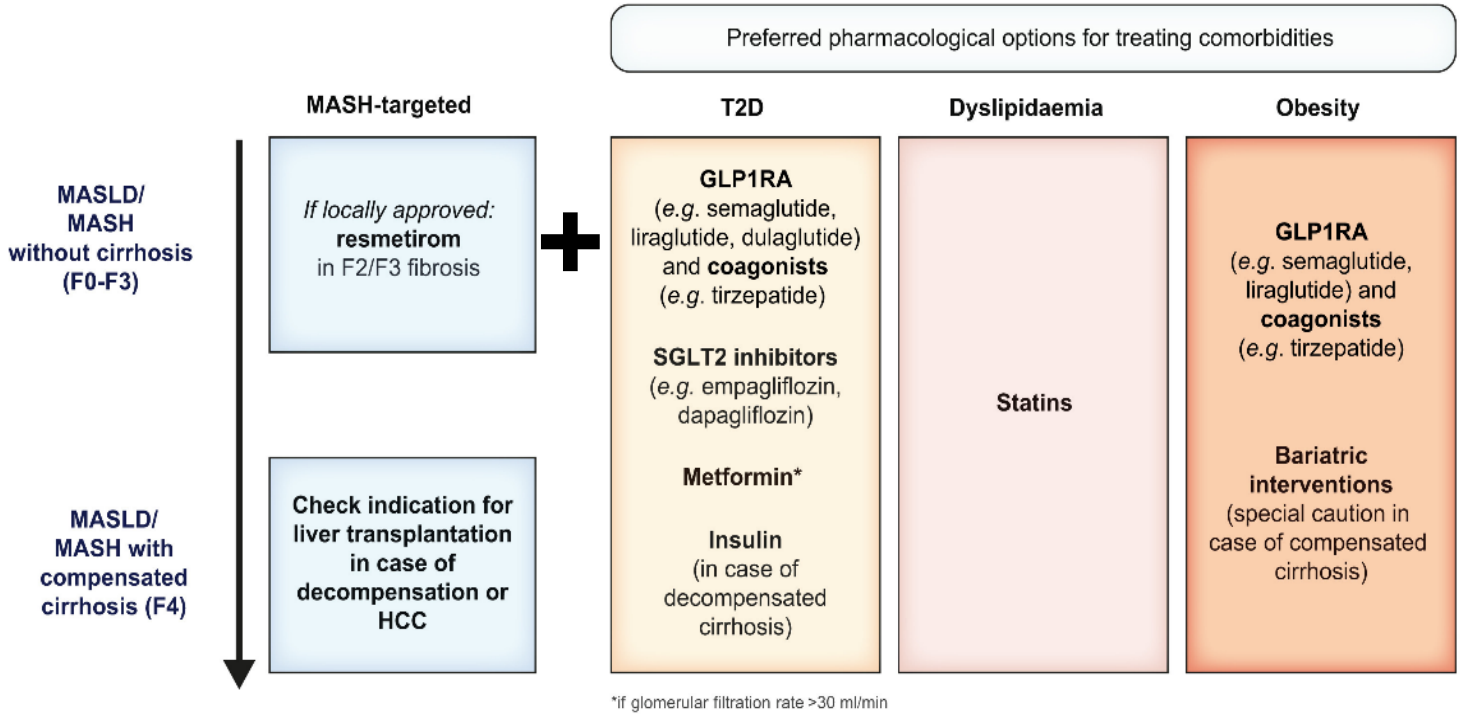
Abbreviations: ICER, incremental cost-effectiveness ratio; ITT, intent to treat; MASH, metabolic dysfunction-associated steatohepatitis; NIT; non-invasive test; TE, technical engagement

Treatment pathway for MASH and proposed positioning of resmetirom

Company

- Resmetirom anticipated to be used in conjunction with diet and exercise and other SoC therapies

Company's proposed positioning of resmetirom in the treatment pathway



EAG

- Company's description of treatment pathway broadly appropriate
- No licensed therapy available for the treatment of MASH
- People are offered lifestyle modification interventions such as dietary changes, weight loss and exercise

Link to NICE recommendations for GLP-1 RAs

- Would the diet and exercise counselling offered alongside resmetirom differ to what is currently provided as part of SoC?
- Would resmetirom be prescribed in secondary care or primary care?

NICE

Abbreviations: EAG, external assessment group; GLP-1 RA, glucagon-like peptide-1 receptor agonist; MASH, metabolic dysfunction-association steatohepatitis; MASLD, metabolic dysfunction-associated steatotic liver disease; SoC, standard of care

Key issue 1: Current and anticipated use of GLP-1 RAs

Background

- Semaglutide is not relevant comparator → NICE evaluation for semaglutide in this indication (ID6458) ongoing
- GLP-1 RAs commonly used in patients with obesity or T2DM (14.2% at baseline in MAESTRO-NASH)
- Unclear whether resmetirom would be prescribed to people already receiving a GLP-1 RA

EAG

- Many patients eligible for resmetirom could also be eligible for, or already having, semaglutide
- Semaglutide may have beneficial effects on fibrosis → uncertain whether both would be used concomitantly
- Clinical advisers - resmetirom unnecessary if patients lose weight / have reduced liver stiffness on a GLP-1 RA

Company

- Concomitant semaglutide and resmetirom use would be clinically plausible for people with both metabolic disease and MASH because they are mechanistically complementary rather than substitutive
- Resmetirom is a liver-directed therapy, whereas semaglutide is a systemic cardiometabolic therapy
- GLP-1 RAs may improve metabolic risk factors and reduce liver fat but not established as antifibrotic therapies

Clinical expert comments:

- MoAs could be considered complementary and concomitant use may be beneficial for some patients
- In practice, need to consider whether both agents would be started simultaneously or sequentially
- GLP-1 RA dose would need to have been stabilised for at least 24 weeks to consider concomitant use

- Would resmetirom be started in parallel with management of the metabolic syndrome manifestations or subsequently?
- How should this be reflected in the model?

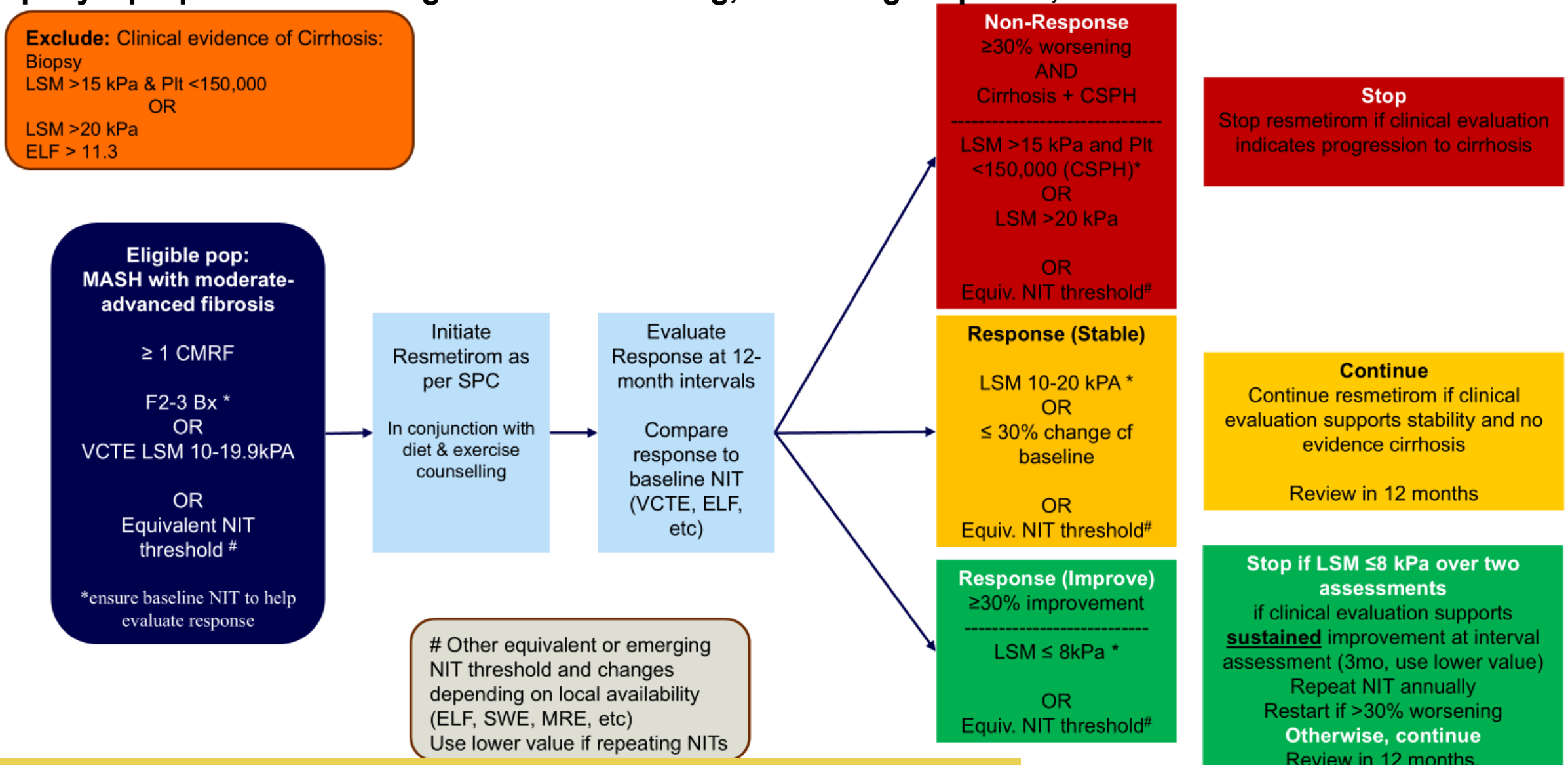
NICE

Abbreviations: GLP-1 RA, glucagon-like peptide-1 receptor agonist; MASH, metabolic dysfunction-association steatohepatitis; MoA, mechanism of action; T2DM, type 2 diabetes mellitus

Key issue 2: Use of resmetirom in clinical practice guided by NITs (1/3)

Link to use of NITs

Company's proposed clinical algorithm for initiating, evaluating response, and discontinuation of resmetirom



- Is the company's proposed clinical algorithm for initiating, evaluating response, and discontinuation of resmetirom appropriate?

Abbreviations: Bx, biopsy; CMRF, cardiometabolic risk factor; ELF, enhanced liver fibrosis; LSM, liver stiffness measurement; NIT, non-invasive test; VCTE, Vibration-Controlled Transient Elastography

Key issue 2: Use of resmetirom in clinical practice guided by NITs (2/3)

EAG

Use of NIT criteria

- Has concerns about specific NIT criteria proposed by company → only [redacted] of trial population meet VCTE criteria, raising concerns about generalisability of trial population and suitability of criteria.
- Clinical advice raised concerns about no. of patients eligible for treatment under these criteria, and many would be at low risk of subsequent disease. Evidence from several large cohort studies demonstrate risk of cirrhosis and other events is low in many patients with LSM >10 kPa → criteria could lead to over treatment

Stopping rules and discontinuation

- Likely that repeat NIT testing would be required for clinicians to implement company's stopping rules → Prefers 1 additional FibroScan test and consultation, and 3 months additional resmetirom cost while NIT results confirmed
- Agrees with treatment discontinuation upon progression to HCC/DCC given stakeholder clinical consensus
- Uncertain about treatment continuation in people with F4 CC. **No fibrosis-stage stopping rule in MAESTRO-NASH** and ongoing MAESTRO-NASH-OUTCOMES trial is evaluating resmetirom in people with CC.
- Unsure if appropriate to stop treatment upon fibrosis regression to F0 or F1. **SmPC does not specify this stopping rule** and stakeholder opinion during TE did not demonstrate strong support for such a rule
  - Concerned about feasibility of implementing this stopping rule in clinical practice given NITs limited ability to reliably distinguish between fibrosis stages and do not provide detailed information on MASH resolution

Abbreviations: CC, compensated cirrhosis; DCC, decompensated cirrhosis; HCC, hepatocellular carcinoma; CMRF, cardiometabolic risk factor; ELF, enhanced liver fibrosis; LSM, liver stiffness measurement; NIT, non-invasive test; SmPC, summary of product characteristics; VCTE, Vibration-Controlled Transient Elastography

Key issue 2: Use of resmetirom in clinical practice (3/3)

Clinical expert comments at Technical Engagement:

NIT assessment in clinical practice

- Currently, fibrosis NIT assessment is a two-stage process:
  1. Indirect fibrosis risk score (FIB-4) with a high negative predictive value
  2. Second-line testing with FibroScan VCTE or ELF
- Repeated FIB-4 testing annually is effective for mitigating against "missed cases"

Stopping rules and discontinuation

- Appropriate to stop resmetirom treatment upon progression to ALD, including CC
- Mixed responses on if appropriate to stop resmetirom treatment on fibrosis regression *without MASH resolution*:
  - Clinical expert 1: Would make sense to continue therapy pending updates from long-term trial data
  - Clinical expert 2: There are no high performing tests for MASH that are independent of fibrosis. More relevant to consider whether treatment should be discontinued if fibrosis regresses. Must consider if underlying drivers of disease have been addressed through lifestyle changes/weight loss

a. What tests are used in clinical practice for MASH?
b. Is it appropriate to assume no additional treatment eligibility costs in the resmetirom arm?
c. Is it appropriate to stop resmetirom treatment when fibrosis regresses to F0 or F1?
d. Is it appropriate to stop resmetirom treatment when people progress to advanced liver disease, including CC?
e. Are there any other considerations for discontinuation that should be incorporated into the modelling?
f. Should repeat testing costs be applied to assess treatment response? If so, is one extra outpatient FibroScan assessment sufficient, and should 3 or 6 months of additional resmetirom cost be assumed?

Abbreviations: ALD, advanced liver disease; CC, compensated cirrhosis; CMRF, cardiometabolic risk factor; CVD, cardiovascular disease; ELF, enhanced liver fibrosis; LSM, liver stiffness measurement; MASH, metabolic dysfunction-associated steatohepatitis; NIT, non-invasive test; VCTE, Vibration-Controlled Transient Elastography

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Key clinical trial: MAESTRO-NASH (1/2)

Link to baseline characteristics

MAESTRO-NASH is an ongoing placebo-controlled phase 3 RCT

MAESTRO-NASH study design and outcomes

	MAESTRO-NASH
Study type	Placebo-controlled phase 3 RCT
Population	Adults with biopsy-confirmed NASH and fibrosis stage 1B, 2 or 3 and with ≥3 cardiometabolic risk factors
Intervention	80mg and 100mg resmetirom; oral tablet, once daily
Comparator	Placebo; oral tablet, once daily
Duration	54 months (ongoing); dual primary outcomes assessed at week 52 and presented in company submission
Week 52 primary outcomes*	1. MASH resolution without worsening of fibrosis 2. ≥1-point improvement in fibrosis stage without worsening of NAS
Month 54 primary outcome (data not yet available)	Time to composite clinical event: all-cause mortality, liver transplant, and significant hepatic events
Locations	246 global sites including 13 NHS sites in UK
Used in model?	Yes

*MASH resolution defined as hepatocellular ballooning score of 0, a lobular inflammation score of 0 or 1, and a reduction in the NAS by at least 2 points

Abbreviations: NAS, non-alcoholic fatty liver disease activity score; MASH, metabolic dysfunction-associated steatohepatitis

Key clinical trial: MAESTRO-NASH (2/2)

MASH resolution with no worsening of fibrosis and fibrosis improvement with no worsening of NAS occurred in significantly more resmetirom-treated patients vs. placebo-treated patients

MAESTRO-NASH dual primary endpoint results (mITT-LB-W52 population, n=955)*

	% response Resmetirom 80 mg (n = 316)	% response Resmetirom 100 mg (n = 321)	% response Placebo (n = 318)	% difference Resmetirom 80 mg vs Placebo (95% CI)	% difference Resmetirom 100 mg vs Placebo (95% CI)
MASH resolution with no worsening of fibrosis					
Primary	25.9	29.9	9.7	16.4 (11.0, 21.8)	20.7 (15.3, 26.2)
Consensus (sensitivity)**	24.4	27.7	7.9	16.8 (11.3, 22.4)	20.7 (15.0, 26.3)
Fibrosis improvement with no worsening of NAS					
Primary	24.2	25.9	14.2	10.2 (4.8, 15.7)	11.8 (6.4, 17.2)
Consensus (sensitivity)**	24.4	25.5	12.3	12.2 (6.3, 18.2)	13.4 (7.4, 19.3)

*mITT-LB-W52 population excludes 11 patients who had a delay in their week 52 biopsy because of COVID-19.

**A consensus read (sensitivity analysis) of biopsies was done if disagreement between pathologists as to whether either primary endpoint was met.

Note that company model uses more restricted trial population (PLB-W52) to derive transition probabilities

Abbreviations: CI, confidence interval; NAS, non-alcoholic fatty liver disease activity score; MASH, metabolic dysfunction-associated steatohepatitis

Key issue 3: Generalisability of the clinical trial (1/2)

EAG: Nearly all MAESTRO-NASH patients had liver fibrosis assessed using a baseline liver biopsy, which is not required or desirable as a diagnostic test for MASH with fibrosis in the UK

Company response at Technical Engagement

Use of baseline liver biopsy in MAESTRO-NASH

- Liver biopsy was used for trial eligibility and endpoint assessment, and was required by regulators
- In UK clinical practice patient identification will use NITs but biopsy does not undermine external validity of trial

EAG response at Technical Engagement

Use of baseline liver biopsy in MAESTRO-NASH

- NITs will be used to identify patients eligible for resmetirom. NITs estimate probability of clinically significant fibrosis but cannot distinguish fibrosis stages with same accuracy as biopsy.
- NITs cannot reliably distinguish between intermediate fibrosis stages (e.g. F1 vs F2) and do not provide detailed information on MASH resolution → remains unclear how use of NITs affects estimation of treatment effects
- [redacted]% of trial population met proposed NIT FibroScan VCTE criteria → not fully aligned with scope.
- Treatment effect based on NIT could be reduced in clinical practice if a proportion of patients without fibrosis stage 2 or 3 are treated (clinical expert TE response)
- In company subgroup analysis requested by EAG that restricts population to only those who meet proposed NIT-based eligibility criteria: outcomes are similar to those of whole population and modest reduction in ICER

Abbreviations: EAG, external assessment group; ELF, enhanced liver fibrosis; FIB-4, Fibrosis-4 Index; ICER, incremental cost-effectiveness ratio; MASH, metabolic dysfunction-associated steatohepatitis; NIT, non-invasive test; TE, technical engagement; VCTE, Vibration-Controlled Transient Elastography

Link to assessment of trial population against eligibility criteria in literature

Key issue 3: Generalisability of the clinical trial (2/2)

EAG: MAESTRO-NASH only included patients with ≥ 3 CMRFs

Company response at Technical Engagement

- Clinical expert opinion and local data suggest that UK patients referred to secondary care have several CMRFs→ MAESTRO-NASH population reflective of population referred to secondary care
- It would be inequitable to require a specific number of CMRFs for eligibility for resmetirom
- Provided new evidence from UK Biobank: Metabolic characteristics observed in MAESTRO-NASH resemble an "at-risk MASH" subgroup (MASH with stage 2 or higher fibrosis) defined in analysis of UK Biobank dataset.
- MAESTRO-NASH cohort and UK Biobank "at-risk MASH" cohort have similar demographic profiles.

EAG response at Technical Engagement

- Agrees that patients eligible for resmetirom likely to have multiple CMRFs. Notes TE clinical expert testimony indicated that most people with MASH and moderate-to-advanced liver fibrosis have three or more CMRFs.
- However, NICE scope does not restrict inclusion to patients with 3 CMRFs and some eligible patients may have fewer than 3 CMRFs → further limits generalisability of trial evidence

- How is the use of NITs likely to affect the generalisability of the observed treatment effect to UK clinical practice?
- How does the requirement for ≥3 CMRFs affect the generalisability of MAESTRO-NASH?
- Is MAESTRO-NASH acceptable for decision making?

Abbreviations: CMRF, cardiometabolic risk factor; EAG, external assessment group; NIT, non-invasive test; MASH, metabolic dysfunction-association steatohepatitis

Key issue 4: Reliance on surrogate endpoints

Company response at Technical Engagement:

- Fibrosis stage is well-established prognostic factor in MASH, with higher stages associated with increased risk of severe liver disease, major adverse liver outcomes, and mortality. Literature review demonstrates the relationship between fibrosis stage and liver-related morbidity and mortality
- FDA and EMA accepted the primary endpoints in MAESTRO-NASH as valid surrogate endpoints*, acknowledging challenges of capturing long-term outcomes and unmet need

EAG response at Technical Engagement:

- Main drivers of the model (reduced comorbid events, avoidance of liver complications (DCC and HCC), and improved survival) are not observed directly in the trial. Outcomes are inferred indirectly through intermediate changes in fibrosis stage, MASH resolution and risk factors (BMI, LDL-C, HDL-C, and triglycerides)
- Fibrosis stage/ MASH resolution not validated as surrogate outcomes→ modelled clinical outcomes uncertain
- Possible that improvements in fibrosis stage partially but not fully reduce risk of future morbidity and mortality, e.g., due to architectural damage, microvascular changes, and persistent metabolic drivers of disease

Clinical expert comments:

- Longitudinal studies consistently show correlation between fibrosis stage and longer-term outcomes
- Less evidence for MASH resolution but data shows association between steatohepatitis grade and fibrosis stage

*Note that surrogate endpoints were accepted by FDA/EMA for accelerated approval/conditional MA, respectively

Are fibrosis improvement and MASH resolution acceptable surrogate endpoints?
To what extent does the reliance on surrogate endpoints generate uncertainty?

Abbreviations: BMI, body mass index; DCC, decompensated cirrhosis; EMA, European Medicines Agency; FDA, Food and Drug Administration; HCC, hepatocellular carcinoma; HDL-C, High-Density Lipoprotein Cholesterol; LDL-C, Low-Density Lipoprotein Cholesterol; MA, marketing authorisation; MASH, metabolic dysfunction-associated steatohepatitis

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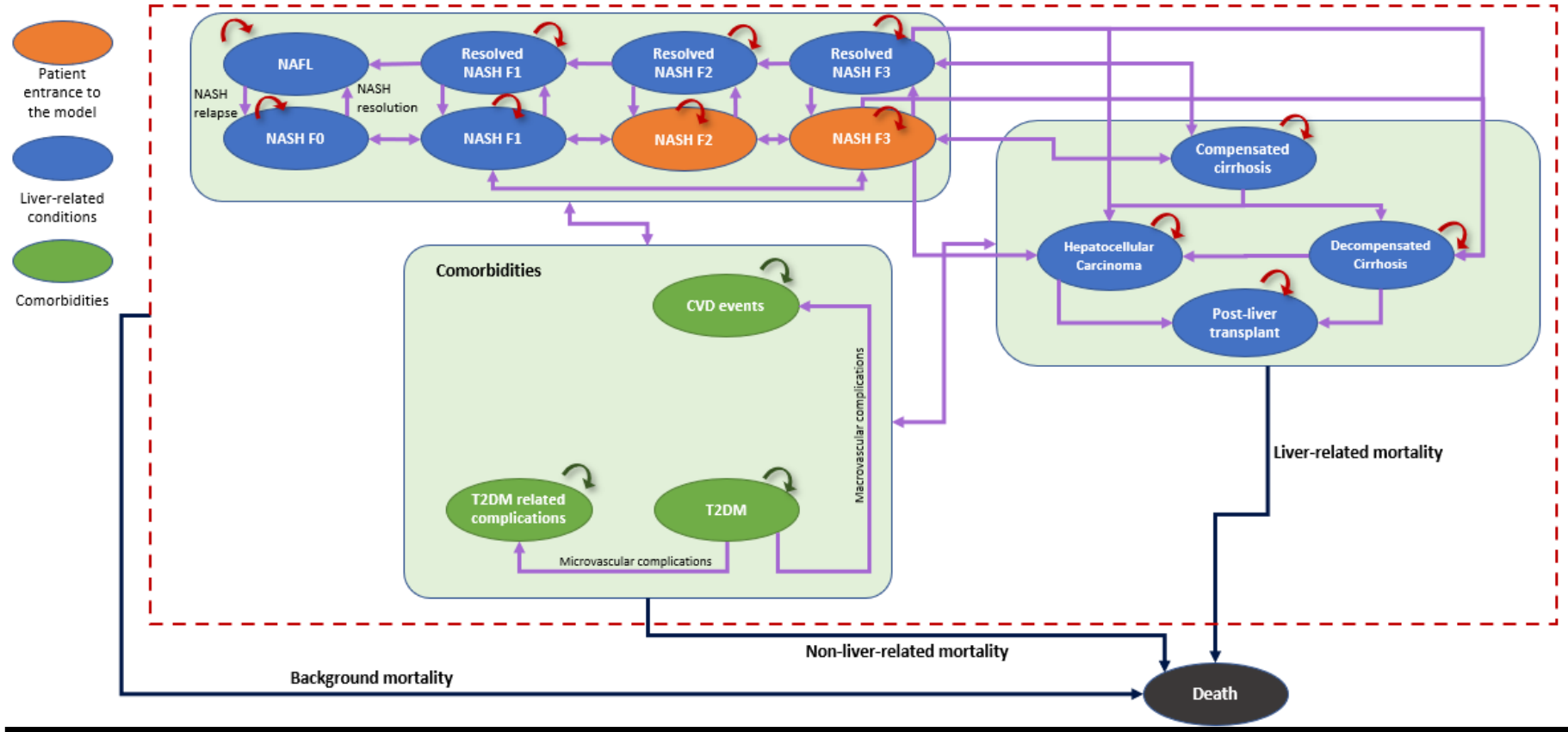
Overview of company's economic model

Individual patient simulation model of resmetirom versus SoC (lifestyle changes)

Model structure



Resmetirom is modelled to affect QALYs by:

- Avoidance of advanced fibrosis
- Avoidance of HCC and liver transplants
- Improved survival

Resmetirom is modelled to affect costs by:

- Increasing drug acquisition costs
- Reducing advanced fibrosis care costs

EAG

- Model structure and approach broadly consistent with previous CEAs and captures key aspects of MASH.
- Individual patient simulation provides greater flexibility by enabling simultaneous modelling of liver and non-liver related outcomes but substantially increases model complexity. Unclear whether additional complexity justified.

Is the company's modelling approach appropriate?

Abbreviations: CEA, cost-effectiveness analysis; CVD, cardiovascular disease; HCC, hepatocellular carcinoma; MASH, metabolic dysfunction-associated steatohepatitis; SoC, standard care; T2DM, type 2 diabetes; QALY, quality-adjusted life year

Key issue 5: Validation of company model

Background

Before Technical Engagement, EAG had many concerns about the programming of the model which made the internal validity of the model uncertain, including:

- It was unclear what internal validation and cross-checking had been done
- Some black box tests indicated errors in the R code, e.g. for life years calculations
- Queries requiring clarification about the coding of the model, e.g. inputs read in multiple locations, variables duplicated, and ordering of code obscuring logical calculations

Company response at Technical Engagement:

- Submitted revised model with requested corrections, answered questions on the model and completed TECH-VER validation checklist
- Combined all input data into a single input parameters workbook and simplified reading procedure in R
- Streamlined R code and provided detailed document summarising model workflow and log of model changes
- Added options for scenario analysis and further updated model to correct error in cost calculation

EAG response at Technical Engagement:

- Updates and model validation have substantially improved the model's usability and transparency.
- Several thousand lines of R code have been added at TE, so EAG has not been able to fully check the model.
- While the model appears to work correctly, the EAG cannot be certain if there are any unidentified errors.

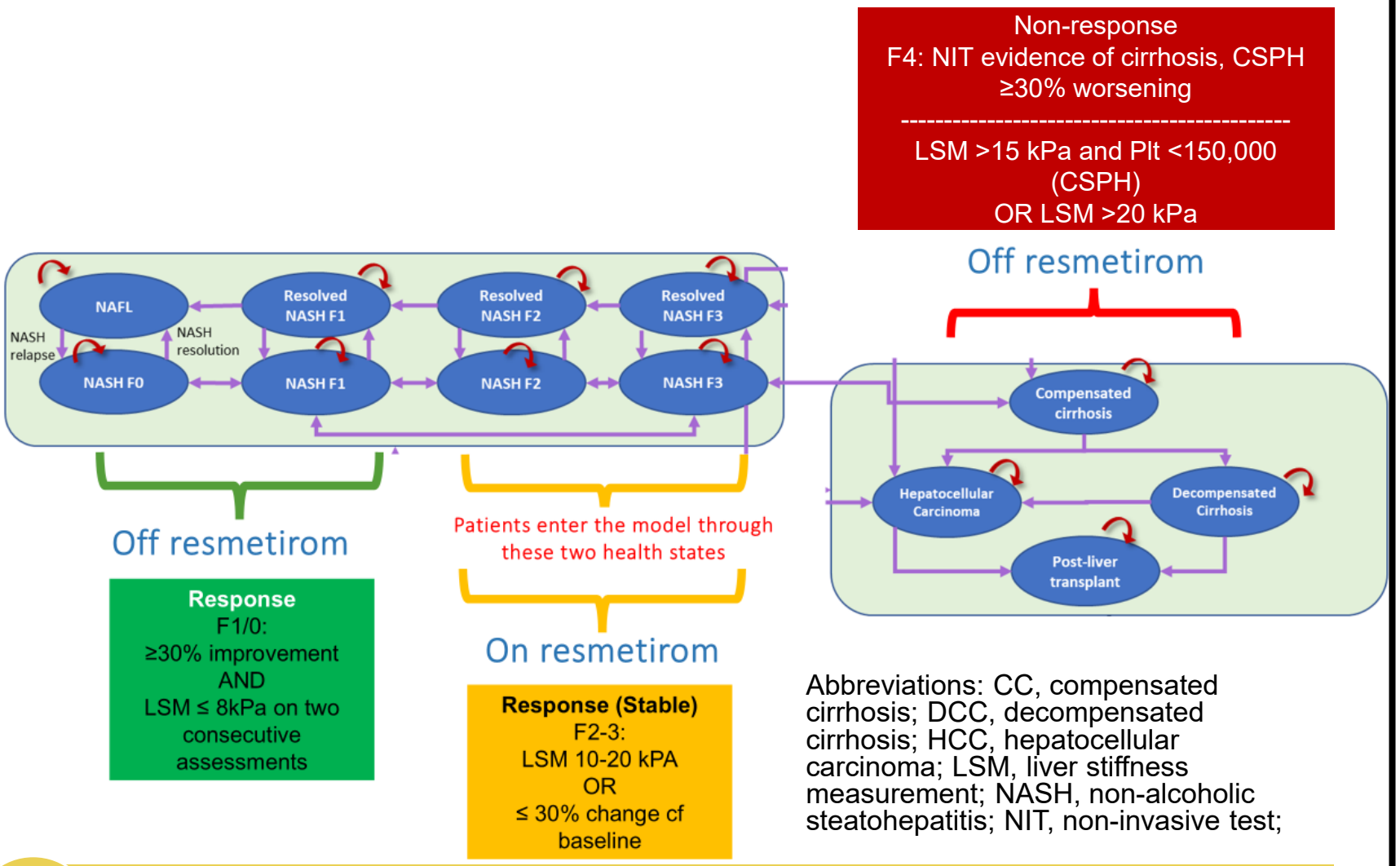
Is the company's model acceptable for decision making?

NICE

Abbreviations: EAG, external assessment group; TE, technical engagement

Key issue 6: NIT criteria used as proxy for fibrosis stage in the model

VCTE NIT thresholds mapped to resmetirom model structure



Abbreviations: CC, compensated cirrhosis; DCC, decompensated cirrhosis; HCC, hepatocellular carcinoma; LSM, liver stiffness measurement; NASH, non-alcoholic steatohepatitis; NIT, non-invasive test;

Is it appropriate to use the proposed NIT criteria as proxy for histologically assessed fibrosis stage in the model?

EAG

- Proposed NIT criteria assumed to correspond directly to fibrosis stage but NITs cannot reliably distinguish between intermediate fibrosis stages and do not capture MASH resolution
- Structural misalignment between model and clinical practice with implications for identification of target population and estimation of treatment effects → unclear if model predictions based on histological endpoints representative of likely outcomes in clinical setting using NIT

Key issue 7: Natural history and face validity of model progression rates (1/2)

Company rejects natural history evidence but EAG considers that current implementation of treatment effects generates clinically implausible predictions

Background

- Before Technical Engagement, EAG raised concerns about company's approach to modelling natural history, which relies on repeating transitions from SoC arm of MAESTRO-NASH, and rejection of natural history evidence

Company response at Technical Engagement:

- Pooled progression rates from natural history studies are not representative of target population because they mix patients with different risk profiles and baseline disease stages
- Rejects Le et al as NH source because results are in opposite direction to what company considers plausible and because rapid fibrosis progression was observed in MAESTRO-NASH advanced fibrosis population
- Found anomalous estimates and substantive flaws in Le et al
- Provided 4 scenario analyses that incorporate NH evidence from Le et al and Ng et al into model with relative risk applied for resmetirom
- Considers scenario analyses potentially informative but they come from aggregate data in heterogenous MASH populations and do not reflect costs and benefits of resmetirom

Link to critique of NH studies

Abbreviations: EAG, external assessment group; MASH, metabolic dysfunction-associated steatohepatitis; NAFLD, non-alcoholic fatty liver disease; NH, natural history; RCT, randomised controlled trial; SoC, standard of care

Key issue 7: Natural history and face validity of model progression rates (2/2)

EAG response to Technical Engagement:

- Scenarios have limited interpretability as alternative estimates of treatment effect because they distribute treatment benefit across entire cohort, instead of linking it to people who have MASH resolution
- However, scenarios are informative for assessing face validity of model predictions under SoC
- Comparison of health state occupancy across four natural history scenarios and company base case reveal clear and consistent differences: patients in SoC arm of the company base case spend substantially more time in F0/NAFL health states and less time in F2 and F3 than in any of the natural history scenarios

Comparison of health state occupancy in SoC arm

	F0/NAFL	F1/F1R	F2/F2R	F3/F3R	F4 CC	DCC	HCC	Post liver transplant	Total
Company base case	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Scenario 1 (Le et al)	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Scenario 2 (Ng et al)	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Scenario 3 (Le et al and Ng et al combined, max 1 stage change per cycle)	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Scenario 4 (Le et al and Ng et al combined, max 2 stages change per cycle)	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]

- Is it appropriate to validate progression rates in the model using NH cohorts from Le et al or Ng et al?
- Are there any other NH studies that could be used to validate the model progression rates?
- Do the model's predictions about progression under standard care have face validity?

Abbreviations: EAG, external assessment group; MASH, metabolic dysfunction-associated steatohepatitis; NAFL, non-alcoholic fatty liver; NH, natural history; SoC, standard of care

Key issue 8: Population used for transition probabilities

To derive transition probabilities, company prefers paired liver biopsy cohort, EAG prefers ITT

	Company preferred population	EAG preferred population
Preferred population for deriving transition probabilities	PLB-W52 F2, F3 (N=739)	mITT-LB-W52 (N=955)
Description	mITT-W52 minus: • N=173 without complete biopsy records at baseline and at week 52 • N=43 stage F1B fibrosis	mITT-W52 (primary analysis) minus N=11 with delayed week 52 biopsy
Rationale	Transition probabilities could not be derived for patients with incomplete data	PLB-W52 cohort unlikely to be representative of full trial cohort
MASH resolution with no worsening of fibrosis (primary analysis), Risk difference		
Resmetirom 80mg vs placebo	[redacted]	16.4 (95% CI, 11.00 to 21.8)
Resmetirom 100mg vs placebo	[redacted]	20.7 (95% CI, 15.3 to 26.2)
Fibrosis improvement with no worsening of NAS (primary analysis), Risk difference		
Resmetirom 80mg vs placebo	[redacted]	10.2 (95% CI, 4.8 to 15.7)
Resmetirom 100mg vs placebo	[redacted]	11.8 (95% CI, 6.4 to 17.2)

Which population is most appropriate to inform transition probabilities?

Links to baseline characteristics and company and EAG positions

Abbreviations: CI, confidence interval; EAG, external assessment group; NAS, non-alcoholic fatty liver disease activity score; MASH, metabolic dysfunction-associated steatohepatitis

Key issue 9: Repeated application of transition probabilities

Company and EAG have different approaches to extrapolating beyond 12-month follow-up data

Company- and EAG-preferred assumptions for MASH resolution after year 1

	Company	EAG
Preferred assumption for MASH resolution after year 1	Repeat application of 12-month MASH resolution transition probabilities in both arms for entire time horizon	Assume MASH resolution occurs only in first annual cycle of model in both arms
Rationale	• Constant annual rate of MASH resolution is biologically and clinically plausible and there is no expectation of treatment effect waning	• Company biological rationale relies on several assumptions not empirically established • Evidence from long-term follow-up of SoC patients that weight loss plateaus after first year • MAESTRO-NASH PD data shows that reductions in liver fat occur within 16 weeks, indicating early biological effect

Clinical expert comments at Technical Engagement:

Clinical expert 1:

- Limited data to support or refute assumption of same MASH resolution probability throughout time horizon.
- MASH resolution would tend to happen within first year of treatment, but fibrosis improvement would be slower.

Clinical expert 2:

- Would expect some plateauing of weight loss over time, but likely to be considerable inter-individual variation.

- Is a constant annual probability of MASH resolution biologically and clinically plausible?
- How should MASH resolution be modelled after year 1?

Abbreviations: MASH, metabolic dysfunction-associated steatohepatitis; PD, pharmacodynamic; SoC, standard of care; THR-β; thyroid hormone receptor-beta

Key issue 10: Transition probabilities to advanced liver complications

Company- and EAG-preferred annual probabilities to advanced liver complications

Transition	Company preferred probability and source	EAG preferred probability and source
F3 to DCC	0.029 (Davidson et al)	0.006 (Vilar-Gomez et al)
F3 to HCC	0.002 (Vilar-Gomez et al)	0.002 (Vilar-Gomez et al)
F4 to DCC	0.076 (Davidson et al)	0.063 (Vilar-Gomez et al)
F4 to HCC	0.057 (Shang et al, Table 4)	0.031 (Shang et al, Table 3)
DCC to HCC	0.043 (Shang et al, Table 4)	0.029 (Shang et al, Table 3)
DCC to LT (Year 1)	0.018 (Shang et al, Table 4)	0.020 (Shang et al, Table 3)
DCC to LT (Year 2+)	0.014 (Shang et al, Table 4)	0.004 (Shang et al, Table 3)

EAG

F3 to DCC and F4 to DCC:

- EAG notes that data from Davidson et al is unpublished and not reported in manuscript
- Davidson et al F3 to DCC value is substantially higher than reported elsewhere → EAG prefers to use Vilar-Gomez et al value for F3 to DCC. For consistency, EAG also prefers Vilar-Gomez et al for F4 to DCC transition

Transitions informed by Shang et al

- EAG concerned that specific data used from Shang et al may be inappropriate as company calculations rely on events from Year 2+ in Table 4 where the at-risk period is undefined. EAG prefers to use data from Table 3 of Shang et al, which reports cumulative incidence over 5 years.

Which transition probabilities should be used for advanced liver complications?

Abbreviations: DCC, decompensated cirrhosis; F3, fibrosis stage 3; F4, fibrosis stage 4/compensated cirrhosis; HCC, hepatocellular carcinoma; LT, liver transplant

Key issue 11: Utility values and MASH resolution increment

Link to expert comments

Background

- During TE, company accepted EAG recommendation to use MAESTRO-NASH trial-derived values for F1-F3 (with and without MASH resolution) and Papatheodoridi et al for F4 (compensated cirrhosis)
- Company and EAG differ in modelling approach: company prefers beta distribution, EAG prefers Gaussian

Company- and EAG- preferred utilities

Health state	Company utility	EAG utility	Papatheodoridi
NAFL	[redacted]	[redacted]	0.786
F0 (MASH unresolved)	[redacted]	[redacted]	0.786
F1 (MASH unresolved)	[redacted]	[redacted]	0.786
F1 (MASH resolved)	[redacted]	[redacted]	0.786
F2 (MASH unresolved)	[redacted]	[redacted]	0.786
F2 (MASH resolved)	[redacted]	[redacted]	0.786
F3 (MASH unresolved)	[redacted]	[redacted]	0.777
F3 (MASH resolved)	[redacted]	[redacted]	0.777
F4 CC	[redacted]	0.725	0.725
DCC	0.540	0.540	-

EAG

F0 to F3

- Company mean utility values not fully consistent with disease progression
- Prefers to assume F0 to F3 utilities independent of fibrosis stage

F4 compensated cirrhosis

- Company crosswalked Papatheodoridi et al EQ-5D-5L values to 3L. But EAG confirmed with authors that values were already crosswalked to 3L

MASH resolution increment

- Considers evidence for independent utility benefit weak but retained in base case

- For F0 to F3 utility values, which modelling approach is most appropriate? Which F4 compensated cirrhosis utility value is most appropriate?
- Should a MASH resolution increment be applied?

Abbreviations: CC, compensated cirrhosis; DCC, decompensated cirrhosis; EAG, external assessment group; MASH, metabolic dysfunction-associated steatohepatitis; NAFL, non-alcoholic fatty liver; TE, technical engagement

Key issue 12: Extrahepatic treatment effects

EAG prefers to assume no further treatment-related change in BMI after year 1

	Company position	EAG position
LDL-C and HDL-C	• Trial-based changes in LDL-C and HDL-C applied in first cycle, then from cycle 2 evolve according to background trends	• Company approach assumes permanent treatment-related difference in LDL-C and HDL-C • No statistically significant difference in HDL-C observed in MAESTRO-NASH
BMI	• BMI evolves annually in the model based on background trends derived from NHS Digital population data, combined with modest treatment effects observed in trial while patients on therapy.	• Prefers to assume no further treatment-related change in BMI after year 1 • Model imposes persistent and increasing treatment effect on BMI, resulting in continuous weight decline for all patients over entire time horizon in both arms → not clinically plausible
CVD event risks	• Risk of CVD events calculated using risk equations, which are linked to fibrosis stage. • Considers CVD structure conservative, limiting risk increases largely to people with ALD or ongoing inflammatory activity.	• Limited evidence to support existence of independent effect of fibrosis stage on CVD outcomes → not appropriate to model fibrosis stage as directly affecting CVD event risks

How should LDL-C, HDL-C and BMI be modelled after year 1?
Is it appropriate to model fibrosis stage as directly affecting CVD event risks?

Abbreviations: ALD, advanced liver disease; BMI, body mass index; CVD, cardiovascular disease; HDL-C, high-density lipoprotein cholesterol; LDL-C, low-density lipoprotein cholesterol; MoA, mechanism of action

Resmetirom for treating moderate-to-advanced liver fibrosis (without cirrhosis) caused by metabolic dysfunction-associated steatohepatitis (MASH)

- ❑ Background and key issues
- ❑ Clinical effectiveness
- ❑ Modelling and cost effectiveness
- ✓ **Other considerations**
- ❑ Summary

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Managed access

- **Company has not made a managed access proposal for this topic**
- **Committee cannot make a managed access recommendation unless the company has submitted a proposal and this has been reviewed by NICE.**

The committee can make a recommendation with managed access if:

- the technology cannot be recommended for use because the evidence is too uncertain
- the technology has the **plausible potential** to be cost effective at the **currently agreed price**
- new evidence that could **sufficiently support the case for recommendation** is expected from ongoing or planned clinical trials, or could be collected from people having the technology in clinical practice
- data could feasibly be collected within a reasonable timeframe (up to a **maximum of 5 years**) without **undue burden**.

Uncaptured benefits

Company mentioned:

- System-level benefits of alleviation of resource pressures on NHS from avoidance of CC, DCC, HCC and LT only partially reflected in modelling.
- MASH resolution and fibrosis regression likely to reduce productivity losses associated with MASH.
- Resmetirom demonstrated favourable effects on lipids and blood pressure → long-term cardiometabolic benefit may be underestimated given limitations of risk equations in MASH and limited trial follow-up data.
- Multiple disease-specific HRQoL measures collected in MAESTRO-NASH → meaningful improvements demonstrated in domains that are only partially reflected in EQ-5D, e.g. fatigue, emotional wellbeing, disease-related worry, and stigma.
- Access to effective and simple-to-take pharmacotherapy may address some health inequalities. MASH disproportionately affects populations with multiple comorbidities and incidence of fatty liver-related death highest in groups with higher deprivation.

Abbreviations: CC, compensated cirrhosis; DCC, decompensated cirrhosis; HCC, hepatocellular carcinoma; HRQoL, health-related quality of life; LT, liver transplant; MASH, metabolic dysfunction-associated steatohepatitis; T2DM, type 2 diabetes

Resmetirom for treating moderate-to-advanced liver fibrosis (without cirrhosis) caused by metabolic dysfunction-associated steatohepatitis (MASH)

- ❑ Background and key issues
- ❑ Clinical effectiveness
- ❑ Modelling and cost effectiveness
- ❑ Other considerations
- ✓ **Summary**

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Summary of company and EAG base case assumptions (1/2)

Assumption	Company base case	EAG base case
Population used for transition probabilities	PLB-W52 F2/F3	mITT-LB-W52
Eligibility assessment costs	No eligibility assessment costs	Include additional costs in resmetirom arm (1 extra visit and 1 FibroScan VCTE)
Stopping rules	No additional costs on stopping treatment	Add 3 months resmetirom costs for F0/F1 regression or F3 progression, plus 1 visit and 1 FibroScan
MASH resolution	Cycle 1 transitions for MASH repeated across entire time horizon	MASH resolution only possible in first cycle/year of model
Using 80mg and 100mg dose data	Treatment effects modelled separately for 80mg and 100mg doses	Treatment effect pool data from 80mg and 100mg doses
Utilities	• Utility values for F0 to F3 sourced from MAESTRO-NASH • F4 CC utility set to 0.64 • Include MASH increment	• Utility values for F0 to F3 sourced from Gaussian analysis of MAESTRO-NASH independent of fibrosis stage • F4 CC utility set to 0.725 • Include MASH increment

Abbreviations: CC, compensated cirrhosis; ICER, incremental cost-effectiveness ratio; MASH, metabolic dysfunction-associated steatohepatitis; VCTE, Vibration-Controlled Transient Elastography

Summary of company and EAG base case assumptions (2/2)

Assumption	Company base case	EAG base case
Transitions to advanced liver complications	• Transition probabilities for F3 to DCC and F4 to DCC based on Davidson et al. • Transition probabilities for F4 to HCC, DCC to HCC, DCC to liver transplant, and HCC to liver transplant are based on Shang et al. (Table 4).	• Transition probabilities for F3 to DCC and F4 to DCC based on Vilar-Gomez et al. • Transition probabilities for F4 to HCC, DCC to HCC, DCC to liver transplant, and HCC to liver transplant based on Shang et al. (Table 3).
BMI	Repeat cycle 1 weight changes throughout time horizon	No further treatment-related change in BMI applied after year 1
Base case ICER (deterministic)	£35,034 per QALY gained (EAG corrected)	£57,755 per QALY gained

Abbreviations: BMI, body mass index; DCC, decompensated cirrhosis; HCC, hepatocellular carcinoma; HDL-C, high-density lipoprotein cholesterol; ICER, incremental cost-effectiveness ratio; LDL-C, low-density lipoprotein cholesterol

Cost-effectiveness results are presented in Part 2 of the committee meeting because of the confidential price of resmetirom

Resmetirom for treating moderate-to-advanced liver fibrosis (without cirrhosis) caused by metabolic dysfunction-associated steatohepatitis (MASH)

Supplementary appendix

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Key issues and questions for committee (1/3)

Issue	ICER impact
Key issue 1: Treatment pathway/current and anticipated use of GLP-1 RAs in the UK • Would the diet and exercise counselling offered alongside resmetirom differ to what is currently provided as part of SoC? • Would resmetirom be prescribed in secondary care or primary care? • Would resmetirom be started in parallel with management of the metabolic syndrome or subsequently? How should this be reflected in the model?	Unknown
Key issue 2: Use of resmetirom in clinical practice • What tests are used in clinical practice for MASH? • Is it appropriate to assume no additional treatment eligibility costs in the resmetirom arm? • Is the company's proposed clinical algorithm for initiating treatment and evaluating response appropriate? • Is it appropriate to stop resmetirom treatment when fibrosis regresses to F0 or F1? • Is it appropriate to stop resmetirom treatment when people progress to advanced liver disease, including CC? • Are there any other considerations for discontinuation that should be incorporated into the modelling? • Should repeat testing costs be applied to assess treatment response? If so, is one extra outpatient FibroScan assessment sufficient, and should 3 or 6 months of additional resmetirom cost be assumed?	Large

Abbreviations: CC, compensated cirrhosis; GLP-1 RA, glucagon-like peptide-1 receptor agonist; ICER, incremental cost-effectiveness ratio; MASH, metabolic dysfunction-associated steatohepatitis; NIT, non-invasive test; T2DM, type 2 diabetes mellitus

Key issues and questions for committee (2/3)

Issue	ICER impact
Key issue 3: Generalisability of the clinical trial • How is the use of NITs likely to affect the generalisability of the observed treatment effect to UK clinical practice? • How does the requirement for ≥3 CMRFs affect the generalisability of MAESTRO-NASH? • Is MAESTRO-NASH acceptable for decision making?	Unknown
Key issue 4: Reliance on surrogate endpoints • Are fibrosis improvement and MASH resolution acceptable surrogate endpoints? • To what extent does the reliance on surrogate endpoints generate uncertainty?	Unknown
Key issue 5: Validation of the company model • Is the company's model acceptable for decision making?	Unknown
Key issue 6: NIT criteria as proxy for fibrosis stage in the model • Is it appropriate to use the proposed NIT criteria as proxy for histologically assessed fibrosis stage in the model?	Unknown
Key issue 7: Natural history and face validity of model progression rates • Is it appropriate to validate progression rates in the model using NH cohorts from Le et al or Ng et al? • Are there any other NH studies that could be used to validate the model progression rates? • Do the model's predictions about progression under standard care have face validity?	Large

Abbreviations: CMRF, cardiometabolic risk factor; ICER, incremental cost-effectiveness ratio; MASH, metabolic dysfunction-associated steatohepatitis; NIT, non-invasive test;

Key issues and questions for committee (3/3)

Issue	ICER impact
Key issue 8: Population for transition probabilities • Which population is most appropriate to inform transition probabilities?	Moderate
Key issue 9: Repeated application of transition probabilities • Is a constant annual probability of MASH resolution biologically and clinically plausible? • How should MASH resolution be modelled after year 1?	Moderate
Key issue 10: Transition probabilities to advanced liver complications • Which transition probabilities should be used for advanced liver complications?	Moderate
Key issue 11: Utility values and MASH resolution increment • For F0 to F3 utility values, which modelling approach is most appropriate? • Which F4 compensated cirrhosis utility value is most appropriate? • Should a MASH resolution increment be applied?	Moderate
Key issue 12: Extrahepatic treatment effects • How should LDL-C, HDL-C and BMI be modelled after year 1? • Is it appropriate to model fibrosis stage as directly affecting CVD event risks?	Small

Abbreviations: BMI, body mass index; CVD, cardiovascular disease; HDL-C, high-density lipoprotein cholesterol; ICER, incremental cost-effectiveness ratio; LDL-C, low-density lipoprotein cholesterol; MASH, metabolic dysfunction-associated steatohepatitis;

Issues resolved at Technical Engagement

Issue	Resolved at TE?
Misinterpretation of Singh et al (2015)	Yes
Health state costs and interpretation of the Davidson study	Yes
Differences in dosing of resmetirom between trial and clinical practice	Yes
Deviations from HTA lab recommendations	Yes

Abbreviations: HTA, health technology assessment; ICER, incremental cost-effectiveness ratio; TE, technical engagement

Old vs updated nomenclature

Old nomenclature:		Updated nomenclature:
NAFLD (non-alcoholic fatty liver disease)	→	MASLD (metabolic dysfunction-associated steatotic liver disease)
NASH (non-alcoholic steatohepatitis)	→	MASH (metabolic dysfunction-associated steatohepatitis)

Abbreviations: MASH, metabolic dysfunction-associated steatohepatitis; MASLD, metabolic dysfunction-associated steatotic liver disease; NASH, non-alcoholic steatohepatitis; NAFLD, non-alcoholic fatty liver disease

Glossary

ALD, advanced liver disease (characterised by CC, DCC, HCC, or need for liver transplant)

CC, compensated cirrhosis (severely scarred liver that can still maintain its core functions)

DCC, decompensated cirrhosis (liver scarring has progressed to a point that the liver can no longer maintain its core functions)

ELF, Enhanced Liver Fibrosis (blood test that combines three serum biomarkers)

FIB-4, Fibrosis-4 Index (non-invasive clinical score that combines age, AST, ALT and platelet count)

FibroScan VCTE, vibration-controlled transient elastography (imaging-based ultrasound test)

HCC, hepatocellular carcinoma

MASH/NASH, metabolic dysfunction-associated steatohepatitis/non-alcoholic steatohepatitis (Active form of disease characterised by hepatocellular ballooning and/or lobular inflammation)

MASLD/NAFLD, metabolic dysfunction-associated steatotic liver disease/ non-alcoholic fatty liver disease (Steatotic liver disease and presence of ≥ 1 cardiometabolic criterion, with exclusion of excessive alcohol intake and other causes of steatosis)

NAS, non-alcoholic fatty liver disease activity score

NIT, non-invasive test

Link to main slides

Summary of current non-invasive diagnostic testing for fibrosis caused by MASH

1st line test

FIB-4	Simple, non-invasive clinical score that can be usually calculated from routine blood tests. Combines age, AST, ALT and platelet count

2nd line test

FibroScan VCTE	Imaging-based ultrasound test

OR

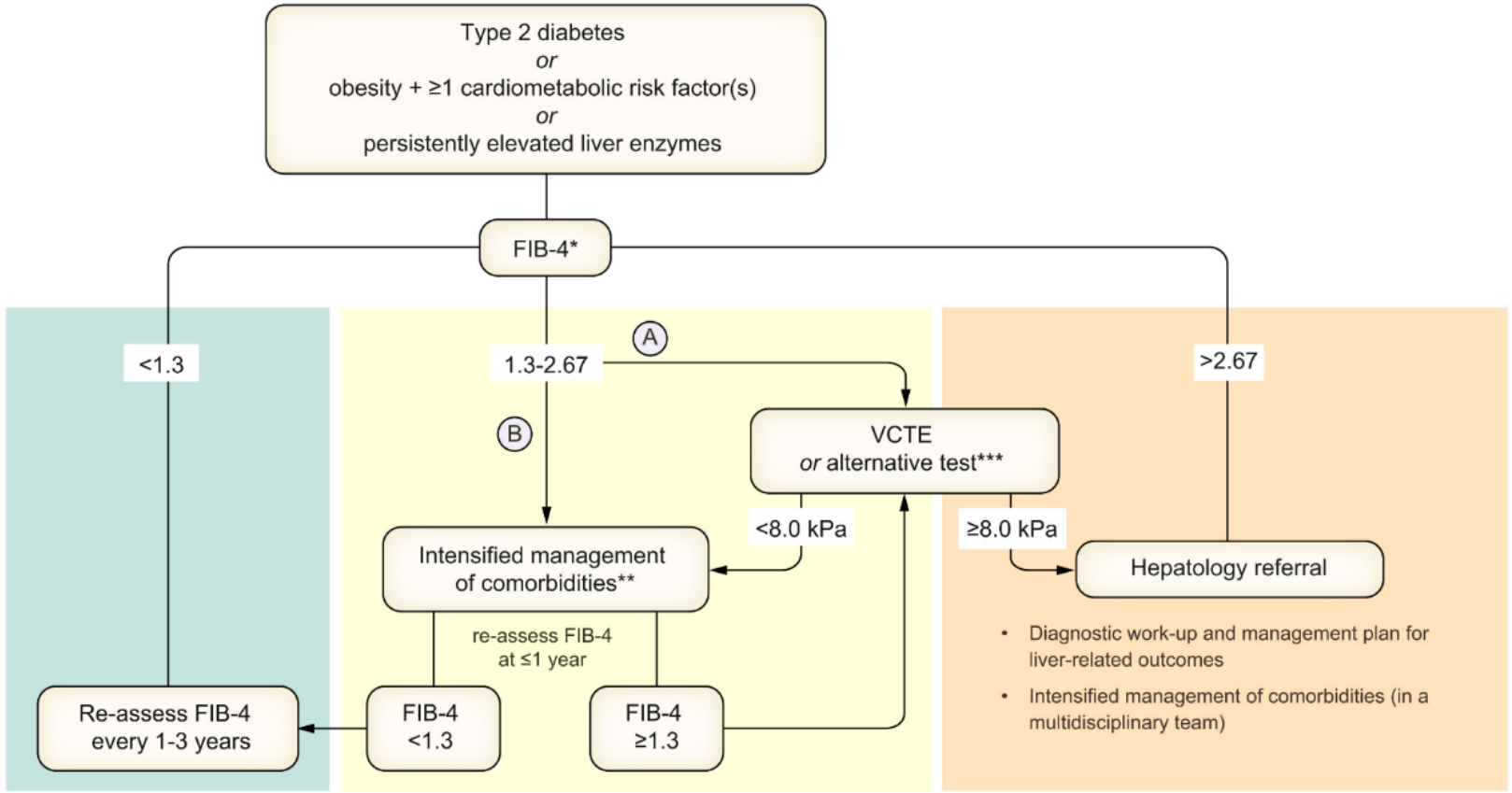
ELF	Blood test that combines three serum biomarkers

Abbreviations: ALT, Alanine Aminotransferase; AST, Aspartate Aminotransferase; ELF, enhanced liver fibrosis; FIB-4, Fibrosis-4 index; MASH, metabolic dysfunction-associated steatohepatitis; VCTE, Vibration-Controlled Transient Elastography

Diagnostic pathway for MASH

Link to treatment pathway

Proposed 2024 EASL–EASD–EASO strategy for non-invasive evaluation of advanced fibrosis risk and liver-related outcomes in individuals with metabolic risk factors or suspected steatotic liver disease



* FIB-4 thresholds valid for age ≤65 years (for age >65 years: lower FIB-4 cut-off is 2.0)
** *e.g.* lifestyle intervention, treatment of comorbidities (*e.g.* GLP1RA), bariatric procedures
*** *e.g.* MRE, SWE, ELF, with adapted thresholds
Ⓐ and Ⓑ are options, depending on medical history, clinical context and local resources

Abbreviations: EASD, European Association for the Study of Diabetes; EASL, European Association for the Study of the Liver; EASO, European Association for the Study of Obesity

GLP-1 RA NICE recommendations to date (1/2)

Link to main slides

TA875 Semaglutide for managing overweight and obesity: Semaglutide is recommended as an option for weight management, including weight loss and weight maintenance, alongside a reduced-calorie diet and increased physical activity in adults, only if:

- it is used for a maximum of 2 years, and within a specialist weight management service providing multidisciplinary management of overweight or obesity (including but not limited to tiers 3 and 4), and
- they have at least 1 weight-related comorbidity and:
  - a body mass index (BMI) of at least 35.0 kg/m2, or
  - a BMI of 30.0 kg/m2 to 34.9 kg/m2 and meet the criteria for referral to specialist overweight and obesity management services in NICE's guideline on overweight and obesity management.

Use a lower BMI threshold (usually reduced by 2.5 kg/m2) for people from South Asian, Chinese, other Asian, Middle Eastern, Black African or African-Caribbean ethnic backgrounds.

TA1026 Tirzepatide for managing overweight and obesity: Tirzepatide is recommended as an option for managing overweight and obesity, alongside a reduced-calorie diet and increased physical activity in adults, only if they have:

- an initial body mass index (BMI) of at least 35 kg/m2 and
- at least 1 weight-related comorbidity

Use a lower BMI threshold (usually reduced by 2.5 kg/m2) for people from South Asian, Chinese, other Asian, Middle Eastern, Black African or African-Caribbean ethnic backgrounds.

GLP-1 RA NICE recommendations to date (2/2)

Link to main slides

TA924 Tirzepatide for treating type 2 diabetes: Tirzepatide is recommended for treating type 2 diabetes alongside diet and exercise in adults when it is insufficiently controlled only if:

- triple therapy with metformin and 2 other oral antidiabetic drugs is ineffective, not tolerated or contraindicated, and
- they have a body mass index (BMI) of 35 kg/m2 or more, and specific psychological or other medical problems associated with obesity, or
- they have a BMI of less than 35 kg/m2, and:
  - insulin therapy would have significant occupational implications, or
  - weight loss would benefit other significant obesity-related complications.

Use lower BMI thresholds (usually reduced by 2.5 kg/m2) for people from South Asian, Chinese, other Asian, Middle Eastern, Black African or African-Caribbean family backgrounds.

ID6441 Semaglutide for reducing the risk of major adverse cardiovascular events in people with cardiovascular disease and overweight or obesity: Semaglutide (up to a maintenance dose of 2.4 mg once weekly) can be used, within its marketing authorisation, alongside a reduced-calorie diet and increased physical activity, as an option for reducing the risk of a major adverse cardiovascular event (that is, cardiovascular death, non fatal myocardial infarction or non-fatal stroke) in adults with both:

- established cardiovascular disease (CVD), defined as at least 1 of the following:

− previous myocardial infarction

− previous ischaemic or haemorrhagic stroke

− symptomatic peripheral arterial disease (they have intermittent claudication with an ankle-brachial index of less than 0.85 at rest, or have had a peripheral arterial revascularisation procedure or an amputation because of atherosclerotic disease), and

- a body mass index (BMI) of at least 27 kg/m2.

MAESTRO-NASH baseline characteristics (1/3)

Link to main slides

Demographic and baseline characteristics (mITT-W52 population, n = 966)

	Resmetirom 80 mg (n = 322)	Resmetirom 100 mg (n = 323)	Placebo (n = 321)
Age, years	55.9 ± 11.5	57.0 ± 10.8	57.1 ± 10.5
Sex, male, no. (%)†	140 (43.5)	141 (43.7)	143 (44.5)
Race, no. (%)†			
White	291 (90.4)	291 (90.1)	281 (87.5)
Black or African American	5 (1.6)	5 (1.5)	9 (2.8)
Asian	10 (3.1)	9 (2.8)	9 (2.8)
Other‡	12 (3.7)	11 (3.4)	18 (5.6)
Missing	4 (1.2)	7 (2.2)	4 (1.2)
Ethnicity, Hispanic or Latino, no. (%)†	71 (22.0)	81 (25.1)	52 (16.2)
Body weight, kg	100.1 ± 22.3	101.9 ± 22.9	100.2 ± 23.1
BMI, kg/m^2	35.5 ± 6.4	36.2 ± 7.4	35.3 ± 6.5
T2DM, no. (%)	224 (69.6)	213 (65.9)	210 (65.4)
Hypertension, no. (%)	243 (75.5)	254 (78.6)	257 (80.1)
Dyslipidaemia, no. (%)	229 (71.1)	236 (73.1)	224 (69.8)
Hypothyroidism, no. (%)§	39 (12.1)	46 (14.2)	45 (14.0)
History of atherosclerotic cardiovascular disease (ASCVD), no. (%)	20 (6.2)	23 (7.1)	14 (4.4)

NICE

Abbreviations: ALT, alanine aminotransferase; ASCVD, atherosclerotic cardiovascular disease; AST, aspartate aminotransferase; BMI, body mass index; CAP, Controlled Attenuation Parameter; F1-F3, fibrosis stages 1-3; GGT, gamma-glutamyl transferase; LDL-C, low-density lipoprotein-cholesterol; LSM, liver stiffness measurement; MRE, magnetic resonance elastography; MRI-PDFF, MRI-based proton density fat fraction; NAS, NAFLD Activity Score; T2DM, type 2 diabetes mellitus; VCTE, Vibration-Controlled Transient Elastography

MAESTRO-NASH baseline characteristics (2/3)

Link to main slides

Additional baseline characteristics (mITT-W52 population, n = 966)

	Resmetirom 80 mg (n = 322)	Resmetirom 100 mg (n = 323)	Placebo (n = 321)
10-year ASCVD risk score, %¶	14.7 ± 12.0	14.5 ± 12.1	15.4 ± 11.6
FibroScan VCTE/LSM, kPall	13.3 ± 6.8	13.6 ± 7.1	12.9 ± 5.5
Median (Q1, Q3)	11.5 (9.5, 14.9)	11.9 (9.5, 15.9)	11.7 (9.4, 14.8)
FibroScan CAP, dB/m**	346.1 ± 37.2	349.4 ± 38.7	347.2 ± 37.0
MRI-PDFF, %††	18.2 ± 6.8	17.2 ± 6.6	17.8 ± 6.8
MRE, kPa	3.5 ± 0.94	3.7 ± 1.1	3.5 ± 0.97
FIB-4‡‡	1.4 ± 0.68	1.5 ± 0.73	1.4 ± 0.68
LDL-C, mg/dL	106.6 ± 37.4	103.0 ± 36.8	106.8 ± 41.1
ALT, U/L	52.8 ± 27.3	56.3 ± 34.0	54.7 ± 34.8
AST, U/L	38.2 ± 19.3	42.5 ± 25.2	40.7 ± 24.6
Gamma-glutamyl transferase (GGT), U/L	84.3 ± 111.3	84.6 ± 99.0	75.7 ± 85.0
Baseline liver biopsy, no. (%)			
NAS ≥ 5§§	266 (82.6)	288 (89.2)	253 (78.8)
F1B fibrosis¶¶	16 (5.0)	15 (4.6)	18 (5.6)
F2 fibrosis¶¶	107 (33.2)	100 (31.0)	112 (34.9)
F3 fibrosis¶¶	194 (60.2)	203 (62.8)	186 (57.9)

Abbreviations: ALT, alanine aminotransferase; ASCVD, atherosclerotic cardiovascular disease; AST, aspartate aminotransferase; BMI, body mass index; CAP, Controlled Attenuation Parameter; F1-F3, fibrosis stages 1-3; GGT, gamma-glutamyl transferase; LDL-C, low-density lipoprotein-cholesterol; LSM, liver stiffness measurement; MRE, magnetic resonance elastography; MRI-PDFF, MRI-based proton density fat fraction; NAS, NAFLD Activity Score; T2DM, type 2 diabetes mellitus; VCTE, Vibration-Controlled Transient Elastography

MAESTRO-NASH baseline characteristics (3/3)

Link to main slides

Additional baseline characteristics (mITT-W52 population, n = 966)

	Resmetirom 80 mg (n = 322)	Resmetirom 100 mg (n = 323)	Placebo (n = 321)
HbA1c, %	6.6 ± 1.1	6.6 ± 1.1	6.5 ± 1.0
Total cholesterol, mg/dL	179.6 ± 43.4	176.9 ± 46.0	180.0 ± 50.0
HDL-C, mg/dL	43.8 ± 12.6	44.0 ± 12.9	43.8 ± 13.3
Apoliprotein B (ApoB), mg/dL	98.4 ± 27.8	95.9 ± 27.8	97.8 ± 32.0
Lipoprotein(a) (Lp(a)), nmol/L	44.7 ± 61.1	43.8 ± 60.8	42.2 ± 62.7
ELF score	9.7 ± 0.89	9.8 ± 0.86	9.7 ± 0.86
Triglycerides, mg/dL	189.2 ± 112.5	188.7 ± 153.8	184.1 ± 125.8
Alkaline phosphatase, U/L	74.9 ± 27.1	73.9 ± 23.0	71.5 ± 23.7
Bilirubin, mg/dL†	0.63 ± 0.27	0.66 ± 0.32	0.66 ± 0.31
Platelets, 10^9/L†	236.6 ± 67.9	230.6 ± 59.1	233.6 ± 60.4
Albumin, g/dL†	4.4 ± 0.32	4.3 ± 0.27	4.4 ± 0.29
Homeostatic Model Assessment of Insulin Resistance (HOMA-IR)	11.9 ± 11.8	10.6 ± 8.3	11.0 ± 12.3
GLP-1 RA, no. (%)	54 (16.8)	41 (12.7)	42 (13.1)
SGLT2i, no. (%)	55 (17.1)	39 (12.1)	36 (11.2)
Statin, no. (%)	149 (46.3)	166 (51.4)	158 (49.2)

Abbreviations: ApoB, apolipoprotein B; ELF, Enhanced Liver Fibrosis; GLP-1 RA, glucagon-like peptide-1 receptor agonist; HbA1c, glycated haemoglobin; HDL-C, high-density lipoprotein-cholesterol; HOMA-IR, homeostatic model assessment of insulin resistance; Lp(a), lipoprotein(a); SGLT2i, sodium–glucose cotransporter-2 inhibitors.

Overview of MAESTRO-NAFLD-1

MAESTRO-NAFLD-1 study design and outcomes

	MAESTRO-NAFLD-1
Study type	Placebo-controlled phase 3 RCT
Population	Adults with MASLD and presumed MASH
Intervention	80mg and 100mg resmetirom; oral tablet, once daily
Comparator	Placebo; oral tablet, once daily
Duration	52 weeks
Primary outcome	Incidence of adverse events
Locations	77 locations in the United States
Used in model?	No

Abbreviations: MASLD, metabolic dysfunction-associated steatotic liver disease; MASH, metabolic dysfunction-associated steatohepatitis; RCT, randomised controlled trial

‘Fast progressor’ phenotype

Company cites emerging evidence on ‘fast progressor’ phenotype

Company response at Technical Engagement:

- Cites literature showing ~18–25% of patients progress quickly and highlights emerging research using biomarkers, polygenic scores, and clustering to explore factors associated with rapid progression.
- TARGET-NASH (longitudinal cohort study) analyses suggest patients with higher baseline fibrosis experience faster onset of adverse liver outcomes.
- Cites evidence that cardiometabolic factors, particularly T2DM and hypertension, are key drivers of fibrosis severity, disease progression and liver-related outcomes.
- Findings support concept of fast progression but validated tools for identifying patients in practice not available.

EAG response at Technical engagement:

- Acknowledges that MASH is a heterogeneous condition and some patients may progress faster than others.
- Recognises that cited literature suggests some patients may represent phenotype of “fast progressors”
- However, evidence is emergent and there is no established clinical consensus on clearly defined phenotype.
- Importantly, there are currently no validated tools to reliably identify such a patient group, and therefore no robust basis on which to target treatment to those most likely to benefit.

Clinical expert comments :

- Clinical expert 1: Some people seem to progress more rapidly than others and some have ALD at younger age.
- Clinical expert 2: Higher BMI, T2DM, hypertension and elevated AST/ALT risk factors for faster progression but subgroup not currently easily identified in clinical practice.

- Is a ‘fast progressor’ phenotype identifiable in clinical practice?
- If so, is this subgroup relevant for decision making?

Abbreviations: ALD, advanced liver disease; AST/ALT, aspartate aminotransferase/alanine aminotransferase; BMI, body mass index; MASH, metabolic dysfunction-associated steatohepatitis; T2DM, Type 2 diabetes Mellitus

Link to main slides

Comparison of baseline characteristics for MAESTRO-NASH cohorts

	mITT-W52 (N=966)*	mITT-LB-W52 (N=955)	PLB-W52 (N=782)	PLB-W52 with F2/F3 (N=739)
Sample selection	Randomised, received at least 1 treatment dose	mITT-W52 minus N=11 delayed week 52 biopsies	mITT-W52 minus N=173 with no baseline biopsy (N=15) and/or no week 52 biopsy (N=166)	PLB-W52 minus N=43 stage F1B fibrosis
Liver biopsy status				
Patients with baseline biopsy	[redacted]	[redacted]	782	739
Patients with week 52 liver biopsy	[redacted]	[redacted]	782	739
Baseline characteristics				
Age, mean (years)	56.6	[redacted]	[redacted]	[redacted]
Female (%)	56.1	[redacted]	[redacted]	[redacted]
Type 2 diabetes mellitus (%)	67.0	[redacted]	[redacted]	[redacted]
Hypertension (%)	78.1	[redacted]	[redacted]	[redacted]
Fibrosis stage F1B (%)	5.1	[redacted]	[redacted]	[redacted]
Fibrosis stage F2 (%)	33.0	[redacted]	[redacted]	[redacted]
Fibrosis stage F3 (%)	60.4	[redacted]	[redacted]	[redacted]

EAG-preferred cohort

Company-preferred cohort

Key issue 8: Summary of EAG and company positions

Link to main slides

EAG position

- Company's PLB-W52 cohort unlikely to be representative of full trial cohort (biased transition probabilities).
- PLB-W52 population likely subject to attrition bias: company's analytical approach assumes that missing data are missing completely at random but this is highly implausible, as sample availability is related to trial discontinuations, which are often due to adverse events or lack of treatment response.
- Proportion of patients with F3 fibrosis higher in PLB-W52 vs mITT-LB-W52 cohort (66.4% vs 60.4%).
- EAG prefers mITT-LB–W52 (reflects the pre-specified primary analysis and unbiased treatment effect.
- Acknowledges that company has explored robustness of results using different imputation methods but these analyses do not resolve concern that missing data may have influenced magnitude of the treatment effect

Company position

- PLB-W52 cohort necessary because transition probabilities could not be derived for patients with incomplete data. In mITT-LB-W52 where two histological assessors disagreed on MASH resolution status, "MASH resolution 0/1" variable recorded as 0.5, which could not be programmed in microsimulation.
- Highly unlikely that PLB-W52 unfairly favours resmetirom → Missingness not always attributable to AEs or loss of response, and discontinuation due to perceived loss of response unlikely to be major contributor to missing data because of requirement for histological assessment.
- Positive treatment effect for resmetirom is observed consistently across pre-specified subgroups and appears robust to alternative approaches for handling missing data.
- Demographic and baseline characteristics of PLB–W52 and mITT-LB–W52 cohorts broadly comparable.

Abbreviations: AE, adverse event; MASH, metabolic dysfunction-associated steatohepatitis

Link to main slides

Proportion of trial population meeting treatment eligibility criteria proposed at BASL MASLD SIG consensus meeting

Noureddin 2024 thresholds and M-NASH baseline NITs (VCTE, ELF, Magnetic Resonance Elastography (MRE)) (n = 966)

NIT / Threshold	Expert Recommendation	Resmetirom 100mg (n = 323)	Resmetirom 80mg (n = 322)	Placebo (n = 321)
VCTE ≤ 9.9 kPa	No recommendation provided	[redacted]	[redacted]	[redacted]
VCTE (≥ 10, ≤ 15 kPa)	Treat	[redacted]	[redacted]	[redacted]
VCTE (≥ 15.1, ≤ 19.9 kPa)	Consider	[redacted]	[redacted]	[redacted]
VCTE (≥ 20 kPa)	Do Not Treat	[redacted]	[redacted]	[redacted]
MRE ≤ 3.2 kPA	No recommendation provided	[redacted]	[redacted]	[redacted]
MRE (≥ 3.3, ≤ 4.2 kPa)	Treat	[redacted]	[redacted]	[redacted]
MRE (≥ 4.3, ≤ 4.9 kPa)	Consider	[redacted]	[redacted]	[redacted]
MRE (≥ 5 kPa)	Do Not Treat	[redacted]	[redacted]	[redacted]
ELF ≤ 9.1 kPA	No recommendation provided	[redacted]	[redacted]	[redacted]
ELF (≥ 9.2, ≤ 10.4)	Treat	[redacted]	[redacted]	[redacted]
ELF (≥ 10.5, ≤ 11.3)	Consider	[redacted]	[redacted]	[redacted]
ELF (> 11.3)	Do Not Treat	[redacted]	[redacted]	[redacted]
VCTE	NA	[redacted]	[redacted]	[redacted]
MRE	NA	[redacted]	[redacted]	[redacted]
ELF	NA	[redacted]	[redacted]	[redacted]
VCTE or MRE or ELF	Treat, detected by at least one NIT	[redacted]	[redacted]	[redacted]

Abbreviations: BASL, The British Association for the Study of the Liver; ELF, Enhanced Liver Fibrosis; kPa, Kilopascal; MASLD, metabolic dysfunction-association steatotic liver disease; MRE, magnetic resonance elastography; NIT, non-invasive test; VCTE, Vibration-Controlled Transient Elastography

Company and EAG critiques of natural history studies (1/2)

Link to main slides

Company and EAG critiques of natural history studies

NH study	Study type	Company critique of study	EAG critique of study
Singh et al 2015	Meta-analysis of NAFLD studies, which identified 11 cohort studies including 411 patients	• Authors reported limited ability to estimate fibrosis progression rates in people with intermediate or advanced fibrosis at baseline • People with advanced disease may be less likely to undergo repeat histologic examination → potential underestimation of progression rates in these patients.	• Acknowledges study limitations and recognises potential for bias • Singh et al broadly supports findings in Le et al, indicating that progression to advanced liver disease typically occurs over prolonged period • Limitations do not provide support for assumption that fibrosis progression accelerates at higher fibrosis stages
Ng et al 2022	Meta-analysis of placebo arms from MASH RCTs, which identified 29 studies including 1522 patients	• Suggested as alternative NH source and included in scenario analysis • Across studies, approximately 1/5 of patients experienced progression in a similar time frame as observed in the MAESTRO -NASH (12 months)	No specific critique

Abbreviations: EAG, external assessment group; MASH, metabolic dysfunction-associated steatohepatitis; NAFLD, non-alcoholic fatty liver disease; NH, natural history; RCT, randomised controlled trial; SoC, standard of care

Company and EAG critiques of natural history studies (2/2)

Link to main slides

Company and EAG critiques of natural history studies (continued)

NH study	Study type	Company critique of study	EAG critique of study
Le et al 2023	Meta-analysis of NAFLD studies, which identified 54 RCTs and observational studies including 26,738 patients	• Concerns regarding reliability and applicability of study • Rejection as NH source not based solely on the clinical implausibility of findings (that progression slows with advancing fibrosis) but also reflects observations of rapid fibrosis progression in the MAESTRO-NASH advanced fibrosis population • Clinical advice from 10 UK experts across hepatology, gastroenterology, and endocrinology does not support the EAG's interpretation of study findings • Provides evidence from several published sources, including Luthra et al, indicating that incidence of cirrhosis, liver transplantation, and other clinical outcomes increases with fibrosis stage	• Notes company's concerns regarding reliability of NH estimates • While anomalies in calculations are apparent, discrepancies do not invalidate broad conclusions of study. • Findings reported by Le et al suggest that fibrosis progression generally occurs over many years, which contrasts with company's characterisation of this population as requiring urgent intervention • While studies in Le et al represent a heterogeneous population, not clear that these populations are less representative of target population than patients recruited to MAESTRO-NASH • Studies cited by company estimate the risk of clinical outcomes conditional on fibrosis stage at index, rather than the rate of transition between fibrosis stages

Abbreviations: : EAG, external assessment group; NAFLD, non-alcoholic fatty liver disease; NH, natural history; RCT, randomised controlled trial;SoC, standard of care

Key issue 11: Utility values and MASH resolution increment expert comments

Clinical expert comments at Technical Engagement :

- There is a step-change in quality of life when liver disease progresses to compensated cirrhosis, and particularly to decompensation. There are also household impacts and significant burden for close relatives.

Patient expert comments at Technical Engagement :

- Some patients unaware of what fibrosis stage they have unless staging explained to them
- Patients with earlier stage disease often report and fluctuating fatigue, reduced stamina, but many can still maintain work, family responsibilities, and social activities
- Move from F3 to F4 represents noticeable shift in day-to-day life. Compensated cirrhosis brings fatigue, reduced stamina and emotional strain but most people can still manage a degree of independence.
- Move to decompensated cirrhosis often described as a dramatic. Once decompensation occurs, QoL typically deteriorates sharply.
- MASH resolution would lead to a clear, meaningful and life-enhancing improvement in QoL. People feel better physically, think more clearly, participate more in daily life, and experience significant reduction in fear and uncertainty. Even if not all symptoms disappear, shift from active disease to stability described as transformative.
- Carers affected emotionally, socially and financially, and often need to stop work or take time off.

Link to main slides

Abbreviations: MASH, metabolic dysfunction-associated steatohepatitis; QoL, quality of life;