

Single Technology Appraisal

Resmetirom for treating moderate to advanced liver fibrosis (without cirrhosis) caused by metabolic dysfunction-associated steatotic liver disease [ID6529]

Committee Papers

NATIONAL INSTITUTE FOR HEALTH AND CARE EXCELLENCE

SINGLE TECHNOLOGY APPRAISAL

Resmetirom for treating moderate to advanced liver fibrosis (without cirrhosis) caused by metabolic dysfunction-associated steatotic liver disease [ID6529]

Contents:

The following documents are made available to stakeholders:

The [final scope and final stakeholder list](#) are available on the NICE website.

Pre-technical engagement documents

1. [Company submission](#) from Madrigal Pharmaceuticals
2. [Company summary of information for patients \(SIP\)](#) from Madrigal Pharmaceuticals
3. [Clarification questions and company responses](#)
4. [Patient group, professional group and NHS organisation submissions](#) from:
 - a. [British Liver Trust](#)
 - b. [British Association for the Study of the Liver \(BASL\)](#)
 - c. [British Hepatology Pharmacy Group](#)
 - d. [UK Clinical Pharmacy Association](#)
 - e. [NHS England](#)
5. [External Assessment Report](#) prepared by [York Technology Assessment Group](#)
6. [External Assessment Report – factual accuracy check](#)

Post-technical engagement documents

7. [Technical engagement response from company](#)
 - a. [Company response to technical engagement](#)
 - b. [Company response to EAG clarification questions on the company's technical engagement response](#)
8. [Technical engagement responses and statements from experts:](#)
 - a. [Professor Quentin Anstee, Honorary Consultant Hepatologist – clinical expert, nominated by Madrigal Pharmaceuticals UK Ltd](#)
 - b. [Dr Richard Aspinall, Consultant Hepatologist – clinical expert, nominated by NHS England](#)

- c. [Ms Vanessa Hebditch – patient expert, nominated by British Liver Trust](#)
 - d. [Ms Sara Harding – patient expert, nominated by British Liver Trust](#)
9. **[Technical engagement responses from stakeholders:](#)**
 - a. [British Association for the Study of the Liver \(BASL\)](#)
10. **[External Assessment Report critique of company response to technical engagement prepared by York Technology Assessment Group](#)**
 - a. [EAR critique of company Technical Engagement response](#)
 - b. [Addendum 1](#)
 - c. [Addendum 2](#)
 - d. [Addendum 3](#)
11. **[Additional input from Clinical Experts](#)**

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NATIONAL INSTITUTE FOR HEALTH AND CARE EXCELLENCE

Single technology appraisal

**Resmetirom for treating moderate to advanced liver
fibrosis (without cirrhosis) caused by metabolic
dysfunction-associated steatohepatitis [ID6529]**

Company evidence submission

September 2025

File name	Version	Contains confidential information	Date
ID6529 Resmetirom for treating moderate to advanced liver fibrosis (without cirrhosis) caused by metabolic dysfunction- associated steatohepatitis	1	Yes	12 th September 2025

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Company evidence submission: Resmetirom for treating moderate to advanced liver fibrosis (without cirrhosis) (MASLD) ID6529

ID6529 Resmetirom for treating moderate to advanced liver fibrosis (without cirrhosis) caused by metabolic dysfunction- associated steatohepatitis	1	Yes	12th September 2025

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Abbreviations

Abbreviation	Definition
AASLD	American Association for the Study of Liver Diseases
AE	Adverse event
ALEH	Latin American Association for the Study of the Liver
ALT	Alanine aminotransferase
ApoB	Apolipoprotein B
ApoC-III	Apolipoprotein C-III
ASCVD	Atherosclerotic cardiovascular disease
AST	Aspartate aminotransferase
BASL	British Association for the Study of the Liver
BIM	Budget-impact model
BMI	Body mass index
Bol	Burden of illness
BSG	British Society of Gastroenterology
CAP	Controlled Attenuation Parameter
CC	Compensated cirrhosis
CDF	Cancer Drugs Fund
CEA	Cost-effectiveness analysis
CEAC	Cost-effectiveness acceptability curve
CFB	Change from baseline
CHD	Coronary heart disease
CI	Confidence interval
CK-18	Cytokeratin-18
CKD	Chronic Kidney Disease
CLDQ	Chronic Liver Disease Questionnaire
Col	Cost of illness
CPK	Creatine phosphokinase
CPRD	Clinical Practice Research Datalink
CRN	Clinical Research Network
CTCAE	Common Terminology Criteria for Adverse Events
CVD	Cardiovascular disease
DALY	Disability-adjusted life year
DCC	Decompensated cirrhosis
DIO1	Type 1 iodothyronine deiodinase
DIO3	Type 3 iodothyronine deiodinase
DP	Decision problem
DSA	Deterministic sensitivity analysis
DSU	Decision Support Unit

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EAG	Evidence Assessment Group
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
EC	European Commission
ECG	Electrocardiogram
eCRF	Electronic case report form
EEPRU	Economics of Health and Social Care Systems Policy Research
EHR	Electronic Health Record
ELF	Enhanced Liver Fibrosis
EMA	European Medicines Agency
EQ-5D	Euroqol-5 Dimensions
ESLD	End-stage liver disease
EU	European Union
F	Fibrosis
FDA	Food and Drug Administration
FIB-4	Fibrosis-4
FT3	Free triiodothyronine
FT4	Free thyroxine
GGT	Gamma-glutamyl transferase
GLP-1 RA	Glucagon-like peptide-1 receptor agonist
GP	General practitioner
HbA1c	Glycated haemoglobin
HCC	Hepatocellular carcinoma
HCHS	Hospital & Community Health Services
HCRU	Healthcare resource utilisation
HDL-C	High-density lipoprotein-cholesterol
HES	Hospital Episode Statistics
HOMA-IR	Homeostatic model assessment of insulin resistance
HR	Hazard ratio
HRQoL	Health-related quality of life
HSE	Health Survey for England
HSUV	Health state utility value
HTA	Health Technology Assessment
ICER	Incremental cost-effectiveness ratio
ICER	Institute for Clinical and Economic Review
ILI	Intensive lifestyle intervention
IMF	Innovative Medicines Fund
IPD	Individual patient data
IQM	IQVIA QualityMetric
IRP	International Reliance Procedure
IS	Ischaemic stroke
ITC	Indirect treatment comparison
ITT	Intent-to-treat
LDL-C	Low-density lipoprotein-cholesterol

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LDQoL	Liver Disease Quality of Life
Lp(a)	Lipoprotein(a)
LS	Least squares
LSM	Liver stiffness measurement
LT	Liver transplantation
LYG	Life-years gained
MACE	Major adverse cardiovascular event
MALO	Major adverse liver outcome
MASH	Metabolic dysfunction-associated steatohepatitis
MASL	Metabolic dysfunction-associated steatosis liver
MASLD	Metabolic dysfunction-associated steatotic liver disease
MCID	Minimal clinically important difference
MedRA	Medical Dictionary for Regulatory Activities
MELD	Model for End-Stage Liver Disease
MHRA	Medicines and Healthcare products Regulatory Agency
MI	Myocardial infarction
mITT	Modified intent-to-treat
MMRM	Mixed model for repeated measurements
MRE	Magnetic resonance elastography
MRI	Magnetic resonance imaging
MRI-PDFF	MRI-based proton density fat fraction
MSM	Microsimulation model
N/A	Not applicable
NAFLD	Non-alcoholic fatty liver disease
NAS	NAFLD Activity Score
NASH	Non-alcoholic steatohepatitis
NCI	National Cancer Institute
NFS	NAFLD Fibrosis Score
NG	NICE guideline
NHB	Net health benefit
NHS	National Health Service
NICE	National Institute for Health and Care Excellence
NIT	Non-invasive test
NMB	Net monetary benefit
NR	Not reported
OCA	Obeticholic acid
OLE	Open-label extension
ONS	Office for National Statistics
OR	Odds ratio
PIIINP	Procollagen type III N-terminal propeptide
PAS	Patient Access Scheme
PLD	Patient level data
PPPY	Per patient per year
ProC3	Propeptide of type III collagen
PSA	Probabilistic sensitivity analysis

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PSS	Personal Social Services
PSSRU	Personal Social Services Research Unit
QALY	Quality-adjusted life year
QoL	Quality of life
RCT	Randomised controlled trial
rT3	Reverse T3
SAE	Serious adverse event
SAP	Statistical analysis plan
SBP	Systolic blood pressure
SD	Standard deviation
SE	Standard error
SGLT2	Sodium-glucose co-transporter 2
SHBG	Sex hormone-binding globulin
SLR	Systematic literature review
SmPC	Summary of product characteristics
SoC	Standard of care
STA	Single technology appraisal
T2DM	Type 2 diabetes mellitus
TA	Technology appraisal
TC	Total cholesterol
TE	Transient elastography
TEAE	Treatment-emergent adverse event
THR- α	Thyroid hormone receptor-alpha
THR- β	Thyroid hormone receptor-beta
TIMP-1	Tissue inhibitor of metalloproteinases-1
TRAE	Treatment-related adverse event
TSD	Technical Support Document
TSH	Thyroid-stimulating hormone
UK	United Kingdom
U.S.	United States
VCTE	Vibration-Controlled Transient Elastography
VLDL	Very low-density lipoprotein
WPAI	Work Productivity and Activity Impairment
WTP	Willingness to pay

1. Decision problem, description of the technology and clinical care pathway

- **Metabolic dysfunction-associated steatohepatitis (MASH)** is a chronic progressive liver disease representing the advanced stages of metabolic dysfunction-associated steatotic liver disease (MASLD), and can lead to liver fibrosis, cirrhosis, hepatocellular carcinoma (HCC), liver transplantation (LT), and liver-related mortality (1,2).
- The **main prognostic factor in MASH** is fibrosis stage; increasing fibrosis severity is associated with decreased health-related quality of life (HRQoL) and greater liver-related and all-cause mortality (3,4).
- **No licensed treatments** currently exist for MASH in the United Kingdom (UK); management is limited to lifestyle modification and treatment of comorbidities (e.g., type 2 diabetes mellitus (T2DM), obesity, dyslipidaemia), as well as highly limited (fewer than 5% of cases (5)) unlicensed use of antidiabetic agents such as pioglitazone and vitamin E (6).
- **Real-world adherence to lifestyle modification is poor** and off-label pharmacological options (e.g., pioglitazone, vitamin E, and glucagon-like peptide-1 receptor agonists [GLP-1 RAs]) are associated with safety concerns or poor persistence (7–11).
- **Resmetirom is the first disease-specific pharmacological treatment for pre-cirrhotic MASH with moderate to advanced liver fibrosis (fibrosis stages F2 to F3)** and is indicated to be used in conjunction with diet and exercise (12).
- Resmetirom works directly in the liver by selectively stimulating **thyroid hormone receptor-beta (THR-β)**, improving critical hepatic processes and reducing fibrosis, a key driver of disease progression in MASH (13,14).
- Resmetirom has been **approved by the U.S. Food and Drug Administration (FDA) (March 2024)** (15) and has been **granted conditional marketing authorisation by the European Commission (EC) (August 2025)** for the treatment of adults with non-cirrhotic MASH with moderate to advanced liver fibrosis, to be used in conjunction with diet and exercise (16).

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- The **efficacy and safety of resmetirom** have been demonstrated in MAESTRO-NASH (NCT03900429), a pivotal phase III trial evaluating resmetirom in patients with biopsy-confirmed MASH and fibrosis stages F1B-F3 (17).
- The proposed use of resmetirom in the UK is aligned with the conditional EC marketing authorisation: **adults with non-cirrhotic MASH with moderate to advanced liver fibrosis (fibrosis stages F2-F3) in conjunction with diet and exercise.**
- Resmetirom is expected to **fill a major unmet need for patients with MASH who have moderate to advanced fibrosis (stages F2-F3)** by offering a liver-directed, disease-modifying therapy. By reducing hepatic fat and improving key liver processes, it has shown potential to improve fibrosis and thereby reduce long-term risk of progression.

1.1 Decision problem

The objective of this appraisal is to determine the clinical and cost-effectiveness of resmetirom (Madrigal Pharmaceuticals, Inc.) for the treatment of adults with non-cirrhotic metabolic dysfunction-associated steatohepatitis (MASH) with moderate to advanced liver fibrosis (fibrosis stages F2-F3).

Resmetirom does not currently have a marketing authorisation in the United Kingdom (UK) for treatment of MASH (formerly known as non-alcoholic steatohepatitis [NASH]). On March 14, 2024, it was approved by the U.S. Food and Drug Administration (FDA) as the first treatment indicated in conjunction with diet and exercise for the treatment of adults with non-cirrhotic non-alcoholic steatohepatitis (NASH) with moderate to advanced liver fibrosis (consistent with stages F2 to F3 fibrosis) (15). In August 2025, the European Commission (EC) granted conditional marketing authorisation for resmetirom for the treatment of adults with non-cirrhotic MASH with moderate to advanced liver fibrosis (fibrosis stages F2 to F3), in conjunction with diet and exercise (16). This decision means that resmetirom is now the first and only approved therapy in the European Union (EU) for the treatment of MASH.

This submission is aligned with the technology's conditional marketing authorisation in the EU. Resmetirom's anticipated indication in the UK is for use in conjunction with diet and exercise for the treatment of adults with non-cirrhotic MASH with moderate to advanced liver

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fibrosis (fibrosis stages F2-F3). The decision problem addressed in this submission is provided in Table 1, which outlines any differences from the National Institute for Health and Care Excellence (NICE) final scope (18).

Table 1 The decision problem

	Final scope issued by NICE	Decision problem addressed in the company submission	Rationale if different from the final NICE scope
Population	Adults with non-cirrhotic, moderate to advanced liver fibrosis (consistent with stage 2 or 3) caused by MASH.	Adults with non-cirrhotic MASH with moderate to advanced liver fibrosis (fibrosis stages F2-F3).	N/A – In line with final NICE scope.
Intervention	Resmetirom in addition to established clinical management.	Resmetirom in addition to established clinical management.	N/A – In line with final NICE scope.
Comparator(s)	Established clinical management without resmetirom, which may include: • lifestyle modification interventions (such as advice on healthy diet, weight loss when required, and regular exercise); • unlicensed use of pioglitazone and vitamin E. Semaglutide (subject to a NICE evaluation).	Established clinical management without resmetirom, including: • lifestyle modification interventions (such as advice on healthy diet, weight loss when required, and regular exercise) – use of pioglitazone and vitamin E may be permitted in conjunction.	As per NICE’s methods and process guide (19), appropriate comparators should be technologies that are recommended by NICE and available for routine use in the National Health Service (NHS). At the time of this submission, semaglutide is not currently licensed in the UK or recommended for MASH. Including it as a comparator falls outside of NICE’s established procedural framework, which states “technologies that do not have regulatory approval for the population defined in the scope if they are considered to be established clinical practice for the population in the NHS”. Semaglutide, pioglitazone, and vitamin E are not therapies established in clinical practice for the treatment of

			patients with MASH fibrosis stages F2-F3. Please see paragraph following this table for rationale around active comparators.
Outcomes	The outcome measures to be considered include: • resolution of MASH • change in fibrosis stage • progression to cirrhosis • occurrence of hepatic decompensation events, including development of ascites, hepatic encephalopathy, variceal bleeding • liver transplantation (LT) • hepatocellular carcinoma (HCC) • overall survival • adverse effects of treatment • health-related quality-of-life (HRQoL).	The outcome measures considered include: • MASH resolution • improvement (reduction) and progression (worsening) in fibrosis stage • improvement in NAFLD Activity Score (NAS) • change in lipid profile • change in magnetic resonance imaging (MRI)-based proton density fat fraction (PDFF) • change in liver function tests • change in MASH inflammation and fibrosis biomarkers • change in metabolic, liver, and cardiovascular assessments • non-invasive imaging outcomes	Outcome measures included in this submission are based on those outcomes that have been included in the pivotal clinical trial of resmetirom for the indication of interest (MAESTRO-NASH [NCT03900429]) (17), or have been included in the economic modelling. These endpoints have been recommended by the FDA (20) and by the European Medicines Agency (EMA) (21). They were also endorsed during the HTA Lab report for this topic (22). Individual clinical events associated with DCC (ascites, hepatic encephalopathy, variceal bleeding) were not individually modelled owing to a lack of reliable event probabilities; instead these events were modelled in aggregate based on average costs and disutility obtained from prior health economic evaluations in this therapy area. Non-invasive imaging outcomes (e.g., MRI -PDFF) are included in the clinical write-up because they were captured in

		• progression to cirrhosis and decompensated cirrhosis (DCC) with associated DCC events • LT • HCC • overall survival • adverse effects of treatment • HRQoL.	the pivotal trial, however they are not expected to be reflected in the diagnostic or therapeutic pathway for MASH in the NHS and are therefore not included in the economic evaluation.
Economic analysis	The reference case stipulates that the cost-effectiveness of treatments should be expressed in terms of incremental cost per quality-adjusted life year (QALY). The reference case stipulates that the time horizon for estimating clinical and cost-effectiveness should be sufficiently long to reflect any differences in costs or outcomes between the technologies being compared. Costs will be considered from an NHS and Personal Social Services (PSS) perspective. The availability of any commercial arrangements for the intervention, comparator and subsequent treatment technologies will be taken into account.	The economic analysis adheres to the NICE reference case.	N/A – In line with final NICE scope.

Subgroups to be considered	If the evidence allows, the following will be considered: • subgroups by liver fibrosis stage; • people with type 2 diabetes mellitus (T2DM).	The following subgroups are considered: • people with T2DM.	Subgroup analyses are provided for the pivotal trial results by fibrosis stage and T2DM, however the economic model does not estimate cost-effectiveness in subpopulations by fibrosis stage. This is because the study remains protocol-blinded through month 54 (17), and to preserve the integrity of the confirmatory clinical outcomes analyses, detailed arm-level data on fibrosis stage progression cannot be disclosed.

Abbreviations: DCC, decompensated cirrhosis; EMA, European Medicines Agency; F2-F4, fibrosis stages 2-4; FDA, Food and Drug Administration; HCC, hepatocellular carcinoma; HRQoL, health-related quality of life; HTA, Health Technology Assessment; LT, liver transplantation; MASH, metabolic dysfunction-associated steatohepatitis; MRI, magnetic resonance imaging; N/A, not applicable; NAS, NAFLD Activity Score; NHS, National Health Service; NICE, National Institute for Health and Care Excellence; PDFF, proton density fat fraction; PSS, Personal Social Services; QALY, quality-adjusted life year; T2DM, type 2 diabetes mellitus.

Exclusion of pioglitazone and vitamin E as standalone comparators

As outlined in our Decision Problem (DP) consultation and later pre-submission meetings with NICE, the submitted economic evaluation of resmetirom does not include vitamin E or pioglitazone as standalone comparators. Neither vitamin E nor pioglitazone is licensed in the UK for the treatment of MASH, and their use in routine NHS practice is limited. NICE's updated draft guidance (NG49) indicates that these treatments are not commonly prescribed (23), primarily due to concerns over long-term safety and the limited strength of supporting evidence. Furthermore, the key pivotal pharmacotherapy trials in MASH, including MAESTRO-NASH for resmetirom (17) and REGENERATE for obeticholic acid (24), did not prohibit or stratify for use of off-label agents such as pioglitazone or vitamin E in any study arm. Instead, they regarded such interventions as part of the standard of care (SoC) to which the new pharmacotherapy was to be added rather than comparators in their own right. This approach was agreed with regulators in each case. Including pioglitazone and vitamin E as standalone comparators has limited relevance to NHS clinical practice and would introduce substantial, avoidable uncertainty into any economic analysis.

Exclusion of semaglutide as comparator

As per NICE's methods and process guide (19), appropriate comparators should be technologies that are recommended by NICE and available for routine use in the NHS. At the time of this submission—and based on the most recent NICE update (9 July 2025)—semaglutide has no UK marketing authorisation, is not currently recommended by NICE for MASH, and its own STA is not scheduled to begin until November 2025. Given this timeline, it is unlikely that semaglutide will receive a NICE recommendation prior to the current appraisal's decision point, and less likely still that it will achieve a state of supply and local funding commensurate with 'available for routine use' in the MASH indication.

1.2 Description of the technology being evaluated

Resmetirom is an orally active treatment that works directly in the liver by stimulating thyroid hormone receptor-beta (THR- β) to improve critical hepatic processes and reduce fibrosis (13,25). The stimulation of THR- β allows for the expression of genes that improve critical processes in the liver. Resmetirom works to improve lipid metabolism and reduces inflammation directly in the liver. This helps to address drivers of disease progression, reduce liver damage, and improve liver health (13,14).

Table 2 presents a description of resmetirom for the indication being appraised. Please see Appendix A for details of the summary of product characteristics (SmPC). The document is included in the submission reference package.

Table 2 Technology being evaluated

UK approved name and brand name	UK approved name: Resmetirom Brand name: Rezdiffra®
Mechanism of action	Summary: Resmetirom is an orally active treatment that works directly in the liver by stimulating THR-β to improve critical hepatic processes and reduce fibrosis (13,25). The stimulation of THR-β allows for the expression of genes that improve critical processes in the liver. Resmetirom works to improve lipid metabolism and reduces inflammation directly in the liver. This helps to address drivers of disease progression, reduce liver damage, and improve liver health (13,14). Detailed Description: Thyroid hormones, such as free thyroxine (FT4) and free triiodothyronine (FT3), are key regulators of lipid metabolism in the liver (26). THR-β is the major form of the thyroid hormone receptor in the liver, and stimulation of this receptor reduces intrahepatic triglycerides. Free T3 binds to THR-β that activates THR-β signalling that regulates genes that lead to increased hepatic lipase production; this will catalyse the breakdown of triglycerides into non-esterified fatty acids that undergo beta oxidation. This intrahepatic thyroid hormone activity is regulated by circulating hormone concentrations together with the action of liver deiodinases. Within the liver, T4 can be converted by deiodinase type 1 (DIO1) into the active form T3, or by deiodinase type 3 (DIO3) into the inactive reverse T3 (rT3) (27). rT3, which is a marker of

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	hepatic inflammation, is higher, and FT3/rT3 is lower in the MASH compared with the non-MASH population; the ratio of FT3/rT3 declines with advancing fibrosis state (28). Even when circulating thyroid hormone concentrations stay within the normal range, the intracellular signalling components—such as transporters, deiodinases, and receptors—can be disrupted in MASH (29). THR-β also regulates mitophagy and mitochondrial biogenesis, cholesterol biosynthesis, de novo lipogenesis, hepatic low-density lipoprotein (LDL) receptor expression (which increases serum cholesterol clearance), and glucose homeostasis (30,31). These metabolic pathways are frequently impaired in patients with MASLD and MASH (30). Among patients with MASH, the liver has low THR-β activity, causing mitochondrial dysfunction, increased inflammation, and accumulation of lipids. This results in hepatocyte damage/death and progression of fibrosis (14). THR-β signaling activity decreases with advancing fibrosis stage and may predict future hepatic decompensation. Resmetirom is a partial agonist of THR-β that promotes lipophagy and hepatic fatty acid β-oxidation, thereby reducing liver fat (14). It is approximately 28 times more selective than FT3 for THR-β versus thyroid hormone receptor-alpha (THR-α), which is mainly expressed in the heart and bones (32). In vitro studies have demonstrated resmetirom's preferential use of the organic anion transporting polypeptides 1B1 receptor for hepatocyte uptake and stronger activation of THR-β (33,34). Moreover, oxygen consumption rate studies found that both T3 and resmetirom increased basal and maximal respiration, accompanied by an increase in the production of adenosine triphosphate, reflecting higher oxidation of substrates (33). While it is known that increased hepatic THR-β agonism increases the level of hepatic DIO1 (35,36), additional in vitro and in vivo data suggest that resmetirom upregulates the expression of DIO1, supporting its role not only as a thyromimetic but also in potentially increasing the conversion of T4 to T3 (34).

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	Treatment with resmetirom reduces rT3 and increases the ratio of FT3/rT3 in individuals with MASH and F2/F3 fibrosis (28).
Marketing authorisation/CE mark status	Resmetirom (Rezdiffra, Madrigal Pharmaceuticals, Inc.) does not currently have a marketing authorisation in the UK for treating non-cirrhotic MASH with moderate to advanced liver fibrosis. On March 14, 2024, it was approved by the U.S. FDA as the first treatment of liver fibrosis due to non-cirrhotic MASH (15). In August 2025, the EC granted conditional marketing authorisation for Rezdiffra in conjunction with diet and exercise for the treatment of adults with non-cirrhotic MASH with moderate to advanced liver fibrosis (fibrosis stages F2 to F3) (16). Madrigal is currently applying for UK marketing authorisation of resmetirom in the same indication, via the Medicines and Healthcare products Regulatory Agency (MHRA) International Reliance Procedure (IRP).
Indications and any restriction(s) as described in the summary of product characteristics (SmPC)	The anticipated indication in the UK for resmetirom is in conjunction with diet and exercise for the treatment of adults with non-cirrhotic MASH with moderate to advanced liver fibrosis (F2-F3). Resmetirom should not be used in patients with DCC, including patients with moderate or severe (Child-Pugh B or C) hepatic impairment.
Method of administration and dosage	Resmetirom is available in 60 mg, 80 mg, and 100 mg film-coated tablets. The recommended dosage of resmetirom is based on actual body weight. For patients weighing: • < 100 kg, the recommended dosage is 80 mg orally once daily. • ≥ 100 kg, the recommended dosage is 100 mg orally once daily. Resmetirom tablets should be swallowed whole with water (with or without food) and should not be split, crushed, chewed, or dissolved. No dose titration or escalation period is required for resmetirom. The dose of resmetirom may need to be modified if the patient is required to take a concomitant medication. Concomitant use of resmetirom with

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	strong CYP2C8 inhibitors (e.g., gemfibrozil) is not recommended. If resmetirom is used concomitantly with a moderate CYP2C8 inhibitor (e.g., clopidogrel), the dosage of resmetirom should be reduced from 100 mg to 80 mg for patients weighing ≥ 100 kg and from 80 mg to 60 mg for patients weighing < 100 kg. Resmetirom should be taken four hours before or after any required bile acid sequestrants.
Additional tests or investigations	Before initiating treatment with resmetirom, patients typically need to undergo non-invasive tests (NITs) to confirm a diagnosis of non-cirrhotic MASH with moderate to advanced liver fibrosis (F2-F3) and rule out other liver diseases. Liver biopsy is not routinely required for diagnosis or monitoring. NITs such as transient elastography (TE) (FibroScan®) to assess liver stiffness, TE used to assess Controlled Attenuation Parameter (CAP), ultrasound, MRI-PDFF, magnetic resonance elastography (MRE), shear-wave elastography, and Enhanced Liver Fibrosis (ELF) test are used to assess steatosis or fibrosis. A liver biopsy is not required for clinical management of individuals with MASLD, unless NITs are indeterminant (37). Patients should be monitored during treatment with resmetirom for elevations in liver tests and for the development of liver-related adverse reactions. Monitor for symptoms and signs of hepatotoxicity (e.g., fatigue, nausea, vomiting, right upper quadrant pain or tenderness, jaundice, fever, rash, and/or eosinophilia [$> 5\%$] (38). Changes in fibrosis and steatosis can be tracked using imaging-based NITs, which may serve as indicators of therapeutic response. Thyroid function test monitoring is not anticipated to be required as part of the SmPC.
List price and average cost of a course of treatment	The indicative price of resmetirom is █████ per day across all doses. At its list price, the annual drug acquisition costs for resmetirom are estimated to be █████ per year of treatment.
Patient access scheme (if applicable)	N/A

Abbreviations: CAP, Controlled Attenuation Parameter; DCC, decompensated cirrhosis; DIO1, type 1 iodothyronine deiodinase; DIO3, type 3 iodothyronine deiodinase; EC, European Commission; ELF, Enhanced Liver Fibrosis; FDA, Food and Drug Administration; FT3, free triiodothyronine; FT4, free thyroxine; IRP, International Reliance Procedure; LDL, low-density lipoprotein; MASH, metabolic dysfunction-associated

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steatohepatitis; MASLD, metabolic dysfunction-associated steatotic liver disease; MHRA, Medicines and Healthcare products Regulatory Agency; MRE, magnetic resonance elastography; MRI, magnetic resonance imaging; MRI-PDFF, MRI-based proton density fat fraction; N/A, not applicable; NIT, non-invasive test; PAS, Patient Access Scheme; rT3; reverse triiodothyronine; SmPC, summary of product characteristics; TE, transient elastography; THR- α , thyroid hormone receptor-alpha; THR- β , thyroid hormone receptor-beta; UK, United Kingdom; U.S., United States.

1.3 Health condition and position of the technology in the treatment pathway

1.3.1 Disease overview

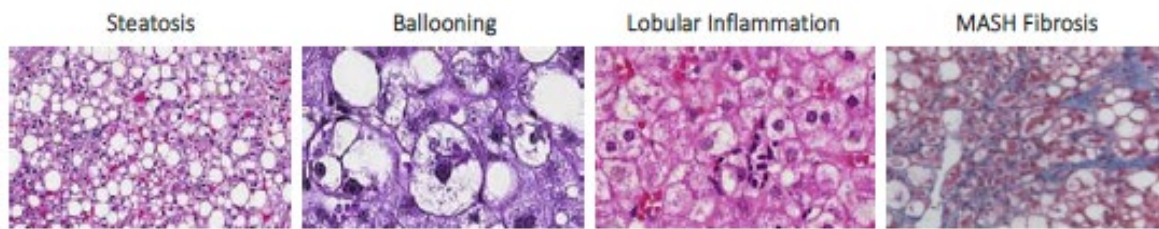
1.3.1.1 Background

MASLD is an umbrella term that covers metabolic dysfunction-associated steatosis liver (MASL), MASH, and MASH with fibrosis. MASH is a progressive, inflammatory subtype of MASLD that has hallmark histopathological features of hepatic steatosis defined by imaging or histology, lobular inflammation, hepatocellular ballooning and hepatic injury as shown in Figure 1 (1,2,39). MASH is chronic, progressive and can lead to fibrosis, increasing the risk of major complications, such as cirrhosis, HCC, LT and liver-related mortality. Additionally, MASH is associated with an elevated risk of cardiovascular disease (CVD) and chronic kidney disease (CKD) (1,2,40–42).

Figure 2 summarises the MASLD group of conditions by increasing severity (6,37,43,44).

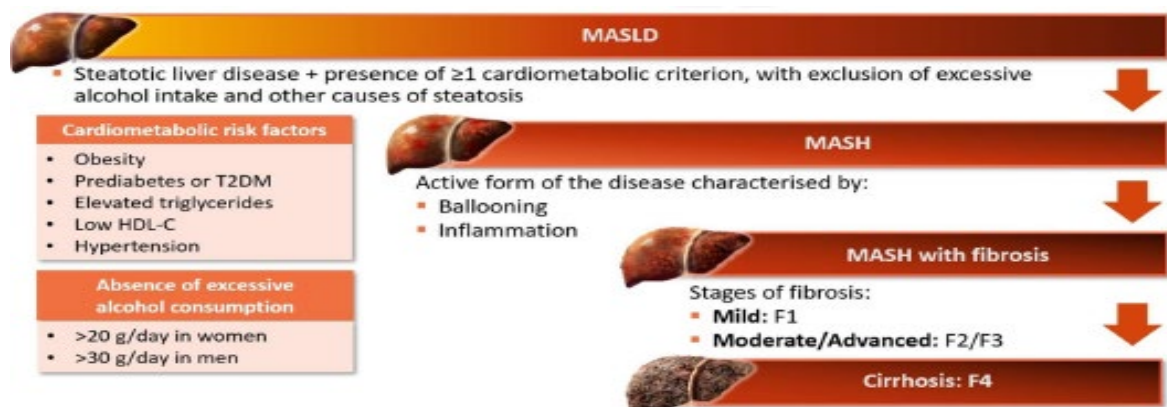
- Isolated fatty liver (F0 fibrosis), where there is a reversible build-up of fat in the liver but without damage or scarring.
- MASH (F0 or F1) where there are distinct changes in tissues of the liver (hepatocellular ballooning and lobular inflammation) but no or very little scarring, which is considered reversible.
- MASH with moderate or advanced (stage F2 or F3) fibrosis, where persistent inflammation causes scar tissue around the liver and nearby blood vessels, but the liver is still able to function normally.
- Cirrhosis (F4), where the liver shrinks and becomes heavily scarred. Liver damage at this state may be wholly or semi-irreversible. F4 typically begins as compensated cirrhosis (CC) which may be asymptomatic, but the state can generate acute and life-threatening symptoms if it develops to DCC; furthermore, the risk of liver failure, HCC, and the need for LT are elevated.

Figure 1 Histological findings consistent with MASH



Abbreviations: MASH, metabolic dysfunction-associated steatohepatitis.

Figure 2 Overview of the progression to MASH from a healthy liver



Abbreviations: F1-F4, fibrosis stages 1-4; HDL-C, high-density lipoprotein-cholesterol; MASH, metabolic dysfunction-associated steatohepatitis; MASLD, metabolic dysfunction-associated steatotic liver disease; T2DM, type 2 diabetes mellitus.

A note on nomenclature

MASLD and MASH are newly defined terms that replace NAFLD and NASH (37,45). This change was led by a panel of experts from international liver societies, including the American Association for the Study of Liver Diseases (AASLD), the European Association for the Study of the Liver (EASL), and the Latin American Association for the Study of the Liver (ALEH). NAFLD and NASH were considered stigmatising and inaccurately descriptive and therefore this initiative aimed to replace these terms with a name that better reflects the disease's metabolic origins. MASLD is preferred to NAFLD because it is more specific about the main associated risk factors of excess weight and metabolic diseases.

1.3.1.2 Disease progression

The natural history of MASLD shows that the transition from MASL to MASH and fibrosis involves episodes of inflammation, leading to the progression of fibrosis with occasional periods of regression (46). The pattern of inflammatory episodes is unclear, and the anticipated time to progression from MASL to MASH is highly variable and may be

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influenced by genetic components and lifestyle factors (46–49). MASH itself is progressive (46,50), but its natural history – in particular the speed of fibrosis progression from stage to stage, and eventual emergence of cirrhosis is highly heterogeneous, depending on individual patient risk factors and comorbidities.

A firmer understanding of typical progression in MASH – particularly between asymptomatic stages where fibrosis progresses or regresses – is still limited due partly to the heterogeneity of surveillance research methods used (e.g., selected measurement instruments, timeframe and coverage of data collection) and partly to the heterogeneity of populations selected for study – their baseline risk profiles, the treatments they receive, and their response to treatment.

Only regular screening across wide populations of patients with MASH or suspected MASH could deliver accurate estimates of progression (or regression) rates between individual fibrosis stages. Such data remain scarce; attempts to pool these data to develop estimates of transition rates between individual stages (e.g., from F2 to F3 or vice-versa) have yielded mixed results, as will be covered in our consideration of potential evidence sources for the economic model (Section 3.2).

Despite these challenges, regardless of the precise rates involved, it is apparent that MASH is associated with serious long-term consequences for patients. One study observed that over a two-year period, approximately 20% of patients with MASH who had advanced fibrosis (F3) were expected to progress to F4 (CC) and among F4 (CC) patients, it was estimated that 20% of them would develop DCC or HCC within a three-to-six year timespan (51).

Davidson et al. 2025 (5,52) studied UK primary care data (Clinical Practice Research Datalink [CPRD]) linked to Hospital Episode Statistics (HES) and attempted to fill in an epidemiological profile of MASH progression in the UK. A sample of patient historical data covering a 10-year period between 2011 and 2021 was studied (5,52).

During this timeframe, 8.4 to 8.8% of patients with a MASH diagnosis (any stage) were observed to progress to CC, and 6.5% to 7.2% of patients with MASH progressed to DCC. Most progression events occurred within two years of the study index date when looking at progression to CC (61.1 to 69.3%) and progression to DCC (52.3 to 58.4%). Around 0.4 to 0.7% of patients with MASH progressed to HCC during the timeframe and 13.2 to 14.2% progressed to end-stage liver disease (ESLD) (a collective definition including CC, DCC, LT, and HCC). The analysis was best suited to capturing symptomatic acute events or

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diagnoses arising at later stages of fibrosis and cirrhosis, and did not distinguish how patients were identified initially – e.g., incidentally identified during early-stage disease or after targeted testing for suspected disease linked with other risk markers. Therefore, the study again did not provide the level of detail required for economic modelling in patients with MASH and F2 or F3 fibrosis. However, the analyses provided useful supporting evidence for the position that the rate of progression toward ESLD is greater at more severe levels of fibrosis, and is highest at stage F4. This underscores the critical importance of early detection, effective therapies, and interventions to prevent disease progression at earlier stages before a patient develops cirrhosis (53,54).

Existing evidence from clinical trials and registries also supports the concept of a high-risk MASH population, whose comorbidities and prognostic profile make them likely to progress more rapidly to ESLD than other patients with MASH. Clinical trial and real-world data have shown that between 17 and 22% of patients with non-cirrhotic MASH may progress to ESLD within approximately three years, around half may develop features of ESLD within one year, and 80% may have DCC within around three years (55,56). Currently the only way to identify and safeguard such potential ‘rapid progressors’ is to increase early screening and intervention in identified cases.

1.3.1.3 Patient characteristics and clinical features

Patients with MASLD and MASH typically have multiple comorbidities, including obesity, metabolic syndrome, and T2DM, which are also risk factors for fibrosis progression. A pooled analysis in people with confirmed histological MASH reported the most common comorbidity to be hypertriglyceridaemia, followed by hyperlipidaemia, metabolic syndrome, hypertension, and then T2DM (Table 3) (57). Similar findings were reported in the CPRD-HES study (5,52).

Comorbidities may also be risk factors for MASH progression, with increased waist circumference, T2DM, increased glycated haemoglobin (HbA1c), hypertension, and high low-density lipoprotein-cholesterol (LDL-C) reported to be risk factors for progression of fibrosis (23).

Table 3 Overall pooled prevalence of frequent comorbidities in people with MASH

Comorbidity	MASH % (95% CI)
T2DM	43.63 (30.28–57.98)
Hyperlipidaemia	72.13 (54.59–84.78)

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Hypertriglyceridaemia	83.33 (36.87–97.72)
Hypertension	67.97 (56.31–77.74)
Metabolic syndrome	70.65 (54.64–82.79)

Abbreviations: CI, confidence interval; MASH, metabolic dysfunction-associated steatohepatitis; T2DM, type 2 diabetes mellitus.

1.3.1.4 Association between liver fibrosis and outcomes

Liver fibrosis is a major prognostic factor in patients with MASH; patients with fibrosis are at an increased risk of all-cause mortality compared with patients without fibrosis, and the risk of liver-related mortality increases exponentially with each stage of fibrosis (46).

Several studies have shown an association between worsening fibrosis and mortality. A cohort study that evaluated 646 patients with MASLD found that fibrosis was a significant predictor of mortality compared with a matched control group without MASLD, with increasing fibrosis stage associated with worsening mortality (58). Similar findings were reported in a nationwide matched-cohort study from Sweden wherein MASLD was associated with a higher risk of mortality than matched controls across all stages of MASLD, with worsening histological severity increasing the risk of mortality (59). Indeed, the excess risk of overall mortality increased from 10.7% in patients with simple steatosis (i.e., MASL), to 18.5% in patients with MASH without fibrosis, 25.6% in patients with non-cirrhotic fibrosis, and 49.4% in patients with cirrhosis, compared with population controls. The study also found a significant relationship between mortality risk caused by extra-hepatic cancer, cirrhosis, CVD, or HCC, with progressive increases in histological severity – from MASH without fibrosis, to non-cirrhotic fibrosis, to cirrhosis (Table 4) (59).

Table 4 Increased risk of mortality from different causes in patients with MASLD vs. matched population comparators

	Incidence rate difference per 1,000 person-years			
	Simple steatosis	MASH without fibrosis	MASH with non-cirrhotic fibrosis	MASH with cirrhosis
Extra hepatic cancer	4.4	3.9	4.5	6.5
Cirrhosis	1.2	3.0	5.5	22.3
CVD	0.7	2.7	1.8	8.2
HCC	0.7	1.3	2.5	5.5

Abbreviations: CVD, cardiovascular disease; HCC, hepatocellular carcinoma; MASH, metabolic dysfunction-associated steatohepatitis.

The association between fibrosis stage and long-term clinical outcomes, covering all major advanced liver outcomes (MALO) including cirrhosis, cirrhosis-related decompensation (ascites, encephalopathy, and variceal bleeding), HCC, need for LT, and liver-related death,

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has been well established. A systematic literature review (SLR) conducted in 2025 reported on the association between histological fibrosis stage and long-term clinical outcomes in patients with MASH (60). Significant associations between fibrosis stage and liver-related events were reported in all five studies reporting liver-related events, and significant associations between fibrosis stage and progression to cirrhosis were reported in all four studies reporting on cirrhosis (60).

Another U.S. study of patients with MASLD (n = 215) reported that patients with fibrosis stage 3 had a significantly higher rate of progression from MASH to cirrhosis compared with those with fibrosis stage 0–1 (hazard ratio [HR]: 2.0; 95% CI 1.3–3.1) (61).

1.3.1.5 Epidemiology of MASH

MASH – estimated by a range of publications as detailed below – has a prevalence between 0.02% and 5% and is believed to be substantially underdiagnosed in the UK population, particularly among patients in milder, asymptomatic fibrosis stages. Suspected MASH is typically identified through a combination of clinical, laboratory, and imaging findings, with appropriate exclusion of other liver conditions (62). Given the challenges, and the geographic diversity of diagnostic approaches (either due to clinical choices or dictated by resource constraints) applied across the NHS, published estimates of MASH epidemiology vary depending on the definitions applied and the true prevalence is currently unknown (63–65). Careful consideration is therefore required when interpreting reported epidemiological estimates.

Some UK-specific epidemiological data are available from published modelling studies (66,67) and a more recent analysis used UK CPRD data (5,52). The Davidson et al. 2025 analysis of CPRD and HES data used different disease definition codes to identify adult patients with incident MASH during the study period: 1) ≥ 1 MASH-coded primary or secondary care record (n = 2,696); 2) ≥ 1 MASH-coded inpatient record OR ≥ 2 MASH-coded outpatient or primary care records (n = 2,101); 3) ≥ 1 MASLD-coded primary or secondary care record AND a subsequent liver biopsy (n = 2,041); and 4) ≥ 1 MASLD-coded primary or secondary care record AND ≥ 2 subsequent elastography or fibrosis scores (n = 1,587).

Incidence rates per 100,000 person-years increased throughout the ten-year study period from 2011 to 2021; from 0.61–1.34 in 2011 to 2.04–2.70 in 2020 using Definitions 1–3, and from 0.02 in 2013 to 4.44 in 2019 using Definition 4. Prevalence per 100,000 people increased from 4.31–12.02 in 2011 to 18.55–26.60 in 2020 using Definitions 1–3. As seen in

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this study, using different definitions to identify MASH patients can yield potentially wide ranges in prevalence estimates, highlighting a challenge in quantifying the epidemiological burden to the NHS in England and Wales.

Morgan et al. 2021 elicited clinical expert opinion to generate estimates of overall adult MASH prevalence ranging from 2.2% to 4.1% in 2018 (66). Despite this, the study suggested that only a minority (around 20%) of all MASH patients are formally diagnosed within the healthcare system – between 0.23 and 0.44 million depending on the assumed prevalence. Diagnosis was also estimated according to fibrosis severity, with diagnosis in earlier stages being limited (2.0% in F0 and F1, 16.5% in F2) and dramatically higher in later stages. In fact, the study suggested that 58.3% of all prevalent F3 cases and 100% of F4 cirrhosis cases – even if asymptomatic and with CC – would be identified. Based on our own elicitations of clinical expert opinion, these latter diagnosis rates are considered unrealistically high. However, the research serves to reflect an aspiration of NHS clinicians to proactively identify F3 and F2 fibrosis, as well as the more immediately acute F4 cirrhosis.

Schattenberg et al. 2021, in a multi-country modelling study, estimated the epidemiology of MASH across five countries including the UK (67). The analysis applied previously published prevalence assumptions (68,69) to national population data and distributed cases across fibrosis stages and diagnosis rates. The assumptions were comparable with those used in Morgan et al. 2021 (66), but the Schattenberg et al. 2021 paper also estimated absolute number of UK patients by fibrosis stage (67). Within an assumed diagnosed population, the study estimated between 38,655 and 71,714 for F2, and between 84,969 and 157,635 for F3, depending on the prevalence scenario. F4 patient numbers were estimated at between 86,437 and 160,358.

Taken together, these studies do share some common features, but they also highlight the potential for large discrepancies in modelled prevalence and incidence, without giving an idea of which paper has the overestimate and which the underestimate. Therefore, to generate a plausible set of patient numbers for our subsequent budget-impact model (BIM), we undertook further work in the field to compare modelled figures to real numbers of patients currently managed in clinic.

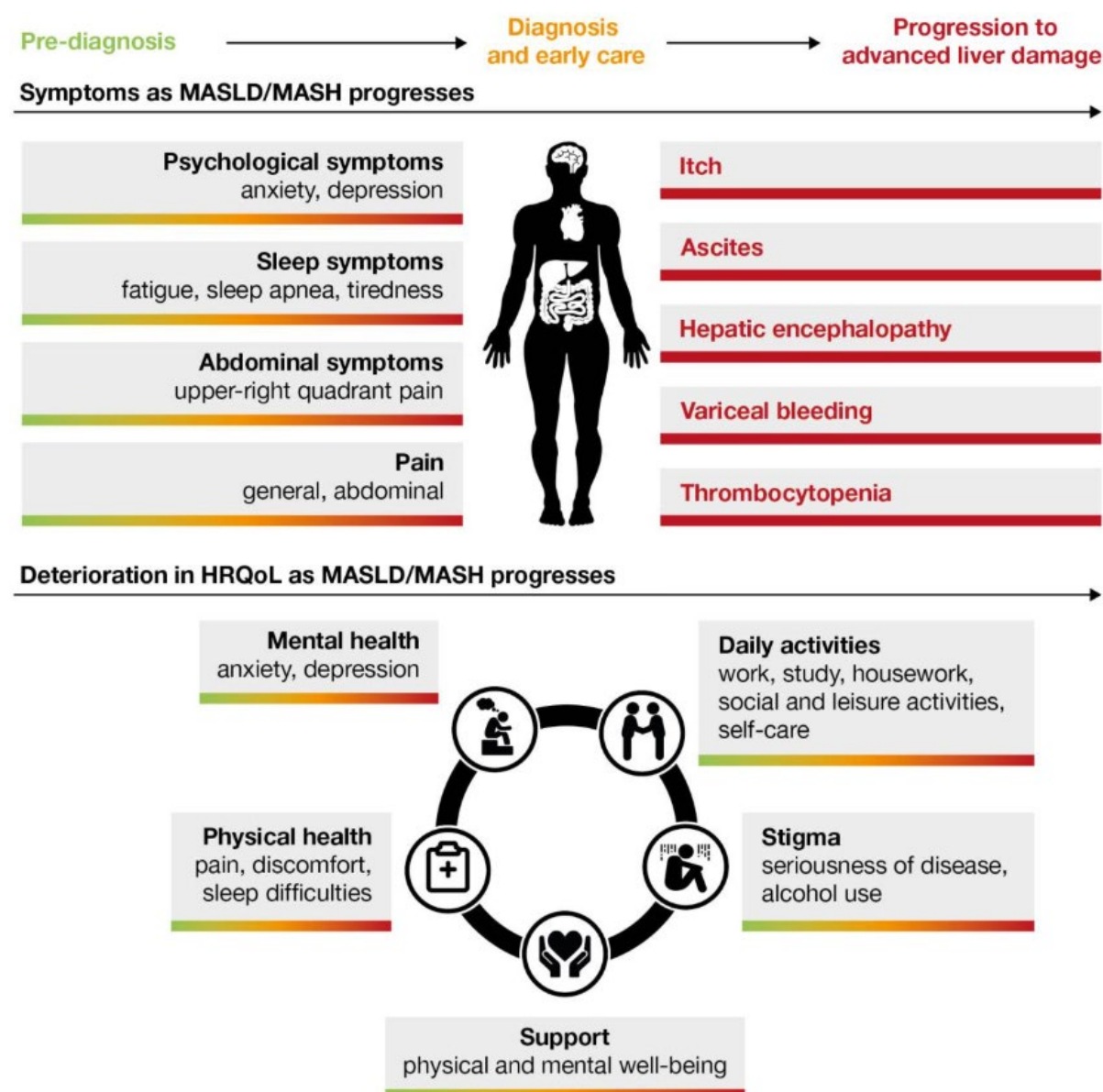
1.3.1.6 Disease burden

Humanistic burden

In patients with MASH who have developed ESLD, HRQoL impacts are profound and easier to quantify because the condition is symptomatic. However, as investigated in Section 3.4, patients with MASH report that the disease impacts many aspects of their lives even in earlier stages, through diminished physical functioning, work performance, ability to perform daily living tasks, and quality of family and personal relationships. A recent review of studies carried out in the U.S. and EU5 (70) found that patients with MASH self-report worse HRQoL than that of the general population and list symptoms including fatigue/tiredness (38–78%) and abdominal pain (13–61%), while other commonly-reported symptoms included poor sleep quality, sleep apnoea, weakness/lethargy, anxiety/depression, weight gain, cognition problems, abdominal bloating, pruritis and jaundice (70). Although the impact on HRQoL was typically observed to worsen with increasing severity of fibrosis, this pattern was statistically observable as a general trend; heterogeneity was seen between countries as well as individual stages of fibrosis (70).

Another factor affecting HRQoL is the stigma surrounding liver disease, with family and friends but also physicians often assuming patients with MASH are likely alcoholic, questioning their honesty regarding their alcohol intake (71,72). An overview of symptoms and HRQoL as MASLD/MASH progresses, as derived from the study by Eskridge et al. 2023 (72), is presented in Figure 3 below.

Figure 3 Overview of symptoms and HRQoL as MASLD/MASH progresses



Abbreviations: HRQoL: health-related quality of life; MASH, metabolic dysfunction-associated steatohepatitis; MASLD, metabolic dysfunction-associated steatotic liver disease.

Economic burden

A recent burden-of-illness (BoI) study of MASH in the UK (Morgan et al. 2021 (66)) estimated that the diagnosed MASH population had a total economic impact between £2.3 and £4.2 billion in 2018. Had all MASH cases been diagnosed, these costs would have been £7.0–£13.0 billion. Costs varied by disease severity, with more advanced fibrosis stages accounting for a disproportionate share. Patients with MASH and F3 fibrosis contributed £479–£889 million (21%), compared with those with F4 CC £553–£1,026 million (24%) or F4 DCC £164–£303 million (7%). On a per-patient basis, economic costs were estimated at £9,420–£9,450. Of the total, health system costs were estimated at £200–£359 million, Company evidence submission: Resmetirom for treating moderate to advanced liver fibrosis (without cirrhosis) (MASLD) ID6529

comprised mostly of secondary care (£126–£224 million; 62%) and diagnostic testing (£48–£90 million; 25%) and being mostly attributable to F4 patients (35%). The UK government covered 79% of the health system costs, while individuals and families bore 15% and other parties 6%. Per-patient, health system costs were £803–£828.

Productivity losses represented the largest component of the economic burden, estimated at £2.0–£3.7 billion. Advanced disease stages again accounted for a greater proportion, with F3 and F4 CC stages responsible for 21% and 23% of productivity costs, respectively. On average, productivity losses amounted to £8,285 per patient, with the largest contributors being foregone income (58%) and reduced productivity while at work (presenteeism, 46%).

Other economic costs attributable to MASH were £81–£149 million, comprising carer costs (£14–£25 million), deadweight losses (£58–£107 million), and funeral costs (£10–£18 million). Deadweight losses, borne by society as a whole, made up the majority of this category. The monetised value of wellbeing loss was estimated at £5.6–£10.5 billion, equating to approximately £23,400 per person.

The CPRD-HES study by Davidson et al 2025 combined information from the Diagnostic Imaging Dataset as well as death registrations from the Office for National Statistics (ONS) to estimate healthcare resource utilisation (HCRU) and costs among adults with incident MASH in England between 2011 and 2020 (5,52). The study was conducted to support recommendations from NICE regarding the incorporation of up-to-date, UK-specific MASH health state costs into cost-effectiveness models. Annualised all-cause and MASH-related HCRU and costs (inflated to 2021–2022 GBP) were estimated. Among 2,696 patients identified (mean follow-up 52 months), 40.9% had T2DM, 61.8% were overweight or obese, 19.2% had CVD, and 12.9% progressed to cirrhosis. Use of pharmacological therapies was low (e.g., pioglitazone use in 3.1% pre-index and 1.9% post-index). Mean all-cause and MASH-related primary care consultations were 16.8 and 0.1 per patient per year (PPPY), with corresponding annualised costs of £602 and £3, respectively. Patients with T2DM or who progressed to cirrhosis had notably higher all-cause primary care consultations and costs (e.g., £768 vs. £487 for T2DM vs. non-T2DM; £779 vs. £575 for cirrhosis vs. non-cirrhosis). However, MASH-related costs remained low across subgroups (5,52).

In secondary care, mean all-cause inpatient admissions, outpatient visits, and emergency visits were 1.3, 5.8, and 0.5 PPPY, respectively. MASH-related admissions and visits were less frequent (0.2 and 1.1 PPPY for inpatient and outpatient visits, respectively). Mean annualised inpatient, outpatient, and emergency care costs were £1,592, £702, and £78 for

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all-cause use, and £447 and £152 for inpatient and outpatient visits, respectively, for MASH-related use (5,52).

Subgroup analyses showed higher resource use and costs in patients with T2DM or cirrhosis. For example, patients with cirrhosis had nearly three times the inpatient costs of those without (£3,620 vs. £1,290) and twice the number of inpatient admissions (2.4 vs. 1.1 PPPY) (5,52).

The Davidson et al. 2025 analysis excluded patients with ESLD occurring at or shortly after index from the dataset (5,52). The timeframe of analysis (ten years) as well as the selection of a patient population that included milder fibrosis stages, meant that only a small proportion of patients were identified as having progressed to ESLD states (8.6% to CC and 6.5% to DCC) – so the specialist costs associated with treating the long-term consequences of MASH (including LT or treatment of HCC) are likely an underestimate relative to the population of this decision problem. However, the research reinforces the substantial economic burden of MASH in England, with a trend that healthcare costs rise significantly among patients with advanced disease, particularly those with cirrhosis or T2DM.

1.3.1.7 Clinical pathway of care

NICE has published guidance on the diagnosis and management of NAFLD in 2016 (23) and an update, including for the nomenclature change to MASLD and its considerations of metabolic comorbidities, is currently in progress as of September 2025 (73). As such, parts of the 2016 guidance may now be outdated, particularly as the ongoing update aims to provide comprehensive recommendations across all NHS-funded care settings (73).

The British Society of Gastroenterology (BSG) guidelines on abnormal liver function blood tests for primary care and the NHS MASLD guidelines for secondary care are also used for shaping clinical care pathways in the UK (74–76). The BSG and the British Association for the Study of the Liver (BASL) have a special interest group for MASLD which has developed a series of evidence-based quality standard recommendations (76). The joint guidelines of EASL, the European Association for the Study of Diabetes (EASD), and the European Association for the Study of Obesity (EASO), offer comprehensive recommendations for MASLD, including for NITs, lifestyle interventions, incretin therapies for comorbidities, and resmetirom for non-cirrhotic MASH with significant fibrosis; it is accessible to clinicians across Europe, including those in England and Wales (37).

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1.3.1.8 Diagnosis of MASH and detection/staging of liver fibrosis

As reported in NICE guideline NG49 ('Non-alcoholic fatty liver disease (NAFLD): assessment and management'), diagnostic practice in MASH and MASLD varies widely and includes clinical, biochemical, and radiographic tests (23). It has also been reported that screening for MASLD is considered cost-effective and should be undertaken in the absence of alcohol-related liver disease (77,78).

The diagnosis of MASLD is determined by the presence of a fatty liver on ultrasound, given other causes of a fatty liver have been ruled out. If the screening ultrasound reveals a non-fatty liver, NICE recommends reassessment for MASLD every 3 years. The presence of advanced liver fibrosis should be assessed using the ELF test, with a score ≥ 10.51 in the setting of MASLD indicating advanced fibrosis (23).

The 2024 EASL/EASD/EASO MASLD guidelines (37), the 2022 BSG/BASL quality standards (74,76), as well as many other international or national guidelines recommend case finding or routine screening for MASLD with liver fibrosis in the presence of T2DM, obesity with an additional metabolic risk factor, or abnormal liver function tests (37,74,76,79–84).

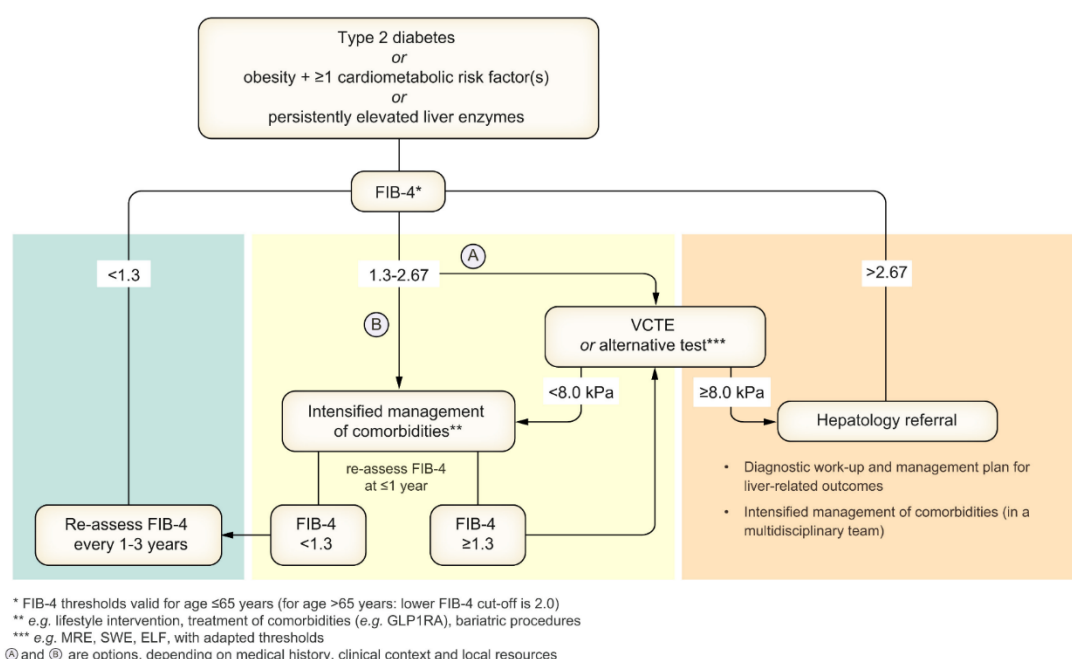
In the real-world setting, a routine work-up is often started with an ultrasound and assessment of liver enzymes. In clinical practice, especially in England and Wales, sequential testing strategies using NITs are employed to optimise patient management in line with guideline recommendations. For patients with MASH at fibrosis stages F2 and F3, NITs are increasingly recommended to assess disease severity, monitor progression, and guide treatment decisions. The FIB-4 score and TE (e.g., FibroScan) are widely used due to their accessibility and validated performance in detecting moderate to advanced fibrosis (37). The CAP measurement, which is available as an additional feature on TE (e.g., FibroScan) can also quantify the degree of steatosis. If not available or in cases where a valid TE cannot be performed, other secondary risk assessment tools such as ELF test or MRE may be considered (37).

The 2024 EASL-EASD-EASO and many other European Clinical Practice Guidelines recommend a stepwise strategy for evaluating liver fibrosis in patients with presumed or confirmed MASLD (23,37,85–87). As described in the 2024 EASL-EASD-EASO guidelines, the emerging guidance is to consider initiating primary risk assessment using simple non-proprietary blood-based scores (e.g., FIB-4, NAFLD Fibrosis Score [NFS], SAFE) amongst high-risk populations (e.g., people living with diabetes, people with obesity with ≥ 1 metabolic

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comorbidity) with no evidence of other steatosis-inducing chronic liver diseases. Given the high prevalence of MASLD in these groups, the focus is on determining whether patients may have moderate (F2 or higher) or advanced (F3 or higher) fibrosis rather than confirming fat accumulation (37). If these scores indicate a moderate or higher risk (e.g., FIB-4 > 1.3, SAFE > 0), further evaluation with advanced imaging techniques, such as imaging-based elastography, is advised to assess the stage of liver fibrosis.

Figure 4 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



Abbreviations: FIB-4: Fibrosis-4; VCTE, Vibration-Controlled Transient Elastography.

When advanced imaging techniques are not available or not indicated for the patient (e.g., due to severe obesity, contraindication), proprietary blood-based tests can be considered (e.g., ELF, FibroTest, ADAPT). Additionally, serial monitoring using NITs is recommended and can be used in combination with all available clinical and laboratory data to assess disease progression, regression, or stability to inform clinical management strategies. Commonly-used blood-based and imaging-based tests in both specialty (i.e., hepatology, gastroenterology) and non-specialty (i.e., primary care) settings are summarised in Table 5.

Table 5 Key non-invasive tests for staging liver fibrosis and steatosis in MASLD

Test Type	Test Name	Description
Blood-Based	FIB-4 Score	Score that combines age, aspartate aminotransferase (AST), alanine aminotransferase (ALT), and platelet count in a non-

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		proprietary algorithm to assess risk of advanced liver fibrosis (F ≥ 3).
	NFS	Score that combines age, body mass index (BMI), diabetes status, ALT, AST, platelet count, and albumin in a non-proprietary algorithm to assess risk of advanced liver fibrosis (F ≥ 3).
	ELF	Proprietary blood test to assess liver fibrosis and predict likelihood of future liver-related events derived from a single score based on three extracellular matrix-based biomarkers: hyaluronic acid, procollagen type III amino terminal propeptide, and tissue inhibitor of metalloproteinases 1.
	FibroTest	Proprietary blood test to assess liver steatosis, inflammation, and fibrosis based on measurement of 10 blood-based biomarkers.
Imaging-Based	TE	TE (e.g., FibroScan) is an ultrasound-guided technology that uses external mechanical force to induce shear waves in a specific region of the liver. The speed of the induced shear waves can be used to quantify liver stiffness, a surrogate of liver fibrosis. In addition, the quantification of the amplitude of the shear wave signal (e.g., CAP), a surrogate of liver fat, is often captured during the same exam.
	Point Shear Wave Elastography or 2D Shear Wave Elastography	A multivendor ultrasound imaging-based technology that uses focused acoustic force to induce shear waves in a specific point or region of the liver. The speed of the induced shear waves can be used to quantify liver stiffness, a surrogate of liver fibrosis. In addition, the quantification of the amplitude of the shear wave signal, a surrogate of liver fat, is often captured during the same exam.
	MRE	MRI-based test to quantify liver stiffness through shear waves generated by continuous mechanical stimulation. Elevated stiffness is associated with higher stages of liver fibrosis.

Abbreviations: ALT, alanine aminotransferase; AST, aspartate aminotransferase; BMI, body mass index; CAP, Controlled Attenuation Parameter; ELF, Enhanced Liver Fibrosis; F, fibrosis; FIB-4, Fibrosis-4; MRE, magnetic resonance elastography; MRI, magnetic resonance imaging; NFS, NAFLD Fibrosis Score; TE, transient elastography.

Patients may need to be referred to a hepatologist, who will determine whether an extra procedure is necessary (37). A liver biopsy is not routinely recommended but may be necessary in certain clinical scenarios where non-invasive methods do not provide sufficient information; in the UK analysis of adults with a MASH-coded primary and/or secondary care recorded diagnosis using the CPRD-HES database (n = 2,696), just over a quarter of patients received a liver biopsy (28.6 %) (5,52). The proportion of patients who undergo liver biopsy is expected to decline over the time by improving access to and accuracy of NITs. Such a shift from relying on biopsy to NITs facilitates higher rates of diagnosis at primary care level and improves efficiency (54). Addressing regional variations in access to routine testing (driven both by resource constraints and local practice) will in our view be a key public health challenge associated with the introduction of any new pharmacotherapy to the NHS in England and Wales.

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1.3.1.9 Current treatment pathway

The subset of patients with MASH who have moderate to advanced fibrosis (fibrosis stages F2 to F3) is typically managed in a hospital or specialist care setting, while for the earlier stages of MASLD, including MASH with mild fibrosis, care is usually managed by general practitioners (GPs) (43). Some of the elements of care are common between earlier stages of MASLD and individuals with MASH with moderate to advanced fibrosis. Patients at all stages require lifestyle modification interventions, including healthy eating, weight loss (if indicated), and regular exercise.

There are currently no medicines approved for MASLD or MASH in England and Wales or therapies that are considered to be established clinical practice for the population in the NHS. Medicines for associated comorbid conditions such as high blood pressure, high cholesterol, T2DM, and obesity may be offered to treat those specific conditions. The 2016 NICE guideline NG49 mentions pioglitazone and vitamin E as treatment options (23). As set out during the scoping consultation, these agents are regarded as part of the SoC to which resmetirom would be added rather than active comparators in their own right. Surgical interventions have limited application in this field; bariatric surgery to promote weight loss and improve MASH may be suitable for a small proportion of patients. Also, patients who progress to cirrhosis and who develop liver failure may be considered for a transplant, though the average waiting list for a liver on the NHS in England and Wales is approximately 5-7 months (88).

As previously highlighted, consensus recommendations on quality standards for the management of MASLD were published by the BASL and the BSG NAFLD Special Interest Group in 2022 (76). It is recommended that services should be established at the local level (i.e., before referral to the gastroenterology or liver clinic) to investigate suspected liver disease (based on ultrasound or persistent, unexplained abnormal liver enzymes) using NITs, and the possibility of liver fibrosis should be considered in individuals with T2DM or metabolic syndrome. Validated, widely-available NITs with high negative predictive value (e.g., FIB-4 or NFS) are recommended as community-based screening for risk of liver fibrosis in the community, with sequential ELF testing, TE, or acoustic radiation forced impulse to distinguish those with intermediate and high risk.

Patients stratified as high risk for advanced fibrosis or cirrhosis based on NITs should be referred to a hepatologist. Liver biopsy should be considered if NITs do not provide enough information to evaluate MASH severity and determine whether patients should be considered for potential drug therapies. Patients at low risk of significant fibrosis should be referred to a general practitioner. Company evidence submission: Resmetirom for treating moderate to advanced liver fibrosis (without cirrhosis) (MASLD) ID6529

managed in the community, with a focus on lifestyle advice and CVD risk reduction, and reassessment of fibrosis using NITs after 3 years.

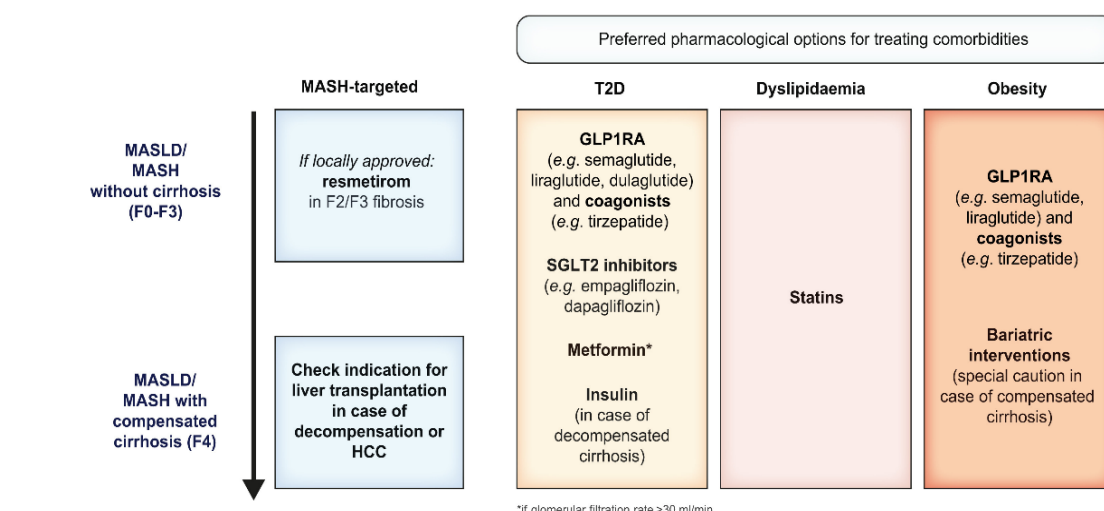
1.3.1.10 Positioning of resmetirom

Resmetirom is anticipated to be indicated for use in conjunction with diet and exercise for the treatment of adults with non-cirrhotic MASH with moderate to advanced liver fibrosis (fibrosis stages F2 to F3), which aligns with the proposed positioning in this submission as well as the pivotal phase III randomised controlled trial (RCT) MAESTRO-NASH, which evaluated resmetirom in adults with biopsy-confirmed MASH and fibrosis stages F1B to F3 (17).

Resmetirom is expected to be the first licensed pharmacological treatment in this indication, and its positioning is supported by feedback from UK clinical experts whom have highlighted the significant unmet need in this patient population. Based on the mechanism of action described in Table 2 (Section 1.2), and the results of MAESTRO-NASH (17), resmetirom is expected to be used to reduce the risk of progression (relative to only lifestyle management) to more advanced fibrosis stages, cirrhosis, complications of liver fibrosis, liver failure, and mortality for patients with non-cirrhotic MASH with moderate to advanced fibrosis (fibrosis stages F2 to F3). Resmetirom has been shown to reduce progression and offer fibrosis stage improvement and resolution of MASH (17); Section 2.6.1). As described in previous parts of Section 1.3.1.6, once a patient with MASH progresses and becomes cirrhotic, there is a significant increase in HRQoL, disease, and economic burden. Therefore, preventing progression to cirrhosis and ESLD in patients eligible for resmetirom is critical—both for patient outcomes and to reduce the burden of MASH on NHS resources. The role of resmetirom within the MASH treatment pathway is distinct from the management of established ESLD, which may involve hepatology referral, cirrhosis surveillance, or LT.

The 2024 EASL–EASD–EASO Guidelines outline the management of MASLD and MASH, highlighting lifestyle modification as first-line therapy, and—where locally approved—the use of resmetirom in patients with F2–F3 liver fibrosis (37).

Figure 5 Resmetirom in the treatment pathway



Abbreviations: F0-F4, fibrosis stages 0-4; GLP-1 RA, glucagon-like peptide-1 receptor agonist; HCC, hepatocellular carcinoma; SGLT2, sodium-glucose co-transporter 2; T2D, type 2 diabetes.

1.3.1.11 Limitations of current treatment and unmet need

As described in Section 1.3.1.2, patients with MASH with moderate to advanced liver fibrosis (fibrosis stages F2 to F3) are at risk of disease progression and therefore require early treatment to avoid cirrhosis, ESLD, and mortality. There are no UK-licensed, NICE-recommended treatments for MASH, nor ones that are specifically liver-directed; instead, disease management focuses on lifestyle modifications, whilst some patients may receive treatments prescribed to manage existing comorbid diseases. Lifestyle modification is the most common treatment for people with MASH. However, real-world adherence to strict exercise routines is low, and few patients with MASH receive nutritional counseling (7). Off-label pharmacological treatments are sparsely used by liver specialists.

Weight loss is a major treatment goal in the management of MASH and forms part of the SoC to which resmetirom is expected to be added. EU guidelines from the EASL-EASD-EASO recommend dietary and behavioural therapy-induced weight loss to address liver injury (37). Evidence remains insufficient to show an effect of weight reduction by lifestyle modification on advanced fibrosis or cirrhosis, and current estimates suggest that only 30% of patients with MASLD achieve > 5% weight loss within 3 months via lifestyle modifications (7). Pharmacological weight loss therapies, including GLP-1 RAs, are anticipated over time to become integrated to the SoC in this context, but, at present, none of them has a UK marketing authorisation for treating MASH, and the NHS uptake of GLP-1 RAs for obesity treatment itself has fallen short of even the restrictive, BMI-limited implementation arrangements agreed between NHS, NICE and their manufacturers (89).

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Supporting the positioning of resmetirom as a new agent that is anticipated to be added to the existing SoC, rather than replacing individual treatments within it, in the MAESTRO-NASH study, the majority (46–51%) of patients were receiving statins at baseline, 13–17% were receiving GLP-1 RAs, and 11–17% were receiving sodium–glucose co-transporter 2 inhibitors (SGLT2is) (17).

The lack of efficacy of currently available treatments is reflected in the fact that MASH is one of the leading causes of LT. A 2022 U.S. study that evaluated 116,292 patients who underwent LT with a known aetiology of chronic liver disease (excluding those with HCC) indicated that MASH was the second most common cause at 27%. Among patients with HCC, nearly a third (31%) were reported to have MASH, which was the most common cause. Furthermore, the proportion of patients undergoing LT due to MASH has seen a large increase since 2013, reflecting the increasing burden of MASH as well as improved ascertainment of underlying disease prior to transplantation (90).

Due to global trends in the prevalence of obesity, the prevalence of MASH is also anticipated to increase in the future, based on recent models (65). Patients with MASLD/MASH experience poorer HRQoL than healthy comparator cohorts (70,72). Further, the costs associated with MASH management are substantial and increase with disease progression (5,52). Consequently, there is a major need for a MASH-specific therapy that may decrease MASH-related HCRU and healthcare costs to the NHS and improve HRQoL for people with MASH. Treatment should be specifically liver-directed and address all components of the liver pathophysiology of MASH, specifically liver steatosis, and fibrosis, while also improving relevant CVD risk factors such as reductions in LDL-C, apolipoprotein B (ApoB), and triglycerides, which in turn reduces CVD risk.

1.4 Equality considerations

Mortality due to MASLD is overrepresented in the most deprived populations in England (91). Access to specialist services is unevenly distributed in England, with heterogeneous treatment pathways and access to medicines that may potentially compound this inequality rather than address it (92). Although resmetirom itself is not expected to introduce equality issues that would differentially impact patients protected by equality legislation, its implementation in the NHS should be viewed against the context of current regional and socioeconomic inequalities in liver health.

2. Clinical effectiveness

Overview of presented data:

- An **SLR** was conducted in **February 2025** (updated **July 2025**) to identify all relevant clinical evidence on the **efficacy and safety of resmetirom** and relevant comparators in **adults with MASH and liver fibrosis (either diagnosed or suspected)** (Appendix B). The **MAESTRO-NASH phase III RCT** (NCT03900429) was identified as the primary source of clinical effectiveness evidence for this submission (17).
- The efficacy and safety of **resmetirom** for the treatment of **adults with non-cirrhotic MASH with moderate to advanced liver fibrosis (fibrosis stages F2–F3)** was demonstrated in the pivotal, multicentre, **randomised, double-blind, placebo-controlled phase III MAESTRO-NASH trial** (17).
- The **MAESTRO-NASH** population (n = 966) had a high disease burden: 807/966 (**83.5%**) had **NAS ≥ 5** at baseline, 598/966 (**60.4%**) had stage **F3 fibrosis**, and most had multiple metabolic risk factors (**T2DM = 67.0%**, **hypertension = 78.1%**, **dyslipidaemia = 71.3%**).
- At **week 52**, **NASH resolution with no worsening of fibrosis** (one of the dual primary endpoints) was achieved in **25.9%** of patients receiving **resmetirom 80 mg** and **29.9%** receiving **resmetirom 100 mg**, compared with **9.7%** receiving placebo (**p < 0.001** for both comparisons).
- At **week 52**, **≥ 1-stage Fibrosis improvement with no worsening of NAS** (the other dual primary endpoint) was achieved in **24.2%** (80 mg) and **25.9%** (100 mg) of patients, compared with **14.2%** for placebo (**p < 0.001** for both comparisons). Taken together with the NASH resolution results, these findings indicate that a substantial proportion of patients experienced improvement in at least one key histological endpoint.
- Additional histological benefits at **week 52** included higher rates of **≥ 2-point NAS improvement with no fibrosis worsening** (**41.3% [80 mg]**, **44.9% [100 mg]** vs. **21.2% placebo**) and higher rates of **fibrosis improvement by ≥ 2 stages** (**8.3% [80 mg]**, **10.1% [100 mg]** vs. **2.8% placebo**).

- **Resmetirom** treatment significantly reduced **LDL-C** at **week 24** (**–13.6% [80 mg]**, **–16.3% [100 mg]** vs. **+0.1% placebo**; **p < 0.001** for both), with effects maintained at **week 52**; improvements were also seen in other **lipid parameters**, **MRI-PDFF**, and **liver enzymes**.
- Safety analyses in the **F2–F3 population** showed **resmetirom** was generally **well tolerated**; the incidence of **serious adverse events (SAEs)** was **low** and **similar between treatment and placebo groups**.

Key clinical benefits of resmetirom:

- Resmetirom represents the **first pharmacological treatment** to demonstrate clinically meaningful improvements in both **NASH resolution and fibrosis improvement**, addressing critical unmet needs in this progressive disease.
- Provides improvement in liver histology and reductions in atherogenic lipids, potentially lowering the long-term risk of both **liver-related and cardiovascular morbidity and mortality**.
- Offers clinically meaningful benefit in a population with **high baseline disease burden** (moderate to advanced fibrosis, multiple metabolic risk factors), where therapeutic options have been limited.
- Demonstrates a **favourable safety profile** and good tolerability, supporting its use in routine clinical practice.
- By reducing progression of fibrosis and improving cardiometabolic risk factors, resmetirom has the potential to **delay or prevent progression to cirrhosis, LT, and cardiovascular events**, leading to improved HRQoL and reduced burden on the NHS.

2.1 Identification and selection of relevant studies

An SLR was conducted to identify all relevant clinical evidence on the efficacy and safety of resmetirom and relevant comparators for the treatment of adults with non-cirrhotic MASH with moderate to advanced liver fibrosis (fibrosis stages F2 to F3). A detailed description of the SLR methodology and search strategies is presented in Appendix B. The SLR comprised a de novo SLR performed in February 2025 and an SLR update performed in July 2025. Population inclusion criteria in the SLR encompassed adult patients (18 years or older) with a diagnosis of MASH and liver fibrosis (any stage), or adult patients (18 years or older) with MASLD and presumed/suspected MASH. Therefore, the target population for the SLR was broader than the population relevant to the current decision problem.

Overall, a total of 54 records were included (see Appendix B), reporting on 42 unique clinical studies. Three clinical studies have currently generated results on resmetirom for the treatment of MASH or MASLD (presumed MASH), comprising:

- A phase II RCT of resmetirom 80 mg vs. placebo in patients with MASH (NCT02912260, reported across three records (93–95)). The trial included a double-blind, randomised phase, and an open-label extension (OLE) phase of 80 mg initially, followed by 80 mg or 100 mg;
- A phase III RCT of resmetirom 80 mg vs. resmetirom 100 mg vs. placebo in patients with MASH (NCT03900429 [MAESTRO-NASH], reported across three records (17,96,97));
- A phase III RCT of resmetirom 80 mg vs. resmetirom 100 mg vs. placebo in patients with MASLD and presumed MASH (NCT04197479 [MAESTRO-NAFLD-1] (98)).

Further information on the MAESTRO-NASH trial (NCT03900429) is provided in the sections that follow. MAESTRO-NASH was the pivotal phase III trial of resmetirom vs. placebo (resmetirom 80 mg = 322, resmetirom 100 mg = 323, and placebo = 321) (17). NCT02912260 was deprioritised because of the much smaller sample size (resmetirom = 84, placebo = 41) compared to the phase III study, as well as the fact that patients were only randomised to one treatment dosage, i.e., 80 mg. Additionally, a large proportion of patients in the respective arms of the phase II study were at fibrosis stage F1, which is inconsistent with moderate to advanced disease in the decision problem for resmetirom (93).

MAESTRO-NAFLD-1 (NCT04197479) was deprioritised in both clinical and economic sections because of its focus on a population of adults with MASLD, who had presumed Company evidence submission: Resmetirom for treating moderate to advanced liver fibrosis (without cirrhosis) (MASLD) ID6529

MASH as opposed to confirmed, diagnosed utilising solely non-invasive biomarkers and imaging (98).

2.2 List of relevant clinical effectiveness evidence

The primary source of clinical effectiveness evidence for resmetirom for the indication of interest, as utilised in the economic model, is the phase III RCT of resmetirom 80 mg vs. resmetirom 100 mg vs. placebo in patients with MASH (NCT03900429 [MAESTRO-NASH] (17)).

An overview of the MAESTRO-NASH study is provided in Table 6.

Table 6 Clinical effectiveness evidence

Study	MAESTRO-NASH (NCT03900429)
Study design	Randomised, double-blind, placebo-controlled, phase III trial (multicentre)
Population	Adults with biopsy-confirmed MASH and fibrosis stages 1B, 2, or 3
Intervention(s)	Resmetirom 80 mg; Resmetirom 100 mg
Comparator(s)	Placebo
Indicate if study supports application for marketing authorisation	Yes
Indicate if study used in the economic model	Yes
Rationale if study not used in model	N/A
Reported outcomes specified in the decision problem (decision problem outcomes are denoted in bold type)	- MASH resolution - Improvement (reduction) and progression (worsening) in fibrosis stage - Improvement in NAS - Change in lipid profile - Change in MRI-PDFF - Change in liver function tests - Change in MASH inflammation and fibrosis biomarkers - Change in metabolic, liver, and cardiovascular assessments - Non-invasive imaging outcomes - Progression to cirrhosis and DCC with associated DCC events - LT - HCC - Overall survival - Adverse effects of treatment - HRQoL.
All other reported outcomes	All outcomes specified in the decision problem have been reported

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Abbreviations: DCC, decompensated cirrhosis; F1-F3, fibrosis stages 1-3; HCC, hepatocellular carcinoma; HRQoL, health-related quality of life; LT, liver transplantation; MASH, metabolic dysfunction-associated steatohepatitis; MRI-PDFF, MRI-based proton density fat fraction; N/A, not applicable; NAS, NAFLD Activity Score.

2.3 Summary of methodology of the relevant clinical effectiveness evidence

2.3.1 Data presented in the submission – MAESTRO-NASH

The evidence on the effectiveness of resmetirom used in the cost-effectiveness analysis (CEA) (Section 3) is derived exclusively from the completed MAESTRO-NASH trial (17), from which we also obtained patient-level data to inform the economic modelling described in Section 3.2.

2.3.1.1 Trial methodology

Table 7 Summary of trial methodology for MAESTRO-NASH

Trial Number (Acronym)	NCT03900429 (MAESTRO-NASH)
Location	Conducted at 245 sites across 15 countries including the U.S., UK, Germany, France, Canada, Spain, Australia, Austria, Belgium, Switzerland, Italy, Israel, Hungary, Poland, and Mexico.
Trial design	Randomised, double-blind, placebo-controlled, phase III trial. Patients were randomised 1:1:1 to resmetirom 80 mg, resmetirom 100 mg, or placebo. The trial included a 52-week histology endpoint period and a 54-month clinical outcome period. Note: Results for the 54-month analysis are not currently available.
Eligibility criteria for participants	Key eligibility criteria included: Adults ≥ 18 years with biopsy-confirmed NASH and fibrosis stage 1B, 2, or 3; NAS ≥ 4 (with ≥ 1 in each component); CAP ≥ 280 dB/m and liver stiffness measurement (LSM) ≥ 8.5 kPa on FibroScan; ≥ 3 of 5 metabolic risk factors. No more than 15% of the total enrollment could have F1 fibrosis mostly F1B, and no more than 3% of the total enrollment could have F1A or F1C fibrosis (only if N-terminal type III collagen pro-peptide (ProC3) level ≥ 14 ng/mL). Key exclusion criteria were alcohol consumption > 20 g/day for women; > 30 g/day for men, HbA1c level > 9.0 % at screening, causes of chronic liver disease other than non-cirrhotic NASH.
Settings and locations where the data were collected	245 clinical trial sites across North America, Europe, Australia, and Israel. Data were collected from academic medical centres and community-based practices participating in the trial.
Study periods and trial drugs	Screening began in March 2019. Dual primary endpoints assessed at week 52; clinical outcomes endpoint at 54 months. Trial drugs: Resmetirom 80 mg and 100 mg (oral, once daily), compared with placebo.

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Prior and concomitant medication	The following were prohibited: regular use of drugs historically associated with NAFLD, which include, but are not limited, to the following: amiodarone, methotrexate, systemic oral glucocorticoids, tamoxifen, oestrogens at doses greater than those used for hormone replacement or contraception, anabolic steroids except testosterone replacement, valproic acid, and known hepatotoxins for more than 4 weeks within the last 8 weeks prior to the initial screening, GLP-1 RAs unless stable, drugs affecting thyroid function unless stable or per protocol exceptions, high-dose vitamin E unless stable. The following were permitted: medications for comorbid conditions (e.g. T2DM, hypertension, dyslipidaemia) if stable.
Primary outcome	Dual primary endpoints at week 52: (1) NASH resolution (ballooning = 0, inflammation $\leq$ 1, and $\geq$ 2-point NAS reduction) without worsening of fibrosis; (2) $\geq$ 1-stage fibrosis improvement without worsening of NAS.
Secondary outcomes used in the model/ specified in the scope	Key secondary endpoint: Percent change in LDL-C at week 24. Others include: change in MRI-PDFF, liver enzymes, lipid profile, thyroid and sex hormones, liver stiffness (FibroScan and MRE), liver/spleen volume, ELF score, HRQoL, safety and AEs.
Pre-planned subgroups	Subgroups stratified by fibrosis stage (F1B/F2/F3), baseline NAS, age, sex, and T2DM status at baseline. Subgroup analyses presented for histological endpoints.

Abbreviations: AE, adverse event; CAP, Controlled Attenuation Parameter; ELF, Enhanced Liver Fibrosis; F1-F3, fibrosis stages 1-3; GLP-1 RA, glucagon-like peptide-1 receptor agonist; HbA1c, glycated haemoglobin; HRQoL, health-related quality of life; LDL-C, low-density lipoprotein-cholesterol; LSM, liver stiffness measurement; MRE, magnetic resonance elastography; MRI-PDFF, MRI-based proton density fat fraction; NAFLD, non-alcoholic fatty liver disease; NAS, NAFLD Activity Score; NASH, non-alcoholic steatohepatitis; ProC3, Propeptide of type III collagen; T2DM, type 2 diabetes mellitus.

2.3.1.2 Trial design

MAESTRO-NASH was a multicentre, double-blind, randomised, placebo-controlled study. Patients who qualified for study inclusion were randomised in a 1:1:1 manner to receive MGL-3196 (resmetirom) 100 mg, MGL-3196 80 mg, or matching placebo given orally once daily in the morning for up to 54 months. The randomisation was stratified by baseline T2DM status (presence/absence) and fibrosis stage (1, 2, 3). Randomisation was performed with the use of an interactive web-response system. Liver biopsies were planned for all patients at screening, 52 weeks, and 54 months after starting treatment.

Throughout the trial, patients received nutrition and exercise counselling according to current recommendations (84,99). Patients were unaware of the trial-group assignments, as were site personnel, personnel of contract research organisations, and sponsor personnel who were conducting the trial, administering the investigational product, and performing clinical assessments. Selected persons were aware of the trial-group assignments to facilitate dispensation of resmetirom or placebo. All trial personnel were unaware of the results of

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post-baseline tests that could reveal the trial-group assignments, including levels of total and free thyroxine (T4), sex hormone–binding globulin (SHBG), and lipids as well as MRI-PDFF.

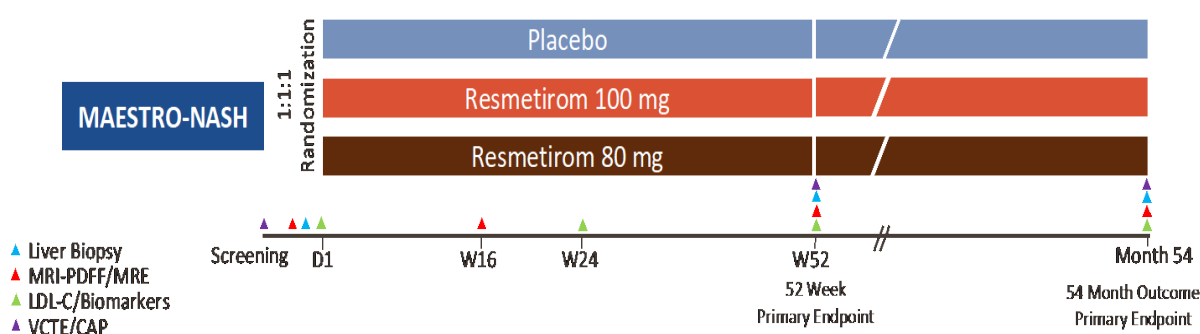
Screening biopsy results were used as baseline values for histological variables, and a second biopsy was performed at week 52. Biopsy specimens on glass slides were assessed centrally by two independent expert pathologists (the second and third authors) to determine the NAS and fibrosis stage (according to NASH Clinical Research Network [CRN] criteria (100)). For the primary analysis, all screening or baseline biopsy specimens and week 52 biopsy specimens on glass slides were re-read independently by both pathologists in large unpaired groups of screening or baseline biopsy specimens (50 to 100 slides per group, spiked with biopsy specimens obtained from patients who had screening failure) or a separate matched set of week 52 biopsy specimens (50 to 100 slides per group). The pathologists were unaware of the trial-group assignments, patient characteristics, and each other's assessments.

A consensus review was conducted as a supportive analysis wherein the two pathologists read blinded (to time of biopsy and identification code) digitised images for cases in which there was disagreement on the primary read with respect to response status for the two primary endpoints or a reduction in fibrosis by at least two stages. Only the NAS or fibrosis components that determined the response for which there was disagreement between the pathologists were re-read.

The dual primary endpoints at week 52 were NASH resolution (achievement of a hepatocellular ballooning score of 0, a lobular inflammation score of 0 or 1, and a reduction in the NAS by ≥ 2 points) with no worsening of fibrosis, and Fibrosis improvement (reduction) by at least one stage with no worsening of the NAS. The key secondary endpoint was the percent change from baseline in the LDL-C level at week 24.

The study design for MAESTRO-NASH is depicted in Figure 6.

Figure 6 MAESTRO-NASH study design



Abbreviations: CAP, Controlled Attenuation Parameter; LDL-C, low-density lipoprotein-cholesterol; MRE, magnetic resonance elastography; MRI-PDFF, MRI-based proton density fat fraction; VCTE, Vibration-Controlled Transient Elastography.

2.3.1.3 Population and eligibility criteria

The population for this study was male and female patients ≥ 18 years of age with biopsy-proven NASH. The population comprised patients diagnosed as 'high-risk' fibrosis stage 1 (F1B plus high-risk F1A/F1C) or fibrosis stages 2 or 3. The study design was to limit the number of F1B plus high-risk F1A/F1C patients to no more than 15%; however, the F1A/F1C population comprised $\leq 3\%$ of the total population and was only eligible for participation with a screening PRO-C3 lab value that was > 14 ng/mL. The F3 population would comprise at least 50% of the total population. Only F2 and F3 patients were included in the primary efficacy analyses. Analyses of the F1 population was considered exploratory. The key inclusion and exclusion criteria for MAESTRO-NASH are presented in Table 8.

Table 8 Key eligibility criteria for MAESTRO-NASH

Key inclusion criteria	Key exclusion criteria
≥ 18 years of age; ≥ 3 out of 5 metabolic risk factors using a modified version of the International Diabetes Foundation criteria (101), and a pre-screening VCTE; FibroScan within the past 3 months with values consistent with CAP ≥ 280 dB/m and LSM ≥ 8.5 kPa (alternatively a historic liver biopsy within 6 months of randomisation that was confirmed as eligible by the study's central pathologist); - Histological evidence of NASH;	- Alcohol consumption > 20 g/day for women, > 30 g/day for men; - HbA1c level $> 9.0\%$ at screening; - Causes of chronic liver disease other than non-cirrhotic NASH.

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Key inclusion criteria	Key exclusion criteria
- NAS ≥ 4 with a score of ≥ 1 for each component (steatosis, hepatocyte ballooning, lobular inflammation); - The majority F2/F3 and at least 50% of the total enrollment having F3 fibrosis; - Weight was required to be stable ($< 5\%$ change in 3 months); - Doses of GLP-1 RAs were required to be stable for at least 6 months before biopsy.	

Abbreviations: CAP, Controlled Attenuation Parameter; F2-F3, fibrosis stages 2-3; GLP-1 RA, glucagon-like peptide-1 receptor agonist; HbA1c, glycated haemoglobin; LSM, liver stiffness measurement; NAFLD, non-alcoholic fatty liver disease; NAS, NAFLD Activity Score; NASH, non-alcoholic steatohepatitis; VCTE, Vibration-Controlled Transient Elastography.

Appendix J provides the full inclusion and exclusion criteria for the MAESTRO-NASH study, which outlines the characteristics of patients eligible for enrollment.

Screening

Potential patients to be screened for this study had to:

- not have any history of significant alcohol consumption;
- have at least three metabolic risk factors using a slightly modified version of the International Diabetes Foundation criteria (101);
- have either:
 - both AST and FibroScan requirements:
 - AST > 17 IU (women) and AST > 20 IU (men) **AND** a FibroScan within 3 months of planned screening showing KpA ≥ 8.5 CAP ≥ 280 .

OR

have a historic liver biopsy < 2 years old demonstrating fibrosis stage 1B, 2 or 3 with NASH (NAS ≥ 4 , all components).

2.3.1.4 Study settings and locations

The MAESTRO-NASH study was a multinational, multicentre, phase III RCT with sites across several countries in North America, Europe, and Australia (245 sites in 15 countries in total). The trial was carried out in secondary and tertiary care settings, including academic medical centres and specialist hepatology clinics, ensuring broad geographic and clinical

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representation of patients with non-cirrhotic MASH and moderate to advanced liver fibrosis (stages F2–F3).

2.3.1.5 Trial drugs and concomitant medications

MGL-3196 and matching placebo are available as a tablet for oral administration. The tablet is manufactured in 60, 80, and 100 mg dose strengths. The range of dose strengths provided all of the doses used in the study.

In patients assigned to 100 mg or 80 mg arms, doses were decreased by 20 mg to 80 or 60 mg, respectively, at week 12 in the case of $\geq 30\%$ decrease from baseline in FT4 to < 0.7 ng/dL, observed on two consecutive regularly scheduled visits four weeks apart, specifically, at weeks 4 and 8. In subjects assigned to the MGL-3196 100 mg arm who were dose reduced to 80 mg at week 12, if FT4 at weeks 16 and 20 continued to be $\geq 30\%$ decreased from baseline and < 0.7 ng/dL, the dose could be further decreased to 60 mg at week 24. No dose reductions would be made later than week 24 and the patient's dose would not be reduced to < 60 mg. In the open-label treatment arm of the study in patients with hepatic impairment, doses as low as 40 mg were allowed. During the trial itself, these dose adjustments occurred only rarely.

Concomitant medication was defined as any prescription or over-the-counter preparation, including vitamins, over-the-counter medications, and supplements. Each concomitant medication received from 30 days before the first dose of study drug, initiated during the study as well as to 30 days following the last dose of all study drug(s) must have been recorded in the electronic case report form (eCRF).

A complete list of medications prohibited during the MAESTRO-NASH study is provided in Appendix J.

2.3.1.6 Outcomes used in the economic model or specified in the scope

All efficacy endpoints were assessed in the F2 and F3 patients. These objectives were assessed in F1 patients in an exploratory fashion.

Dual primary efficacy endpoints

For the week 52 analysis, the dual primary objectives were:

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1. To determine the effect of once-daily, oral administration of 80 or 100 mg MGL-3196 vs. matching placebo on NASH, as measured by:

The resolution of NASH associated with an at least 2-point reduction in NAS and without worsening of fibrosis by liver biopsy after 52 weeks of treatment (week 52 dual primary endpoint). Resolution includes:

- The total absence of ballooning (score = 0) and absent or mild inflammation (score 0 to 1) (associated with an at least 2-point reduction in NAS);
- No worsening of fibrosis, defined as any progression ≥ 1 stage.

For F1B patients, a change to F2 is not considered 1-stage worsening.

Note: A “**NASH resolution responder**” in this study was defined as ballooning = 0, inflammation = 0,1, and at least a 2-point reduction in NAS with no worsening of fibrosis stage as compared with the baseline liver biopsy.

2. To determine the effect of once-daily, oral administration of 80 or 100 mg MGL-3196 vs. placebo on the histological improvement from baseline demonstrated by at least a 1-point improvement in fibrosis (NASH CRN system (100)) by liver biopsy with no worsening of NAS (total of three NAS components: ballooning, inflammation, and steatosis) at week 52. For F1B patients, a 1-point improvement in fibrosis would be a change to F0. For F2 patients, a 1-point improvement in fibrosis would be a change to F1A or F1C (a change of F2 to F1B is not considered a 1-point improvement).

Note: A “**Fibrosis responder**” in this study was defined as at least a 1-point reduction in fibrosis stage with no worsening of NAS as compared with the baseline liver biopsy.

Key secondary efficacy endpoint

For the week 52 analysis, the key secondary endpoint was the percent change from baseline in the LDL-C level at week 24.

Other secondary and exploratory endpoints

All secondary and exploratory endpoints assessed in the MAESTRO-NASH trial are presented in Appendix J, with definitions of key endpoints. These span histological, biomarker, and imaging assessments, metabolic and cardiovascular outcomes, liver-related clinical events, survival, safety, and HRQoL.

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2.3.1.7 Patient datasets and baseline characteristics

The MAESTRO-NASH clinical study protocol specified and ran statistical analyses based on several analysis 'populations' (i.e., datasets or subsets) defined by clinical, diagnostic, and data-gathering criteria, as summarised below. Datasets or subsets relevant to this submission are highlighted with a grey field.

- **Intent-to-Treat Population (ITT):** included all patients who were randomised in the study. Treatment groups were defined by randomised assignment (including dose level), regardless of the actual treatment received. This group forms a master population from which the following populations are taken.
- **Safety Population (n = 966):** included all F1B, F2, and F3 patients in the ITT population who received at least 1 dose of study drug. Treatment assignment was determined by actual treatment received on day 1. This population was used for all safety analyses including those presented in Harrison et al 2024 (17).
- **Modified Intent-to-Treat Population (mITT):** included all F1B, F2, and F3 patients who were randomised in the study. Treatment groups were defined by randomised assignment (including dose level), regardless of actual treatment received. The mITT population will be used for the month 54 primary efficacy analysis and all other month 54 efficacy analyses that are not based on liver biopsies (data not available).
- **Week 52 mITT Population (mITT-W52) (n = 966):** included all patients in the mITT population that were randomised on or before July 31, 2021. Treatment groups were defined by randomised assignment (including dose level), regardless of actual treatment received. The mITT-W52 population was used for all week 52 efficacy analyses that were not based on liver biopsies, as presented in Harrison et al. 2024 (17).
- **Liver Biopsy mITT Population (mITT-LB-W52) (n = 955):** this population was used for the main week 52 efficacy analyses that were based on liver biopsies, including the dual primary endpoints reported in Harrison et al. 2024 (17). The mITT-LB-W52 dataset was a subset of mITT-w52 that excluded eleven (n = 11) patients who had unacceptably delayed week 52 biopsies due to the COVID-19 pandemic.
- **Paired Liver Biopsy Population at Week 52 (PLB-W52) (n = 782):** this limited patients in the mITT-W52 population to include only those who took at least one dose of study medication, had a baseline liver biopsy, and finished the week 52 visit with an acceptable (i.e., considered interpretable by central reader) liver biopsy. Analyses for this population were presented Table S9 in the online supplement to Harrison et

al. 2024 (17), and patient-level data from MAESTRO-NASH in this population were used to derive key transition estimates in the economic model.

Detailed history

From March 2019 to July 2021, 966 patients with F1B, F2, or F3 fibrosis at baseline were randomised to resmetirom 80 mg (n = 322), resmetirom 100 mg (n = 323), or placebo (n = 321) – this formed the mITT and “Safety” populations for analysis (n = 966). A total of 84 patients who had a fibrosis stage of F1A or F1C at baseline were randomly assigned to receive 80 mg of resmetirom (30 patients), 100 mg of resmetirom (26 patients), or placebo (28 patients) as an exploratory analysis population for safety and efficacy.

A total 11 of 966 patients had a delay in their week 52 biopsy for reasons related to COVID-19, were considered to have missing data completely at random, and were removed for analyses based on biopsy, consistent with regulatory guidance regarding COVID-19. The resulting population of 955 patients (called “Primary biopsy analysis population (mITT-LB-W52)”) was used for the main biopsy-related analyses in Harrison et al. 2024 (17), and had n = 316 in the 80 mg resmetirom group, n = 321 in the 100 mg resmetirom group, and n = 318 in the placebo group (17).

The demographic and baseline characteristics for the population at baseline are presented in Table 9 and Table 10 below. Most patients were white (89.3%) with a high incidence of metabolic risk factors (hypertension, 78.1%; dyslipidaemia, 71.3%; T2DM, 67.0%). A total of 21.1% of the patients were Hispanic; only 2.0% of the patients were black. The mean ($\pm$ SD) age of the patients was 56.6 ± 10.9 years and the mean BMI (the weight in kilograms divided by the square of the height in metres) was $35.7 \pm 6.8 \text{ kg/m}^2$. Baseline biopsies indicated that 83.5% of the patients had a NAS ≥ 5 , 5.1% had F1B, 33.0% had F2, and 60.4% had F3 fibrosis. Common baseline medications were generally balanced across treatment arms (Table 9 and Table 10). At the time of database lock for the week 52 endpoints, adherence to the trial regimen was high (92% with $> 80\%$ adherence).

Further demographic and baseline characteristics by fibrosis stage are presented in Appendix J, while further details of the PLB-W52 population are described in Section 3.2.1.

Table 9 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/m²	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)
10-year ASCVD risk score, %¶	14.7 ± 12.0	14.5 ± 12.1	15.4 ± 11.6
FibroScan VCTE/LSM, kPa	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.

*Plus-minus values are means ± SD. Percentages may not total 100 because of rounding.

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†Data on sex, race, and ethnic group were reported by the patient.

‡“Other” includes American Indian or Alaska Native, Native Hawaiian or other Pacific Islander, and all other non-specified race or ethnic group categories.

§Shown are patients who were receiving thyroxine-replacement therapy at screening.

¶The risk of cardiovascular events was derived from multiple risk factors, including age, sex, race, systolic blood pressure, diastolic blood pressure, total cholesterol, HDL-C, LDL-C, history of diabetes, smoking status, hypertension treatment, statin treatment, and aspirin therapy. Persons are preliminarily classified on the basis of estimated risk: a 10-year risk of ASCVD of less than 5% is low risk; 5 to 7.4% is borderline risk; 7.5 to 19.9% is intermediate risk; and 20% or more is high risk.

||Liver stiffness was measured by means of VCTE. Values of more than 8.5 are considered to be indicative of fibrosis of stage F2 or higher.

**CAP is a method for the non-invasive assessment of steatosis, which measures the increased attenuation of ultrasound waves when traveling through steatotic hepatic tissue, as compared with normal liver tissue. The maximum value is 360 dB per metre; for this trial, a reading of more than 280 dB per metre was considered to be high.

††MRI-PDFF is a magnetic resonance imaging–derived non-invasive, quantitative biomarker to assess liver fat content. A reading of more than 5% is considered to be high.

‡‡The Fibrosis-4 index score is derived from platelet count, AST level, age, and ALT level. Scores of more than 2.67 are considered to be indicative of advanced fibrosis and an elevated risk of liver-related events.

§§The NAS is assessed on a scale of 0 to 8, with higher scores indicating more severe disease; the components of this measure are steatosis (assessed on a scale of 0 to 3), lobular inflammation (assessed on a scale of 0 to 3), and hepatocellular ballooning (assessed on a scale of 0 to 2). NAS of 4 or more are considered to indicate at-risk NASH.

¶¶Fibrosis stages range from F0 (no fibrosis) to F4 (cirrhosis). A stage of F1B indicates moderate fibrosis, pericentral area only. Five patients in each group who were scored as having F3 fibrosis at eligibility and who were rescored as having F4 fibrosis at baseline by one or both central pathologists were evaluated in the F3 group.

Table 10 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
Apolipoprotein 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)

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	Resmetirom 80 mg (n = 322)	Resmetirom 100 mg (n = 323)	Placebo (n = 321)
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.

*Plus-minus signs are mean $\pm$ SD.

†Safety population.

2.4 Statistical analysis and definition of study groups in the relevant clinical effectiveness evidence

2.4.1 Statistical analysis overview

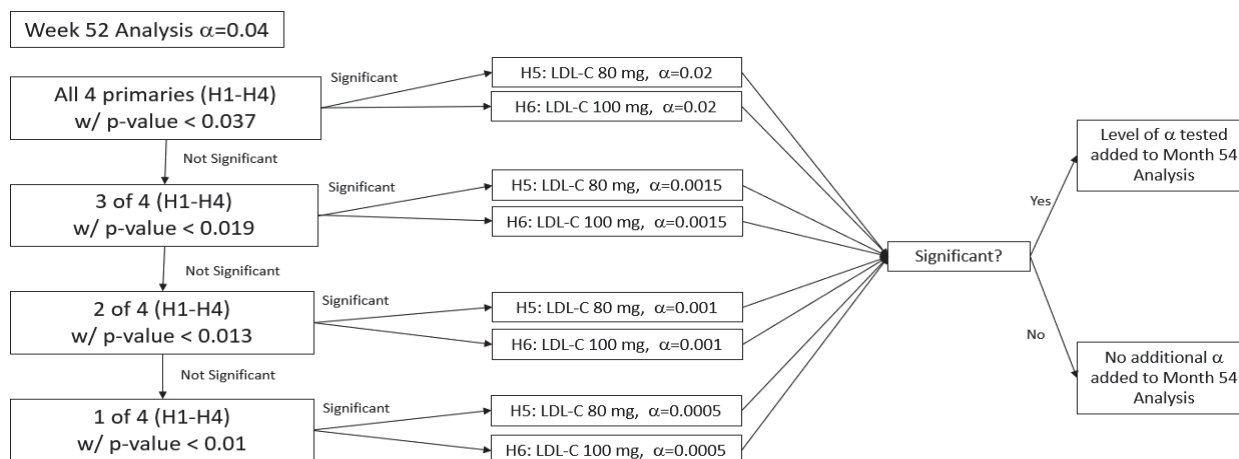
On the basis of a sample size of at least 780 patients, the trial had more than 90% power to detect a difference between each dose of resmetirom and placebo with the use of a stratified Cochran–Mantel–Haenszel test, under the assumption that NASH resolution with no worsening of fibrosis would occur in 7.2% of the patients receiving placebo and 19.8% of those receiving resmetirom and that fibrosis improvement by at least one stage with no worsening of the NAS would occur in 14% of the patients receiving placebo and 26% of those receiving resmetirom (93). No comparisons were planned between the two resmetirom dose groups.

The trial recruited additional patients to further expand the safety profile of resmetirom, support more robust subgroup analyses, and allow for uncertainty in the assumed treatment effects relative to placebo. Multiplicity was controlled with the use of a weighted Bonferroni approach ($\alpha = 0.04$ at week 52 and $\alpha = 0.01$ at month 54). In addition, a two-stage gatekeeping procedure was used to control α at 0.04 for the week 52 family of endpoints. Recycling of α to the month 54 analysis, as appropriate, is planned.

The primary statistical analysis model used the Cochran–Mantel–Haenszel test to determine response with respect to the biopsy endpoints. Patients with missing biopsies were considered to have not had a response. Disagreement was incorporated into a statistical Cochran–Mantel–Haenszel model that provided partial credit for cases in which pathologists disagreed on response status for any biopsy endpoint. Multiple sensitivity analyses were conducted, including multiple imputation and tipping-point analysis. All reported p-values were two-sided. For endpoints not included in the hierarchical plan to adjust for multiple testing, 95% CIs were reported without p-values; 95% CIs should not be used in place of Company evidence submission: Resmetirom for treating moderate to advanced liver fibrosis (without cirrhosis) (MASLD) ID6529

hypothesis tests. An overview of the statistical testing process for primary and key secondary endpoints is presented in Figure 7 below.

Figure 7 Statistical testing process for primary and key secondary efficacy endpoints at week 52



Abbreviations: LDL-C, low-density lipoprotein-cholesterol.

2.4.2 Analysis populations

Details of the analysis populations are provided in Section 2.3.1.7.

2.4.3 Sample size

The sample size was estimated using a 2-sided, $\alpha = 0.01$ Cochran-Mantel-Haenszel test to provide 95% power for testing each MGL-3196 dose vs. placebo. A placebo response rate of 8% and MGL 3196 response rates of 22% were assumed for both the 80 and 100 mg doses. The response rates assumed for placebo and MGL-3196 were based (conservatively) on the MGL-3196 phase II NASH study (93). It was assumed that up to 10% of patients would dropout before having a week 52 liver biopsy (although one may be obtained at the early termination visit); patients with a missing week 52 biopsy were to be counted as non-responders. As reported in Section 2.4.1, the response rates adjusted for patients who dropped out were 7.2% for the placebo group and 19.8% for each MGL 3196 dose group. A minimum of 780 total patients (260 in each arm) was needed to reach the desired power for the primary endpoint.

2.4.4 Statistical analysis

A summary of statistical analyses for MAESTRO-NASH is presented in Table 11.

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Table 11 Summary of statistical analyses

Trial number (acronym)	Hypothesis objective	Statistical analysis	Sample size, power calculation	Data management, patient withdrawals
NCT03900429 (MAESTRO-NASH)	The trial had two co-primary efficacy hypotheses at week 52: 1. Resmetirom is superior to placebo in achieving NASH resolution with no worsening of fibrosis; 2. Resmetirom is superior to placebo in achieving ≥ 1-stage fibrosis improvement with no worsening of NAS.	The proportion of patients with a NASH resolution response in each MGL-3196 dose group was compared to placebo using a relative risk analysis from a Cochran-Mantel-Haenszel χ^2 test that was stratified by baseline T2DM status (presence/absence) and baseline fibrosis stage (2 or 3). The analysis was performed on the week 52 population. Patients without week 52 biopsy data in the analysis window due to early study termination or any other reason were counted as non-responders. Sensitivity analyses were performed to assess the robustness of the non-responder imputations for missing biopsies. Separate analyses were performed to compare each MGL-3196 dose to placebo. Corresponding estimates of the relative risk were provided along with 95% CIs.	For the primary endpoints, a minimum of 780 total patients was needed (260 in each arm) to reach the desired power. The sample size was estimated using a 2-sided, $\alpha = 0.01$ Cochran-Mantel-Haenszel test to provide 95% power for testing each MGL-3196 dose vs. placebo. A placebo response rate of 8% and MGL 3196 response rates of 22% were assumed for both the 80 and 100 mg doses. It was assumed that up to 10% of patients would dropout before having a week 52 liver biopsy (although one may be obtained at the early termination visit); patients with a missing week 52 biopsy were to be counted as non-responders. The response rates adjusted for patients who dropped out were 7.2% for the placebo group and 19.8% for each MGL 3196 dose group.	Electronic data capture was used for data management with regular monitoring. Patients who withdrew were included in appropriate analyses. Withdrawals were accounted for in the imputation strategy. Reasons for discontinuation were collected and documented.

Abbreviations: CI, confidence interval; ITT, intent-to-treat; mITT, modified intent-to-treat; NAS, NAFLD Activity Score; NASH, non-alcoholic steatohepatitis; T2DM, type 2 diabetes mellitus.

Week 52 primary analysis – Dual primary endpoints

NASH resolution response

The proportion of patients with a NASH resolution response in each MGL-3196 dose group was compared to placebo using a relative risk analysis from a Cochran-Mantel-Haenszel χ^2 test that was stratified by baseline T2DM status (presence/absence) and baseline fibrosis stage (2 or 3). The analysis was performed on the week 52 population. Patients without week 52 biopsy data in the analysis window due to early study termination or any other reason were counted as non-responders. Sensitivity analyses were performed to assess the robustness of the non-responder imputations for missing biopsies. Separate analyses were performed to compare each MGL-3196 dose to placebo. Corresponding estimates of the relative risk were provided along with 95% CIs.

Fibrosis ≥ 1 stage improvement

Histological improvement from baseline demonstrated by at least a one-point improvement in fibrosis (NASH CRN system (100)) with no worsening of NAS (total of three NAS components – ballooning, inflammation and steatosis) at the 52-week liver biopsy (fibrosis ≥ 1 stage responder) was analysed using Cochran-Mantel-Haenszel χ^2 tests stratified by the baseline randomisation factors. Analyses were performed separately for each MGL-3196 dose vs. placebo.

Secondary and exploratory endpoints

Key secondary endpoint

The LDL-C percent change from baseline at week 24 was analysed using a mixed model for repeated measurements (MMRM) based on the week 52 population using all three arms in same model. The model included terms for treatment, visit (weeks 4, 12, 16 and 24), presence of diabetes at baseline, baseline fibrosis stage, and treatment-by-visit interaction where treatment was 100 mg, 80 mg, or placebo. The week 8 assessment was excluded from the MMRM analysis because patients would not be fasted at this visit. An unstructured covariance matrix was used in the MMRM model. Sensitivity analyses to evaluate the effect of missing lab data was performed as defined in the statistical analysis plan (SAP).

Note: The analysis of the week 24 LDL-C key secondary endpoint was conducted at the time of the week 52 primary analysis.

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Other secondary and exploratory endpoints

The SAP pre-specified a range of additional secondary and exploratory endpoints for the week 52 analysis. These endpoints were assessed descriptively and, where applicable, through statistical analyses consistent with the SAP.

Analysis of safety

Safety analyses were performed in the safety population in patients with F2 or F3 NASH at baseline as the primary safety analysis. Results from patients with F1B or high-risk F1A/F1C NASH at baseline would be presented separately. Combined safety (all randomised patients) would also be presented.

The safety endpoints for this study included: AEs, clinical laboratory assessments, vital signs, 12-lead electrocardiograms (ECGs), concomitant medications, clinical assessments, and Model for End-Stage Liver Disease (MELD) scores. The National Cancer Institute (NCI) Common Terminology Criteria for Adverse Events (CTCAE) Version 4.03 (102) was used for assessing the severity of AEs and laboratory tests.

The AEs were coded using a current version of the Medical Dictionary for Regulatory Activities (MedDRA) (103). A treatment-emergent AE (TEAE) was defined as an AE which is new or worsening after the patient has received the first dose of study drug and onset within 30 days after the last dose of study medication. A general summary of patients with AEs, TEAEs, and serious adverse events (SAEs) were tabulated with numbers and percentages of patients and repeated for severity and relationship to study drug per treatment group. The number of AEs leading to withdrawal and SAEs leading to death were summarised. The incidence of AEs, TEAEs, and SAEs were summarised by body system and treatment group.

2.5 Critical appraisal of the relevant clinical effectiveness evidence

The MAESTRO-NASH study (17) was assessed using the Cochrane Risk of Bias 2.0 tool (104) across five domains. The overall risk of bias was judged to be low, indicating high methodological rigour and low concern for bias. A summary of judgements across domains is provided in Table 12 below. Full results of the critical appraisals for all studies included in the SLR of clinical evidence are presented in Appendix B.

Table 12 Summary of MAESTRO-NASH critical appraisal

Domain	Risk of Bias Judgement	Comments
1. Randomisation process	Low	Random sequence generation and allocation concealment were adequate; no baseline imbalances were observed.
2. Deviations from intended interventions	Low	Trial was double-blind; participants, carers, and personnel were unaware of group allocation; appropriate analysis used.
3. Missing outcome data	Low	Some missing data, but evidence suggests minimal risk of bias due to missingness.
4. Measurement of the outcome	Low	Outcome measures were appropriate and applied equally; outcome assessors were blinded.
5. Selection of the reported result	Low	Analyses were consistent with the pre-specified plan; no evidence of selective reporting.
Overall	Low	

2.6 Clinical effectiveness results of the relevant studies

2.6.1 Results of dual primary endpoints

The primary endpoint analysis, carried out in the mITT-LB-W52 population (n = 955), NASH resolution with no worsening of fibrosis was achieved in significantly more resmetirom-treated patients vs. placebo-treated patients (25.9% [80 mg] and 29.9% [100 mg] vs. 9.7% [placebo]; $p < 0.001$ vs. placebo for both). A ≥ 1 -stage fibrosis improvement with no worsening of NAS was also achieved in significantly more resmetirom-treated vs. placebo-treated patients (24.2% [80 mg] and 25.9% [100 mg] vs. 14.2% [placebo]; $p < 0.001$ for both comparisons with placebo; Table 13 and Figure 8). A consensus read (sensitivity analysis) of digitised images of biopsies where there was disagreement between the pathologists as to whether there was a response with respect to either primary endpoint yielded similar results to those of the primary analysis. Similar results were obtained individually by each pathologist on reads of glass (primary) and in multiple sensitivity analyses (Table 14-Table 17). Results in the population of patients with eligible biopsies at baseline and week 52,

pertinent to the economic analysis described in Section 3, were generally supportive of the primary analyses (Table 3, Appendix J).

Table 13 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 between Resmetirom 80 mg and Placebo (95% CI)†	p-value	% difference between Resmetirom 100 mg and Placebo (95% CI)†	p-value
NASH resolution with no worsening of fibrosis							
Primary	25.9	29.9	9.7	16.4 (11.0, 21.8)	< 0.001	20.7 (15.3, 26.2)	< 0.001
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)	< 0.001	11.8 (6.4, 17.2)	< 0.001
Consensus (sensitivity)	24.4	25.5	12.3	12.2 (6.3, 18.2)		13.4 (7.4, 19.3)	

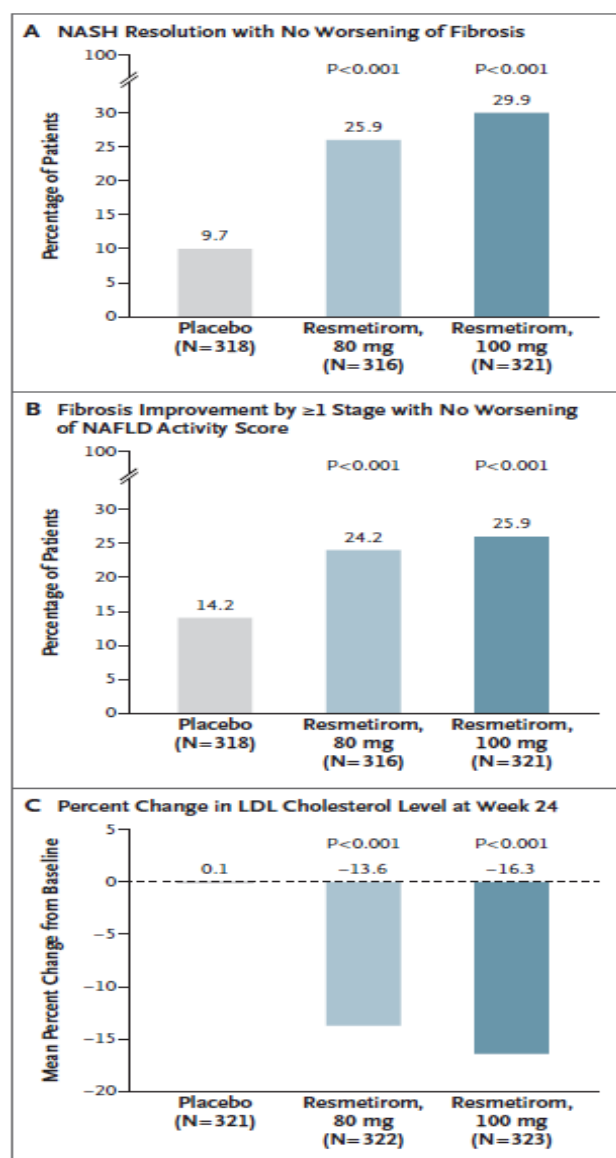
Abbreviations: CI, confidence interval; NAS, NAFLD Activity Score; NASH, non-alcoholic steatohepatitis.

*Of the 966 patients in the primary population, 11 patients (6 in the 80 mg resmetirom group, 3 in the 100 mg resmetirom group, and 2 in the placebo group) had a delay in their week 52 biopsy for reasons related to COVID-19 and were not evaluated for the endpoints shown here. NASH resolution was defined as a hepatocellular ballooning score of 0, a lobular inflammation score of 0 or 1, and a reduction in the NAS by at least 2 points.

†The widths of the CIs have not been adjusted for multiplicity and may not be used for hypothesis testing.

Data for patients with missing response data at week 52 were imputed under the missing at random assumption by running a simulation (100 times) which produces a correlated pair of binary 0/1 data for each patient that represents the patient's response status for each pathologist. The statistics were then calculated for each imputation using the same approach as for the primary endpoint. The normalised results from each dataset were combined using Rubin's rule. Patients that were F3 at eligibility and re-evaluated as F4 at baseline by either pathologist are included in this analysis.

Figure 8 Dual primary and key secondary endpoints (mITT-LB-W52 population, n = 955)



Abbreviations: LDL, low-density lipoprotein; NASH, non-alcoholic steatohepatitis.

Table 14 Sensitivity analysis of dual primary endpoints: multiple imputation (mITT-LB-W52 population, n = 955)

	% response Resmetirom 80 mg (n = 316)	% response Resmetirom 100 mg (n = 321)	% response Placebo (n = 318)	% difference between Resmetirom 80 mg and Placebo (95% CI)	% difference between Resmetirom 100 mg and Placebo (95% CI)
NASH resolution with no worsening of fibrosis					
Multiple imputation (sensitivity)	31.0	36.0	13.5	17.7 (11.3, 24.1)	23.2 (16.8, 29.6)
Fibrosis improvement with no worsening of NAS					

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	% response Resmetirom 80 mg (n = 316)	% response Resmetirom 100 mg (n = 321)	% response Placebo (n = 318)	% difference between Resmetirom 80 mg and Placebo (95% CI)	% difference between Resmetirom 100 mg and Placebo (95% CI)
Multiple imputation (sensitivity)	29.2	31.9	17.9	11.4 (5.1, 17.8)	14.1 (7.9, 20.4)

Abbreviations: CI, confidence interval; NAS, NAFLD Activity Score; NASH, non-alcoholic steatohepatitis.

Data for patients with missing response data at week 52 were imputed under the missing at random assumption by running a simulation (100 times) which produces a correlated pair of binary 0/1 data for each patient that represents the patient's response status for each pathologist. The statistics were then calculated for each imputation using the same approach as for the primary endpoint. The normalised results from each dataset were combined using Rubin's rule.

Patients that were F3 at eligibility and re-evaluated as F4 at baseline by either pathologist are included in this analysis.

Table 15 Sensitivity analysis of dual primary endpoint (NASH resolution): generalised estimating equation model (mITT-LB-W52 population, n = 955)

	Resmetirom 80 mg (n = 316)	Resmetirom 100 mg (n = 321)	Placebo (n = 318)
NASH resolution at week 52, no. (%)*			
(1,1)	62 (19.6)	62 (19.3)	18 (5.7)
(1,0)	24 (7.6)	55 (17.1)	22 (6.9)
(0,1)	16 (5.1)	13 (4.0)	4 (1.3)
(0,0)	214 (67.7)	191 (59.5)	274 (86.2)
Odds ratio (OR) of resmetirom group to placebo†	3.5	4.2	
95% CI of the OR	(2.3, 5.2)	(2.8, 6.2)	
Difference in percentage of responders, Cochran–Mantel–Haenszel, resmetirom group – placebo (SD)†	17.5 (3.0)	21.3 (3.0)	
95% CI of the difference	(11.7, 23.3)	(15.4, 27.2)	

Abbreviations: CI, confidence interval; NASH, non-alcoholic steatohepatitis; OR, odds ratio; SD, standard deviation.

*The ordered pair indicates (result according to pathologist A, result according to pathologist B). 1 indicates yes/responder; 0 indicates no/non-responder.

†The OR and difference in percentage of responders, 95% CIs, and p-values were obtained by fitting a generalised estimating equation model with treatment arm, baseline T2DM status, baseline fibrosis stage, and pathologist by treatment interaction as factors, logit link function and a compound symmetric covariance structure, under the assumption that the scores from the two pathologists are repeated measurements for the same patient with some within-patient correlation structure.

Patients with no valid biopsy within the week 52 window are considered non-responders for the week 52 analysis, as are patients who experience a composite clinical endpoint (e.g., LT, death) prior to their week 52 biopsy.

Patients that were F3 at eligibility and re-evaluated as F4 at baseline by either pathologist are included in this analysis.

Table 16 Sensitivity analysis of dual primary endpoint (Fibrosis improvement): generalised estimating equation model (mITT-LB-W52 population, n = 955)

	Resmetirom 80 mg (n = 316)	Resmetirom 100 mg (n = 321)	Placebo (n = 318)
Fibrosis improvement at week 52, no. (%)*			
(1,1)	52 (16.5)	51 (15.9)	28 (8.8)
(1,0)	21 (6.6)	34 (10.6)	21 (6.6)
(0,1)	28 (8.9)	30 (9.3)	13 (4.1)
(0,0)	215 (68.0)	206 (64.2)	256 (80.5)
OR of resmetirom group to placebo†	2.0	2.1	
95% CI of the OR	(1.4, 2.9)	(1.5, 3.0)	
Difference in percentage of responders, Cochran–Mantel–Haenszel, resmetirom group - placebo (SD)†	9.7 (2.7)	11.0 (2.7)	
95% CI of the difference	(4.4, 15.0)	(5.7, 16.3)	

Abbreviations: CI, confidence interval; OR, odds ratio; SD, standard deviation.

*The ordered pair indicates (result according to pathologist A, result according to pathologist B). 1 indicates yes/responder; 0 indicates no/non-responder.

†The OR and difference in percentage of responders, 95% CIs, and p-values were obtained by fitting a generalised estimating equation model with treatment arm, baseline T2DM status, baseline fibrosis stage, and pathologist by treatment interaction as factors, logit link function and a compound symmetric covariance structure, under the assumption that the scores from the two pathologists are repeated measurements for the same patient with some within-patient correlation structure.

Patients with no biopsy within the week 52 window or experience a composite clinical endpoint (e.g., LT, death) prior to their week 52 biopsy are considered non-responders for the week 52 analysis.

Patients that were F3 at eligibility and re-evaluated as F4 at baseline by either pathologist are included in this analysis.

Table 17 Sensitivity analysis of dual primary endpoints: Tipping point (mITT-LB-W52 population, n = 955)

	% response Resmetirom 80 mg (n = 316)	% response Resmetirom 100 mg (n = 321)	% response Placebo (n = 318)	% difference between Resmetirom 80 mg and Placebo (95% CI)†	p-value	% difference between Resmetirom 100 mg and Placebo (95% CI)†	p-value
NASH resolution							
Placebo – 0% imputed responders (Primary Analysis)	25.9	29.9	9.7	16.4 (11.0, 21.8)*	< 0.001	20.7 (15.3, 26.2)*	< 0.001
Placebo – 30% imputed responders	25.9	29.9	13.7	12.4 (6.5, 18.3)	< 0.001	16.7 (10.9, 22.6)	< 0.001
Placebo – 60% imputed responders	25.9	29.9	17.8	8.3 (2.2, 14.4)	0.0154	12.7 (6.6, 18.8)	< 0.001
Placebo – 67% imputed responders	25.9	29.9	18.8	7.4 (1.2, 13.5)	0.0377	11.7 (5.6, 17.9)	< 0.001

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	% response Resmetirom 80 mg (n = 316)	% response Resmetirom 100 mg (n = 321)	% response Placebo (n = 318)	% difference between Resmetirom 80 mg and Placebo (95% CI)†	p-value	% difference between Resmetirom 100 mg and Placebo (95% CI)†	p-value
Placebo – 90% imputed responders	25.9	29.9	21.9	4.2 (-2.0, 10.4)	0.3693	8.6 (2.4, 14.8)	0.0130
Placebo – 100% imputed responders	25.9	29.9	23.4	2.6 (-3.5, 8.8)	0.4047	7.0 (0.9, 13.2)	0.0246
Fibrosis improvement							
Placebo – 0% imputed responders (Primary Analysis)	24.2	25.9	14.2	10.2 (4.8, 15.7)*	< 0.001	11.8 (6.4, 17.2)*	< 0.001
Placebo – 10% imputed responders	24.2	25.9	15.6	8.8 (3.2, 14.4)	0.0048	10.4 (4.8, 15.9)	< 0.001
Placebo – 20% imputed responders	24.2	25.9	16.8	7.5 (1.8, 13.3)	0.0201	9.1 (3.4, 14.8)	0.0038
Placebo – 25% imputed responders	24.2	25.9	17.5	6.9 (1.1, 12.7)	0.0398	8.5 (2.7, 14.2)	0.0084
Placebo – 30% imputed responders	24.2	25.9	18.1	6.2 (0.3, 12.1)	0.0762	7.8 (1.9, 13.6)	0.0181
Placebo – 35% imputed responders	24.2	25.9	18.9	5.5 (-0.5, 11.5)	0.1410	7.1 (1.2, 13.0)	0.0378

Abbreviations: CI, confidence interval; NASH, non-alcoholic steatohepatitis.

*Calculated using a stratified Cochran–Mantel–Haenszel approach. Patients with missing response at week 52 are considered non-responders in both active and placebo groups.

†Active patients with missing response at week 52 are considered non-responders. Placebo patients with missing response at week 52 had their response imputed by running a simulation (100 times) which produces a correlated pair of binary 0/1 data that represents the patient's response for each pathologist. The statistics were then calculated for each imputation using the same approach as in preceding footnote. The normalised results from each dataset were combined using Rubin's rule.

Note: Patients who experience a composite clinical endpoint (e.g., liver transplant, death) prior to their week 52 biopsy. Patients that were F3 at eligibility and re-evaluated as F4 at baseline by either pathologist are included in this analysis. To account for multiplicity, 0.037 is considered to be the threshold for significance in this table.

2.6.2 Results of additional biopsy endpoints

Multiple additional biopsy endpoints were also achieved with resmetirom treatment (Table 18) including a 2-stage reduction in fibrosis and both NASH resolution and Fibrosis improvement. The rates of response were higher at each endpoint in resmetirom-treated patients relative to paired placebo. At week 52, fewer patients in the resmetirom groups compared with the placebo group experienced fibrosis worsening (Figure 9). All NAS components were improved by resmetirom relative to placebo (Figure 10).

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Table 18 Additional biopsy endpoints (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 from placebo (95% CI)†	% difference Resmetirom 100 mg from placebo (95% CI)†
≥ 2-point improvement in NAS with no worsening of fibrosis (with ≥ 1 point in ballooning or inflammation)					
% Response	41.3	44.9	21.2	20.2 (13.8, 26.5)	23.8 (17.4, 30.2)
≥ 2-point improvement in NAS with improvement in fibrosis (with ≥ 1 point in ballooning or inflammation)					
% Response	18.8	21.2	8.5	10.5 (5.8, 15.3)	13.0 (8.3, 17.7)
Improvement in each NAS component					
% Response	23.3	27.9	7.2	16.1 (11.1, 21.0)	20.9 (15.8, 25.9)
2-stage fibrosis improvement					
% Response	8.3	10.1	2.8	5.6 (2.5, 8.7)	7.4 (3.9, 10.8)
NASH resolution and fibrosis improvement					
% Response	14.2	16.0	4.9	9.5 (5.4, 13.6)	11.6 (7.5, 15.8)

Abbreviations: CI, confidence interval; NAS, NAFLD Activity Score; NASH, non-alcoholic steatohepatitis.

*Of the 966 patients in the primary population, 11 patients (6 in the 80 mg resmetirom group, 3 in the 100 mg resmetirom group, and 2 in the placebo group) had a delay in their week 52 biopsy for reasons related to COVID-19 and were not evaluated for the endpoints shown here.

†The widths of the CIs have not been adjusted for multiplicity and may not be used for hypothesis testing.

Figure 9 Percentage of patients who were F1B or F2 at baseline with worse (progressed to ≥ F3), stable (no change), or improved fibrosis stage at week 52 based on liver biopsy (mITT-LB-W52 population, n = 955)

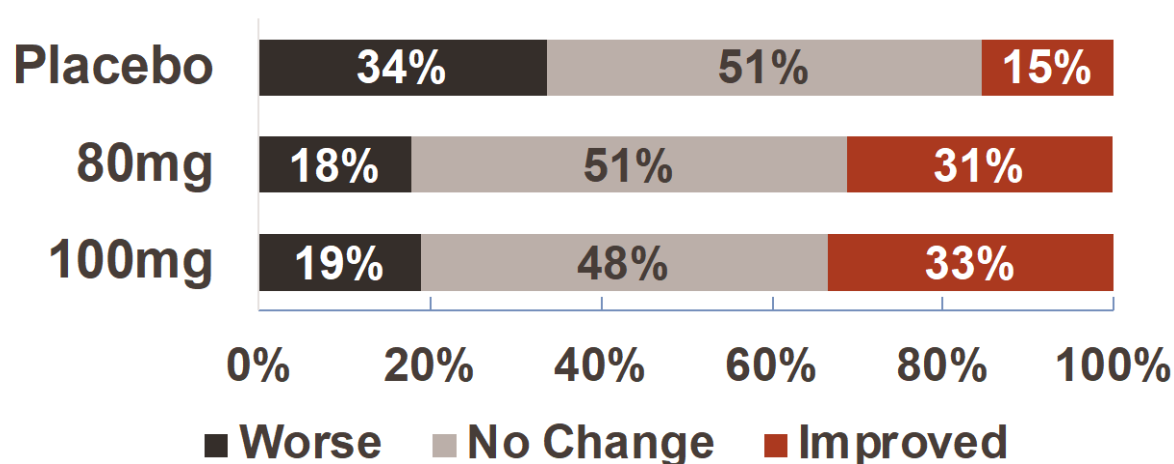
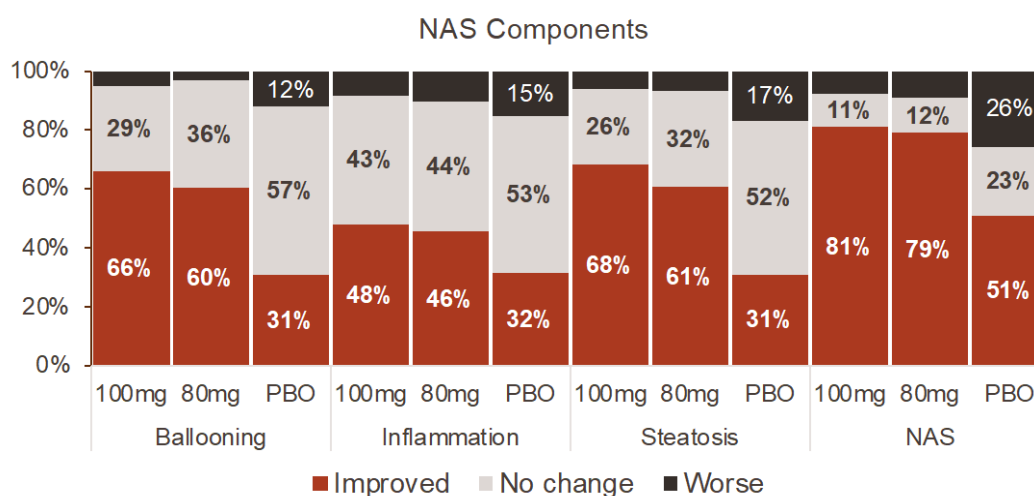


Figure 10 Percent of patients with worsened, stable (no change), or improved individual components of the NAS (ballooning, inflammation, steatosis) (mITT-LB-W52 population, n = 955)



Abbreviations: NAS, NAFLD Activity Score.

2.6.3 Results of secondary endpoints analysed in mITT-W52 population (n = 966)

Biochemical and imaging outcomes

LDL-C levels were reduced from baseline at week 24 among resmetirom-treated patients (-13.6% [80 mg]; -16.3% [100 mg]) vs. placebo-treated patients (0.1%; $p < 0.001$ vs. placebo for both (Table 19 and Figure 8)); these effects were maintained at week 52 (Table 19, Table 20, and Figure 11). At week 24, triglycerides (in patients with baseline triglyceride levels > 150 mg/dL), non-HDL-C, ApoB, apolipoprotein C-III (ApoC-III), and Lp(a) levels were reduced from baseline in the resmetirom groups compared with the placebo group; these effects were maintained at week 52 (Table 19, Table 20, and Figure 11).

In addition, liver enzymes including ALT, AST, and GGT were reduced by resmetirom relative to placebo (Table 19). Resmetirom treatment resulted in improvements from baseline in multiple NITs including MRI-PDFF at weeks 16 and 52 (Table 19 and Figure 12) and FibroScan CAP at week 52 (Table 4, Appendix J, and Figure 12). Liver stiffness (VCTE or MRE) was reduced from baseline with resmetirom treatment compared with placebo (Table 4, Appendix J, and Figures 1 and 2, Appendix J). More resmetirom-treated patients were FibroScan VCTE and MRE responders at week 52 compared with placebo-treated patients (Figures 1 and 2, Appendix J). By week 16, both liver and spleen volume were

reduced from baseline with resmetirom treatment; this effect was maintained at week 52 (Figure 3, Appendix J).

ELF and components of ELF were improved by resmetirom treatment relative to placebo (Table 4, Appendix J, and Figure 4, Appendix J). Additionally, cytokeratin-18 (CK-18) and adiponectin, as well as the inactive reverse triiodothyronine improved among resmetirom-treated patients compared with placebo-treated patients (Table 4, Appendix J).

Table 19 Key secondary and other secondary endpoints (mITT-W52 population, n = 966)

	Least squares (LS) mean % change from baseline (CFB) (SE) Resmetirom 80 mg (n = 322)	LS mean % CFB (SE) Resmetirom 100 mg (n = 323)	LS mean % CFB (SE) Placebo (n = 321)	LS mean % CFB difference between Resmetirom 80 mg and Placebo (95% CI)	p-value	LS mean % CFB difference between Resmetirom 100 mg and Placebo (95% CI)	p-value
LDL-C (mg/dL)							
Week 24* – no.	285	280	294				
Baseline mean (SD)	106.6 (37.8)	102.9 (37.6)	106.2 (41.4)				
Week 24 (% CFB)	-13.6 (1.7)	-16.3 (1.7)	0.11 (1.7)	-13.7 (-17.5, -10.0)	< 0.001	-16.4 (-20.1, -12.6)	< 0.001
Week 52 – no.	276	262	284				
Baseline mean (SD)	106.9 (37.9)	102.9 (36.8)	106.1 (41.7)				
Week 52 (% CFB)	-13.7 (1.8)	-19.5 (1.8)	-0.4 (1.7)	-13.3 (-17.3, -9.3)		-19.0 (-23.0, -15.1)	
ApoB (U/L)							
Week 24 – no.	285	280	294				
Baseline mean (SD)	98.4 (28.1)	95.9 (28.3)	97.5 (32.1)				
Week 24 (% CFB)	-16.8 (1.3)	-19.8 (1.3)	0.39 (1.3)	-17.2 (-20.0, -14.4)		-20.2 (-22.9, -17.4)	
Week 52 – no.	276	262	284				
Baseline mean (SD)	98.5 (27.6)	95.6 (27.8)	97.1 (32.1)				
Week 52 (% CFB)	-16.2 (1.5)	-22.3 (1.5)	0.59 (1.4)	-16.8 (-20.0, -13.7)		-22.9 (-26.0, -19.7)	
Triglycerides (mg/dL) (baseline triglycerides > 150 mg/dL)							
Week 24 – no. II	170	146	144				
Baseline mean (SD)	237.9 (120.7)	244.7 (132.8)	261.5 (146.0)				
Week 24 (% CFB)	-22.7 (4.0)	-21.7 (4.3)	-2.6 (4.1)	-20.1 (-28.3, -11.8)		-19.1 (-27.8, -10.3)	
Week 52 – no.	165	134	140				
Baseline mean (SD)	241.0 (122.4)	252.1 (160.2)	256.5 (145.7)				
Week 52 (% CFB)	-22.5 (4.2)	-28.4 (4.4)	-3.5 (4.2)	-19.0 (-27.9, -10.1)		-24.9 (-34.1, -15.7)	

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	Least squares (LS) mean % change from baseline (CFB) (SE) Resmetirom 80 mg (n = 322)	LS mean % CFB (SE) Resmetirom 100 mg (n = 323)	LS mean % CFB (SE) Placebo (n = 321)	LS mean % CFB difference between Resmetirom 80 mg and Placebo (95% CI)	p-value	LS mean % CFB difference between Resmetirom 100 mg and Placebo (95% CI)	p-value
Lp(a) (nmol/L) (baseline Lp(a) > 10 nmol/L)							
Week 24 – no.¶	200	187	200				
Baseline mean (SD)	62.0 (67.5)	58.7 (64.6)	57.9 (70.2)				
Week 24 (% CFB)	-30.4 (3.8)	-35.9 (4.0)	-0.84 (3.5)	-29.5 (-37.6, -21.5)		-35.1 (-43.5, -26.6)	
Week 52 – no.	193	172	194				
Baseline mean (SD)	64.5 (68.4)	57.6 (62.7)	57.7 (70.0)				
Week 52 (% CFB)	-34.0 (4.9)	-37.5 (5.6)	-5.0 (4.6)	-29.5 (-39.4, -19.6)		-32.4 (-43.1, -21.8)	
MRI-PDFF, % fat fraction							
Week 16 – no.	228	218	224				
Baseline mean (SD)	18.2 (6.8)	17.2 (6.5)	17.9 (6.6)				
Week 16 (% CFB)	-37.8 (2.2)	-42.1 (2.2)	-6.4 (2.2)	-31.4 (-36.3, -26.4)		-35.7 (-40.7, -30.7)	
Week 52 – no.	233	222	230				
Baseline mean (SD)	18.2 (6.8)	17.2 (6.7)	17.9 (6.6)				
Week 52 (% CFB)	-35.4 (2.8)	-46.6 (2.8)	-8.7 (2.7)	-26.7 (-32.9, -20.6)		-37.9 (-44.2, -31.7)	
ALT (U/L)#							
Baseline – no.†	265	264	244				
Baseline mean (SD)	59.1 (25.4)	65.4 (33.5)	63.1 (26.7)				
Week 48 (CFB)	-20.4 (2.2)	-24.8 (2.3)	-8.5 (2.3)				
Week 48 (% Change from baseline)††	-26.6 (3.7)	-33.2 (3.9)	-6.9 (3.8)	-19.7 (-27.7, -11.6)		-26.3 (-34.5, -18.1)	
AST (U/L)							
Baseline – no.	265	264	244				
Baseline mean (SD)	41.5 (18.6)	48.5 (26.0)	44.9 (20.8)				
Week 48 (CFB)	-13.9 (1.7)	-15.8 (1.7)	-6.0 (1.7)				
Week 48 (% CFB)††	-22.1 (3.9)	-28.3 (3.9)	-2.9 (3.8)	-19.3 (-27.2, -11.3)		-25.4 (-33.5, -17.4)	

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	Least squares (LS) mean % change from baseline (CFB) (SE) Resmetirom 80 mg (n = 322)	LS mean % CFB (SE) Resmetirom 100 mg (n = 323)	LS mean % CFB (SE) Placebo (n = 321)	LS mean % CFB difference between Resmetirom 80 mg and Placebo (95% CI)	p-value	LS mean % CFB difference between Resmetirom 100 mg and Placebo (95% CI)	p-value
GGT (U/L)							
Baseline – no.	265	264	244				
Baseline mean (SD)	87.3 (122.2)	92.4 (109.4)	80.1 (87.2)				
Week 48 (CFB)	-31.3 (3.9)	-32.7 (4.0)	-7.3 (3.9)				
Week 48 (% CFB) ^{††}	-25.0 (5.5)	-31.9 (6.3)	3.3 (5.2)	-28.3 (-37.3, -19.3)		-35.2 (-45.5, -25.0)	

Abbreviations: ALT, alanine aminotransferase; ApoB, apolipoprotein B; AST, aspartate aminotransferase; CFB, change from baseline; CI, confidence interval; GGT, gamma-glutamyl transferase; LDL-C, low-density lipoprotein-cholesterol; Lp(a), lipoprotein(a); LS, least squares; MRI-PDFF, MRI-based proton density fat fraction; SD, standard deviation; SE, standard error.

*Key secondary endpoint.

#multiply imputed values.

||Data are for patients with a baseline triglyceride level of more than 150 mg per decilitre.

¶||Data are for patients with a baseline Lp(a) level of more than 10 nmol per litre.

†Data are for patients with a baseline ALT level of 30 U per litre or more.

Direct LDL-C was measured. Data were missing for one patient in the 80 mg resmetirom group for the LDL-C, ApoB, triglycerides, and Lp(a) analyses.

Table 20 Change from baseline in lipids, lipoproteins, and lipid particles at weeks 24 and 52 (MITT-W52 population, n = 966)

	LS mean % CFB (SE) Resmetirom 80 mg (n = 322)	LS mean % CFB (SE) Resmetirom 100 mg (n = 323)	LS mean % CFB (SE) Placebo (n = 321)	LS mean % CFB difference between Resmetirom 80 mg and Placebo (95% CI)	LS mean % CFB difference between Resmetirom 100 mg and Placebo (95% CI)
LDL-C, mg/dL (baseline LDL-C > 100 mg/dL)					
Week 24 – no.	148	133	150		
Baseline mean (SD)	135.6 (26.5)	134.4 (27.3)	136.8 (34.0)		
Week 24 (% CFB)	-21.3 (2.0)	-20.6 (2.0)	-5.9 (1.9)	-15.4 (-19.3, -11.6)	-14.7 (-18.6, -10.8)
Week 52 – no.	147	125	144		
Baseline mean (SD)	135.2 (26.0)	133.3 (27.4)	136.9 (34.2)		
Week 52 (% CFB)	-25.3 (2.2)	-27.1 (2.3)	-9.6 (2.1)	-15.7 (-20.0, -11.4)	-17.5 (-22.0, -13.1)
ApoB, mg/dL (baseline LDL-C > 100 mg/dL)					
Week 24 – no.	148	133	150		
Baseline mean (SD)	117.9 (22.2)	116.9 (24.0)	118.3 (29.8)		
Week 24 (% CFB)	-21.9 (1.7)	-22.1 (1.8)	-3.7 (1.6)	-18.1 (-21.4, -14.9)	-18.4 (-21.8, -15.0)
Week 52 – no.	147	125	144		
Baseline mean (SD)	117.4 (20.9)	115.7 (24.1)	118.1 (29.9)		
Week 52 (% CFB)	-25.0 (2.0)	-26.6 (2.0)	-6.5 (1.9)	-18.5 (-22.4, -14.6)	-20.1 (-24.1, -16.1)
ApoC-III					
Week 24 – no.	282	272	288		
Baseline mean (SD)	10.9 (4.7)	10.7 (5.3)	10.5 (5.6)		
Week 24 (% CFB)	-10.6 (3.6)	-14.1 (3.1)	8.1 (3.1)	-18.7 (-27.1, -10.4)	-22.2 (-29.0, -15.4)
Week 52 – no.	272	255	279		
Baseline mean (SD)	10.9 (4.7)	10.7 (5.5)	10.3 (5.5)		
Week 52 (% CFB)	-10.0 (3.8)	-17.1 (3.3)	9.8 (3.3)	-19.8 (-28.4, -11.1)	-26.9 (-34.1, -19.6)
Non-HDL-C					
Week 24 – no.	285	280	294		

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	LS mean % CFB (SE) Resmetirom 80 mg (n = 322)	LS mean % CFB (SE) Resmetirom 100 mg (n = 323)	LS mean % CFB (SE) Placebo (n = 321)	LS mean % CFB difference between Resmetirom 80 mg and Placebo (95% CI)	LS mean % CFB difference between Resmetirom 100 mg and Placebo (95% CI)
Baseline mean (SD)	135.6 (43.2)	131.8 (44.7)	135.7 (50.6)		
Week 24 (% CFB)	-15.2 (1.5)	-17.7 (1.6)	0.16 (1.5)	-15.4 (-18.8, -12.0)	-17.9 (-21.2, -14.5)
Week 52 – no.	276	262	284		
Baseline mean (SD)	136.1 (43.1)	132.4 (46.7)	135.2 (50.6)		
Week 52 (% CFB)	-15.7 (1.7)	-22.1 (1.7)	-0.40 (1.6)	-15.3 (-19.0, -11.7)	-21.7 (-25.2, -18.1)
HDL-C					
Week 24 – no.	285	280	294		
Baseline mean (SD)	43.9 (12.5)	43.5 (12.8)	43.8 (13.5)		
Week 24 (% CFB)	2.7 (1.5)	2.9 (1.5)	1.7 (1.5)	0.98 (-2.3, 4.2)	1.2 (-2.1, 4.5)
Week 52 – no.	276	262	284		
Baseline mean (SD)	44.1 (12.5)	43.6 (12.7)	44.1 (13.3)		
Week 52 (% CFB)	4.7 (1.4)	4.6 (1.5)	2.7 (1.4)	2.1 (-0.99, 5.1)	2.0 (-1.2, 5.1)
HDL particles, umol/L					
Week 52 – no.	266	252	275		
Baseline mean (SD)	30.5 (6.5)	31.0 (6.0)	30.8 (6.2)		
Week 52 (% CFB)	5.2 (1.3)	2.3 (1.3)	1.6 (1.2)	3.6 (0.80, 6.3)	0.69 (-2.1, 3.5)
HDL particle size, nm					
Week 52 – no.	266	252	275		
Baseline mean (SD)	8.9 (0.46)	9.0 (0.46)	9.0 (0.45)		
Week 52 (% CFB)	0.90 (0.28)	0.40 (0.28)	0.30 (0.27)	0.60 (-0.01, 1.2)	0.10 (-0.51, 0.71)

	LS mean % CFB (SE) Resmetirom 80 mg (n = 322)	LS mean % CFB (SE) Resmetirom 100 mg (n = 323)	LS mean % CFB (SE) Placebo (n = 321)	LS mean % CFB difference between Resmetirom 80 mg and Placebo (95% CI)	LS mean % CFB difference between Resmetirom 100 mg and Placebo (95% CI)
LDL particles, nmol/L					
Week 52 – no.	266	252	275		
Baseline mean (SD)	1322.9 (438.5)	1273.5 (440.1)	1282.5 (476.1)		
Week 52 (% CFB)	-16.8 (1.7)	-20.0 (1.7)	-0.69 (1.6)	-16.1 (-19.8, -12.4)	-19.4 (-23.1, -15.6)
LDL particle size, nm					
Week 52 – no.	260	251	273		
Baseline mean (SD)	20.4 (0.59)	20.3 (0.59)	20.4 (0.60)		
Week 52 (% CFB)	-0.32 (0.17)	-0.35 (0.17)	0.04 (0.16)	-0.36 (-0.73, 0.01)	-0.39 (-0.76, -0.02)
Large HDL particles, umol/L					
Week 52 – no.	265	251	275		
Baseline mean (SD)	5.5 (2.9)	5.5 (2.9)	5.8 (2.9)		
Week 52 (% CFB)	12.3 (5.5)	4.5 (5.6)	12.2 (5.3)	0.06 (-11.9, 12.0)	-7.7 (-19.8, 4.4)
Large LDL particles, nmol/L					
Week 52 – no.	234	213	239		
Baseline mean (SD)	366.8 (263.0)	330.2 (265.6)	355.7 (257.3)		
Week 52 (% CFB)	47.8 (25.3)	55.6 (26.0)	86.4 (24.3)	-38.6 (-93.6, 16.3)	-30.8 (-87.0, 25.4)
Large very low-density lipoprotein (VLDL) and chylomicron particles, nmol/L					
Week 52 – no.	266	252	275		
Baseline mean (SD)	8.2 (5.8)	8.2 (8.9)	8.3 (8.7)		
Week 52 (% CFB)	-5.7 (4.9)	-9.1 (5.0)	11.2 (4.7)	-16.8 (-27.5, -6.2)	-20.2 (-31.1, -9.4)
Medium HDL particles, umol/L					
Week 52 – no.	260	245	271		
Baseline mean (SD)	5.5 (4.1)	5.7 (4.6)	5.1 (4.1)		
Week 52 (% CFB)	88.2 (28.0)	130.2 (28.7)	65.1 (27.1)	23.1 (-38.2, 84.4)	65.2 (2.9, 127.5)

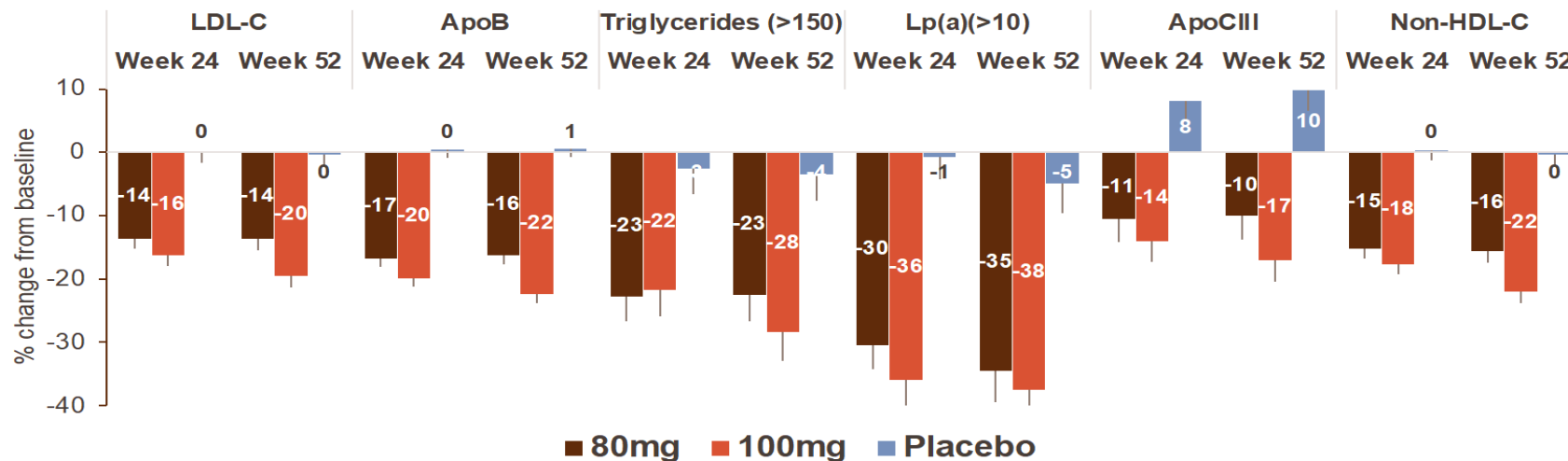
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	LS mean % CFB (SE) Resmetirom 80 mg (n = 322)	LS mean % CFB (SE) Resmetirom 100 mg (n = 323)	LS mean % CFB (SE) Placebo (n = 321)	LS mean % CFB difference between Resmetirom 80 mg and Placebo (95% CI)	LS mean % CFB difference between Resmetirom 100 mg and Placebo (95% CI)
Medium VLDL particles, nmol/L					
Week 52 – no.	253	240	260		
Baseline mean (SD)	25.0 (25.2)	23.2 (25.6)	23.1 (27.6)		
Week 52 (% CFB)	-18.7 (52.0)	-27.4 (53.5)	115.8 (50.6)	-134.5 (-249.6, -19.5)	-143.2 (-259.8, -26.7)
Small LDL particles, nmol/L					
Week 52 – no.	266	252	275		
Baseline mean (SD)	880.7 (336.3)	882.0 (360.3)	850.0 (356.9)		
Week 52 (% CFB)	-3.3 (9.2)	6.6 (9.5)	21.7 (8.9)	-25.0 (-45.2, -4.7)	-15.0 (-35.5, 5.5)
Small VLDL particles, nmol/L					
Week 52 – no.	260	250	270		
Baseline mean (SD)	25.8 (15.0)	27.1 (17.0)	27.4 (15.3)		
Week 52 (% CFB)	62.9 (38.2)	26.3 (39.0)	41.6 (36.9)	21.3 (-62.8, 105.4)	-15.3 (-100.2, 69.5)
VLDL and chylomicron particles, nmol/L					
Week 52 – no.	266	252	275		
Baseline mean (SD)	57.2 (32.4)	57.1 (38.8)	57.1 (38.2)		
Week 52 (% CFB)	-11.2 (4.3)	-20.2 (4.4)	8.2 (4.1)	-19.4 (-28.8, -10.0)	-28.4 (-37.9, -18.9)
VLDL particle size, nm					
Week 52 – no.	266	252	274		
Baseline mean (SD)	55.5 (6.5)	55.3 (6.9)	54.7 (7.3)		
Week 52 (% CFB)	1.9 (0.92)	3.4 (0.94)	2.0 (0.89)	-0.05 (-2.1, 2.0)	1.4 (-0.65, 3.4)
VLDL and chylomicron triglycerides, mg/dL					
Week 52 – no.	266	252	275		
Baseline mean (SD)	114.1 (68.6)	113.5 (92.1)	113.6 (91.7)		
Week 52 (% CFB)	-14.7 (3.1)	-17.9 (3.1)	4.9 (3.0)	-19.6 (-26.3, -12.9)	-22.8 (-29.6, -16.0)

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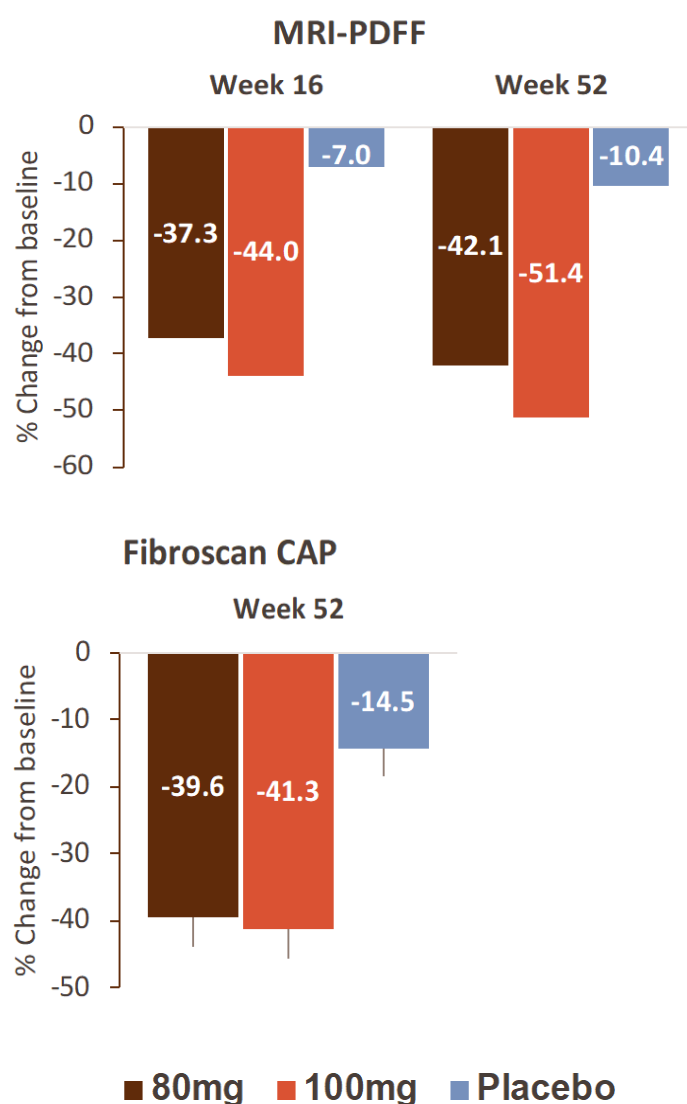
Abbreviations: ApoB, apolipoprotein B; ApoC-III, apolipoprotein C-III; CFB, change from baseline; CI, confidence interval; HDL-C, high-density lipoprotein-cholesterol; LDL-C, low-density lipoprotein-cholesterol; LS, least squares; SD, standard deviation; SE, standard error; VLDL, very low-density lipoprotein.

Figure 11 Percent change from baseline in lipids and lipoproteins at weeks 24 and 52 (mITT-W52 population, n = 966)



Abbreviations: ApoB, apolipoprotein B; ApoC-III, apolipoprotein C-III; HDL-C, high-density lipoprotein-cholesterol; LDL-C, low-density lipoprotein-cholesterol; Lp(a), lipoprotein(a).

Figure 12 Percent change from baseline in hepatic fat as measured by MRI-PDFF at weeks 16 and 52, and steatosis as measured by FibroScan CAP at week 52 (mITT-W52 population, n = 966)



Abbreviations: CAP, Controlled Attenuation Parameter; MRI-PDFF, MRI-based proton density fat fraction.

HRQoL

HRQoL was assessed in MAESTRO-NASH using the Chronic Liver Disease Questionnaire–NAFLD (CLDQ-NAFLD) and the Liver Disease Quality of Life (LDQoL) instrument (96). A total of 966 patients were included in the ITT population (resmetirom 100 mg, n = 323; resmetirom 80 mg, n = 322; placebo, n = 321). There were 125 (50%) patients in the resmetirom 100 mg group, 109 (42%) in the 80 mg group, and 53 (19%) in the placebo group who met the primary histological endpoint of NASH resolution OR improvement of histological fibrosis as measured via baseline/week 52 paired biopsies (available for n = 782; of those, n = 696 had CLDQ-NAFLD and n = 714 had LDQoL).

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At weeks 24 and 52, patients treated with resmetirom 80 mg or 100 mg reported improvements in the CLDQ-NAFLD Worry domain (mean change +0.21 to +0.24; $p < 0.05$). At week 52, patients achieving primary histological endpoints (resmetirom 80 mg and 100 mg pooled) demonstrated improvements in HRQoL: CLDQ-NAFLD Worry domain (+0.46; 41% achieved the minimal clinically important difference [MCID]); LDQoL Role Emotional (+3.0; 28% MCID), Health Distress (+8.1; 38% MCID), Stigma (+3.5; 39% MCID), and LDQoL total score (+2.2; 35% MCID) (all $p < 0.05$). Comparable or greater improvements were observed among histological responders in the individual 80 mg and 100 mg resmetirom groups, whereas no meaningful improvements were observed in the placebo group or in non-responders. Similar or more pronounced benefits were reported in patients with baseline F3 fibrosis who achieved histological response (96).

In summary, resmetirom treatment was associated with statistically significant and clinically meaningful HRQoL improvements among patients with NASH who achieved histological response. Furthermore, among resmetirom-treated groups, there was no dose dependency so that changes in HRQL scores were similar between 100 mg and 80 mg doses.

2.7 Subsequent treatments used in the relevant studies

No data on subsequent treatments were collected or reported in the MAESTRO-NASH trial. The trial protocol and clinical study report focused solely on outcomes of the randomised treatments (resmetirom and placebo). Information on the number and type of subsequent drug or non-drug treatments, lines of therapy, and duration of use was not available. Consequently, no further details are provided in this section.

2.8 Subgroup analysis

Subgroup analyses of the primary endpoints revealed consistent results across subgroups (based on baseline fibrosis stage, baseline NAS, T2DM status, age, and sex) with more resmetirom-treated patients achieving either NASH resolution or Fibrosis improvement compared with placebo-treated patients. The 100 mg resmetirom group generally outperformed the 80 mg group except in patients ≥ 65 years. Of note, there was no impact of concomitant GLP-1 RA, statin therapy, or thyroxine replacement therapy on achievement of NASH resolution or fibrosis improvement in the resmetirom groups. Patients with $\geq 30\%$ liver fat reduction or increase in the exposure biomarker SHBG by $\geq 120\%$ had a greater response at both endpoints (17).

Subgroups were pre-planned, with data reported for the mITT population. A summary of results for the subgroups is presented in Appendix C.
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2.9 Meta-analysis

A meta-analysis was not conducted for this submission. Although the SLR of clinical evidence identified multiple studies in the MASH population, MAESTRO-NASH was the only trial of resmetirom that met the population criteria defined in the NICE scope. This trial also included the relevant comparator arm specified in the scope. The results from MAESTRO-NASH were, therefore, sufficient to inform the economic model without the need to pool data across multiple trials.

Given that the relevant treatment comparison could be derived directly from the MAESTRO-NASH results, quantitative evidence synthesis was not necessary. Details of patient flow in the MAESTRO-NASH trial, together with a summary of all studies identified in the SLR of clinical evidence, their associated treatments, and the corresponding risk of bias assessments, are presented in Appendix B.

2.10 Indirect and mixed treatment comparisons

No indirect treatment comparison (ITC) was conducted as part of this submission. All relevant clinical efficacy and safety data required for the economic evaluation were available directly from the MAESTRO-NASH trial, which provides head-to-head comparisons of resmetirom versus placebo in the indicated population. As such, an ITC was not necessary to support the CEA.

2.11 Adverse reactions

In the MAESTRO-NASH trial, AEs were reported by the vast majority of patients across all treatment groups. Among those receiving resmetirom, 91.6% to 91.9% experienced at least one AE, compared with 92.8% of those receiving placebo (Table 21). The majority of events were mild to moderate in severity (17).

The most commonly reported AEs were gastrointestinal in nature—particularly diarrhoea and nausea—as well as COVID-19 infection (Table 22 and Table 23). Gastrointestinal symptoms generally began at the start of treatment. Approximately half of all diarrhoea cases were described as worsening of pre-existing symptoms or intermittent/loose stools. No cases of severe diarrhoea were recorded. The median duration of diarrhoea was 15 to 20 days and did not vary by resmetirom dose. No further increase in the incidence of diarrhoea or nausea was observed after the initial treatment period when comparing resmetirom with placebo.

The incidence of SAEs was similar across trial groups: 10.9% in the 80 mg resmetirom group, 12.7% in the 100 mg group, and 11.5% in the placebo group (Table 21 and Table 24). Three SAEs were considered treatment-related and were balanced across the resmetirom and placebo arms. There was no numerical increase in cancer incidence in patients receiving resmetirom compared with placebo, and no cases of drug-induced liver injury were reported.

At week 52, trial discontinuations due to AEs were more common in the 100 mg resmetirom group than in the other two trial groups (6.8% in the 100 mg resmetirom group, 1.9% in the 80 mg resmetirom group, and 2.2% in the placebo groups). Thereafter, trial discontinuations were similar across the trial groups.

Resmetirom treatment was not associated with changes in heart rate, body weight, or arrhythmias (Table 5, Appendix J). A modest reduction in blood pressure was observed among resmetirom-treated patients. Levels of sex hormones remained largely unchanged from baseline (Table 6, Appendix J). Independent of thyroxine-replacement status, resmetirom treatment led to reductions in FT4 of approximately 16–19%, with no effect on thyrotropin or the active thyroid hormone, FT3 (Table 7, Appendix J). In addition, no increases in fracture incidence or clinically meaningful changes in bone mineral density T scores were observed (Table 8, Appendix J).

Table 21 Safety summary (Safety Population, n = 966)

no. (%)	Resmetirom 80 mg (n = 322)	Resmetirom 100 mg (n = 323)	Placebo (n = 321)
≥ 1 AE	296 (91.9)	296 (91.6)	298 (92.8)
Grade 1 (mild)	73 (22.7)	66 (20.4)	77 (24.0)
Grade 2 (moderate)	180 (55.9)	183 (56.7)	169 (52.6)
≥ Grade 3 (severe)	43 (13.4)	47 (14.6)	52 (16.2)
≥ 1 drug-related AEs*	124 (38.5)	134 (41.5)	88 (27.4)
≥ 1 SAE	35 (10.9)	41 (12.7)	36 (11.2)
≥ 1 drug-related SAE*	2 (0.6)	0	1 (0.3)
TEAEs leading to study discontinuation prior to week 52†	6 (1.9)	22 (6.8)	7 (2.2)
TEAEs leading to study discontinuation (entire treatment period)†	9 (2.8)	25 (7.7)	11 (3.4)
Fatal AE	1 (0.3)	2 (0.6)	1 (0.3)
3-pt MACE (adjudicated)‡	1 (0.3)	1 (0.3)	1 (0.3)
Other cardiovascular event (adjudicated)‡	0	1 (0.3)	3 (0.9)

Abbreviations: AE, adverse event; MACE, major adverse cardiovascular event; SAE, serious adverse event; TEAE, treatment-emergent adverse event.

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*Shown are events that were considered by investigators to be related to resmetirom or placebo.

†Data are for events that emerged after the first dose of resmetirom or placebo and within 30 days after the last dose.

‡MACE were defined as nonfatal stroke, non-fatal myocardial infarction (MI), and death from cardiovascular causes. All cardiovascular events were adjudicated.

Table 22 Adverse events affecting > 10% of patients in any group (Safety Population, n = 966)

Preferred Term, no. (%)	Resmetirom 80 mg (n = 322)	Resmetirom 100 mg (n = 323)	Placebo (n = 321)
Diarrhoea	87 (27.0)	108 (33.4)	50 (15.6)
COVID-19	69 (21.4)	54 (16.7)	66 (20.6)
Nausea	71 (22.0)	61 (18.9)	40 (12.5)
Arthralgia	48 (14.9)	35 (10.8)	40 (12.5)
Back pain	35 (10.9)	27 (8.4)	38 (11.8)
Urinary tract infection	33 (10.2)	27 (8.4)	27 (8.4)
Fatigue	33 (10.3)	26 (8.0)	28 (8.7)
Pruritus	26 (8.1)	37 (11.5)	22 (6.9)

Table 23 Adverse events reported in ≥ 5% of patients in any group (Safety Population, n = 966)

Preferred Term, no. (%)	Resmetirom 80 mg (n = 322)	Resmetirom 100 mg (n = 323)	Placebo (n = 321)
Abdominal pain upper	23 (7.1)	27 (8.4)	29 (9.0)
Headache	30 (9.3)	25 (7.7)	27 (8.4)
Vomiting	28 (8.7)	35 (10.8)	17 (5.3)
Type 2 diabetes	24 (7.5)	26 (8.0)	25 (7.8)
Abdominal pain	23 (7.1)	29 (9.0)	18 (5.6)
Constipation	21 (6.5)	28 (8.7)	17 (5.3)
Muscle spasms	14 (4.3)	22 (6.8)	22 (6.9)
Hypertension	16 (5.0)	13 (4.0)	25 (7.8)
Dizziness	20 (6.2)	19 (5.9)	11 (3.4)
Nasopharyngitis	14 (4.3)	20 (6.2)	14 (4.4)
Pain in extremity	12 (3.7)	12 (3.7)	23 (7.2)
Upper respiratory tract infection	23 (7.1)	8 (2.5)	17 (5.3)
Rash	12 (3.7)	21 (6.5)	12 (3.7)
Cough	14 (4.3)	18 (5.6)	12 (3.7)
Abdominal distension	14 (4.3)	13 (4.0)	17 (5.3)
Procedural pain	16 (5.0)	9 (2.8)	19 (5.9)
Gastroesophageal reflux disease	16 (5.0)	7 (2.2)	8 (2.5)
Decreased appetite	5 (1.6)	16 (5.0)	4 (1.2)
Sinusitis	10 (3.1)	13 (4.0)	17 (5.3)

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Table 24 Serious adverse events (Safety Population, n = 966)

System organ class*, no. (%)	Resmetirom 80 mg (n = 322)	Resmetirom 100 mg (n = 323)	Placebo (n = 321)
Patients with at least one treatment-emergent SAE	35 (10.9)	41 (12.7)	37 (11.5)
Infections and infestations	12 (3.7)	5 (1.5)	13 (4.0)
COVID-19	1 (0.3)	1 (0.3)	2 (0.6)
COVID-19 pneumonia	2 (0.6)	0	3 (0.9)
Gastrointestinal disorders	3 (0.9)	7 (2.2)	7 (2.2)
Acute Gallstone-related disorders#	3 (0.9)	3 (0.9)	1 (0.3)
Injury, poisoning and procedural complications	3 (0.9)	8 (2.5)	4 (1.2)
Post-procedural haemorrhage	1 (0.3)	1 (0.3)	2 (0.6)
Cardiac disorders	3 (0.9)	3 (0.9)	7 (2.2)
Respiratory, thoracic and mediastinal disorders	3 (0.9)	4 (1.2)	6 (1.9)
Musculoskeletal and connective tissue disorders	7 (2.2)	1 (0.3)	4 (1.2)
Nervous system disorders	3 (0.9)	8 (0.6)	6 (1.9)
General disorders and administration site conditions	2 (0.6)	5 (1.5)	3 (0.9)

Abbreviations: SAE, serious adverse event.

*Included SAEs where category was not unblinding.

#Includes a combination of acute cholecystitis, gallstone-related pancreatitis, or choledolithiasis.

Individual SAEs that were unblinding for treatment of individual patients are not shown because MAESTRO-NASH is a blinded ongoing 54-month outcome study.

2.12 Ongoing studies

Details of all ongoing studies of resmetirom are presented below.

2.12.1 MAESTRO-NASH (NCT03900429)

The MAESTRO-NASH trial is ongoing, with extended follow-up to 54 months (17). This is a pre-specified analysis to evaluate durability of histological benefit and clinical outcomes such as progression to cirrhosis, hepatic decompensation, transplantation, and mortality. These 54-month data are not yet publicly available.

2.12.2 MAESTRO-NASH-OUTCOMES (NCT05500222)

The MAESTRO-NASH-OUTCOMES is a multi-national, double-blind, placebo-controlled trial studying the efficacy of 80 mg once-daily resmetirom in patients with MASH cirrhosis by

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measuring the time to experiencing a composite clinical outcome event (105). In this trial, composite clinical outcome events are defined as follows: all-cause mortality, LT, and significant hepatic events, including potential hepatic decompensation events (ascites, hepatic encephalopathy, or gastroesophageal variceal haemorrhage), and confirmed increase of MELD score from < 12 to ≥ 15 . Recruitment has now been completed, with baseline characteristics of the patients recently presented (106).

2.12.3 MAESTRO-NAFLD-OLE (NCT04951219)

A 52-week OLE following MAESTRO-NAFLD-1, evaluating long-term safety and biomarker data for resmetirom (105). It has two arms of resmetirom 80 mg and 100 mg once daily for 12 weeks after which all patients will receive 100 mg resmetirom for the rest of the trial. This study is currently recruiting patients and will be completed in 2026.

These forthcoming data will help inform the long-term safety profile of resmetirom and begin to characterise its impact on hard clinical endpoints in MASH cirrhosis.

2.13 Interpretation of clinical effectiveness and safety evidence

2.13.1 Principal findings

Evidence from the pivotal phase III MAESTRO-NASH trial (17) demonstrates that resmetirom provides statistically and clinically significant benefits over placebo in adults with non-cirrhotic MASH with moderate to advanced liver fibrosis (fibrosis stage F2 to F3). At week 52, both the 80 mg and 100 mg doses achieved higher rates of NASH resolution without worsening of fibrosis (25.9% and 29.9%, respectively) compared with placebo (9.7%; $p < 0.001$ for both), and greater proportions of patients achieved ≥ 1 -stage Fibrosis improvement without worsening of NAS (24.2% and 25.9% vs. 14.2%; $p \leq 0.001$). Therefore, resmetirom demonstrated superiority over placebo on the pre-specified dual primary histological endpoints at week 52.

These dual histological endpoints are widely recognised as important predictors of long-term clinical outcomes in MASH, given their association with reduced risk of progression to cirrhosis, hepatic decompensation, and liver-related mortality, and are consistent with those proposed by regulatory agencies as reasonably likely to predict longer-term clinical benefit in phase III MASH trials (107,108). These effects were supported by multiple sensitivity analyses and were consistent across subgroups defined by fibrosis stage, baseline NAS,

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age, sex, and T2DM status, highlighting resmetirom's utility in a population that commonly presents with multiple comorbidities. Resolution of MASH and improvements in fibrosis suggest that the treatment has the potential to halt or reverse disease progression at a stage where patients are only one or two steps from cirrhosis, a point at which therapeutic options are extremely limited and irreversible damage occurs. By intervening earlier, resmetirom addresses a critical unmet need in this population.

Resmetirom also improved additional histological endpoints, reduced fibrosis worsening, and led to favourable changes in NAS components. Clinically relevant improvements in lipid parameters (including LDL-C, non-HDL-C, triglycerides, ApoB, and Lp(a)) and MRI-PDFF were observed as early as week 24 and maintained at week 52. These lipid-lowering effects were consistent with those reported in earlier studies (93,98). Given the high cardiovascular risk in patients with MASH, many of whom also have T2DM, such reductions are clinically meaningful. While direct evidence linking resmetirom to improved cardiovascular outcomes is not yet available, the observed changes in ApoB and LDL-C are of a magnitude that, in other settings, has been associated with improved cardiovascular outcomes (109,110). As CVD is the leading cause of death in patients with MASH (111), these effects represent an added clinical value beyond liver-related outcomes.

The safety profile of resmetirom was consistent with that observed in earlier trials (93,98). Gastrointestinal AEs, particularly diarrhoea and nausea, were more frequent with resmetirom than placebo but were generally mild to moderate, transient, and self-limiting. Discontinuations due to AEs were low overall but higher in the 100 mg group (6.8%) compared with 80 mg (1.8%) and placebo (2.2%). The incidence of SAEs was similar across treatment groups (10.9–12.7%), indicating no evidence of increased serious safety risks. These findings support the overall tolerability of resmetirom as a therapy for patients with MASH with moderate to advanced fibrosis (fibrosis stages F2 to F3). This is of particular importance in a chronic, progressive disease such as MASH, where ongoing therapy is needed to sustain histological and clinical benefit.

Collectively, the evidence indicates that resmetirom is a well-tolerated, liver-targeted therapy that achieves clinically meaningful histological improvements aligned with regulatory expectations, while also providing additional benefits on cardiovascular risk factors and patient HRQoL. Notably, patients achieving histological response with resmetirom also reported HRQoL gains (96), underscoring that benefits extend beyond surrogate endpoints to outcomes directly relevant to daily life. By addressing both liver disease progression and the burden of comorbidities, resmetirom has the potential to modify the clinical course of

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MASH, reduce the risk of cirrhosis and liver-related events, and deliver substantial benefit for patients with moderate to advanced fibrosis.

2.13.2 Strengths and limitations of the clinical evidence

2.13.2.1 Strengths

- **Robust trial design:** MAESTRO-NASH is one of the largest phase III trials conducted to date in MASH, enrolling 966 patients across 245 sites in 15 countries. The study used a randomised, double-blind, placebo-controlled design with stratified randomisation and a pre-specified SAP, minimising risk of bias.
- **Histological endpoints of regulatory relevance:** The dual primary endpoints—resolution of steatohepatitis without worsening fibrosis, and Fibrosis improvement ≥ 1 stage without worsening of steatohepatitis—are accepted by regulatory agencies as surrogate markers reasonably likely to predict long-term clinical benefit (107,108). Histology was centrally read by two independent pathologists with adjudication, reducing risk of inter-observer variability.
- **Multiplicity control and sensitivity analyses:** The trial incorporated pre-specified hierarchical testing to control for multiplicity, and sensitivity analyses consistently supported the robustness of the findings. Results remained directionally consistent across key subgroups, including patients with and without T2DM, different baseline fibrosis stages (F2 and F3), and sex.
- **Comorbidity representation:** The enrolled population had a high prevalence of obesity (mean BMI 35.7 kg/m²), T2DM (67.0%), hypertension (78.1%), and dyslipidaemia (71.3%). These features closely mirror the patient population seen in NHS clinical practice in England and Wales, supporting external validity.
- **Broad secondary and exploratory outcomes:** In addition to histology, the trial demonstrated consistent improvements in non-invasive imaging (MRI-PDFF, FibroScan CAP, liver stiffness), serum biomarkers (ELF, CK-18, adiponectin), and lipid parameters (LDL-C, ApoB, triglycerides). These results provide mechanistic support for the observed histological benefits and reinforce the likelihood of long-term clinical benefit.
- **Safety and tolerability:** Resmetirom was generally well tolerated, with

discontinuation rates comparable to placebo. No clinically significant effects were
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observed on heart rate, arrhythmia, sex hormones, or bone mineral density. Thyroid hormone changes were consistent with the drug's mechanism (reductions in FT4 without effect on FT3 or thyroid-stimulating hormone [TSH]) and were not associated with adverse clinical outcomes.

2.13.2.2 Limitations

- **Duration of histological follow-up:** The dual primary endpoints were assessed at 52 weeks. While this does not directly demonstrate long-term clinical outcomes, the trial includes a 54-month extension with repeat biopsies and outcome measures. These data will provide further evidence of durability, but the short-term histological benefits already observed are accepted surrogates of clinical benefit.
- **Inclusion of F1B patients:** A small proportion of patients (5%) with F1B fibrosis were enrolled. These patients were pre-specified for exploratory analyses, and the efficacy results in the F2–F3 population — the target group for UK practice — were consistent and robust.
- **Reliance on surrogate endpoints:** Like all MASH therapies in development, efficacy was assessed using histological surrogate markers rather than long-term outcomes such as cirrhosis or mortality. However, these endpoints are regulatory-accepted (107,108) and strongly linked to progression risk. The ongoing studies of resmetirom will strengthen this evidence base.

2.13.3 Applicability of clinical evidence to practice

2.13.3.1 Patient characteristics

The MAESTRO-NASH trial population (n = 966) is broadly reflective of patients with non-cirrhotic MASH and moderate to advanced fibrosis who are likely to be treated in NHS clinical practice. The mean age was 56.6 years, with 43.5% male patients. Almost all patients were overweight or obese (mean BMI 35.7 kg/m²) and the prevalence of metabolic comorbidities was high: 67.0% had T2DM, 78.1% hypertension, and 71.3% dyslipidaemia.

According to clinical expert feedback derived as part of a clinical advisory board meeting held in London on 9 December 2024 with leading UK clinicians (*further details available upon request*), these characteristics align closely with the typical profile of patients with progressive MASH in the England and Wales, where metabolic syndrome and T2DM are key

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risk factors for advanced fibrosis. Importantly, ~60% of patients had stage F3 fibrosis and ~33% had F2, ensuring representation of the target moderate to advanced fibrosis population (F2–F3) consistent with the NICE decision problem. Only ~5% of patients had F1B fibrosis, minimising heterogeneity and strengthening relevance to the intended UK licensed population.

Although MAESTRO-NASH was an international trial (245 sites across 15 countries), the UK was among the participating countries, ensuring inclusion of patients reflective of NHS clinical practice. The majority of participants were white (89%), with only 2% identifying as black. The comorbidity burden and metabolic risk profile observed were consistent with those typically seen among patients at similar disease stages in UK hepatology clinics, according to expert clinical input. In the trial, all patients received background lifestyle intervention (diet and exercise), reflecting standard UK practice (23).

2.13.3.2 Analysis sets

The primary analysis dataset (mITT-W52 population, n = 966) included all randomised patients whose fibrosis stage was F1B to F3 fibrosis. Importantly, subgroup analyses demonstrated consistent efficacy across age, sex, diabetes status, and fibrosis stage, supporting generalisability to UK clinical practice. Patients with F1A/F1C or cirrhosis were not included in the analysis (unless specific criteria were met), making the main results analyses more relevant to the decision problem for resmetirom.

2.13.3.3 Service provision

Resmetirom is an oral, once-daily therapy that can be administered in the outpatient setting. Treatment would be initiated and monitored by clinicians experienced in the management of liver disease, such as hepatologists or gastroenterologists, in line with the proposed UK licensed indication for the treatment of non-cirrhotic MASH with moderate to advanced liver fibrosis (fibrosis stages F2 to F3).

Unlike injectable therapies, resmetirom does not require infusion facilities or specialist nursing support, and therefore its introduction is not expected to necessitate additional infrastructure within the NHS. Monitoring requirements are aligned with current routine practice for patients with liver disease and include standard liver function tests. Given the drug's mechanism of action, periodic assessment of lipid profile and thyroid function may also be recommended.

The main service delivery consideration is the identification of eligible patients. Current NICE guidelines recommend using NITs to assess fibrosis stage. Increased adoption of these non-invasive tools in secondary care is likely to support implementation of resmetirom in clinical practice.

Overall, resmetirom is expected to integrate into existing NHS hepatology services without significant additional resource requirements, with the potential to simplify and improve long-term management of MASH by providing an oral, well-tolerated, liver-targeted treatment option. Resource burden in respect of service delivery is mainly a consideration in the context of NHS expanding its current provision and screening capacity to detect more patients who could be eligible for therapy with resmetirom.

3. Cost-effectiveness

3.1 Published cost-effectiveness studies

A SLR was conducted to identify published economic evaluations of treatments for MASH/NASH and liver fibrosis or MASLD/NAFLD. To ensure all relevant research was captured, the review scope was broader than the clinical indication linked with this submission. SLR methods are detailed in Appendix E and studies identified are summarised in Table 25. Most studies identified by the SLR reported results in terms of cost per quality-adjusted life year (QALY) gained, with a small number focusing on budget impact or cost savings associated with interventions. None of the included cost-effectiveness studies were conducted from a UK NHS perspective.

Table 25 Summary list of published cost-effectiveness studies

Study	Year	Summary of model	Patient population (average age in years)	QALYs (intervention, comparator)	Costs (currency) (intervention, comparator)	ICER (per QALY gained)
Le et al. (112)	2025	Patient-level simulation Markov model	Patients with MASH and fibrosis stage F2-F3; Average age: 57.1	Intervention: Resmetirom: 10.74 QALYs	Resmetirom: \$129,163 total costs (2023, USD)	\$140,134 per QALY gained
				Comparator: SoC: 10.48 QALYs	SoC: \$92,908 total costs	
Pochopien et al. (113)	2024	Cohort simulation Markov model	Patients with NAFLD and NASH, including all fibrosis stage F0-F4; Average age: 47.7 years	Interventions: Small molecule therapy: 12.54 QALYs	Small molecule therapy: \$315,943 total costs (2023, USD)	Small molecule therapy: Dominant; Biologic therapy: \$673,653 per QALY gained; Curative therapy: \$118,829 per QALY gained
				Biologic therapy: 12.65 QALYs	Biologic therapy: \$533,032 total costs	
				Curative therapy: 13.93 QALYs	Curative therapy: \$513,693 total costs	
				Comparator: Lifestyle intervention: 12.34 QALYs	Lifestyle intervention: \$324,873 total costs	
Kim et al. (114)	2024	Markov model	Patients with MASH and fibrosis stage F2-F3	Intervention: Resmetirom: 11.86	Resmetirom: \$799,397 total costs (cost year NR, USD)	NR but calculated at \$112,732 per QALY gained based on reported figures
				Comparator: SoC: 9.97	SoC: \$586,333 total costs	
Fishman et al. (115)	2024	State-transition Markov model	Adults aged 18–64 with diagnosed non-cirrhotic NASH and stage F2–F3 fibrosis	NR	Incremental cost of resmetirom compared to SoC (2023, USD): Year 1: \$2.23 million Year 2: \$4.90 million Year 3: \$9.55 million Total (3 years): \$16.67 million	NR

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Study	Year	Summary of model	Patient population (average age in years)	QALYs (intervention, comparator)	Costs (currency) (intervention, comparator)	ICER (per QALY gained)
Gal et al. (116)	2023	Patient-level simulation with embedded cohort Markov model	Adults with histologically confirmed NASH and fibrosis stage F1–F3; Average age: 55 years	Intervention: Obeticholic acid (OCA): 12.33 QALYs	OCA: \$911,651 total costs (2020, USD)	\$969,949 per QALY gained
				Comparator: SoC: 11.64 QALYs	SoC: \$244,263 total costs	
Jirapinyo et al. (117)	2023	Markov-based state-transition model	Patients with compensated NASH cirrhosis; Average age: 54 years	NR	NR	Endoscopic gastric plication vs. Intensive lifestyle intervention (ILI): \$13,106 per QALY gained
Ansaripour et al. (118)	2023	Markov model	Patients with NASH	NR	NR	Resmetirom vs. Placebo: \$74,108 per QALY gained; Resmetirom vs. OCA: Dominant
Tice et al. (119)	2023	Markov cohort model	Patients with NASH and fibrosis stage F2–F3; Average age: 55 years	Interventions: OCA: 10.47 QALYs	OCA: \$676,000 total costs (2022, USD)	OCA vs. SoC: \$568,000 per QALY gained; Resmetirom vs. SoC: Dominant
				Resmetirom: 10.66 QALYs	Resmetirom: \$416,000 total costs	
				Comparator: SoC: 10.05 QALYs	SoC: \$439,000 total costs	
Javanbakht et al. (120)	2023	Markov cohort model	Patients with NASH and liver fibrosis stage F1–F3; Average age: 50 years	Intervention: Resmetirom: 12.75 QALYs	Resmetirom: \$348,432 total costs (2021, USD)	\$53,929 per QALY gained
				Comparator: Placebo: 11.52 QALYs	Placebo: \$281,668 total costs	

Study	Year	Summary of model	Patient population (average age in years)	QALYs (intervention, comparator)	Costs (currency) (intervention, comparator)	ICER (per QALY gained)
Rustgi et al. (121)	2022	Markov cohort model	Adults with NAFLD fibrosis; Average age: 49 years	Intervention: Drug: 9.45 QALYs	Drug: \$574,238 total costs (2020, USD)	\$2,517,676 per QALY gained
				Comparator: Natural history: 9.27 QALYs	Natural history: \$120,312 total costs	
Tran et al. (122)	2021	State-transition model with microsimulation	Adults (≥ 18 years old) with definite NASH, NAS of at least 4, and stage F2-F3 fibrosis; Average age: 55	Intervention: OCA: 14.79 QALYs	OCA: \$230,345 annual cost (cost year NR, CAD)	\$815,514 per QALY gained
				Comparator: Placebo: 14.65 QALYs	Placebo: \$116,173 annual cost	
Barritt et al. (123)	2020	Markov model	Patients with advanced fibrosis (F3) due to NASH; Average age: 54 years	Intervention: OCA: Incremental 1.61 QALYs compared to the comparator Placebo	Disease management cost-related savings reported only (2019, USD)	NR
Rind et al. (124)	2020	Markov cohort model	Patients with NASH and fibrosis stage F2-F3; Average age: 54 years	Intervention: Obeticholic acid: 9.92 QALYs	Obeticholic acid: \$1,094,000 total costs (2022, USD)	\$1,482,000 per QALY gained
				Comparator: SoC: 9.43 QALYs	SoC: \$367,000 total costs	
Klebanoff et al.* (125)	2019	Markov-based state-transition model	Patients with NASH and compensated cirrhosis; Average age: 54 years	Interventions: ILI: 4.79 QALYs	ILI: \$223,087 total costs	ILI vs. Usual care: Dominated; Laparoscopic sleeve gastrectomy vs. Usual care: \$6,563 per QALY gained; Laparoscopic Roux-en-Y gastric bypass vs. Usual care:
				Laparoscopic sleeve gastrectomy: 5.76 QALYs	Laparoscopic sleeve gastrectomy: \$222,153 total costs	
				Laparoscopic Roux-en-Y gastric bypass: 5.78 QALYs	Laparoscopic Roux-en-Y gastric bypass: \$228,369 total costs	
				Comparator: Usual care: 4.58 QALYs	Usual care: \$214,412 total costs	

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Study	Year	Summary of model	Patient population (average age in years)	QALYs (intervention, comparator)	Costs (currency) (intervention, comparator)	ICER (per QALY gained)
						\$229,919 per QALY gained
Younossi et al. 2019 (126)	2019	Markov models	NASH with advanced fibrosis	Intervention: Hypothetical treatment: 135,482,049 QALYs	At a willingness-to-pay (WTP) threshold of \$50k/QALY, a cure for NASH would create \$250 billion in value over the lifetime of this NASH cohort. At higher thresholds, this value increases to \$500 and \$751 billion, respectively.	NR
				Comparator: SoC: 130,473,311 QALYs		
Muto et al. (127)	2018	Markov model	Entire NASH population; Average age: 40 years	NR	Interventions: Lifestyle modification + Vitamin E showed a reduction in lifetime medical costs, 79,356 total costs yen/patient (cost year NR, Japanese yen) compared to the comparator Lifestyle modification alone.	NR
					Lifestyle modification + Pioglitazone showed a reduction in lifetime medical costs, 84,146 total costs yen/patient compared to the comparator Lifestyle modification alone.	
Klebanoff et al.† (128)	2017	Markov-based state-transition model	Patients with NASH who are overweight or obese; Average age: 45 years	Interventions: ILI: 12.34 QALYs	ILI: \$30,227 total costs (2014, USD)	ILI vs. Usual care: Dominated; Laparoscopic Roux-en-Y
				Laparoscopic Roux-en-Y gastric bypass: 12.52 QALYs	Laparoscopic Roux-en-Y gastric bypass: \$52,518 total costs	

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Study	Year	Summary of model	Patient population (average age in years)	QALYs (intervention, comparator)	Costs (currency) (intervention, comparator)	ICER (per QALY gained)
				Comparator: Usual care: 12.34 QALYs	Usual care: \$24,895 total costs	gastric bypass vs. Usual care: \$1,136,760 per QALY gained
Vreman et al. (129)	2017	Markov model with patient-level simulation	US adults aged 20+ years; general population with varying sugar intake and risk for metabolic diseases	NR Total amount of disability-adjusted life years (DALYs) could be reduced by 4.32%-13.37%. The majority of averted DALYs are due to reduced mortality.	Total costs (2015, USD): Overall costs for the modelled disease states could be reduced by 2.26% by the year 2035 with an intervention that reduces added sugars intake by 20%. The 50% intervention will reduce overall costs by 6.99%.	NR
Chhatwal et al. (130)	2016	Microsimulation model	Patients with NASH at fibrosis stage F1–F3	Intervention: OCA: 11.02 QALYs	Obeticholic acid: \$351,000 total costs (cost year NR, USD)	Obeticholic acid vs. Usual care: \$2.57m per QALY gained
				Comparator: Usual care: 10.91 QALYs	Usual care: \$70,300 total costs	
Pearson et al. (131)	2016	Individual-level state-transition model	Patients with NASH and fibrosis stage F1–F3; Average age: 49 years	Intervention: OCA: 11.02 QALYs	OCA: \$371,000	\$2,748,300 per QALY gained
				Comparator: Placebo: 10.91 QALYs	Placebo: \$70,300	
Mahady et al. (132)	2012	Markov model	Patients with recently diagnosed NASH and advanced fibrosis (F3 or greater); Average age: 50 years	NR	Interventions: Vitamin E: \$51,000 total costs (2010, AUD)	Vitamin E vs. Lifestyle: \$8,475 per QALY gained; Pioglitazone vs. Lifestyle: \$2,748 per QALY gained
					Pioglitazone: \$59,000 total costs	
					Comparator:	

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Study	Year	Summary of model	Patient population (average age in years)	QALYs (intervention, comparator)	Costs (currency) (intervention, comparator)	ICER (per QALY gained)
					Lifestyle: \$46,000 total costs	

Abbreviations: DALY, disability-adjusted life year; F0-F4, fibrosis stages 0-4; ICER, incremental cost-effectiveness ratio; ILI, intensive lifestyle intervention; MASH, metabolic dysfunction-associated steatohepatitis; NAFLD, non-alcoholic fatty liver disease; NAS, NAFLD Activity Score; NASH, non-alcoholic steatohepatitis; NR, not reported; OCA, obeticholic acid; QALY, quality-adjusted life year; SoC, standard of care; WTP, willingness-to-pay.

*Results presented for severe obesity (BMI ≥ 40.0).

†Results presented for overweight population.

3.2 Economic analysis

Existing cost-effectiveness studies identified by the SLR exhibited a trend whereby most were Markov cohort designs but a few, especially the more contemporary papers, used some elements of patient-level microsimulation models (MSMs) to estimate costs and benefits, with or without embedded Markov elements (112,116). To accurately model our pharmacotherapy in this complex disease area, which has simultaneous effects on the liver as well as other comorbidities and risk factors that impact HRQoL, we also elected to develop a *de novo* patient-level MSM.

The MSM was designed to assess the cost-effectiveness of resmetirom compared with SoC in adults with non-cirrhotic MASH and fibrosis stage F2 or F3 in England and Wales. It was our intent in building the model to reflect the heterogeneity and complexity of disease progression in MASH, including transitions between fibrosis stages in all directions, MASH resolution or relapse, and progression to late-stage liver disease. We also incorporated risks associated with key comorbidities, namely T2DM, and CVD; these were modelled using published risk equations including QRISK3 (133), UKPDS-OM2 (134), Framingham (135), and QDiabetes (136). Mortality was stratified into liver-related, comorbidity-related, and age- and sex- specific background rates.

3.2.1 Patient population

The population intended to be simulated matches the anticipated license, namely adults with non-cirrhotic MASH with moderate to advanced fibrosis (fibrosis stages F2 and F3). The MSM was developed using bespoke analyses of patient level data (PLD) obtained from the MAESTRO-NASH study.

As described in Section 2.3.1.7, the MAESTRO-NASH study's SAP defined several analysis 'populations' (i.e., data subsets) to address questions or issues in the research. The subset selected to inform efficacy in the development of our MSM was the **Paired Liver Biopsy Population at Week 52 (PLB-W52)** population (**n = 782**). This group of patients had acceptable central-read biopsy data available both at baseline and week 52; its analysis is reported in Table S9 of the online supplement to Harrison et al. 2024 (17). The **PLB-W52** subset is narrower than the **Liver Biopsy Modified Intent-to-Treat Population (mITT-LB-W52) (n = 955)** which was analysed for primary endpoints in the body text of Harrison et al. 2024 (17). This sample size restriction was necessary because **mITT-LB-W52** included biopsy data regardless of the acceptability of the baseline/week 52 paired sample to central reader, meaning it was suitable for reporting aggregate statistics but not suitable to be

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sampled at a patient level for MSM. Specifically, **mITT-LB-W52** retained patient biopsy records even if the two histological assessors did not agree on MASH resolution status. This uncertainty was readily dealt with in the SAP by recording the “MASH resolution 0/1” variable as 0.5 and making necessary adjustments to data management and statistical tests. At patient level, we did not consider that a comparable alternative could be programmed without significantly increasing complexity, in exchange for little extra benefit in terms of certainty.

Our choice of the **PLB-W52** population therefore, although restricting the available numbers, allowed the MASH and fibrosis component of the MSM to be accurately linked to primary efficacy endpoints at patient level. The model mapped year-1 evidence onto a joint distribution of outcomes (MASH resolution × fibrosis change) to populate a first-year transition matrix and to derive relative risks used beyond year 1.

To explore how the modelled population compared to patient profiles collected in the NHS, we summarised baseline characteristics of MAESTRO-NASH participants after excluding F1B (n = 43) from the paired-biopsy population (n = 782), yielding 739 patients with F2–F3 fibrosis. These were compared with patients in the CPRD-HES study database (n = 2,696). As shown in Table 26, the two populations were broadly similar in age (████ vs. 56 years), sex distribution (████ vs. 54.5% female), and obesity prevalence (████ vs. 44.7%). Ethnic distribution was also comparable, though the CPRD cohort included a higher proportion of South Asian patients (9.5% vs. █████ in MAESTRO-NASH). Some notable differences were observed in comorbidity prevalence. Hypertension was present in nearly 80% of the MAESTRO-NASH population compared with 47.3% in CPRD, and T2DM (n = 489) was twice as common (████ vs. 40.9% in CPRD). Within the MAESTRO-NASH study, the subgroup of patients with T2DM showed an even higher burden of metabolic risk factors, with greater prevalence of hypertension (████ versus CPRD and higher rates of advanced fibrosis (F3: █████ for T2DM vs. █████ for overall for the overall paired-biopsy population).

These findings suggest that while MAESTRO-NASH patients are comparable to England and Wales MASH population in terms of demographics and obesity status, they represent a higher-risk subgroup of this population with more advanced liver disease and cardiometabolic comorbidities. A comprehensive list of patient characteristics at baseline is provided in Appendix K, Tables 1–4.

Table 26 Baseline characteristics of model paired-biopsy population (PLB-W52), T2DM subgroup, and CPRD MASH cohort

Patient characteristics	Paired-biopsy population with F2-F3 (base case; n= 739)	Model patients with T2DM (n= 100)	CPRD MASH cohort (England, n = 2,696) (5)
Age (years)	56	56	56
Female (%)	54.55	54.55	54.55
Ethnicity (%)	White 83.7, South Asian 9.5, Black 2.7, Other/mixed 3.3	White 83.7, South Asian 9.5, Black 2.7, Other/mixed 3.3	White 83.7, South Asian 9.5, Black 2.7, Other/mixed 3.3
F2 (%)	NR	NR	NR
F3 (%)	NR	NR	NR
Weight (kg)	NR	NR	NR
Obesity with BMI ≥ 30 (%)	44.7	44.7	44.7
Hypertension (%)	47.3	47.3	47.3
T2DM (%)	40.9	40.9	40.9
LDL (mg/dl)	NR	NR	NR
HDL (mg/dl)	NR	NR	NR
Total cholesterol (mg/dl)	NR	NR	NR

Abbreviations: BMI, body mass index; CPRD, Clinical Practice Research Datalink; F2-F3, fibrosis stages 2-3; HbA1c, glycated haemoglobin; HDL, high-density lipoprotein; LDL, low-density lipoprotein; MASH, metabolic dysfunction-associated steatohepatitis; N/A, not reported; T2DM, type 2 diabetes mellitus.

3.2.2 Model structure

The *de novo* patient-level MSM was developed in R. Our choice of a microsimulation framework reflects the complexity of MASH, a progressive metabolic condition with heterogeneous trajectories and frequent comorbidities.

Conventional cohort Markov models are constrained by the “memoryless” property, whereby future risk depends only on the current state. This is a limitation in MASH, as outcomes are influenced by both patient history and evolving risk factors (137). MSM allows for simulation of individual patient pathways, capturing heterogeneity in baseline characteristics, treatment response (if possible), and comorbidity risks.

The model structure was informed by published economic evaluations in fatty liver disease. Previous studies (e.g., Javanbakht et al. 2023 (120); Tice et al. 2023 (119); Le et al. 2025 (112)) primarily employed cohort or patient-level Markov models, in which fibrosis transitions were simplified and largely history-independent. By contrast, Chhatwal et al. 2022 (53) demonstrated the feasibility and advantages of full MSMs in this disease area, particularly for reflecting comorbidity interactions and long-term uncertainty. The company's MSM aligns

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more closely with these latter approaches, while retaining some simplifying assumptions due to the lack of longer-term data. Specifically, fibrosis regression and progression were modelled using fixed annual transition probabilities informed by MAESTRO-NASH and other published sources, rather than fully time-dependent hazard functions. This will be discussed in further detail in subsequent sections. Nonetheless, the MSM captures individual patient histories through dynamic updates of risk factors (e.g., lipids profile, BMI), treatment discontinuation, relapse after MASH resolution, and evolving comorbidity risks.

Resmetirom treatment effects (MASH resolution, fibrosis improvement, and changes in cardiometabolic risk factors) were modelled explicitly based on MAESTRO-NASH data, with treatment discontinuation representing an appropriate proxy for waning. No arbitrary waning curves were imposed, avoiding speculative assumptions and maintaining consistency with previous NICE appraisals (see Section 3.3.2.3) where discontinuation was considered a transparent and clinically meaningful assumption in place of waning.

3.2.3 Model health states

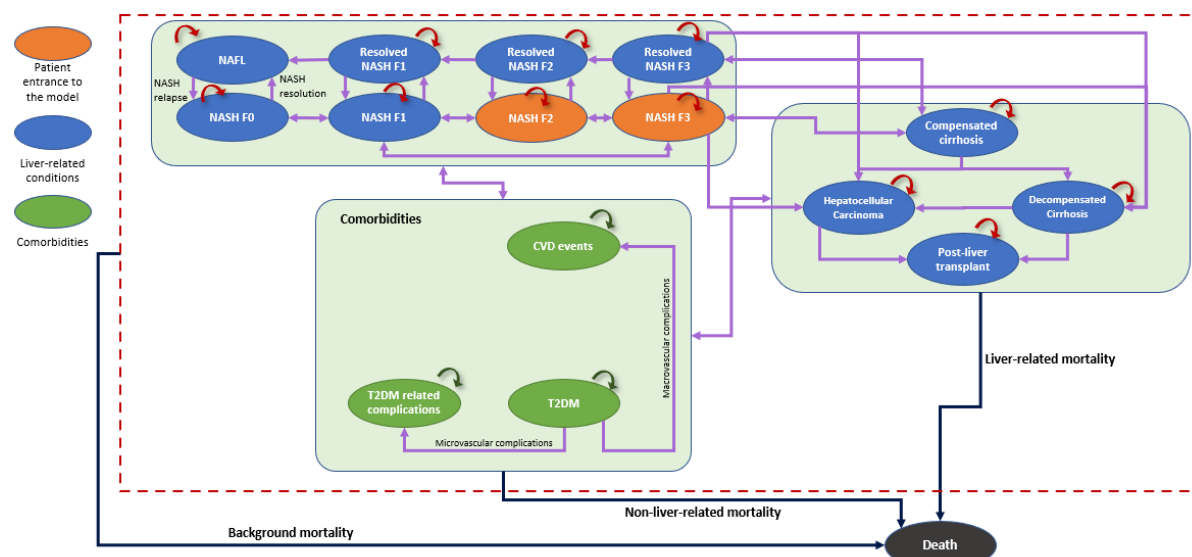
Patients enter the model at fibrosis stages F2 or F3 (F2 MASH or F3 MASH, respectively), sampled from MAESTRO-NASH patient-level data. In each annual cycle, with respect to their liver fibrosis and MASH, individuals can:

- regress, remain stable, or progress in fibrosis stage;
- achieve MASH resolution or relapse to active MASH;
- progress to advanced liver disease (comprised of CC, DCC, HCC, LT);
- experience comorbidities - T2DM or CVD (using established UK equations: QRISK3 for cardiovascular events in non-diabetic patients (133), UKPDS-OM2 for cardiovascular and microvascular events in patients with T2DM (134), Framingham functions for recurrent cardiovascular events (135), and QDiabetes-2018 for diabetes incidence (136));
- die from liver-related (liver complications) or non-liver-related (comorbidities) reasons, or due to background mortality (from age- and sex-related factors).

To implement the above, the MSM includes 16 liver-related and comorbidity health states, shown in Figure 13. The structure was informed by previous fatty liver disease models (e.g.,

Chhatwal et al. 2022 (53)) and tailored to capture the overlap between MASH progression and its major comorbidities.

Figure 13 MSM structure



Abbreviations: CVD: cardiovascular disease; F0-F3: fibrosis stages 0-3; NAFL: non-alcoholic fatty liver; NASH: non-alcoholic steatohepatitis; T2DM: type 2 diabetes mellitus.

The modelled disease pathways span fibrosis stages F0 to F4, CC, DCC, HCC, LT (year 1 and post-transplant), and death. Patients can transition between health states via fibrosis regression or progression, or attainment of MASH resolution (with later potential relapse). Progression to DCC or HCC can occur only from advanced fibrosis stages (F3 and F4). Mortality is modelled to arise from background causes, liver-related complications, or comorbidities.

The model also incorporates comorbidities commonly associated with MASH, specifically T2DM, and CVD (MI and ischaemic stroke [IS]). These were selected because of their strong epidemiological association with MASH and their significant impact on costs, survival, and HRQoL (138). Comorbidities are not represented as stand-alone states but were modelled through risk equations (QRISK3 (133), UKPDS-OM2 (134), Framingham (135), Q-Diabetes (136)) that adjusted transition probabilities and event rates. Relative risk multipliers were applied to baseline QRISK3/UKPDS cardiovascular risk estimates, by fibrosis and liver complication health state (116) (see Table 35).

At model entry, patients start with active MASH and are distributed across fibrosis stages F2 and F3 (“F2 MASH” and “F3 MASH” health states) in proportions corresponding to the baseline fibrosis stage distribution seen in the PLB-W52 analysis population. Baseline

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comorbidity prevalence reflected trial data (17). Any patient who discontinued treatment reverts to SoC transitions but remains at risk of comorbidities as their disease progresses.

To limit complexity while ensuring that the main costs and benefits of treatment were captured, several assumptions were applied:

- **Comorbidities were layered rather than defined by sequential health states.** For example, a patient with F3 fibrosis can simultaneously develop T2DM and later an MI, with incremental costs and disutilities applied in the cycle of onset.
- **T2DM microvascular complications** (e.g., nephropathy, retinopathy, neuropathy) are not modelled as separate states; their impact is captured through cost weights applied to the T2DM state.
- **Resolution of MASH** reduces risks of progression and comorbid events but patients remain at residual background risk, including the possibility of relapse (assumed at 5% annually).
- **Treatment discontinuation** is explicitly modelled based on data from MAESTRO-NASH. Discontinuation is assumed to terminate pharmacological effect, after which patients follow SoC transition probabilities. No treatment legacy effect was assumed.

An annual cycle length is applied in the model. The chosen cycle period is consistent with approaches utilised in previous CEAs of MASH (119,120) and also matches the data collection interval of the MAESTRO-NASH trial (17). A half-cycle correction is also applied.

3.2.4 Structural assumptions

Several simplifying assumptions were necessary to ensure the model remains transparent, tractable and aligned with available evidence. First, fibrosis progression and regression are modelled using fixed annual transition probabilities informed by patient-level data from the PLB-W52 analysis population in MAESTRO-NASH as well as some published sources, rather than developing fully time-dependent hazards. While this may not capture potential acceleration with duration in state, no robust longitudinal data are available for MASH, and the MAESTRO-NASH study had a one-year interval between baseline and final biopsy (17). Second, MASH is modelled to have an annual relapse risk after resolution, which is assumed constant over time. This assumption is conservative, as it prevents patients from accruing permanent benefit after resolution and is varied in sensitivity analyses. Third, comorbidities (T2DM and CVD) are incorporated via validated UK risk equations (QRISK3 Company evidence submission: Resmetirom for treating moderate to advanced liver fibrosis (without cirrhosis) (MASLD) ID6529

(133), UKPDS-OM2 (134), Framingham (135), Qdiabetes (136)) applied across liver disease states, rather than represented as discrete health states. This approach captures heterogeneity in risk while limiting unnecessary complexity. Finally, treatment discontinuation is assumed to represent loss of pharmacological effect; no additional within-treatment waning curve is imposed. This mirrors NICE practice in prior appraisals where Committees have explicitly accepted discontinuation as a proxy for waning—for example TA533 (ocrelizumab) (139) and TA699 (ofatumumab) (140)—with scenario testing used to explore model sensitivity to alternative waning assumptions. We have followed the same principle and presented scenarios with alternative discontinuation rates.

Collectively, these assumptions are expected to yield conservative estimates of resmetirom's cost-effectiveness, as potential benefits are foregone in each of the assumptions applied. Structural uncertainties were further explored in scenario analyses to assess robustness of results.

3.2.5 Intervention technology and comparators

3.2.5.1 Intervention technology

Resmetirom (intervention) is an orally administered, once-daily, selective THR- β agonist, licensed in the U.S., has conditional approval by the EMA (Section 1.1), and is currently under regulatory review in the UK for use in conjunction with diet and exercise for the treatment of adults with non-cirrhotic MASH with moderate to advanced liver fibrosis (fibrosis stages F2-F3).

3.2.5.2 Comparator technology

After discussion at the DP meeting and in line with our Form 1 submission, the economic model included SoC only as comparator. The rationale for this decision was set out in Section 1.1 of this document.

3.2.6 Decision problem alignment

The modelled comparator, SoC, reflects how MASH is currently managed in the NHS. As previously elaborated, vitamin E and pioglitazone are considered part of this SoC and will not be assessed as comparators in their own right. The SoC arm modelled is intended to capture the current clinical pathway into which resmetirom would be introduced. We consider the primary base-case decision problem to address whether this new pharmacotherapy represents a cost-effective addition to the current SoC.

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3.3 Clinical parameters and variables

3.3.1 Resmetirom dose management

Resmetirom dose switching is implemented dynamically within the MSM to reflect the likely prescribing UK SmPC, taking into account patient weight and co-administration of CYP2C8 inhibitors. Dose is determined at baseline and re-evaluated at the start of every model cycle (i.e., each year), with changes applied before clinical transitions are simulated. The algorithm is:

- Patients weighing < 100 kg should initiate treatment with 80 mg once daily.
- Patients weighing $\geq$ 100 kg should initiate treatment with 100 mg once daily.

Dose adjustments are required for resmetirom in patients receiving concomitant therapy with moderate or strong CYP2C8 inhibitors (e.g., gemfibrozil, clopidogrel). In such cases, the dose should be reduced from the weight-based starting regimen:

- Patients otherwise eligible for 100 mg daily should instead receive 80 mg daily.
- Patients otherwise eligible for 80 mg daily should instead receive 60 mg daily.

This adjustment was necessary to account for the pharmacokinetic interaction between resmetirom and CYP2C8 inhibitors, which can increase systemic drug exposure.

Because weight can evolve in the MSM, crossing the 100 kg threshold triggers dose re-assignment at the next cycle start (to 80 mg if < 100 kg; to 100 mg if $\geq$ 100 kg), unless the CYP2C8 rule was active, in which case the inhibitor rule takes precedence.

It is important to note that resmetirom 60 mg was not formally evaluated in the MAESTRO-NASH trial. However, dose adjustments are required in patients receiving concomitant therapy with moderate or strong CYP2C8 inhibitors. Resmetirom is primarily metabolised by the CYP2C8 enzyme; inhibition of this pathway reduces its metabolic clearance, resulting in increased systemic drug exposure. To mitigate the risk of potential adverse effects associated with elevated plasma concentrations, the resmetirom dose was reduced in these patients.

For modelling purposes, we assumed that systemic exposure with 60 mg of resmetirom in the presence of a CYP2C8 inhibitor was approximately equivalent to the exposure achieved with 80 mg in the absence of an inhibitor. Accordingly:

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- When a patient receives 60 mg in combination with a CYP2C8 inhibitor, we applied the efficacy profile observed at 80 mg.
- When a patient eligible for 100 mg daily initiates therapy with a CYP2C8 inhibitor and was subsequently reduced to 80 mg, we applied the 80 mg efficacy profile from that point onwards. Unlike in the 60 mg scenario, we have direct trial evidence for the adjusted dose, so no extrapolation based on exposure equivalence was required.

This approach ensures that efficacy estimates are aligned with expected systemic exposures while maintaining accurate costing, thereby avoiding both underestimation and overestimation of treatment effect in the economic model.

3.3.2 Transition probabilities

Transition probabilities are specified for three categories: **(i) liver-disease transitions** (fibrosis regression, stability, progression, transitions to CC, DCC, HCC, LT); **(ii) comorbidity events** (incident T2DM), first and recurrent CVD); **(iii) mortality** (background, liver-related, and non-liver causes). Where possible, inputs were UK-specific and parameter uncertainty was characterised in the MSM with Beta or Dirichlet distributions. Fibrosis transitions are implemented as fixed annual probabilities based on week 0-52 patient-level data from MAESTRO-NASH, independent of time in state (for more information please see Section 3.3.2.3), with an explicit relapse mechanism for MASH in patients who achieved resolution. In the absence of time-dependent hazards, this approach makes optimal use of the available data from MAESTRO-NASH.

3.3.2.1 Liver-disease transitions

For the first year of treatment, transition probabilities were informed directly by MAESTRO-NASH individual patient data (IPD). Outcomes were classified jointly and comprised MASH resolution status (yes/no) and Fibrosis change (improvement, stability, or worsening). These six mutually exclusive categories provided the multinomial basis for deriving arm-specific transition probabilities.

Table 27 Joint outcomes of MASH resolution and fibrosis changes after 52 weeks of treatment (MAESTRO-NASH, paired-biopsy population)

	MASH resolution					
	Yes			No		
	% Fibrosis improvement	% Fibrosis worsen	% Fibrosis No change	% Fibrosis improvement	% Fibrosis worsen	% Fibrosis No change

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Resmetirom 80 mg (n = 244)	■	■	■	■	■	■
Resmetirom 100 mg (n = 237)	■	■	■	■	■	■
Placebo (n = 258)	■	■	■	■	■	■

Abbreviations: MASH, metabolic dysfunction-associated steatohepatitis.

As Table 27 shows across the trial, MASH resolution occurred in approximately ■ of patients in the resmetirom 80 mg and 100 mg arms vs. approximately ■ in the placebo arm; ≥ 1-stage Fibrosis improvement was observed in approximately ■ of patients in the resmetirom 80 mg and 100 mg arms, and in about ■ of patients in the placebo arm; and fewer patients in the resmetirom arm (~■ of patients in the resmetirom 80 mg and 100 mg arms) experienced Fibrosis worsening than patients in the placebo arm (■), all respectively. In the economic model, these mutually exclusive outcomes were mapped to liver health states within the microsimulation (resolved versus active MASH, with the fibrosis stage updated accordingly), and patients were permitted a single transition per cycle.

Table 28 reports the year-1 transition probabilities for the joint histological outcome that combines MASH resolution with change in fibrosis stage. For each treatment arm (placebo, resmetirom 80 mg, and resmetirom 100 mg), participants at week 52 were classified into four mutually exclusive categories: (i) MASH resolution with ≥ 1-stage fibrosis improvement, (ii) MASH resolution with ≥ 1-stage fibrosis worsening, (iii) no MASH resolution with ≥ 1-stage fibrosis improvement, and (iv) no MASH resolution with ≥ 1-stage fibrosis worsening. The probability of stable fibrosis (no change in fibrosis) was estimated as the residual: one minus the sum of improvement and worsening within the relevant MASH-resolution stratum.

Probabilities were estimated from the pre-specified analysis set (paired-biopsy population). Where a cell contained no observed events in different subpopulations, we applied a Haldane–Anscombe continuity correction (141), calculating $p = (x + 0.5)/(n + 1)$ and then normalised within each arm so that the three probabilities (fibrosis improvement, fibrosis worsening, and stable fibrosis) summed to 1. This preserved the observed correlation between steatohepatitis resolution and fibrosis dynamics without assuming independence. Parameter uncertainty was propagated in sensitivity analyses by drawing from a symmetric Dirichlet posterior with $\alpha = \text{counts} + 0.5$, which is consistent with the Haldane correction and avoids zero-probability cells in probabilistic runs.

A similar approach was used to estimate transition probabilities for the subpopulation of T2DM patients (Table 29).

Table 28 (Year 1) joint transition probabilities (mean (95% CI)); (MAESTRO-NASH, paired-biopsy population; base case)

	MASH resolution	MASH Resolution: YES		MASH Resolution: NO	
		Fibrosis improvement	Fibrosis worsening	Fibrosis improvement	Fibrosis worsening
Placebo	■	■	■	■	■
Resmetirom 100 mg	■	■	■	■	■
Resmetirom 80 mg	■	■	■	■	■

Abbreviations: MASH, metabolic dysfunction-associated steatohepatitis.

Table 29 (Year 1) joint transition probabilities (mean (95% CI)); (MAESTRO-NASH, T2DM subpopulation)

	MASH resolution	MASH Resolution: YES		MASH Resolution: NO	
		Fibrosis improvement	Fibrosis worsening	Fibrosis improvement	Fibrosis worsening
Placebo	■	■	■	■	■
Resmetirom 100 mg	■	■	■	■	■
Resmetirom 80 mg	■	■	■	■	■

Abbreviations: MASH, metabolic dysfunction-associated steatohepatitis.

In the next step, we used results from Singh et al. 2015 (142) to distribute patients falling into categories of fibrosis “improvement” or “worsening” across available fibrosis states (F0 to F4) for both resmetirom and SoC arms identically.

MAESTRO-NASH could not be entirely relied on to inform the magnitude of these fibrosis movements because the study has remained protocol-blinded through month 54, and to preserve the integrity of the confirmatory clinical outcomes analysis (per the FDA-reviewed Subpart H framework (143)), detailed arm-level data on progression to compensated cirrhosis (F4) are not being made available. Therefore, when we performed the base-case analysis on patients with F2+F3, we were not able to present either of these two subpopulations separately (F2 and F3), as the number of patients progressing to F4 could be readily derived through a simple reverse calculation. It is important to emphasise that these progressed patients were fully incorporated within the base-case analysis, ensuring that the overall impact of disease progression to cirrhosis was appropriately captured.

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To maintain consistency across all allowable transitions, we therefore applied baseline stage-specific, annual transition splits from the paired-biopsy meta-analysis by Singh et al. 2015 (142), which is methodologically aligned with our 1-year cycle and provides more stable estimates for ≥ 2 -stage moves than a single trial (Table 30). Operationally, we implemented Dirichlet distributions where there were three or more destinations (e.g., F0 to F1/2/3/4; F1 to F2/3/4) and Beta distributions for binary splits (e.g., F2 to F1 vs. F2 to F0), parameterised to reproduce the meta-analytic means and approximate reported ranges; biologically implausible one-year changes were treated as structural zeros, and the associated uncertainty was explored in probabilistic sensitivity analyses (PSA).

Table 30 Probability distribution of fibrosis stages (F0–F4) allocated to ‘worsening’ and ‘improvement’ outcomes in MAESTRO-NASH, Singh et al. 2015

Health states	Mean	Low value - High value	Distribution
F0 to F1 (worsening)	0.64	0.51 - 0.76	Dirichlet
F0 to F2 (worsening)	0.18	0.15 - 0.22	Dirichlet
F0 to F3 (worsening)	0.09	0.07 - 0.11	Dirichlet
F0 to F4 (worsening)	0.09	0.07 - 0.11	Dirichlet
F1 to F2 (worsening)	0.6	0.48 - 0.72	Dirichlet
F1 to F3 (worsening)	0.33	0.27 - 0.40	Dirichlet
F1 to F4 (worsening)	0.07	0.05 - 0.08	Dirichlet
F2 to F0 (improvement)	0.23	0.08 - 0.38	Beta
F2 to F1 (improvement)	0.77	0.62 - 0.92	Beta
F2 to F3 (worsening)	0.5	0.40 - 0.60	Beta
F2 to F4 (worsening)	0.5	0.40 - 0.60	Beta
F3 to F0 (improvement)	0	0.00 - 0.00	Dirichlet
F3 to F1 (improvement)	0.5	0.40 - 0.60	Dirichlet
F3 to F2 (improvement)	0.5	0.40 - 0.60	Dirichlet
F4 to F0 (improvement)	0	0.00 - 0.00	Dirichlet
F4 to F1 (improvement)	0	0.00 - 0.00	Dirichlet
F4 to F2 (improvement)	0	0.00 - 0.00	Dirichlet
F4 to F3 (improvement)	0	0.00 - 0.00	Dirichlet

Abbreviations: F0-F4, fibrosis stages 0-4. F4 is equal to compensated cirrhosis (CC) in the economic model.

For years 2 and beyond, the same transition framework is retained: directional movement in fibrosis (improve/stable/worsen) was assumed to continue at the rates observed from weeks 0-52 in MAESTRO-NASH and apportioned into stage-specific fibrosis changes using the Singh et al. 2015 splits (142), applied each cycle. An annual treatment discontinuation for resmetirom is also incorporated; individuals who discontinue immediately revert to the SoC transition matrix, with no treatment effect legacy assumed beyond their current health state. Patients in Resolved MASH face a fixed annual relapse probability of 0.050 (0.041- 0.060) (53), and return to Active MASH (with fibrosis stage otherwise evolving per the cycle’s

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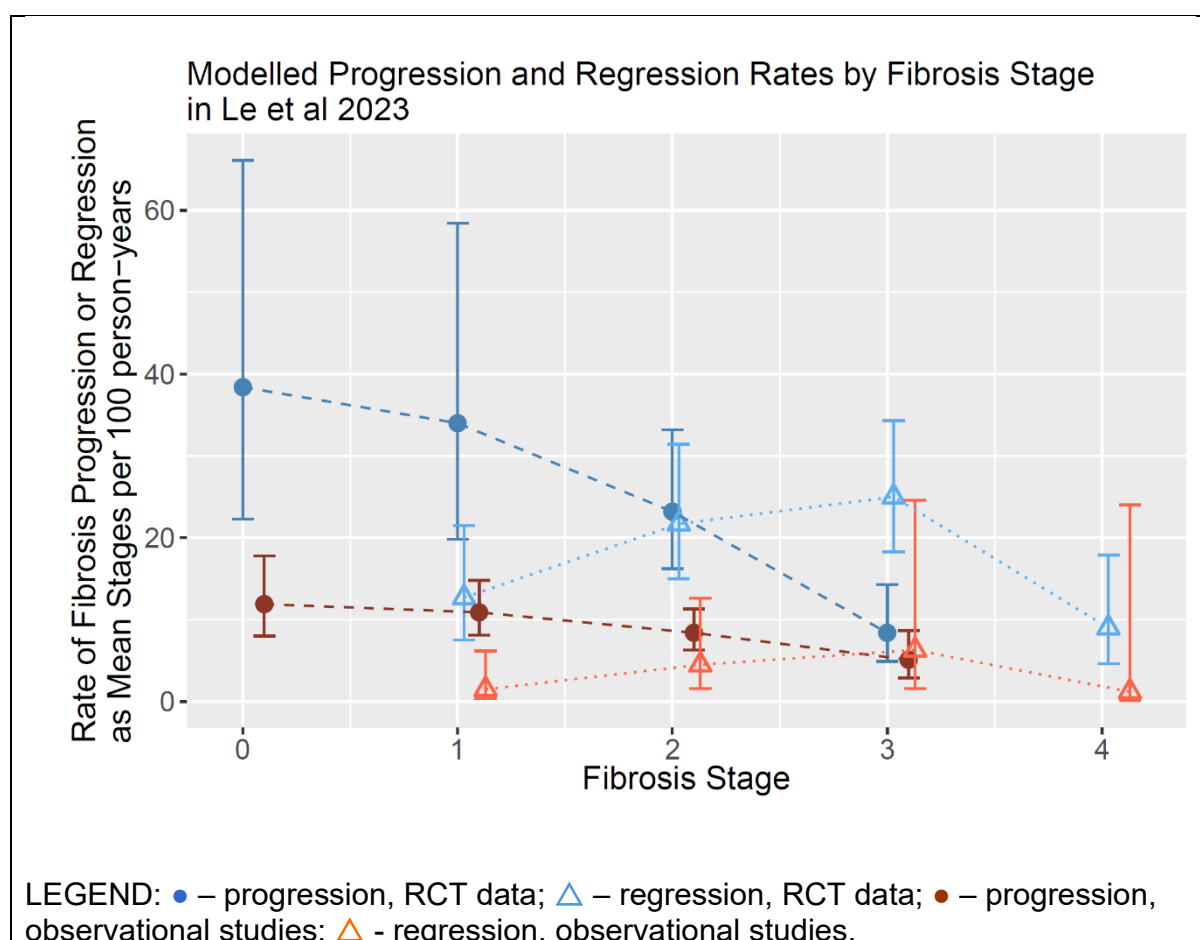
transition rules); this parameter follows external precedent and is varied in sensitivity analyses.

We consider that this method would yield more plausible results than attempting to adapt previously published data sources relating to the natural history of MASH. Our central consideration was that the MAESTRO-NASH trial population – both treatment and placebo arms - aligns well with this decision problem. Our target population comprises patients with MASH with moderate to advanced fibrosis (fibrosis stages F2 to F3). Within MAESTRO-NASH, the metabolic risk profile of participants was notable: ■■■ had three or more metabolic syndrome components and ■■■ had at least two. These components included abdominal obesity, hypertension, elevated fasting glucose, hypertriglyceridemia, and low HDL-C. This meant that the population under study in MAESTRO-NASH could reasonably be characterised as high-risk individuals and, in clinical terms, “fast progressors”, whom are also most likely to receive treatment for MASH on the NHS. The natural history of MASH is highly heterogeneous, so the ability to ground the model in data from this specific high-risk population allowed a more relevant assessment of the value of resmetirom for patients with MASH and moderate to advanced fibrosis (fibrosis stages F2 to F3) within this decision problem.

More recently published studies estimating natural history transition probabilities in MASH or NASH, such as the recent meta-analysis by Le et al. 2023 (144), suffer from several key limitations that reduce their suitability for use in our health economic model. The most recent Le et al. 2023 analysis pooled data from placebo arms of RCTs and real-world observational studies and estimated clinically implausible results for time to progression and regression between fibrosis stages (144). This is due to the mixture of patient populations in this study, which introduced moderate to severe heterogeneity into all transition estimates, and produced several clinically unintuitive point estimates in the matrices published for fibrosis stage. In particular, the mean rate and magnitude of fibrosis progression appeared to decelerate with worsening fibrosis severity, which is the opposite of the trend generally observed and expected in MASH (137).

Figure 14 illustrates the heterogeneity of pooled estimations of fibrosis transition (expressed as mean stages per 100 person-years, for both progression and regression), separated by evidence source from Le et al. 2023 (144).

Figure 14 Summary of fibrosis transition estimates from Le et al. 2023



The use of these pooled estimates for determining time to progression or regression of 1 fibrosis stage (in years) is presented in Table 31. It is worth also noting the low patient numbers and high number of studies for which data have been pooled for each fibrosis stage. For F2 to F3 and F3 to F4 transitions respectively, the authors calculated mean times to progression of 11.9 (95% CI: 8.8–15.9) years and 19.6 (95% CI: 11.5–34.5) years. The authors also reported that time to regress by one stage (in years) was 22.2 (95% CI: 7.9–62.5) years from F2 to F1 and 15.9 (95% CI: 4.1–62.5) years from F3 to F2.

Application of mean progression times from Le et al. 2023 (144) in the MSM would imply that an F3 patient would take approximately 38.1 years on average to improve by 2 fibrosis stages to F1 (15.9 years from F3 to F2 and 22.2 years from F2 to F1). Equally, the Le et al. 2023 data (144) would translate to an F2 patient in the placebo arm of the model taking on average 31.5 years to reach cirrhosis (F4). These values are not supported by the MAESTRO-NASH data and are unlikely to reflect disease progression and regression for this patient population in England and Wales.

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Therefore, taking the MAESTRO-NASH data into account, which form the basis of this economic analysis and this decision problem, it would be mathematically and clinically inappropriate to apply Le et al. 2023 (144) in the economic model to represent the natural history of this disease for the population being modelled.

Table 31 Estimates of time to progression and regression based on pooled incidences among observational studies from Le et al. 2023

NASH stage	Studies/ patients, n	Time to progress by 1 stage (years)	Time to regress by 1 stage (years)
F0	9/41	8.4 (5.6–12.5)	N/A
F1	12/120	9.2 (6.8–12.3)	66.7 (16.1–250.0)
F2	12/92	11.9 (8.8–15.9)	22.2 (7.9–62.5)
F3	8/52	19.6 (11.5–34.5)	15.9 (4.1–62.5)
F4	4/11	N/A	83.3 (4.2–1000.0)

Abbreviations: F0-F4, fibrosis stages 0-4; N/A, not applicable.

Our model uses the most transparent and robust available evidence source, anchored on paired, 52-week biopsy-confirmed transitions observed in the MAESTRO-NASH RCT, and these empirically-observed probabilities applied consistently in subsequent cycles against a background of natural fibrosis progression applied from Singh et al 2015 (142). Applying these transitions within a microsimulation framework allows patient-level heterogeneity, comorbidity risks, and competing hazards of death to be captured, features that cannot be reflected in linear extrapolations from meta-analytic averages.

For these reasons, the decision to use the short-term, trial-derived probabilities from MAESTRO-NASH as the basis for modelling disease progression under SoC was considered the most appropriate option available. Although the SoC arm of MAESTRO-NASH cannot provide a definitive natural history for the condition, it represents the most relevant empirical foundation currently available for modelling regression, stability, and progression of fibrosis in this population.

3.3.2.2 Treatment discontinuation: definitions, rules, and implementation

Treatment discontinuation is modelled via two mechanisms: annual rates sourced from the MAESTRO-NASH trial, and rule-based discontinuation as described below.

Permanent discontinuation

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Patients permanently discontinue resmetirom if they progress to F4 (CC) or any decompensated state (DCC or HCC) – in this situation, resmetirom is stopped for all subsequent cycles and patients revert immediately to the SoC transition matrix with no legacy effect and no further drug costs.

As previously introduced, we applied dose-specific annual resmetirom discontinuation rates derived from all-cause discontinuation rates in MAESTRO-NASH ((17)): 0.028 (0.013 – 0.049) for 80 mg and 0.077 (0.051 – 0.109) for 100 mg.

Temporary discontinuation (eligibility gating)

Patients initiate treatment with resmetirom in health state F2 MASH or F3 MASH (in line with the anticipated product indication). Thereafter, any movement to a lower fibrosis stage < F2 (i.e., both F0 and both F1 health states in the model) triggers temporary discontinuation, regardless of MASH resolution status. Whilst off treatment, patients follow SoC transitions and incur no drug costs. Treatment re-initiation occurs only when a patient returns to F2 or F3 health states (MASH or resolved) and the on-treatment transition matrix and costs are then re-applied from the next cycle.

This above condition reflects the anticipated label that confines active treatment to patients with at least moderate fibrosis. Using < F2 as a stopping rule regardless of MASH status prevents continued therapy in patients whose fibrosis has regressed below the target severity, while preserving label-consistent re-initiation criteria. Linking the treatment stopping rule to earlier stages of fibrosis stages < F2 (i.e., all F0 or F1 health states), which is plausibly assessable with validated NITs, makes the stopping policy implementable, reduces misclassification-driven cycling on/off therapy, and could be aligned with NHS expectations for clear, auditable criteria. In addition, clinical expert opinion (Dr. Queenie Tan, Sheffield Liver Unit) indicates that patients with less severe disease are sent back to primary care and would not be receiving therapy. Therefore, the model excluding treatment for F0 and F1 patients is reflective of expected administration in NHS clinical practice in England and Wales.

3.3.2.3 Treatment effect waning

In the economic analysis, we did not explicitly model any on-treatment waning of resmetirom's effect, in line with the currently available clinical evidence from MAESTRO-NASH. In the MAESTRO-NASH study, patients who remained on therapy for 52 weeks maintained consistent histological benefits, and there was no evidence of declining efficacy

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over the treatment period (17). Without longer-term follow-up data, there was no scientific or empirical basis to impose an arbitrary waning curve while patients continued therapy. Introducing such a function would have required assumptions about the shape, timing, and magnitude of decay that were unsupported by evidence and would have added considerable structural uncertainty to the model. Instead, the model utilises a constant annual treatment discontinuation rate as a proxy for treatment waning, based on the discontinuation rate observed between weeks 0-52 of MAESTRO-NASH. This assumption has been varied in scenario analyses (Section 3.11.3) to assess the impact of uncertainty associated with discontinuation.

It is important to note that the model does not assume any residual legacy effect after treatment discontinuation. Resmetirom's mechanism of action depends on ongoing hepatic THR- β engagement (Section 1.2), and there currently are no data suggesting that histological improvements persist once pharmacological exposure has ceased. In absence of data to support such a legacy effect, patients revert immediately to SoC transition probabilities following discontinuation of resmetirom treatment in the model (either temporarily or permanently), with no continued pharmacological benefit.

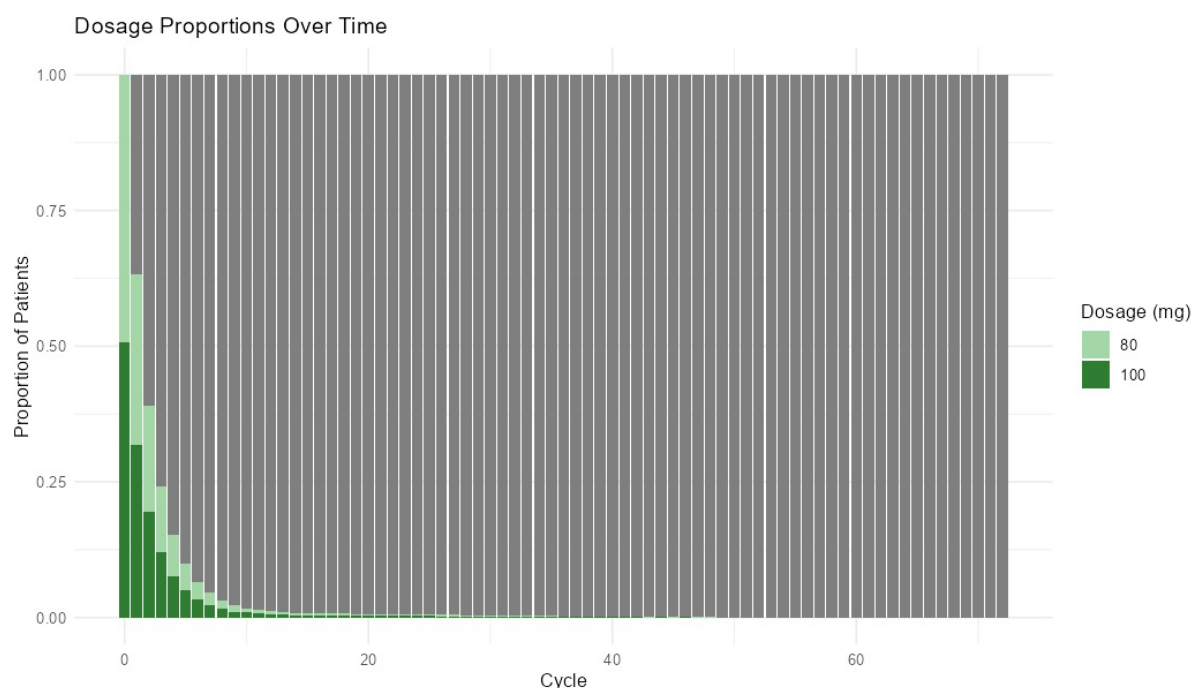
It is important to note that constant per-patient transitions were conditional on health state and treatment status (on-treatment vs. off-treatment/SoC), using probabilities estimated from MAESTRO-NASH. However, we model permanent and temporary discontinuation with a constant annual hazard. Let $p_{on}(t)$ be the proportion of patients remaining on resmetirom at cycle t (for a discrete annual discontinuation rate q , $p_{on}(t) = (1-q)^t$, with temporary discontinuation, $p_{on}(t)$ is **reduced further** in affected cycles). The unconditional cohort-average transition matrix at cycle t is then a mixture of the on-treatment ($\mathbf{P}^{on}$) and SoC ($\mathbf{P}^{SoC}$) matrices:

$$\mathbf{P}_t = p_{on}(t) \mathbf{P}^{on} + [1 - p_{on}(t)] \mathbf{P}^{SoC}$$

As $p_{on}(t)$ declines monotonically overtime, $\mathbf{P}_t$ naturally converges to $\mathbf{P}^{SoC}$. Thus, effective cohort-level treatment effect wanes endogenously as the proportion of patients remaining on treatment falls, while per-patient transitions remain stationary. This is the resulting effect observed in the model: the weighted average probability of (for example) MASH resolution or fibrosis regression declines over time as the treated share falls, even though $\mathbf{P}^{on}$ is fixed.

Figure 15 illustrates the mechanism: the proportion on treatment (resmetirom 80 mg or 100 mg) falls each cycle under the assumed discontinuation hazard; the grey area (off-treatment) increases, and the cohort-average transitions therefore drift towards SoC over time.

Figure 15 Decline in on-treatment proportion over time (resmetirom 80 mg and 100 mg), illustrating cohort-level waning of treatment effect through discontinuation



In this way, treatment discontinuation serves as a proxy for treatment waning: while patients remain adherent, they are modelled to sustain their treatment effect; once they discontinue resmetirom, the effect is lost in full. This approach is aligned with precedent in other NICE appraisals, including multiple sclerosis appraisals (e.g. TA616 (145) and TA624 (146)), where discontinuation was accepted as a pragmatic proxy for waning in the absence of long-term durability data.

From a modelling perspective, this strategy is particularly appropriate because individual treatment histories are tracked (across different fibrosis stages). Thus, discontinuation is directly implemented at the patient level, without requiring speculative assumptions about gradual effect decay or risking double counting of loss of effect.

Additional scenario analyses were conducted to test alternative assumptions about durability in which resmetirom treatment was limited to a maximum time of treatment, after which pharmacological effects ceased—reflecting a treatment-effect waning assumption based on discontinuation (Section 3.11.3). This allowed the evaluation of uncertainty around

implications of time-limited treatment, testing of the waning proxy structural assumption via discontinuation, and evaluation of the effect on cost-effectiveness of resmetirom vs. placebo.

3.3.2.4 Treatment-related adverse events

The incidence of TRAE events in MAESTRO-NASH was low in all treatment arms. AEs in MAESTRO-NASH were largely grade 1–2, transient, resource-light (17) and relatively balanced between treatment arms (Section 2.11). Therefore, to avoid further complexity by applying short-duration disutilities and low costs of low grade events, which would yield negligible QALY and cost impacts and add complexity without affecting conclusions, TRAEs were excluded from the base-case analysis.

While our analyses excluded explicit TRAE modelling due to very low incidence across all arms (including placebo) and uncertain causality, the model did include placeholders that allow the Evidence Assessment Group (EAG) to apply user-defined AE incidence and severity, triggering event-related costs and utility decrements, with uncertainty handled via standard probability distributions.

3.3.2.5 Transition probabilities to advanced liver disease

As fibrosis progresses, the risk of clinically significant outcomes, such as advanced liver disease, increases. The model's late-stage module therefore included DCC, HCC, and LT, together with associated state-specific mortality. This structure reflects the natural history of MASH and provides a pathway from early fibrosis to life-threatening, debilitating, and resource-intensive liver-related outcomes.

In keeping with the clinical understanding that severe complications arise predominantly in advanced stages of fibrosis (F3) or cirrhosis (F4), transitions to DCC and HCC health states were assumed to occur only from F3 (irrespective of MASH resolution) or F4 health states. Annual risks governing movement from F3 or F4 to DCC or HCC health states (and onward to LT or death associated with liver disease) are provided in Table 32 and were applied uniformly across treatment arms; treatment could still influence these events indirectly by preventing or delaying entry into advanced fibrosis. Reliable arm-level data on F4 and subsequent outcomes were not available from MAESTRO-NASH at the time of modelling due to a need to maintain trial integrity. Therefore, late-stage transitions were specified externally and uncertainty was propagated in sensitivity analyses.

Patients in the F3 health states may progress to F4, DCC, or HCC. In the model, identical transition probabilities are applied from F3 to HCC and from F3 to DCC for patients with

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active and resolved MASH. This simplifying assumption reflects the fact that available sources do not provide reliable activity-stratified risks at F3, and fibrosis stage is widely recognised as the dominant predictor of decompensation and HCC. To avoid over-interpreting sparse data or double-counting treatment effects already captured through earlier transitions, equality is adopted in the analysis. Once F4 (CC health state) is reached, the model does not differentiate by MASH status in terms of transition probabilities. The pathobiology at that stage of disease is dominated by cirrhosis, so transitions from F4 (CC) to DCC or HCC, DCC to HCC, DCC to LT, HCC to LT, and post-LT outcomes are modelled identically regardless of prior activity status.

Table 32 Annual transition probabilities to advanced liver complications

Health state transition	Mean annual probability	Low value; High value	Source
F3 & MASH to DCC	0.004	0.003 – 0.005	Vilar-Gomez et al. 2018 (147)
F3 & MASH resolved to DCC	0.004	0.003 – 0.005	Assumed equivalent to patients with MASH
F3 & MASH to HCC	0.003	0.002 – 0.004	Vilar-Gomez et al. 2018 (147)
F3 & MASH resolved to HCC	0.003	0.002 – 0.004	Assumed equivalent to patients with MASH
F4 & MASH to DCC	0.019	0.015 – 0.023	Vilar-Gomez et al. 2018 (147)
F4 & MASH resolved to DCC	0.019	0.015 – 0.023	Assumed equivalent to patients with MASH
F4 & MASH to HCC	0.014	0.011 – 0.017	Vilar-Gomez et al. 2018 (147)
F4 & MASH resolved to HCC	0.014	0.011 – 0.017	Assumed equivalent to patients with MASH
DCC to HCC	0.026	0.021 – 0.031	Ascha et al. 2010 (148)
DCC to liver transplant 1st year	0.43	0.344 – 0.561	Rustgi et al. 2022 (121)
DCC to liver transplant 2nd year	0.43	0.344 – 0.561	Rustgi et al. 2022 (121)
DCC to liver transplant 3rd year	0.43	0.344 – 0.561	Rustgi et al. 2022 (121)
DCC to liver transplant 4th year	0.43	0.344 – 0.561	Rustgi et al. 2022 (121)
DCC to liver transplant +5th year	0.43	0.344 – 0.561	Rustgi et al. 2022 (121)
HCC to liver transplant 1st year	0.557	0.446 – 0.688	Rustgi et al. 2022 (121)
HCC to liver transplant 2nd year	0.557	0.446 – 0.688	Rustgi et al. 2022 (121)
HCC to liver transplant 3rd year	0.557	0.446 – 0.688	Rustgi et al. 2022 (121)
HCC to liver transplant 4th year	0.557	0.446 – 0.688	Rustgi et al. 2022 (121)
HCC to liver transplant +5th year	0.557	0.446 – 0.688	Rustgi et al. 2022 (121)

Abbreviations: DCC, decompensated cirrhosis; F3-F4, fibrosis stages 3-4; HCC, hepatocellular carcinoma; MASH, metabolic dysfunction-associated steatohepatitis. F4 is compensated cirrhosis (CC) in the model.

3.3.2.6 Incorporation of cardiometabolic predictors into modelling of type 2 diabetes and cardiovascular events

To capture the systemic metabolic effects of resmetirom beyond liver histology, we incorporated secondary cardiometabolic outcomes from the MAESTRO-NASH trial data into the microsimulation framework. Trial-reported mean percentage changes from baseline at 52 weeks were available for each treatment arm across multiple risk factors, including LDL-C, HDL-C, non-HDL-C, triglycerides, and body weight (BMI) (Table 33). For the purposes of risk modelling, these outcomes were stratified by five baseline age groups (< 40, 40–49, 50–59, 60–69, ≥ 70 years), which allowed age-specific calibration of risk trajectories also in subpopulations of patients with T2DM (Table 34).

Table 33 Mean percentage change from baseline in cardiometabolic risk factors at week 52 by treatment arm and age group (MAESTRO-NASH, Total paired-biopsy population)

Treatment	Age groups	Mean % Change From Baseline				
		(mean % LDL-C)	(mean % HDL-C)	(mean % non-HDL-C)	(mean % triglycerides)	(mean % BMI)
Placebo	< 40	■	■	■	■	■
	40-49	■	■	■	■	■
	50-59	■	■	■	■	■
	60-69	■	■	■	■	■
	> 69	■	■	■	■	■
Resmi. 100 mg	<40	■	■	■	■	■
	40-49	■	■	■	■	■
	50-59	■	■	■	■	■
	60-69	■	■	■	■	■
	> 69	■	■	■	■	■
Resmi. 80 mg	< 40	■	■	■	■	■
	40-49	■	■	■	■	■
	50-59	■	■	■	■	■
	60-69	■	■	■	■	■
	> 69	■	■	■	■	■

Abbreviations: BMI, body mass index; HDL-C, high-density lipoprotein-cholesterol; LDL-C, low-density lipoprotein-cholesterol; non-HDL-C, non-high-density lipoprotein-cholesterol; SoC, standard of care.

Table 34 Mean percentage change from baseline in cardiometabolic risk factors at week 52 by treatment arm and age group (MAESTRO-NASH, Patients with T2DM and paired-biopsy)

Treatment	Age groups	Mean % Change From Baseline				
		(mean % LDL-C)	(mean % HDL-C)	(mean % non-HDL-C)	(mean % triglycerides)	(mean % BMI)

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Placebo	< 40					
	40-49					
	50-59					
	60-69					
	> 69					
Resmi. 100 mg	< 40					
	40-49					
	50-59					
	60-69					
	> 69					
Resmi. 80 mg	< 40					
	40-49					
	50-59					
	60-69					
	> 69					

Abbreviations: BMI, body mass index; HDL-C, high-density lipoprotein-cholesterol; LDL-C, low-density lipoprotein-cholesterol; non-HDL-C, non-high-density lipoprotein-cholesterol; SoC, standard of care.

Data from the MAESTRO-NASH trial show that resmetirom has a clinically meaningful impact on cardiometabolic risk factors, with the most pronounced effects observed in the subgroup of patients with T2DM (Table 34). Across this population, treatment with resmetirom 100 mg resulted in greater reductions in LDL-C, non-HDL-C, triglycerides, glucose, and body weight at week 52, compared with the broader population, which includes both T2DM and non-T2DM patients. Given the higher metabolic burden in patients with T2DM, these findings support the enhanced cardiometabolic benefit of resmetirom in this subgroup. Subgroup-specific effects have been incorporated into the model to align with these observed differences in clinical outcomes.

For each patient simulated in the model, baseline characteristics (age, sex, fibrosis stage, metabolic risk factors) were sampled from the MAESTRO-NASH dataset. Within the first model cycle, arm-specific trial effects were applied to derive individual risk factors relative to baseline.

3.3.2.7 Modelling of lipid changes

At treatment initiation, baseline LDL-C values are adjusted using age- and treatment-specific percentage changes derived from trial data. These effects are assumed to persist for the first year. From year two onwards, LDL-C values are assumed to rise by 0.1 mmol/L per year, reflecting evidence on gradual rebound in cholesterol levels reported by Domanski et al. 2020 (149). HDL-C values are also adjusted at baseline using age- and treatment-specific

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percentage changes. Unlike LDL-C, however, HDL-C is assumed to decline progressively following the first year, with an annual decrease of 0.1 mmol/L. For triglycerides, baseline values are adjusted by age- and treatment-specific percentage changes at initiation. This effect is assumed to last for one year only, after which triglyceride values are assumed to return to baseline. All changes are applied multiplicatively, such that the treatment effect scales with an individual's baseline lipid value. For example, a 20% reduction in LDL-C reduces a baseline of 3.0 mmol/L to 2.4 mmol/L, while the same percentage applied to a baseline of 4.0 mmol/L reduces the value to 3.2 mmol/L. Finally, total cholesterol (TC) is derived from the updated lipid values using the Friedewald equation:

$$\text{TC} = \text{LDL-C} + \text{HDL-C} + \text{Triglycerides} / 5$$

This approach is widely used in both clinical and research settings for estimating TC when direct measurement is not available (Friedewald et al. 1972 (150)).

3.3.2.8 Modelling of body weight (BMI) changes

Baseline BMI values are assigned using age- and sex-specific averages reported by NHS Digital for the general population (151). These averages were specified in 5-year age groups, separately for males and females.

In the absence of treatment, BMI is assumed to change over time in line with background population trends. Age-related changes are modelled as absolute annual increments or decrements, derived from the difference between mean BMI values in adjacent 5-year age bands in the NHS Digital data (151). These differences are distributed evenly across each five-year interval. For example, if mean BMI increases by 1.0 unit between ages 35–39 and 40–44, an annual increase of 0.2 BMI units is applied for individuals in the 35–39 age band. This approach ensures that modelled BMI trajectories reflect observed patterns in the general population.

In addition to these background trends, treatment effects are applied as annual percentage changes in BMI, stratified by age band and treatment group. Three groups were considered: resmetirom 80 mg, and resmetirom 100 mg and SoC. Age- and treatment-specific percentage effects are derived from clinical trial data, with negative values representing reductions in BMI.

Each year, BMI is updated in two steps: (i) population trend: the absolute age–sex increment (or decrement) is added to the prior BMI value. (ii) treatment effect: the resulting BMI is then multiplied by $(1 + p / 100)$, where p is the treatment- and age-specific percentage change. Company evidence submission: Resmetirom for treating moderate to advanced liver fibrosis (without cirrhosis) (MASLD) ID6529

This structure allows BMI trajectories to capture both natural progression with age and the impact of treatment.

Body weight is derived directly from BMI using the standard relation:

$$\text{Weight (kg)} = \text{BMI (kg/m}^2\text{)} \times (\text{Height (m)})^2$$

As height is assumed constant for each individual, all treatment- and age-related changes in BMI translate proportionally to changes in body weight. For example, a 5% reduction in BMI corresponds to a 5% reduction in weight for an individual of fixed height.

3.3.2.9 Glycaemic control (HbA1c)

HbA1c was not included as a time-varying outcome in the model. In MAESTRO-NASH, mean changes in HbA1c across treatment arms were

[REDACTED]. For example, in the overall trial population, placebo patients showed average changes ranging from [REDACTED]% to [REDACTED]% depending on age, while resmetirom-treated patients showed changes between [REDACTED]% and [REDACTED]%.

[REDACTED]
[REDACTED]
[REDACTED]
[REDACTED]
[REDACTED]

Within the model, HbA1c is not a primary driver of outcomes for patients with MASH. Its relevance in this model is limited to its role as a predictor in the QDiabetes risk equation (136), where it contributes to the estimation of incident diabetes. For this reason, and because [REDACTED], HbA1c was assumed [REDACTED].

This assumption is likely to underestimate any beneficial effect of resmetirom on glycaemic control.

[REDACTED]
[REDACTED]
[REDACTED]
[REDACTED]
[REDACTED]

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■ the impact of this assumption is expected to

These updated predictors are then passed to validated UK risk equations to estimate event probabilities for CVD (QRISK3 for individuals without diabetes (133), UKPDS-OM2 for those with diabetes (134), and Framingham functions for recurrent coronary events (135)). Age-stratified trial effects ensure that changes in risk factors are appropriately scaled to the underlying baseline age distribution; for example, lipid and HbA1c reductions in younger patients (< 40 years) translate to lower absolute risk reductions than in patients aged ≥ 60 years, reflecting the age dependency of the equations.

Table 35 Relative risk multipliers applied to baseline QRISK3/UKPDS-OM2 cardiovascular risk estimates, by fibrosis and liver complication health state (Gal et al. 2023)

Health states	Risk Ratio	Lower Bound - Upper Bound	Source
F0–F2	1	Fixed	Gal et al. 2023 (116)
F3	1.1	1 – 1.25	Gal et al. 2023 (116)
CC	1.2	1 – 1.5	Gal et al. 2023 (116)
DCC	1.5	1 - 2	Gal et al. 2023 (116)
HCC	1.5	1 - 2	Gal et al. 2023 (116)
Liver transplant	1.5	1 - 2	Gal et al. 2023 (116)

Abbreviations: CC, compensated cirrhosis; DCC, decompensated cirrhosis; F0-F3, fibrosis stages 0-3; HCC, hepatocellular carcinoma.

Probabilities were converted to annual transition events using stochastic draws at the individual level. Thus, the combined framework linked short-term cardiometabolic improvements observed in MAESTRO-NASH to long-term reductions in diabetes and cardiovascular events, while ensuring that event risk remained strongly dependent on both age group and disease severity.

This approach reflects the pathophysiological interplay between MASH, metabolic dysfunction, and cardiovascular risk, and allows resmetirom's clinical benefits to be captured not only in preventing liver progression but also in reducing systemic complications that are major contributors to morbidity and mortality in this population.

In the model, time paths for risk factors are fixed to the pre-specified update rules described in this section. Trajectories are not varied in the standard deterministic or PSA because: (i)

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long-term treatment effects beyond year 1 are weakly evidenced and heterogeneous across age groups, so imposing wide distributions would risk over-parameterisation and double-counting effects already mediated via validated risk equations (e.g., HbA1c in QDiabetes-2018 (136)); (ii) Model outcomes are driven primarily by downstream events (e.g., cardiovascular events, diabetes incidence, liver progression). If all intermediate risk-factor trajectories (LDL-C, HDL-C, triglycerides, BMI, HbA1c) were varied simultaneously in sensitivity analyses, it would reduce clarity when interpreting results. For example, suppose an analysis showed a higher rate of cardiovascular events; it would be unclear whether this was due to a simulated increase in LDL-C, a higher BMI, a worsening in HbA1c, or some combination of these changes. The model varies them independently without strong correlation data, so the resulting variability may exaggerate uncertainty and obscure which input is truly influential. This creates “noise” rather than insight and does not improve the decision relevance of the sensitivity analysis; and (iii) jointly varying all trajectories materially increases runtime and computational burden, limiting Monte-Carlo replications and replicability for EAG.

3.3.2.10 Mortality probabilities

Mortality in the model is captured through three components: (i) age- and sex-specific background mortality, (ii) liver-related mortality conditional on disease stage, and (iii) excess mortality associated with non-liver comorbidities. Each patient’s risk of death is re-calculated at every annual cycle, and the first fatal event to occur is assigned as the cause of death.

Age- and sex-specific mortality

All individuals in the model were subject to general population background mortality rates derived from the ONS life tables for England and Wales (2017–2019, pre-COVID) (152). These life tables provided annual probabilities of death stratified by single year of age and sex, ensuring that the model’s survival profile reflected the expected demographic mortality in England. The ONS tables were chosen to avoid distortions caused by excess deaths observed during the COVID-19 pandemic period.

Liver-related mortality

Patients in advanced liver states (CC, DCC, HCC, and post-LT) were assigned additional mortality risks specific to those conditions (Table 36). Transition-specific annual probabilities were obtained from previously published natural-history data and supplemented by published studies (e.g. Lidgren et al. 2007 for post-transplant survival (153)). For example,

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patients with DCC faced an annual mortality rate exceeding 10%, while those with HCC were subject to stage-specific survival probabilities that declined with time since diagnosis. Post-transplant survival was divided into the first year after transplant, where the probability of peri-operative mortality is highest, and subsequent years, which follow a reduced but persistent excess risk. These liver-related mortality probabilities were applied in addition to background mortality, with death assigned to the liver-related category if it occurred first.

Table 36 Liver related mortality probabilities

Health state transition	Mean annual probability	Low value; High value	Source
F4 to death	0.021	0.0168 – 0.0252	Pearson et al. 2016 (131) - Ascha et al. 2010 (148)
DCC to death	0.0130	0.1040 – 0.1560	Pearson et al. 2016 (131) - Ascha et al. 2010 (148)
HCC to death year 1	0.144	0.1152 – 0.1728	Thuluvath et al. 2019 (154)
HCC to death year 2	0.044	0.0352 – 0.0528	Thuluvath et al. 2019 (154)
HCC to death year 3	0.012	0.096 – 0.144	Thuluvath et al. 2019 (154)
HCC to death year 4	0.009	0.072 – 0.108	Thuluvath et al. 2019 (154)
HCC to death year 5+	0.008	0.064 – 0.096	Thuluvath et al. 2019 (154)
LT to death	0.098	0.0784 – 0.118	Lidgren et al. 2007 (153)
PLT to death	0.057	0.0456 – 0.0684	Lidgren et al. 2007 (153)

Abbreviations: DCC, decompensated cirrhosis; F4, fibrosis stage 4; HCC, hepatocellular carcinoma; LT, liver transplantation (first year); PLT, post-liver transplantation (subsequent years). F4 is compensated cirrhosis in the model (CC)

Comorbidity-related mortality

Excess mortality associated with non-liver comorbidities was incorporated via event-specific case-fatality rates. Patients who experienced a MI or stroke were assigned an acute probability of death in the year of the event, followed by elevated long-term mortality risks consistent with UK cardiovascular registries. Similarly, patients with incident T2DM accrued increased mortality risk over time, modelled through the UKPDS risk engine. In addition, patients with recurrent cardiovascular events were assigned progressively higher fatality probabilities based on Framingham Recurring coronary heart disease (CHD) functions.

Implementation of mortality competing risk in the model

At each annual cycle, the model evaluated three mutually exclusive death states: (i) age- and sex-specific background mortality (from national life tables), (ii) liver-related mortality conditional on disease stage (e.g., CC, DCC, HCC, post-LT), and (iii) excess mortality from non-liver comorbidities (e.g., MI, stroke, T2DM). These three death probabilities were

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calculated separately and included in the transition matrix alongside the living disease states. For each individual patient and each cycle, the model then selected the next health state at random according to these transition probabilities (samplev()). If a death state was selected, the cause of death was identified by that specific state. This ensured that a patient could not die from more than one cause within the same cycle, while still capturing the correct contribution of each hazard to overall survival.

This competing-risk approach allowed the model to reflect the reality that individuals with MASH face multiple simultaneous hazards: background demographic ageing, progression of liver disease, and cardiovascular or metabolic comorbidities. The approach prevented double counting of deaths, ensured that each patient trajectory included only one terminal event, and generated survival outcomes that were consistent with both trial evidence and published natural-history data.

3.4 Measurement and valuation of health effects

3.4.1 Health-related quality-of-life data from clinical trials

In MAESTRO-NASH, HRQoL was assessed using condition-specific instruments (CLDQ-NASH, SF-LDQoL) and the Work Productivity and Activity Impairment instrument (WPAI-NASH) to capture the humanistic burden of MASH on patients. SF-LDQoL incorporated SF-36v2, enabling derivation of preference-based utilities suitable for cost-utility analysis. Measurements were taken at baseline, week 24, and week 52. The elicitation method was patient self-report; valuation followed UK general-population preferences via mapping to EQ-5D-3L in accordance with NICE's reference case (19) (utilities based on public preferences, expressed as QALYs).

Because EQ-5D was not directly collected in MAESTRO-NASH, we generated preference-based utilities from the SF-36v2 data using published, UK-validated mapping methods (see Section 3.4.2). This approach is consistent with NICE's manual (Section 4.3) (19) and Decision Support Unit (DSU) guidance on mapping and the use of utilities in decision models (TSDs 8, 10, and 12) (155–157).

Utilities (means with 95% CIs) were estimated at the patient level by treatment arm and timepoint, and then analysed by fibrosis stage and MASH-resolution status; these trial-based utilities informed the state and event utilities used in the model in scenario analyses.

3.4.2 Mapping

Because EQ-5D data were not collected in MAESTRO-NASH, SF-36v2 responses were mapped to EQ-5D-3L following the method developed by Rowen et al. 2009 (158), in line with DSU TSD 10 (157) and NICE's preferences when EQ-5D is unavailable. Specifically, the best-performing published regression model from Rowen et al. 2009 (158) was applied to patient-level SF-36v2 domain scores at baseline, week 24, and week 52. UK tariffs were then used to generate EQ-5D-3L-consistent utilities for QALY estimation in the economic analysis.

However, as reported in the following sections, the actual utility values estimated from MAESTRO-NASH (as generated through this validated mapping) have a number of limitations that limit appropriateness for use in the model base case. For example, utilities did not decrease monotonically with worsening fibrosis, and in some cases higher stages showed similar or higher utility than milder stages (e.g., F2 with NASH resolution vs. F1). This pattern lacked clinical face validity, as it overstated HRQoL differences at earlier stages while showing minimal decrements between advanced fibrosis categories. Given these limitations, the mapped trial-based utilities were considered unsuitable for the model base case. Instead, alternative utility values identified in the literature were adopted, as they better reflect the natural progression of MASH and its impact on HRQoL. The trial-derived utilities are nevertheless presented in scenario analyses (Section 3.11.3) to illustrate their minimal effect on ICER results, but they were not selected for the primary analysis.

3.4.3 Health-related quality-of-life studies

A description of the systematic searches for relevant HRQoL data is provided in Appendix F. Details of the identified studies, including those with UK participants and their limitations, are also presented. Additional searches outside of the boundaries of the SLR were also conducted.

Among all published sources, the most relevant for the UK context was NICE guideline NG49 2016 (23), which provides health-state utilities for fibrosis stages, CC and DCC, HCC, and LT. These values have been used by NICE in prior health technology evaluations in fatty liver disease and represent the only health state utility values (HSUVs) formally adopted in national guidance. NG49 therefore provides a benchmark and external validation source (23). However, NG49 utilities may also represent combined heterogeneous NAFLD/NASH cohorts with varying staging methods, and may not be directly applicable to the specific population within MAESTRO-NASH. For these reasons, although NG49 is the strongest

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published reference and appropriate for use in the model base case, MAESTRO-NASH utilities were considered in scenario analyses to demonstrate any uncertainty in the model associated with utility values for F0-F3 health states.

3.4.4 Adverse reactions

As described in Section 3.3.2.4, TRAEs were not included in the economic evaluation. MAESTRO-NASH showed that TRAEs were generally mild to moderate, short-lived, and unlikely to result in sustained QoL decrements or meaningful healthcare costs (17). The model therefore did not apply any disutilities for TRAEs, although placeholders remain should future evidence warrant their inclusion.

3.4.5 Health-related quality-of-life utilities used in the cost-effectiveness analysis (CEA)

HRQoL utilities in the CEA are defined in terms of utility decrements associated with progressive fibrosis and advanced liver outcomes. Patients with earlier stages disease (F0–F2 and MASH resolved) are assumed to have higher utility than patients with MASH, and patients with more advanced fibrosis (F3, F4) and complications (DCC, HCC, LT) experienced progressively greater decrements in utility. This pattern reflects the clinical reality that the burden of MASH increases with worsening hepatic function, symptom burden, and comorbidities such as fatigue, abdominal discomfort, and impaired daily functioning.

Two sets of HSUVs were used to inform the model in the base case or scenario analyses:

- **Base case:** The utility values used in the model were taken from NICE guideline NG49, which provides estimates for fibrosis stages, CC and DCC, HCC and LT (23). NG49 values have been used in prior NICE assessments and provide a policy-consistent, UK-relevant set for decision making (Table 37).
- **Scenario analyses:** The EQ-5D-3L utilities derived from the post-hoc analysis and mapping of the MAESTRO-NASH QoL data (SF-36v2), mapped to EQ-5D-3L as described in Section 3.4.2, were applied in scenario analyses (Table 38).

Utilities are modelled as state-based and time-invariant within a health state in the analyses. Patients' utilities change when they transition between health states (for example, F3 to F4) and when acute events applied temporary decrements (for example, MI or stroke). In the base-case analysis, time-varying age or sex adjustments are not applied to health state utility values. This decision was based on several scientific considerations. First, the model

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explicitly incorporated a range of comorbidities with associated utility decrements that increased in prevalence with age. Applying additional age-related declines in background QoL risked double counting the effect of ageing, thereby artificially lowering utilities. Second, age adjustment introduces a methodological bias whereby treatment strategies that extend survival are systematically underestimated, since longer-lived patients accrue larger background declines in utility unrelated to disease burden. Third, evidence from the DSU report on UK EQ-5D age/sex norms (159) demonstrates substantial variability across data sources (e.g., monotonic decline in HSE 2014 vs. non-monotonic patterns in EEPUR 2020 during the COVID-19 lockdown), indicating considerable uncertainty in the true trajectory of population norms. Moreover, the DSU concluded that alternative age-adjustment approaches had minimal impact on severity metrics (absolute and proportional shortfall) across a large sample of NICE appraisals, suggesting limited decision relevance. For these reasons, and to maintain consistency with the age profile of the populations from which the source utilities were derived, we did not apply age adjustments in the base case. However, to address potential uncertainty, we explored age-adjusted utilities using HSE 2014 norms in a scenario analysis.

Sensitivity analyses (using the MAESTRO-NASH mapped utilities) are presented in Section 3.11 to help assess the uncertainty around utility values used in the base case.

No explicit adjustments were applied to NG49 values beyond probabilistic uncertainty distributions (Beta). Acute event decrements (for example, CVD events) were applied to those state utilities for the duration specified in the model (Table 39). No additional disutilities were modelled for TRAEs, consistent with Section 3.3.2.4. As discussed earlier, placeholders for TRAE disutilities were retained in the model structure but set to zero in the analysis, given the absence of meaningful or persistent impact of TRAEs on HRQoL in MAESTRO-NASH (17).

As mentioned above, patient-level SF-36v2 data were collected at baseline, week 24, and week 52 in the MAESTRO-NASH trial (96), and SF-6D utility values were derived using IQVIA QualityMetric (IQM) scoring software, applying the SF-6D_R2 algorithm — a revised version of the original SF-6D developed by Brazier et al. 2002 (160), based on UK-specific general population preference weights. Our regression analyses demonstrated that both for EQ-5D and, particularly, for SF-6D, MASH resolution was associated with a statistically significant and clinically meaningful improvement in QoL. Given that the SF-6D estimation was directly derived from SF-36 responses and did not require mapping (unlike EQ-5D), these results are more robust and provide clearer evidence of the positive impact of MASH

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resolution on patients' QoL. Data from the MAESTRO-NASH trial, together with HSUVs used in NICE guideline NG49 (23), therefore support incorporating the impact of MASH resolution into the cost-effectiveness model to reflect the QoL benefits for patients achieving resolution with resmetirom or in the SoC arm. However, we did not use these mapped values from MAESTRO-NASH in the base case because the changes in utility associated with worsening fibrosis stage and MASH resolution did not follow a credible pattern and 95% CIs for all values indicated a considerable degree of uncertainty, partly owing to sample size constraints.

To ensure robust model inputs, treatment-specific utility values are not applied in the base case due to sample size limitations at certain fibrosis stages, which would introduce significant uncertainty. Instead, data were pooled across treatment arms, and utility values were estimated by fibrosis stage among all patients, providing a more consistent and reliable set of utility inputs.

Table 37 Summary of utility values for CEA – Base-case analysis

State	Utility value: mean (standard error)	95% CI	Reference in submission (section and page number)	Justification
F0 without MASH (NAFL)	0.870	0.705 – 1.000	NG49 – 611 (23)	Applied in prior NICE evaluations We used NASH (F012)-treated data in NG49 for fibrosis state with MASH resolution
F0 + MASH	0.840	0.680 – 1.000	NG49 – 611 (23)	
F1 without MASH	0.870	0.705 – 1.000	NG49 – 611 (23)	
F1 + MASH	0.840	0.680 – 1.000	NG49 – 611 (23)	
F2 without MASH	0.870	0.705 – 1.000	NG49 – 611 (23)	
F2 + MASH	0.840	0.680 – 1.000	NG49 – 611 (23)	
F3 without MASH	0.870	0.705 – 1.000	NG49 – 611 (23)	
F3 + MASH	0.840	0.680 – 1.000	NG49 – 611 (23)	
F4 (Cirrhosis)	0.600	0.483 – 0.717	NG49 – 611 (23)	
DCC	0.540	0.435 – 0.645	NG49 – 612 (23)	
HCC	0.540	0.435 – 0.645	NG49 – 612 (23)	
PLT First year	0.800	0.646 – 0.954	NG49 – 612 (23)	
PLT subsequent years	0.850	0.688 – 1.000	NG49 – 612 (23)	

Abbreviations: CI, confidence interval; DCC, decompensated cirrhosis; F0-F4, fibrosis stages 0–4; HCC, hepatocellular carcinoma; MASH, metabolic dysfunction-associated steatohepatitis; NAFL, non-alcoholic fatty liver; NG, NICE guideline; PLT, post-liver transplantation.

Table 38 Summary of utility values for CEA – Scenario analysis

State	Utility value: mean (standard error)	95% CI	Reference in submission (section and page number)	Justification
F0 without MASH (NAFL)	0.870	0.705 – 1.000	NG49 – 611 (23)	
F0 + MASH	0.840	0.680 – 1.000	NG49 – 611 (23)	
F1 without MASH (n= [REDACTED])	[REDACTED]	[REDACTED]	MAESTRO-NASH	
F1 + MASH (n= [REDACTED])	[REDACTED]	[REDACTED]	MAESTRO-NASH	
F2 without MASH (n= [REDACTED])	[REDACTED]	[REDACTED]	MAESTRO-NASH	
F2 + MASH (n= [REDACTED])	[REDACTED]	[REDACTED]	MAESTRO-NASH	
F3 without MASH (n= [REDACTED])	[REDACTED]	[REDACTED]	MAESTRO-NASH	
F3 + MASH (n= [REDACTED])	[REDACTED]	[REDACTED]	MAESTRO-NASH	
F4 (Cirrhosis)	0.600	0.483 – 0.717	NG49 – 611 (23)	
DCC	0.540	0.435 – 0.645	NG49 – 612 (23)	
HCC	0.540	0.435 – 0.645	NG49 – 612 (23)	
PLT First year	0.800	0.646 – 0.954	NG49 – 612 (23)	
PLT subsequent years	0.850	0.688 – 1.000	NG49 – 612 (23)	

Abbreviations: CI, confidence interval; DCC, decompensated cirrhosis; F0–F4, fibrosis stages 0–4; HCC, hepatocellular carcinoma; MASH, metabolic dysfunction-associated steatohepatitis; NAFL, non-alcoholic fatty liver; NG, NICE guideline; PLT, post-liver transplantation.

Table 39 Disutility values associated with comorbidities

State	Utility value: mean	95% CI	Reference in submission (section and page number)	Justification
MI disutility	-0.04	-0.05, -0.03	Sullivan et al. 2006 (161)	
Stroke disutility	-0.05	-0.06, -0.04	Sullivan et al. 2006 (161)	
Post MI & Stroke disutility	-0.03	-0.04, -0.02	Sullivan et al. 2006 (161)	
T2DM disutility	-0.03	-0.0296, -0.0444	Liraglutide NICE submission (162)	

Abbreviations: CI, confidence interval; MI, myocardial infarction; T2DM, type 2 diabetes mellitus.

3.5 Cost and healthcare resource use identification, measurement and valuation

The SLR of cost and HCRU studies (Appendix G) identified several publications with potential relevance to the UK NHS context. Following the review, three groups of evidence were distinguished:

The most directly relevant and up-to-date evidence was provided by Davidson et al. 2025 (5), which analysed linked electronic health records in England to describe healthcare utilisation across the MASLD/MASH pathway. This study reported detailed rates of hospitalisation, outpatient hepatology visits, and monitoring procedures, making it highly relevant for capturing current patterns of NHS resource use. These utilisation estimates were used to inform the frequency and structure of healthcare management in the model. Morgan et al. 2021 (66), a UK Col study, provided complementary evidence on the annual direct medical costs of fibrosis and advanced liver outcomes, including CC (i.e., F4 fibrosis stage), DCC, HCC, and LT. Although slightly older, the Morgan et al. 2021 data (66) are valuable for cross-checking unit costs and ensuring alignment with NHS-based valuations.

Several multicounty studies that included UK participants also reported resource use and costs. Younossi et al. 2016 provided estimates for direct medical costs across NAFLD/NASH stages for the EU4 and UK (69). While older, these data offer useful external benchmarks and are particularly relevant for costs associated with LT and post-transplant follow-up, which were not fully detailed in all UK-only sources. Schattenberg et al. 2021 examined costs and drivers of disease burden across the EU5 (including the UK) (67), highlighting the

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rise in inpatient costs and the distribution of costs across outpatient, inpatient, and pharmacy categories. Although unit costs were not UK-specific, the study was valuable for validating the direction and relative magnitude of cost increases with fibrosis progression.

Other studies, such as O'Hara et al. 2020 (163) and Balp et al. 2019 (164), included UK respondents but relied on self-reported data or mixed multinational samples. These studies were not directly suitable for costing within an NHS perspective because of their heterogeneous methodology and absence of NHS-specific unit costs. Similarly, Carruthers et al. 2017 described admissions trends for liver disease in England and provided context on the growing burden of hospitalisation, but did not provide disaggregated unit costs for economic modelling (165).

3.5.1 Intervention and comparators' costs and resource use

In the economic model, the resmetirom arm comprised lifestyle management plus pharmacological treatment, whereas the SoC arm involved lifestyle management alone. Lifestyle interventions (for example, dietary advice, weight management, and exercise programmes) are a component of routine care for all patients with MASH. To avoid double-counting and ensure comparability, the potential costs of lifestyle or nutritional management are assumed to be identical across both arms and are therefore cancelled out in the model. Consequently, the only pharmacological cost applied to the intervention arm was the cost of resmetirom itself.

Resmetirom was costed at an indicative UK list price of £[REDACTED] per treatment day, applied equally to the 80 mg and 100 mg tablet strengths. Costs accrued only while patients were on active treatment; temporary interruptions reduced costs pro rata by time off therapy, and permanent discontinuation stopped further drug costs. Because resmetirom is an oral treatment, no administration cost was included. The comparator (SoC) therefore incurred no drug acquisition cost.

Monitoring and follow-up are assumed to be identical in both arms, consistent with clinical expert advice and current NHS hepatology practice. At baseline, patients underwent non-invasive staging with TE (FibroScan) (£55.42 (166)) and an ELF test (£54.14 (23,166)), with annual ELF monitoring thereafter. These costs are applied equally to both arms.

Resmetirom is expected to be commissioned in secondary care and prescribed within specialist hepatology services, with dispensing mostly through hospital outpatient pharmacy

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or via home delivery, pending discussions with NHS England and wholesalers. Drug wastage is considered negligible given the oral formulation and long shelf-life, and treatment costs are calculated per treatment day at the indicative price.

Clinical expert input confirmed that the number and type of secondary care visits are identical in both the SoC and resmetirom arms once patients are referred from primary care to specialist hepatology. Patients with higher risk disease, such as moderate to advanced fibrosis and MASH (i.e. fibrosis stages F2 and F3), are already under regular specialist follow-up, which includes initial staging, annual testing, and routine clinic review. Resmetirom does not require additional clinic visits beyond those already delivered in standard practice. Consequently, the model assumes no incremental difference in monitoring or referral resource use between arms, with the only differential cost attributable to the pharmacological acquisition of resmetirom.

3.5.2 Health state unit costs and resource use

Health-state costs (Table 40) were derived primarily from Davidson et al. 2025 (5), a recent English electronic health record (EHR)-based study that provides robust estimates of annual NHS costs by fibrosis stage and advanced liver outcomes, inflated to reflect year 2021-2022 costing. These values were selected as the base case because they are contemporary, UK-specific, and aligned with current NHS practice. Where Davidson et al. 2025 (5) did not provide estimates (LT), costs were taken from NICE guideline NG49 (23), which has been used in prior NICE evaluations.

Table 40 Health-state costs used in the economic model

Health state	Mean annual cost (£)	95% CI	Source
F0	1,676	1,341 – 2,011	Davidson et al. 2025 (5)
F1	1,676	1,341 – 2,011	Davidson et al. 2025 (5)
F2	1,676	1,341 – 2,011	Davidson et al. 2025 (5)
F3	1,676	1,341 – 2,011	Davidson et al. 2025 (5)
F4/CC	10,103	8,082 – 12,153	Davidson et al. 2025 (5)
DCC, year 1	6,817	5,454 – 8,181	Davidson et al. 2025 (5)
DCC, year 2+	9,346	7,477 – 11,215	Davidson et al. 2025 (5)
HCC, year 1	4,974	3,979 – 5,967	Davidson et al. 2025 (5)
HCC, year 2+	6,711	5,369 – 8,054	Davidson et al. 2025 (5)
LT (procedure)	76,762	61,410 – 92,115	NICE NG49 (23)
LT (year 1 follow-up)	10,896	8,717 – 13,076	NICE NG49 (23)
LT (year 2+ follow-up)	10,896	8,717 – 13,076	NICE NG49 (23)

Abbreviations: CC, compensated cirrhosis (also F4, fibrosis stage 4); CI, confidence interval; DCC, decompensated cirrhosis; EHR, electronic health record; F0-F3, fibrosis stages 0-3; HCC, hepatocellular carcinoma; LT, liver transplantation; NG, NICE guideline; NHS, National Health Service.

Direct medical costs for MI and stroke were taken from Brennan et al. 2014 (167), a UK CEA that remains a standard source in NICE appraisals. These data provide event-level costs for the first year, subsequent years, and fatal events, ensuring comprehensive coverage of both acute and chronic phases of disease (Table 41).

Table 41 Cardiovascular event costs

Event	Mean annual cost (£)	95% CI	Source
Non-fatal MI, first year	8,956	7,628–10,284	Brennan et al. 2014 (167)
Non-fatal MI, subsequent years	1,117	940–1,293	Brennan et al. 2014 (167)
Fatal MI	2,247	2,159–2,334	Brennan et al. 2014 (167)
Non-fatal stroke, first year	8,980	4,436–13,524	Brennan et al. 2014 (167)
Non-fatal stroke, subsequent years	688	468–909	Brennan et al. 2014 (167)
Fatal stroke	6,202	6,062–6,342	Brennan et al. 2014 (167)

Abbreviations: CI, confidence interval; MI, myocardial infarction.

Microvascular complications of T2DM were valued using NICE guideline NG28 (168) and supporting UK data. Costs for renal complications were sourced from the UK Renal Registry, and retinopathy costs from Alva et al. 2015 (169) assuming equal to costs of blindness.

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Weighted annualised costs were derived by combining first- and subsequent-year estimates to generate consistent annualised inputs (Table 42).

Table 42 Type 2 diabetes microvascular complication costs

Complication	Mean annual cost (£)	95% CI	Source
Nephropathy	12,981	10,562 – 15,646	NG28 (168)
Retinopathy	2,171	1,767 – 2,617	NG28 (168)

Abbreviations: CI, confidence interval; NG, NICE guideline; NHS, National Health Service; UK, United Kingdom.

All costs obtained from published sources were inflated to 2025 GBP (NHS England and Personal Social Services perspective) using the Hospital & Community Health Services (HCHS) pay-and-prices index as reported in Unit Costs of Health and Social Care (PSSRU) (170), applying the inflator from the original cost year reported in each source (or the publication year where the cost year was not stated). Where an HCHS inflator was not applicable, the HM Treasury GDP deflator (latest available at the time of analysis) was used.

3.5.3 Adverse reaction unit costs and resource use

As described in Section 3.3.2.4, TRAEs are not included in the analysis. In MAESTRO-NASH, TRAEs were predominantly mild to moderate and transient, typically resolving within a few days (17), with no evidence of sustained HRQoL impact or meaningful incremental healthcare resource use. On this basis, no costs for TRAEs were applied in the economic model.

The microsimulation structure retains placeholders for AE costs and disutilities, which would allow incorporation of such effects should new evidence emerge. However, for the base case, all TRAE parameters were set to zero in both arms to avoid speculative assumptions.

3.5.4 Miscellaneous unit costs and resource use

No additional unit costs or healthcare resource use beyond those already described in Sections 3.5.1- 3.5.3 were included in the CEA. Specifically, there were no incremental costs modelled for lifestyle interventions, as these were assumed to be identical across both arms; no social care or indirect costs were applied, consistent with NICE's reference case (19); and no subsequent pharmacotherapies were included beyond standard management of advanced liver disease, cardiovascular events, and T2DM complications already costed within the model.

3.6 Severity

In line with NICE's health technology evaluations manual (Sections 6.2.12–6.2.22) (19), the company considered whether a severity modifier should be applied. The target population for resmetirom comprises adults with MASH and moderate to advanced fibrosis (fibrosis stages F2 to F3). Although this condition is progressive, associated with impaired HRQoL, and has an increased risk of advanced liver outcomes, patients retain a substantial life expectancy, and the absolute and proportional QALY shortfalls relative to the general population are not sufficient to qualify for a severity weight.

Accordingly, a severity modifier was not applied in the economic analysis.

3.7 Uncertainty

MASH is a therapeutic area with inherent evidence challenges due to the absence of reliable data sources, a highly heterogeneous patient population, and a high degree of comorbidities impacting disease burden and HRQoL. There also are no previously licensed pharmacological treatments and there is a paucity of robust, evidence driven long-term outcome data, particularly for MASH natural history and rates of and time to progression/regression. These factors affect the ability to robustly assess this disease in an economic analysis and contribute uncertainties to the CEA.

Residual uncertainty remains around long-term treatment durability of resmetirom benefit beyond the trial period over a lifetime horizon. To address this, the economic model incorporated scenario analyses (for example, alternative assumptions on treatment duration and utility sources) and sensitivity analyses.

A further source of uncertainty relates to whether common HRQoL measures can fully capture the benefits of MASH treatment. Generic instruments, including EQ-5D and SF-36, are consistent with NICE's reference case and useful for utility estimation. However, these tools have known limitations in sensitivity to some key dimensions experienced by patients.

In summary, while uncertainty is unavoidable in a condition with limited long-term evidence, the MAESTRO-NASH trial provides a relevant and robust evidence base for decision-making. The model has been structured to test alternative assumptions and account for key uncertainties.

3.8 Managed access proposal

Resmetirom for the treatment of MASH does not fall within the scope of the Cancer Drugs Fund (CDF) or the Innovative Medicines Fund (IMF). A managed access proposal is therefore not applicable for this submission.

3.9 Summary of base-case analysis inputs and assumptions

3.9.1 Summary of base-case analysis inputs

A comprehensive list of all input parameters applied in the base-case analysis has been provided in Appendix K, including:

- Table 5: Probabilities used in the base-case analysis;
- Table 6: Mean percentage change from baseline in cardiometabolic risk factors at week 52;
- Table 7: Cost parameters used in the base-case analysis;
- Table 8: HSUVs used in the base-case analysis.

3.9.2 Assumptions

A summary of the key structural and parameter assumptions applied in the resmetirom economic model, together with their justification, is provided in Table 43.

Table 43 Summary of model assumptions and justifications

Analysis setting	Assumption/Setting	Justification
Population	Base case uses paired-biopsy population from MAESTRO-NASH; subgroup analyses assess the T2DM subgroup).	Paired-biopsy cohort (patients with baseline and week 52 biopsies), was used to ensure robust measurement of histologic response at patient-level. Alternative subgroups are included for scenario analyses per NICE scope.
Comparator	SoC (lifestyle management). No other comparators are included	Please see summary of Decision Problem for full rationale.
Model structure	Patient-level microsimulation model with annual cycles; fixed transition probabilities between fibrosis stages.	MSM allows explicit modelling of patient heterogeneity and competing risks; annual transitions consistent with trial data and natural history evidence.

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Fibrosis transitions	Year 1 probabilities taken from MAESTRO-NASH (paired-biopsy data); same transition matrix applied in subsequent years.	No robust longitudinal data exist for longer-term disease trajectories; applying observed short-term biopsy-confirmed transitions provides evidence-based anchor.
Treatment effect waning	No within-treatment waning assumed; discontinuation = full loss of pharmacological benefit; scenario: treatment limited to finite treatment duration.	Trial data show no decline in efficacy over 52 weeks. Pharmacological mechanism requires ongoing exposure, so discontinuation is a valid proxy for waning (171).
Legacy effect	No residual ("legacy") benefit after discontinuation.	No current evidence that histological improvements persist once drug exposure ceases; conservative assumption consistent with expectations based on mechanism of action.
Monitoring/visits	Monitoring identical in both arms: FibroScan + ELF at baseline, annual ELF thereafter.	Clinical experts confirmed this reflects NHS hepatology practice. Resmetirom does not require extra monitoring according to SmPC; thus, no incremental HCRU difference beyond drug acquisition.
Drug acquisition	Costed at UK list price of £80.27/day (60mg, 80 mg or 100 mg), applied only while on treatment.	Transparent application of published list price. Treatment costs accrue only during active exposure; no administration costs (oral tablet).
Lifestyle management	Lifestyle management (diet, exercise, nutrition advice) assumed identical across arms , cost-neutral.	All patients receive lifestyle management; cancelling out avoids double counting and isolates incremental drug effect.
Utilities (base case)	Health-state utilities taken from NICE NG49 (23); mapped utilities from MAESTRO-NASH QoL analyses used in scenario analyses.	NG49 provides the most policy-consistent UK reference values (23). Post-hoc mapped trial utilities used for scenario due to methodological challenges but provided for completeness.
Utilities (age/sex adjustment)	No time-varying age- or sex-specific decrements applied to base-case health-state utilities; scenario analysis applies HSE 2014 norms.	Base case avoids double-counting ageing effects already captured via comorbidities; prevents methodological bias against survival gains; DSU evidence shows limited impact of alternative age-adjustments on severity metrics and variability across data sources. Maintains consistency with trial-derived utilities; scenario with HSE 2014 norms explores uncertainty.
Within-state utility over time	Utilities constant within each health state; change only occurs at transitions or events.	No evidence for time-dependent decline within states; avoids speculative assumptions; consistent with NICE DSU guidance.

Adverse events	No disutilities or costs applied for TRAEs.	MAESTRO-NASH TRAEs were mostly mild/moderate and transient, with no sustained impact (17); placeholders retained for future evidence.
CVD events	MI and stroke costs/utilities from Brennan et al. 2014 (167).	UK-specific, widely used in NICE CVD appraisals; provides both acute and long-term costs.
T2DM complications	Renal and blindness costs from NICE NG28 (168) and UK Renal Registry.	NICE guidance provides authoritative UK data; annualised estimates applied in model.
Risk-factor trajectories	Time paths for LDL-C, HDL-C, triglycerides, BMI, HbA1c fixed to pre-specified update rules; not varied in deterministic or probabilistic sensitivity analyses.	Long-term treatment effects weakly evidenced and heterogeneous; simultaneous variation risks double-counting effects already mediated via risk equations. Varying all risk factors simultaneously creates interpretability issues and computational burden, generating noise rather than decision-relevant insight.
Mortality	Competing risks framework: background, liver-related, and CVD/T2DM mortality modelled mutually exclusively.	Prevents double-counting of deaths and reflects multiple simultaneous hazards in MASH patients.
Discounting	Costs and QALYs discounted at 3.5% per annum.	NICE reference case.

Abbreviations: BMI, body mass index; CVD, cardiovascular disease; DSU, Decision Support Unit; ELF, Enhanced Liver Fibrosis; HbA1c, glycated haemoglobin; HCRU, healthcare resource utilisation; HDL-C, high-density lipoprotein-cholesterol; HSE, Health Survey for England; ICER, incremental cost-effectiveness ratio; LDL-C, low-density lipoprotein-cholesterol; MAESTRO-NASH, resmetirom phase 3 trial; MASH, metabolic dysfunction-associated steatohepatitis; MI, myocardial infarction; MSM, microsimulation model; NG28, NICE guideline 28 (type 2 diabetes in adults: management, 2015); NG, NICE guideline; QALY, quality-adjusted life year; QoL, quality of life; SmPC, summary of product characteristics; SoC, standard of care; TA, technology appraisal; TRAE, treatment-related adverse event; T2DM, type 2 diabetes mellitus; UKPDS, UK Prospective Diabetes Study.

3.10 Base-case results

The base-case incremental cost-effectiveness ratio (ICER) for resmetirom, compared with SoC alone, was estimated to be £19,487 per QALY gained. This estimate was based on the list price of £[REDACTED] per tablet for resmetirom. All cost-effectiveness results presented in this section—and throughout the remainder of the submission—reflected this price and applied to both the 80 mg and 100 mg formulations. This pricing assumption was consistently used across all economic modelling and scenario analyses to ensure comparability and internal consistency. Moreover, the results presented were based on a cohort of 10,000 sampled patients, simulated using patient characteristics derived from the MAESTRO-NASH trial population.

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3.10.1 Base-case incremental cost-effectiveness analysis results

Total costs were higher with resmetirom compared with SoC alone (lifestyle modifications), at £[REDACTED] vs. £[REDACTED], resulting in an incremental cost of £[REDACTED]. Resmetirom was also associated with greater total health benefits, yielding [REDACTED] QALYs compared with [REDACTED] QALYs for SoC, an incremental gain of [REDACTED] QALYs. These differences in cost and health outcomes resulted in an ICER of £21,422 per QALY gained for resmetirom compared with SoC. Full results are presented in Table 44.

Table 44 Base-case results

Technologies	Total costs (£)	Total LYG	Total QALYs	Incremental costs (£)	Incremental LYG	Incremental QALYs	ICER versus baseline (£/QALY)	ICER incremental (£/QALY)
SoC	[REDACTED]	[REDACTED]	[REDACTED]	NA	NA	NA	NA	NA
Resmetirom	[REDACTED]	[REDACTED]	[REDACTED]	[REDACTED]	[REDACTED]	[REDACTED]	21,422	21,422

Abbreviations: ICER, incremental cost-effectiveness ratio; LYG, life years gained; QALYs, quality-adjusted life year; SoC, standard of care.

At the reference case threshold of £20,000 per QALY, the intervention generated an incremental net health benefit (NHB) of -0.106 QALYs per patient compared with standard care, indicating a marginal negative gain in population health at this threshold. At the higher threshold of £30,000 per QALY, the NHB increased to 0.439 QALYs per patient, reflecting a more substantial margin of cost-effectiveness. These findings confirm that the intervention is cost-effective under both commonly applied NICE thresholds, with greater headroom for health gain when evaluated against the £30,000 threshold (Table 45).

Table 45 Net health benefit - Base-case analysis

Technologies	Total costs (£)	Total QALYs	Incremental costs (£)	Incremental QALYs	NHB at £20,000	NHB at £30,000
SoC	[REDACTED]	[REDACTED]	NA	NA	[REDACTED]	[REDACTED]
Resmetirom	[REDACTED]	[REDACTED]	[REDACTED]	[REDACTED]	[REDACTED]	[REDACTED]

Abbreviations: ICER, incremental cost-effectiveness ratio; LYG, life years gained; NHB, net health benefit; QALYs, quality-adjusted life year; SoC, standard of care.

3.11 Exploring uncertainty

3.11.1 Probabilistic sensitivity analysis

A PSA was conducted to explore the impact of both multivariate and stochastic uncertainty within the model. The simulation was run on 1,000 sampled patients to capture first-order uncertainty, and each patient profile was evaluated across 2,000 probabilistic iterations to account for second-order uncertainty. Results were summarised as the probability of resmetirom being cost-effective at different WTP thresholds, including the NICE reference threshold of £30,000 per QALY.

The mean probabilistic ICER was estimated at £19,495 per QALY gained (Table 46). The ICER scatter plot (Figure 16) illustrated some variation in the size of incremental QALY gains, but the majority of simulations fell within the north-east quadrant, indicating that resmetirom was consistently associated with both higher costs and improved outcomes. This suggests a high degree of certainty regarding the direction of benefit, despite variation in the magnitude of effect. No simulations fell into the quadrants suggesting lower cost or worse outcomes, reinforcing the robustness of the model findings.

Table 46 Probabilistic base-case results for resmetirom vs. SoC
Based on 1,000 sampled patients and 2,000 model iterations

Technologies	Total costs (£)	Total LYG	Total QALYs	Incremental costs (£)	Incremental LYG	Incremental QALYs	ICER versus baseline (£/QALY)
SoC							
Resmetirom							19,495

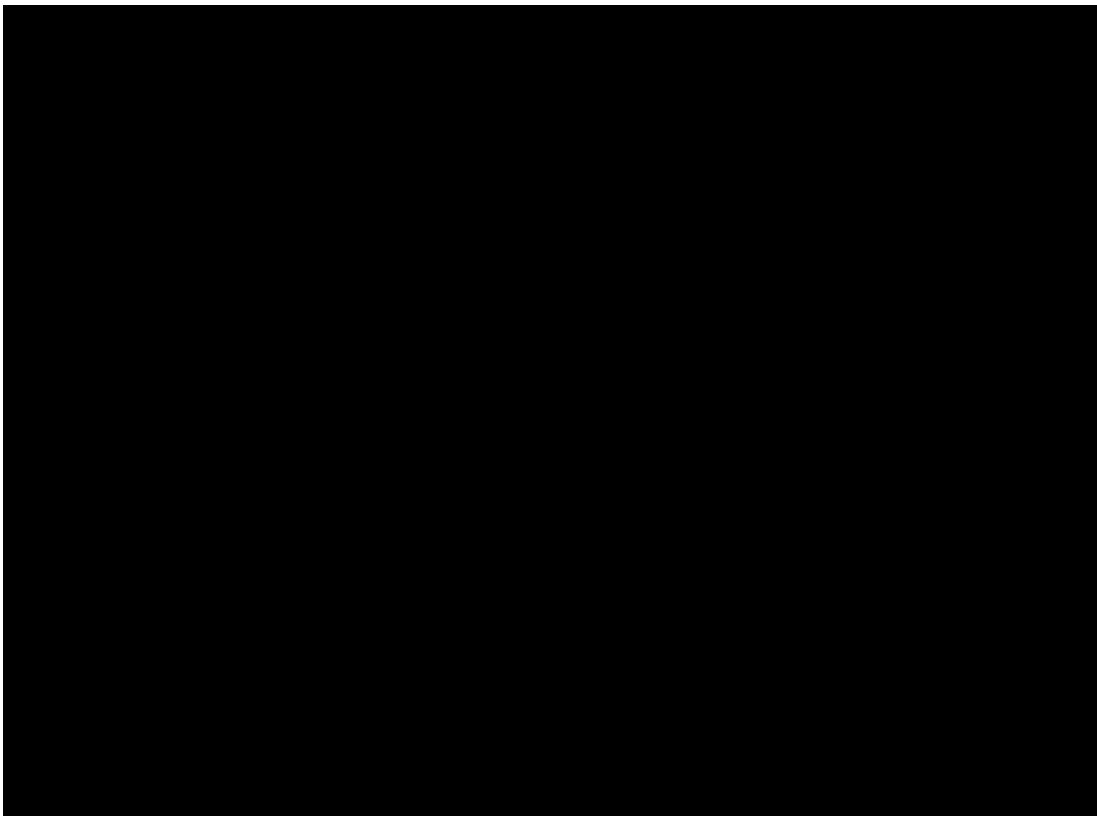
Abbreviations: ICER, incremental cost-effectiveness ratio; LYG, life years gained; NHB, net health benefit; QALYs, quality-adjusted life year; SoC, standard of care.

The cost-effectiveness acceptability curve (CEAC) (Figure 17) showed that resmetirom was likely to be considered cost-effective in % and % of simulations at a threshold of £20,000 and £30,000 per QALY, respectively.

Figure 16 Cost-effectiveness plane for resmetirom vs. SoC



Figure 17 CEAC for resmetirom vs. SoC



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3.11.2 Deterministic sensitivity analysis

A deterministic sensitivity analysis (DSA) was undertaken to explore the impact of parameter uncertainty on cost-effectiveness results. The analysis was implemented within the MSM and reported in terms of incremental net monetary benefit (NMB) at the NICE reference WTP threshold of £30,000 per QALY. Reporting in NMB terms provides a more intuitive interpretation than ICERs, since positive values indicate cost-effectiveness and the magnitude reflects the degree of value relative to the threshold.

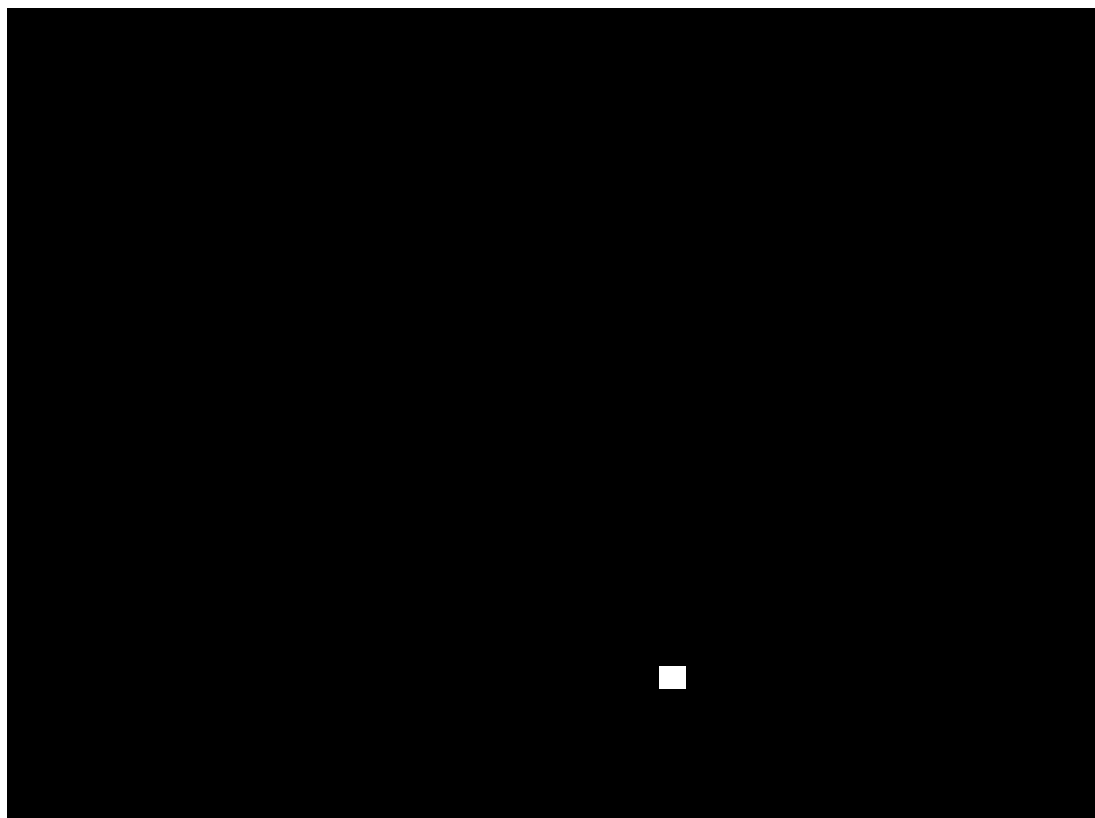
Because the model is a microsimulation, varying individual parameters affects not only mean transition probabilities and utilities but also the distribution of individual patient pathways. This means the DSA results capture both direct parameter shifts and how those shifts interact with patient heterogeneity and competing risks.

The results are presented in Figure 18 as a Tornado chart, ranking the top 25 inputs by their impact on NMB. The analysis shows that the parameters with the greatest influence on model outcomes were:

HSUVs, particularly for NAFL (F0 without MASH) and CC (F4); Transition probabilities for fibrosis improvement, worsening, and stability in subgroups defined by age and treatment response; Parameters related to costs of monitoring or short-term events had comparatively minor effects on NMB.

Importantly, across the full range of plausible input values, the incremental NMB remained positive, supporting the robustness of the base-case conclusion. The yellow band in Figure 18 represents the stochastic variation inherent in the microsimulation approach, reflecting the uncertainty introduced by simulating large numbers of individual patient trajectories. This band illustrates the expected range around the mean NMB attributable to stochastic error, independent of parameter variation. Parameters whose impacts fall entirely within this zone can be considered to have minimal practical influence on model outcomes, whereas parameters whose ranges extend beyond the band represent true drivers of cost-effectiveness uncertainty.

Figure 18 DSA for resmetirom vs. SoC



Transition probabilities for fibrosis progression, regression, and stability were parameterised as Dirichlet distributions, reflecting the multinomial nature of observed trial data (where the sum of probabilities across all transition states equals 1). In the DSA, these Dirichlet-derived parameters were included to ensure that sensitivity analysis preserved the internal dependency between competing transition pathways. For example, increasing the probability of fibrosis regression necessarily decreases the probability of stability or worsening. Including these Dirichlet parameters in the Tornado chart therefore provides a more realistic picture of model uncertainty, compared with varying individual probabilities independently.

Overall, the Tornado chart demonstrates that while the choice of HSUVs and assumptions about fibrosis transitions are influential, the direction of the results is consistent: resmetirom generates positive incremental NMB relative to SoC across plausible parameter ranges.

3.11.3 Scenario analysis

Scenario analyses were performed to test the robustness of the base-case results to alternative assumptions about treatment duration, inclusion of non-liver comorbidities, and the source of HSUVs. These scenarios reflect areas of uncertainty in the evidence base and in economic modelling of MASH and align with NICE expectations for sensitivity testing. The

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key themes for scenario analysis are explained in Table 47. The supplied model in R includes an interface developed in the Shiny application framework, which enables users to select, define and run a wide range of additional combination scenarios.

Table 47 Scenario analyses undertaken

Model setting	Base case	Scenario analysis	Justification
Treatment discontinuation	Patients continue resmetirom for their lifetime, unless they progress beyond F3 or regress below F2. A constant all-cause discontinuation rate is applied based on MAESTRO-NASH.	Option A: the discontinuation rate is halved. Option B: patients discontinue after 2 years.	The first scenario is intended to explore a potential difference in discontinuation rate beyond Year 1, since the all-cause discontinuation in MAESTRO-NASH would likely involve a greater number of AE-related discontinuations than might be observed in the long-term. The 2-year scenario tests the impact of a time-limited treatment effect, consistent with NICE precedent (e.g. TA875 (170)). It serves as an alternative exploration of the impact of treatment waning in the absence of long-term durability data.
Comorbidities included	Model incorporates non-liver comorbidities: cardiovascular events in diabetic and non-diabetic patients, and microvascular events in diabetic patients.	Option A: exclude CVD comorbidities. Option B: exclude all non-liver comorbidities.	These scenarios isolate the value of resmetirom, either for liver outcomes alone, or excluding CVD benefits. It tests the sensitivity of results to uncertainty in how accurately current risk equations capture the effect of MASH and its treatment on cardiometabolic outcomes.
HSUV source	Utilities sourced from NICE guideline NG49 (23) for fibrosis stages and advanced liver disease.	Utilities sourced from MAESTRO-NASH post-hoc analysis ; EQ-5D-3L utilities derived by mapping SF-36v2 domain scores using the	This scenario explores uncertainty in HRQoL measurement. NG49 is conservative and consistent with NICE precedent (23), whereas trial-based mapped utilities may better reflect

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		Rowen et al. 2009 algorithm (158).	the lived experience of patients. The scenario tests whether the choice of HSUV source materially alters cost-effectiveness results.
Combined sensitivity (utilities + comorbidities options)		MAESTRO-NASH utilities + no comorbidities + all discontinue after 2 years	Captures impact of simultaneous alternative assumptions.
Utility decrement	No age/sex adjustment	Applies age- and sex-specific utility decrement to the base case	Reflects NICE's preference for background utility decrements by age/sex in long-term models.

Abbreviations: AE, adverse event; CVD, cardiovascular disease; HRQoL, health-related quality of life; HSUV, health state utility value; MASH, metabolic dysfunction-associated steatohepatitis; NG, NICE guideline.

Results are summarised in Table 48. In the base case, resmetirom yielded an ICER of £21,422_per QALY over a lifetime horizon (for 10,000 sampled patients), remaining well within the NICE WTP threshold (£20,000–£30,000 per QALY).

Overall, the analyses consistently show that resmetirom improves health outcomes compared with SoC, providing an additional [REDACTED] QALYs across scenarios, but at higher costs (incremental costs ranging from ~£[REDACTED]–£[REDACTED]). The resulting ICERs fall between £13,230 and £23,460 per QALY gained, with the lowest ICER observed under a fixed 2-year treatment duration and the highest under assumptions of reduced discontinuation or alternative HSUV inputs. These findings suggest that resmetirom is likely to be cost-effective within typical UK thresholds, with results robust to variations in comorbidity assumptions and utility values.

These findings demonstrate that the base-case cost-effectiveness results are robust across a wide range of structural and parameter assumptions and resmetirom remains within or below the NICE threshold, supporting the base case conclusions.

Table 48 Results of scenario analyses (10,000 sampled patients)

Technologies	Total costs (£)	Total QALYs	Incremental costs (£)	Incremental QALYs	ICER (£/QALY)
Base case (over lifetime)					
SoC	██████	██████	█	█	–
Resmetirom	██████	██████	██████	██████	21,422
Scenario 1: excluding CVD as a comorbidity					
SoC	██████	██████	█	█	–
Resmetirom	██████	██████	██████	██████	22,845
Scenario 2: excluding CVD and T2DM as comorbidities					
SoC	██████	██████	█	█	–
Resmetirom	██████	██████	██████	██████	20,946
Scenario 3: HSUV based on MASTRO_NASH post-hoc analysis					
SoC	██████	██████	█	█	–
Resmetirom	██████	██████	██████	██████	22,020
Scenario 4: HSUV based on MASTRO_NASH post-hoc analysis and excluding CVD as a comorbidity					
SoC	██████	██████	█	█	–
Resmetirom	██████	██████	██████	██████	23,460
Scenario 5: HSUV based on MASTRO_NASH post-hoc analysis and excluding CVD and T2DM as comorbidities					
SoC	██████	██████			
Resmetirom	██████	██████	██████	██████	21,462
Scenario 6: : Applying age- and sex- specific utility decrements					
SoC	██████	██████			
Resmetirom	██████	██████	██████	██████	21,422
Scenario 7: 50% reduction in discontinuation for resmetirom (80 mg and 100 mg)					
SoC	██████	██████	█	█	–
Resmetirom	██████	██████	██████	██████	22,650

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Technologies	Total costs (£)	Total QALYs	Incremental costs (£)	Incremental QALYs	ICER (£/QALY)
Scenario 8: Fixed 2-year treatment duration—all patients discontinue resmetirom after 24 months (80 mg and 100 mg)					
SoC	████████	██████	█	█	—
Resmetirom	████████	██████	██████	██████	13,230

Abbreviations: CVD, cardiovascular disease; HSUV, health state utility value; ICER, incremental cost-effectiveness ratio; QALYs, quality-adjusted life year; SoC, standard of care; T2DM, type 2 diabetes mellitus.

3.12 Subgroup analysis

3.12.1 Diabetic population

For F2 and F3 patients with concomitant T2DM, resmetirom generated ██████ incremental QALYs at an incremental cost of £██████, yielding an ICER of £27,140 per QALY (Table 49). The probabilistic ICER was lower at £23,238 per QALY (Table 51). At thresholds of £20,000 and £30,000 per QALY, the incremental NHB was ██████ and ██████ QALYs, respectively. (Table 50).

The cost-effectiveness plane (Figure 19) demonstrates that almost all PSA iterations are clustered in the north-east quadrant, confirming that resmetirom is consistently associated with both higher costs and higher QALYs compared with SoC. The CEAC (Figure 20) shows that the probability of cost-effectiveness is high in this subgroup: █% at £20,000 per QALY and █% at £30,000 per QALY.

These findings suggest that resmetirom is cost-effective in patients with T2DM, likely reflecting their elevated baseline risk of both hepatic and cardiovascular complications, and the broader benefits of metabolic risk reduction captured in the model.

Table 49 Subgroup analysis results - T2DM

Technologies	Total costs (£)	Total LYG	Total QALYs	Incremental costs (£)	Incremental LYG	Incremental QALYs	ICER versus baseline (£/QALY)
SoC	████████	██████	██████				
Resmetirom	████████	██████	██████	██████	██████	██████	27,140

Abbreviations: ICER, incremental cost-effectiveness ratio; LYG, life years gained; NHB, net health benefit; QALY, quality-adjusted life year.

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Table 50 Subgroup analysis net health benefit –T2DM

Technologies	Total costs (£)	Total QALYs	Incremental costs (£)	Incremental QALYs	NHB at £20,000	NHB at £30,000
SoC	██████	██████	████	████	██████	██████
Resmetirom	██████	██████	██████	██████	██████	██████

Abbreviations: ICER, incremental cost-effectiveness ratio; LYG, life years gained; NHB, net health benefit; QALYs, quality-adjusted life year; SoC, standard of care.

Table 51 Subgroup analysis PSA results - T2DM
Based on 1,000 sampled patients and 2,000 model iterations

Technologies	Total costs (£)	Total QALYs	Incremental costs (£)	Incremental QALYs	ICER versus baseline (£/QALY)
SoC	██████	██████			
Resmetirom	██████	██████	██████	██████	23,283

Abbreviations: ICER, incremental cost-effectiveness ratio; QALY, quality-adjusted life year.

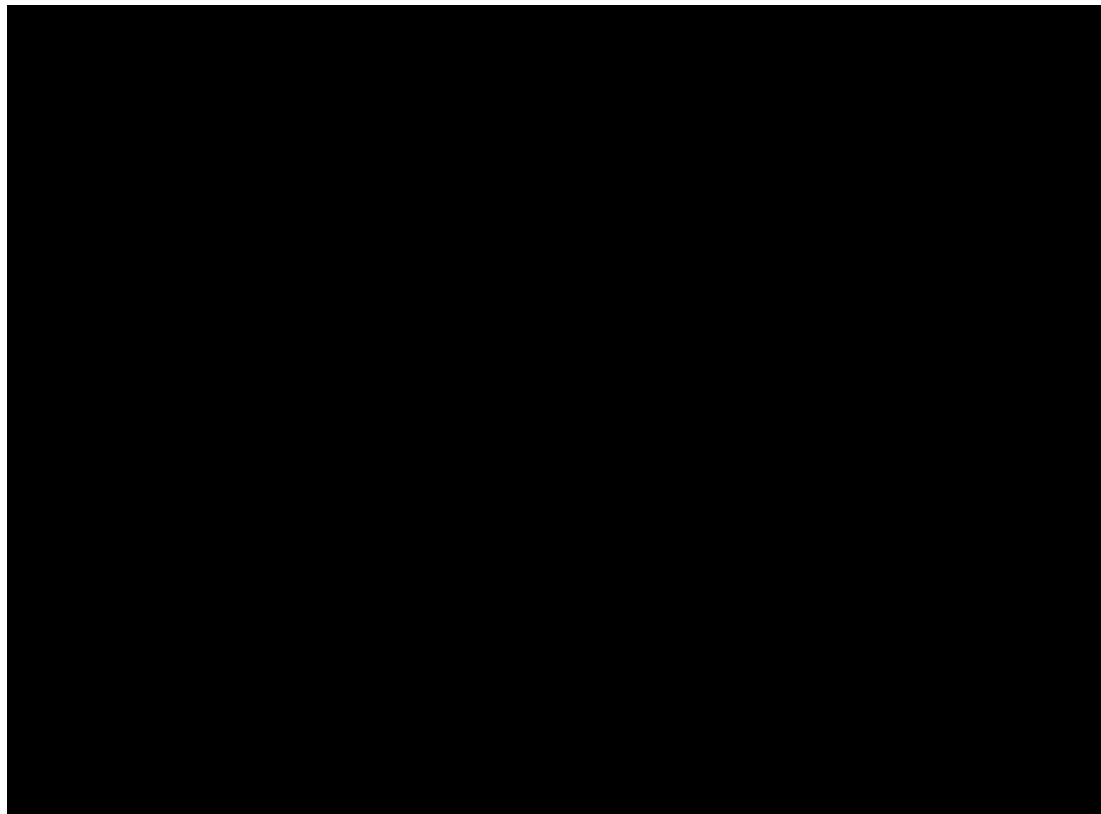
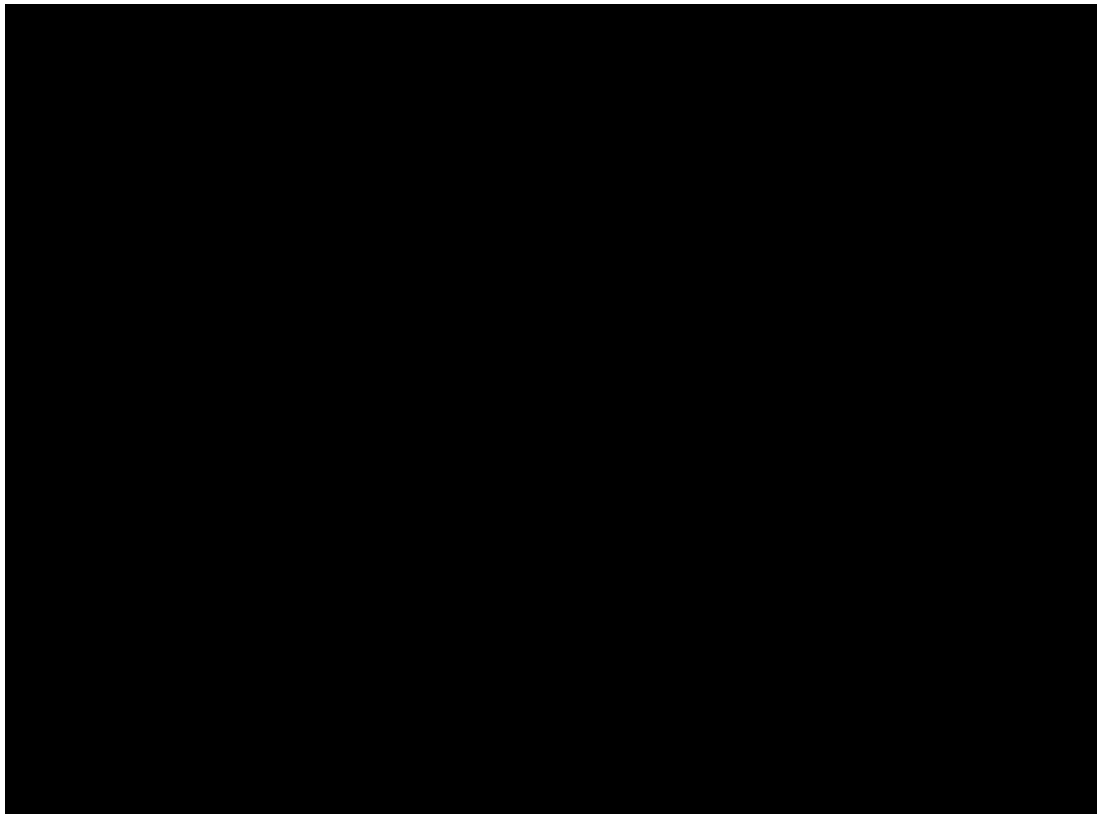
Figure 19 Cost-effectiveness plane for resmetirom vs. SoC: Subgroup of T2DM patients

Figure 20 Cost-effectiveness acceptability curve for resmetirom vs. SoC: Subgroup of T2DM patients



In the T2DM subgroup, resmetirom remained cost-effective in the predefined T2DM subgroup, with an ICER of £27,140 per QALY, which lies toward the upper end of NICE's conventional threshold range. Compared with the overall population, patients with T2DM accrued fewer incremental QALYs under SoC than in the overall trial population (██████ vs. ██████), and incurred higher incremental costs (£██████ vs. £██████). As a result, NHB was negative at the £20,000 threshold but remained positive at £30,000, suggesting that resmetirom delivers value for money in this group but with less headroom than in the base-case analysis.

In patients with T2DM, faster disease progression and higher competing risks mean that there is less time for the benefits of resmetirom to fully translate into QALY gains and avoided costs. Drug acquisition costs are incurred from the start of treatment, but some of the downstream benefits are realised later, and in this population, patients may transition more quickly to severe disease or death before the full effect can accrue. In addition, around 68% of patients in MAESTRO-NASH already had T2DM, meaning that the base case already represents a largely diabetic population, which limits the difference observed between the overall and subgroup analyses. Taken together, these factors explain why

resmetirom remains cost-effective in T2DM, but with a narrower margin compared with the overall trial population.

3.13 Benefits not captured in the QALY calculation

The QALY framework captures survival and HRQoL, but it may underestimate the full value of resmetirom in MASH for several reasons, mainly due to limited available data to model the disease, especially disease progression.

- Avoidance of CC, DCC, HCC, and LT not only improves patient outcomes but also alleviates substantial resource pressures on the NHS (e.g., LT waiting lists, intensive inpatient care). These system-level benefits are only partially reflected in standard cost-utility modelling.
- MASH is associated with significant impairment in work productivity and daily functioning, which is not captured in standard NHS/PSS perspectives. Data from the Global NASH registry (Younossi et al. 2022 (171)) demonstrated that patients with biopsy-proven MASH had markedly worse WPAI than matched controls, confirming the broader humanistic burden of the disease. Complementary evidence from an earlier study (Knight et al. 2018 (172)) quantified this burden: mean absenteeism of 7.2%, presenteeism of 16.3%, and an overall work impairment of 30.8% among MASH patients. Improvements in energy and daily functioning—likely following MASH resolution or fibrosis regression—could meaningfully reduce these productivity losses. However, such gains are not captured in EQ-5D-based QALYs or within the NHS/PSS cost perspective. Including these indirect benefits would likely improve the economic case for resmetirom further.
- Resmetirom demonstrated favourable effects on lipids and blood pressure in MAESTRO-NASH, as highlighted in Section 2.6. While these were linked to cardiovascular risk reductions in our model, the long-term cardiometabolic benefit may still be underestimated given the limitations of current risk equations in MASH populations, as well as the currently limited follow-up data in our own clinical trials.
- The MAESTRO-NASH trial collected multiple disease-specific HRQoL measures (e.g. CLDQ-NAFLD, LDQoL), which demonstrated meaningful improvements in domains such as **fatigue, emotional wellbeing, disease-related worry, and stigma** among histological responders (96). These domains are only partially

reflected in EQ-5D-based utilities. As a result, short-term symptomatic and psychological gains may be under-represented in the analysis QALY estimates.

- MASH disproportionately affects populations with multiple comorbidities, obesity, and T2DM, and the incidence of fatty liver-related death has been shown to be highest in groups with higher deprivation. Access to an effective and simple-to-take pharmacotherapy may address some of these health inequalities - an important NHS priority not accounted for in QALYs.
- In summary, these benefits suggest that the QALY framework may provide a conservative estimate of resmetirom's value. While NG49 utilities (23) anchor the base case in line with NICE methods, additional gains in symptom relief, productivity, cardiometabolic health, and system equity are likely to accrue, supporting the case for resmetirom as a valuable intervention in NHS England.

3.14 Validation

The MSM was validated in line with good practice guidelines and consistent with approaches taken in prior NICE technology appraisals.

- The model was built in R with extensive quality control checks. Transition probabilities were verified to sum to 1 in each cycle, extreme-value testing confirmed expected model behaviour (e.g., no treatment benefit under zero efficacy), and outcomes were reproduced under simplified assumptions. Two independent modellers reviewed the code to confirm internal consistency and accuracy of calculations.
- Model outputs were compared against external cost-effectiveness studies of resmetirom and other MASH interventions. Incremental QALYs in our analysis were higher than those reported in U.S. models such as Le et al. 2025 (112), but the direction of findings was consistent in demonstrating value at accepted WTP thresholds. Differences were explained by methodological choices: our use of biopsy-confirmed MAESTRO-NASH data, the dual-core framework (fibrosis improvement and MASH resolution), and inclusion of cardiometabolic outcomes. Predicted event rates were also compared with UK burden studies (Davidson et al. 2025 (5)) and found to be within plausible ranges.

- The model structure and key assumptions, including the rules governing treatment discontinuation, were reviewed at a UK advisory board involving hepatology specialists and health economic experts.

Despite this validation, some areas of uncertainty remain—most notably the durability of treatment effect beyond the 52-week MAESTRO-NASH data and the potential impact of long-term adherence in routine practice. These limitations are inherent to the evidence base and were explored through extensive scenario and sensitivity analyses to ensure that the cost-effectiveness conclusions are robust across a range of plausible assumptions.

In summary, internal checks, cross-validation with published models and burden studies, and expert review all support that the CEA is technically sound, and consistent with external evidence.

3.15 Interpretation and conclusions of economic evidence

MASH with moderate to advanced fibrosis (fibrosis stages F2 to F3) is a progressive condition that is highly associated the risk of cirrhosis, liver-related complications, and cardiometabolic comorbidities. Currently, there are no licensed pharmacological treatments in the UK, representing a major unmet need in the NHS. Resmetirom, a selective THR- β agonist, is the first therapy to demonstrate statistically significant and clinically meaningful histological improvement in MASH in a large, global phase III trial (MAESTRO-NASH). The current economic evaluation assessed the long-term cost-effectiveness of resmetirom in combination with lifestyle management (diet + exercise) compared with SoC comprising lifestyle management alone.

A patient-level MSM was developed using transition probabilities from the pivotal clinical trial as well as published evidence, UK-specific costs, and utilities sourced from NICE guideline NG49 (23) (with trial-based utilities explored in scenario analyses). The base case adopted a lifetime horizon from the NHS and PSS perspective, with costs and QALYs discounted at 3.5% annually. Cost-effectiveness was expressed as ICERs and NHB. Subgroup analyses explored patients with T2DM.

In the base case, resmetirom was associated with an incremental cost of £[REDACTED] and an incremental gain of [REDACTED] QALYs versus SoC, yielding an ICER of £21,422 per QALY gained (for 10,000 sampled patients). Probabilistic analysis produced consistent results (ICER £19,495 per QALY). At both £20,000 and £30,000 per QALY thresholds, the NHB was positive. In the subgroup of patients with T2DM, resmetirom incurred an incremental cost of

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£[REDACTED] and generated an incremental gain of [REDACTED] QALYs, resulting in an ICER of £27,140 per QALY gained.

This evaluation suggests that resmetirom is likely to be a cost-effective use of NHS resources when compared with SoC, considering the NICE reference WTP threshold range of £20,000–£30,000 per QALY. The use of £30,000 per QALY is justified given the severity of MASH, the absence of effective licensed therapies, and the significant burden of liver and cardiometabolic complications on NHS resources and patient HRQoL.

From a clinical perspective, resmetirom addresses a clear unmet need in the NHS: MASH has no approved pharmacotherapy and its complications drive substantial secondary care costs (including cirrhosis [CC and DCC], HCC, and LT). The safety profile of resmetirom observed in MAESTRO-NASH was favourable, with most TRAEs mild to moderate and transient in nature, and without incremental monitoring requirements beyond current specialist care (17). This supports its feasibility for adoption in secondary care NHS hepatology services, where patients with F2 to F3 stage fibrosis are already monitored. Importantly, treatment is oral, requires no additional infrastructure, and can be delivered within existing pathways.

Our results are broadly consistent with external evaluations, which have generally found resmetirom to be cost-effective relative to usual care when priced within value-based ranges. For example, the U.S. Institute for Clinical and Economic Review (ICER) concluded that resmetirom would meet U.S. WTP thresholds if priced around \$39,600–\$50,100 per year (119). Subsequent conference updates and secondary analyses have reported similar findings of cost-effectiveness under plausible pricing assumptions (114).

Our findings also align and diverge in informative ways from the recent CEA by Le et al. 2025 (112). That US-based agent-level microsimulation, reflecting MASH patients with F2–F3 fibrosis, reported an incremental gain of only 0.26 QALYs at an incremental cost of \$36,255, yielding an ICER of \$140,134 per QALY—well above the U.S. WTP threshold of \$100,000/QALY. Several methodological and contextual differences account for this divergence, the main being that Le et al. 2025 (112) drew on profoundly heterogeneous natural history sources. In addition, their model did not fully incorporate the cardiometabolic benefits of resmetirom, thereby constraining QALY gains compared with our model.

A further important methodological difference—and a key reason our model produces larger QALY gains—is the dual-core representation of histological benefit. MAESTRO-NASH had dual primary endpoints of MASH resolution and Fibrosis improvement, and our model Company evidence submission: Resmetirom for treating moderate to advanced liver fibrosis (without cirrhosis) (MASLD) ID6529

preserves this structure explicitly. Within each fibrosis stage, patients are categorised into resolution or non-resolution sub-states, and transitions are estimated across all observed combinations, with an explicit relapse mechanism. This structure allows two clinically distinct pathways to generate value: (i) reduced risk of progression following fibrosis improvement, and (ii) direct QoL gains and altered progression risk following MASH resolution even in the absence of fibrosis improvement. By contrast, many published models, including Le et al. 2025 (112), summarise histological benefit solely as net movement on the fibrosis ladder, which under-recognises resolution-related benefits. In our model, we carefully avoided double counting by ensuring resolution sub-states were mutually exclusive within each fibrosis stage, and by applying either the utility adjustment or the event-risk modifier, but not both for the same effect.

Taken together, these differences explain why our evaluation produces higher incremental QALY gains and more favourable ICERs than some earlier U.S. models, while still remaining directionally consistent with the broader evidence base that resmetirom offers good value for money when appraised against conventional WTP thresholds.

Uncertainty remains in extrapolating short-term trial outcomes to long-term clinical endpoints. The model assumed fixed annual transition probabilities and treated discontinuation as a proxy for treatment-effect waning, consistent with NICE precedent, but alternative assumptions could alter results. Utility measurement in MASH is challenging: generic instruments may underestimate patient benefit, and mapped trial data introduce additional uncertainty. Subgroup analyses are exploratory, lose randomisation, and in some cases (weight-based dosing) excluded large proportions of the resmetirom-treated population, reducing robustness. Nonetheless, sensitivity and scenario analyses demonstrated that the cost-effectiveness conclusions are stable across a wide range of plausible assumptions.

In conclusion, this analysis indicates that resmetirom is cost-effective compared with SoC in adults with MASH and F2–F3 fibrosis, particularly at the £30,000 per QALY threshold. Resmetirom provides clinically meaningful benefits, addresses a substantial unmet need, and can be delivered safely and efficiently within NHS secondary care. By capturing both fibrosis improvement and MASH resolution, as well as extrahepatic benefits, the dual-core modelling approach reflects the full therapeutic potential of resmetirom, reinforcing its value as a transformative option for NHS England.

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5. Appendices

Appendices A-K are provided as separate files to the main submission dossier.

NATIONAL INSTITUTE FOR HEALTH AND CARE EXCELLENCE

Single technology appraisal

ID6529 Resmetirom for treating moderate to advanced liver fibrosis (without cirrhosis) caused by metabolic dysfunction-associated steatohepatitis

Summary of Information for Patients (SIP)

September 2025

Template version	Date amended	Changes since previous version
2.0	Dec 2023	Clarifications made to guidance notes in section 3i regarding inclusion of statements on cost effectiveness.

File name	Version	Contains confidential information	Date
ID6529 Resmetirom for treating moderate to advanced liver fibrosis (without cirrhosis) caused by metabolic dysfunction-associated steatohepatitis	1	Yes	12 th September 2025

Summary of Information for Patients (SIP):

The pharmaceutical company perspective

What is the SIP?

The Summary of Information for Patients (SIP) is written by the company who is seeking approval from NICE for their treatment to be sold to the NHS for use in England. It is a plain English summary of their submission written for patients participating in the evaluation. It is not independently checked, although members of the public involvement team at NICE will have read it to double-check for marketing and promotional content before it is sent to you.

The **Summary of Information for Patients** template has been adapted for use at NICE from the [Health Technology Assessment International – Patient & Citizens Involvement Group](#) (HTAi PCIG). Information about the development is available in an open-access [IJTAHC journal article](#)

SECTION 1: Submission summary

1a) Name of the medicine (generic and brand name):

Generic name: Resmetirom

1b) Population this treatment will be used by. Please outline the main patient population that is being appraised by NICE:

Adults with non-cirrhotic metabolic dysfunction–associated steatohepatitis (MASH) with moderate to advanced liver fibrosis (stages F2 or F3).

1c) Authorisation: Please provide marketing authorisation information, date of approval and link to the regulatory agency approval. If the marketing authorisation is pending, please state this, and reference the section of the company submission with the anticipated dates for approval.

Marketing authorisation in the UK is pending with approval date to be confirmed.

Resmetirom was approved by the U.S. Food and Drug Administration (FDA) on March 14, 2024 (1), as the first treatment for this condition. In August 2025, the European Commission (EC) granted conditional marketing authorisation in the European Union (EU), alongside diet and exercise, based on unmet medical need (2).

1d) Disclosures. Please be transparent about any existing collaborations (or broader conflicts of interest) between the pharmaceutical company and patient groups relevant to the medicine. Please outline the reason and purpose for the engagement/activity and any financial support provided:

We wish to disclose the existing collaboration and relationship between Madrigal Pharmaceuticals and relevant patient organisations.

- **Collaborating Patient Groups:** British Liver Trust

- **Nature and Purpose of Engagement:** Engagement with this group has focused on understanding the human burden of metabolic dysfunction-associated steatotic liver disease (MASLD)/MASH and the MASH patient journey in the UK. This has included supporting the British Liver Trust to enhance their patient education and support services; awareness campaigns; and policy work to call for better care and earlier detection. These activities are currently ongoing and intended to ensure that UK patient needs and experiences are appropriately considered in the development and delivery of therapies for MASH now and in the future.
- **Financial Support:** Madrigal Pharmaceuticals has provided financial support to the British Liver Trust in the form of a patient advocacy grant for the purposes listed above.
- **Non-Financial Support:** In addition to direct funding, Madrigal did invite British Liver Trust to attend our Patient Advocacy Listening Session meeting at the EASL conference, where they shared their perspectives on the MASH patient journey in the UK.

All collaborations are conducted with a commitment to ethical standards, independence of the patient organisations, and compliance with applicable laws and codes of practice. The purpose of these collaborations is to foster meaningful patient involvement, support disease awareness, and ultimately improve patient outcomes.

SECTION 2: Current landscape

2a) The condition – clinical presentation and impact

Please provide a few sentences to describe the condition that is being assessed by NICE and the number of people who are currently living with this condition in England.

Please outline in general terms how the condition affects the quality of life of patients and their families/caregivers. Please highlight any mortality/morbidity data relating to the condition if available. If the company is making a case for the impact of the treatment on carers this should be clearly stated and explained.

MASH, formerly known as non-alcoholic steatohepatitis (NASH), is a progressive liver disease that generally arises in people with underlying metabolic dysfunction, such as obesity, type 2 diabetes, insulin resistance, and dyslipidaemia. The disease is characterised by fat accumulation in the liver, inflammation, and varying degrees of fibrosis. While many people don't show any symptoms (are asymptomatic) in the early stages, once fibrosis progresses to moderate or advanced levels (stages F2–F3), patients are at substantially increased risk of developing cirrhosis, hepatocellular carcinoma, liver failure, and eventually requiring liver transplantation (3–7).

MASH is now recognised as one of the most common causes of chronic liver disease worldwide and is increasing in prevalence in England in parallel with rising rates of obesity and type 2 diabetes (8).

The condition can have a considerable impact on patients' quality of life (QoL), even before progression to cirrhosis. Symptoms such as fatigue, abdominal pain, and poor physical functioning are common and are often accompanied by psychological distress, including anxiety and depression. Beyond direct liver-related complications, people with MASH are at increased risk of cardiovascular disease, which remains the leading cause of death in this population (9,10).

The disease also affects families and caregivers, particularly as patients reach advanced stages where ongoing monitoring, frequent hospital visits, and, in some cases, transplant evaluation or post-transplant care are required. This can result in emotional strain, reduced productivity, and financial stress for households (9–12).

2b) Diagnosis of the condition (in relation to the medicine being evaluated)

Please briefly explain how the condition is currently diagnosed and how this impacts patients. Are there any additional diagnostic tests required with the new treatment?

MASH is usually suspected in people with risk factors such as obesity, type 2 diabetes, or metabolic syndrome, and is often first identified through abnormal liver function tests or imaging showing fat accumulation in the liver. A definitive diagnosis and staging of fibrosis typically require non-invasive tests such as transient elastography (FibroScan®) or serum biomarker panels (e.g., FIB-4, ELF test). In some cases, a liver biopsy may be performed to confirm disease activity and fibrosis stage, but this becoming less common in the UK as it is invasive, resource-intensive, and not routinely feasible for all patients (13).

Current diagnostic pathways can be lengthy and burdensome, often delaying the identification of patients at moderate to advanced fibrosis stages who are at highest risk of progression and would benefit most from treatment. Many patients remain undiagnosed until their disease has progressed significantly, sometimes only being detected when complications such as cirrhosis arise (13).

No additional diagnostic procedures are required specifically for treatment with resmetirom beyond the standard clinical evaluation of fibrosis stage and disease activity. Diagnosis and patient selection would rely on existing non-invasive tests that are already recommended in clinical practice for the assessment of liver fibrosis (13).

2c) Current treatment options:

The purpose of this section is to set the scene on how the condition is currently managed:

- What is the treatment pathway for this condition and where in this pathway the medicine is likely to be used? Please use diagrams to accompany text where possible. Please give emphasis to the specific setting and condition being considered by NICE in this review. For example, by referencing current treatment guidelines. It may be relevant to show the treatments people may have before and after the treatment under consideration in this SIP.
- Please also consider:
 - if there are multiple treatment options, and data suggest that some are more commonly used than others in the setting and condition being considered in this SIP, please report these data.
 - are there any drug–drug interactions and/or contraindications that commonly cause challenges for patient populations? If so, please explain what these are.

Currently, there are no medicines available on the NHS that are licensed to treat MASH with moderate to advanced liver fibrosis. There is rare use of pioglitazone and vitamin E in an off-label manner as these interventions are not licensed for MASH. Clinical care currently focuses on advice for lifestyle changes such as diet, exercise, and weight loss, together with treatment for related conditions like diabetes and high cholesterol (13,14).

Patients are usually identified in primary care and tested with simple blood or liver scans, and those assessed to potentially have more advanced disease (fibrosis stages F2–F3) are already referred to a liver specialist in hospital. If approved, any decision to commence resmetirom

therapy in a patient with suitable MASH is anticipated to be via the liver specialist hospital clinic, to be established alongside any existing care. After starting resmetirom, patients would continue lifestyle measures and standard care, with regular monitoring (13,14). There are clinical guidelines in place in the USA and Europe with UK clinical guidance in development (led by the British Society for the Study of the Liver [BASL]).

2d) Patient-based evidence (PBE) about living with the condition

Context:

- **Patient-based evidence (PBE)** is when patients input into scientific research, specifically to provide experiences of their symptoms, needs, perceptions, quality of life issues or experiences of the medicine they are currently taking. PBE might also include carer burden and outputs from patient preference studies, when conducted in order to show what matters most to patients and carers and where their greatest needs are. Such research can inform the selection of patient-relevant endpoints in clinical trials.

In this section, please provide a summary of any PBE that has been collected or published to demonstrate what is understood about **patient needs and disease experiences**. Please include the methods used for collecting this evidence. Any such evidence included in the SIP should be formally referenced wherever possible and references included.

People living with MASH and moderate to advanced liver fibrosis often describe symptoms such as tiredness, abdominal discomfort, poor sleep, itching, and problems with concentration or memory. These symptoms can affect everyday life, including the ability to work, exercise, or take part in social activities. Many patients also report feelings of worry, low mood, or stigma related to their condition. Families and carers can be affected too, particularly when the condition becomes more advanced and requires regular hospital visits or preparation for complex care such as transplant (9–12).

In the phase 3 MAESTRO-NASH trial, we collected information directly from patients about how the disease affects their daily lives. This was done using several questionnaires completed at the start of the trial and again during follow-up visits.

We used three main tools:

- CLDQ-NASH (Chronic Liver Disease Questionnaire – NASH): looks at symptoms that are common in MASH, such as fatigue, abdominal discomfort, activity limits, emotional health, worry, and general wellbeing.
- SF-LDQOL (Short Form Liver Disease Quality of Life): combines a general health survey (SF-36) with questions specific to liver disease, allowing us to measure both overall health and liver-related problems.
- WPAI-NASH (Work Productivity and Activity Impairment – NASH): measures how MASH affects people's ability to work and carry out daily activities, including time missed from work, reduced performance at work, and activity limitations at home.

At the beginning of the study, patients reported a lower QoL compared with people in the general population. The biggest problems were low energy, fatigue, and difficulties with daily activities and emotional wellbeing.

By week 52 of the trial, patients who showed improvement in their liver disease (either resolution of MASH or improvement in fibrosis) also reported meaningful improvements in QoL. These included feeling less worried, better emotional wellbeing, improved role functioning, and fewer problems related to stigma and health distress. Patients who did not respond to treatment showed little or no improvement (15).

These findings show that when the disease improves, patients also feel better in ways that matter to them. This evidence highlights the significant impact of MASH on daily life and work, and demonstrates that effective treatment can lead to important improvements in both health and QoL .

SECTION 3: The treatment

3a) How does the new treatment work?

What are the important features of this treatment?

Please outline as clearly as possible important details that you consider relevant to patients relating to the mechanism of action and how the medicine interacts with the body

Where possible, please describe how you feel the medicine is innovative or novel, and how this might be important to patients and their communities.

If there are relevant documents which have been produced to support your regulatory submission such as a summary of product characteristics or patient information leaflet, please provide a link to these.

Resmetirom is a once-daily oral medicine that works directly in the liver. It activates a natural protein in liver cells called the thyroid hormone receptor-beta (THR- β). This receptor helps regulate how the liver processes fats, cholesterol, and sugar. In people with MASH, these processes do not work properly, leading to fat build-up, inflammation, and scarring (fibrosis) in the liver. By stimulating THR- β , resmetirom helps the liver burn fat more efficiently, reduce inflammation, and slow or reverse the development of fibrosis.

Resmetirom is highly selective for THR- β in the liver and does not strongly affect related receptors in the heart or bones. This selectivity is important because it helps target liver disease without causing unwanted side effects in other parts of the body (16–18).

Why resmetirom is innovative

- **First in class:** Resmetirom is the first medicine specifically designed to target THR- β in the liver.
- **Precision mechanism:** Unlike general thyroid hormone treatments, resmetirom is selective to the liver, reducing the risk of side effects elsewhere.
- **Addresses root causes:** It improves multiple pathways—fat metabolism, inflammation, and fibrosis—rather than only treating symptoms.
- **Oral convenience:** It is taken as a tablet, offering patients an easy-to-use treatment compared with more invasive therapies.
- **Potential community benefit:** By slowing or reversing disease progression, resmetirom may help reduce the need for liver transplants and improve QoL for patients and their families.

3b) Combinations with other medicines

Is the medicine intended to be used in combination with any other medicines?

- Yes-/ No

If yes, please explain why and how the medicines work together. Please outline the mechanism of action of those other medicines so it is clear to patients why they are used together.

If yes, please also provide information on the availability of the other medicine(s) as well as the main side effects.

If this submission is for a combination treatment, please ensure the sections on efficacy (3e), quality of life (3f) and safety/side effects (3g) focus on data that relate to the combination, rather than the individual treatments.

Resmetirom is not intended to be used in combination with any other medicine.

3c) Administration and dosing

How and where is the treatment given or taken? Please include the dose, how often the treatment should be given/taken, and how long the treatment should be given/taken for.

How will this administration method or dosing potentially affect patients and caregivers? How does this differ to existing treatments?

How and where the treatment is taken

Resmetirom is given as an oral tablet once daily, with or without food. The recommended dose is anticipated to be 80 mg or 100 mg once daily, depending on patient body weight (80 mg for patients < 100 kg; 100 mg for patients ≥ 100 kg). Treatment is intended to be taken long term in patients with non-cirrhotic MASH with moderate to advanced liver fibrosis (F2–F3), alongside standard care such as lifestyle management and control of cardiometabolic risk factors.

Impact on patients and caregivers

Because resmetirom is an oral, once-daily treatment, it is straightforward and convenient compared with therapies that might require injections, infusions, or complex dose schedules. Daily tablets can easily be incorporated into existing routines for both patients and caregivers. Regular monitoring will still be required (for example, liver function tests, lipid management, and checking for potential drug–drug interactions such as with statins), but the administration itself is simple.

How this differs from existing treatments

At present, there are no licensed disease-specific treatments for MASH with fibrosis in the UK. Current care focuses on lifestyle interventions (diet, exercise, weight loss), management of comorbidities (such as type 2 diabetes or dyslipidaemia) (14). These options may have limited efficacy, tolerability concerns, or require significant effort from patients (e.g., sustaining major lifestyle changes). Resmetirom therefore differs by being the first targeted pharmacological option for this patient group, with a convenient once-daily oral dose that directly addresses the underlying disease process.

3d) Current clinical trials

Please provide a list of completed or ongoing clinical trials for the treatment. Please provide a brief top-level summary for each trial, such as title/name, location, population, patient group size, comparators, key inclusion and exclusion criteria and completion dates etc. Please provide references to further information about the trials or publications from the trials.

Current clinical trials

MAESTRO-NASH (Phase 3 – completed 52-week histology, follow-up ongoing)

This is the main late-stage study of resmetirom. It took place across multiple countries including patients in the UK and included adults with biopsy-confirmed NASH and liver fibrosis stages F1B,

F2, or F3. A total of 966 patients were enrolled and randomly given either resmetirom 80 mg, resmetirom 100 mg, or placebo, taken once daily.

The main goals at 52 weeks were to see if resmetirom could:

1. Clear NASH without making fibrosis worse, and
2. Improve fibrosis by at least one stage without making NASH worse.

Both goals were met compared with placebo. Patients continue to be followed for up to 54 months to assess long-term outcomes.

Reference: *New England Journal of Medicine* 2024 (19); ClinicalTrials.gov identifier **NCT03900429**.

MAESTRO-NAFLD-1 (Phase 3 – safety study, completed)

This trial focused mainly on the safety and tolerability of resmetirom in a broader group of adults with presumed non-alcoholic fatty liver disease (NAFLD)/MASH diagnosed by non-invasive tests, not biopsy. Over 1,200 patients received either resmetirom or placebo once daily.

The study confirmed that resmetirom was generally safe and well tolerated and showed consistent improvements in liver fat, blood lipids, and non-invasive fibrosis tests.

Reference: ClinicalTrials.gov identifier **NCT04197479** (20).

MAESTRO-NASH OUTCOMES (Phase 3 – ongoing)

This is a long-term study designed to find out if resmetirom can reduce major liver outcomes, such as progression to cirrhosis, liver transplant, or death. It is enrolling around 7,000 patients worldwide who have non-cirrhotic MASH with significant fibrosis.

Patients are being randomly assigned to resmetirom or placebo and followed for several years to measure hard clinical outcomes.

Reference: ClinicalTrials.gov identifier **NCT05500222** (21).

3e) Efficacy

Efficacy is the measure of how well a treatment works in treating a specific condition.

In this section, please summarise all data that demonstrate how effective the treatment is compared with current treatments at treating the condition outlined in section 2a. Are any of the outcomes more important to patients than others and why? Are there any limitations to the data which may affect how to interpret the results? Please do not include academic or commercial in confidence information but where necessary reference the section of the company submission where this can be found.

Resmetirom has been tested in a large phase 3 study (MAESTRO-NASH) in adults with NASH/MASH and moderate to advanced scarring (F1B–F3). People took resmetirom once a day (80 mg or 100 mg) or placebo for 52 weeks, on top of standard care.

How well it worked vs. placebo (standard care alone):

- NASH resolved (disappeared on biopsy) without fibrosis getting worse in about 26–30% of people on resmetirom, vs. about 10% on placebo.
- Fibrosis improved by at least one stage without NASH getting worse in about 24–26% on resmetirom, vs. about 14% on placebo.
- Resmetirom also reduced liver fat and improved blood fats (such as low-density lipoprotein-cholesterol and apolipoprotein B), which may be important for long-term liver and heart health (19).

What matters most to patients and why:

Patients and clinicians generally prioritise:

- Slowing or reversing fibrosis to reduce the risk of cirrhosis and serious complications.
- Resolving NASH, showing the underlying disease activity is improving.
- Feeling and functioning better day to day (e.g., less fatigue, better energy and emotional wellbeing). In the resmetirom programme, people who improved on biopsy also reported improvements in QoL measures (15).

How this compares with what is currently used:

In the UK there are no licensed medicines that directly treat MASH. Options used in practice include lifestyle/weight management and, in selected cases, unlicensed use of pioglitazone, or vitamin E (14). These may help some patients, but results on fibrosis improvement are mixed or limited, and side-effects can restrict use. Resmetirom is the first treatment to show clear improvements in both NASH resolution and fibrosis in a large phase 3 trial.

Limitations to keep in mind:

- The main results are at 52 weeks and based on biopsy changes (accepted by regulators but still a surrogate for long-term outcomes).
- A large outcomes study (MAESTRO-NASH OUTCOMES) is ongoing to see whether resmetirom reduces events like progression to cirrhosis, need for transplant, or death (21).

3f) Quality of life impact of the medicine and patient preference information

What is the clinical evidence for a potential impact of this medicine on the quality of life of patients and their families/caregivers? What quality of life instrument was used? If the EuroQol-5D (EQ-5D) was used does it sufficiently capture quality of life for this condition? Are there other disease specific quality of life measures that should also be considered as supplementary information?

Please outline in plain language any quality of life related data such as **patient reported outcomes (PROs)**.

Please include any **patient preference information (PPI)** relating to the drug profile, for instance research to understand willingness to accept the risk of side effects given the added benefit of treatment. Please include all references as required.

In the phase 3 MAESTRO-NASH trial, several tools were used to understand how MASH affects patients' lives and how resmetirom may improve QoL. The CLDQ-NASH questionnaire looked at common liver-related problems such as fatigue, abdominal discomfort, activity limitations, systemic symptoms, emotional wellbeing, and worry. The SF-LDQOL combined a general health survey with questions specific to liver disease, giving a broader picture of both overall and liver-related QoL. The WPAI-NASH measured the effect of MASH on the ability to work and carry out everyday activities, including time off work and reduced productivity. Although the EQ-5D-5L was not collected directly, scores were estimated using published mapping algorithms so that health utility values could be used in cost-effectiveness analyses (15).

At the start of the study, patients with MASH and fibrosis reported a much lower QoL than the general population. The biggest issues were fatigue, low energy, difficulty with daily activities, and emotional distress. These findings confirm the heavy burden of MASH even before cirrhosis develops (15).

After 52 weeks of treatment, patients who responded to resmetirom on biopsy (showing either fibrosis improvement or NASH resolution) experienced meaningful improvements in QoL. For example, patients reported less worry on the CLDQ-NASH, with 41% achieving a clinically important improvement. On the SF-LDQOL, patients also showed gains in emotional wellbeing, reduced health distress, less stigma, and better overall liver-related QoL, with around one-third of patients reaching clinically important thresholds. Importantly, these benefits were not seen in patients receiving placebo or in those who did not respond on biopsy (15).

EQ-5D values estimated through mapping confirmed overall QoL improvements among patients who responded to resmetirom. This demonstrates that clinical benefits observed on biopsy are directly linked to outcomes that matter to patients, such as more energy, reduced emotional burden, and better ability to take part in everyday activities (15).

3g) Safety of the medicine and side effects

When NICE appraises a treatment, it will pay close attention to the balance of the benefits of the treatment in relation to its potential risks and any side effects. Therefore, please outline the main side effects (as opposed to a complete list) of this treatment and include details of a benefit/risk assessment where possible. This will support patient reviewers to consider the potential overall benefits and side effects that the medicine can offer.

Based on available data, please outline the most common side effects, how frequently they happen compared with standard treatment, how they could potentially be managed and how many people had treatment adjustments or stopped treatment. Where it will add value or context for patient readers, please include references to the Summary of Product Characteristics from regulatory agencies etc.

Clinical studies show that resmetirom is generally safe and well tolerated. Most people who took the medicine experienced only mild or moderate side effects, similar to those seen in people who received placebo (a dummy treatment). The most common side effects were mild stomach issues such as diarrhoea or nausea. These usually started soon after treatment began, tended to improve over time, and no severe cases were reported (19).

Serious side effects were uncommon and happened at about the same rate in people taking resmetirom as in those taking placebo. Very few of these events were thought to be caused by the medicine. Only a small number of people stopped treatment because of side effects, mainly in the higher dose group (19).

Importantly, resmetirom was not linked to any heart rhythm problems, weight gain, or drug-induced liver injury. It also showed no negative impact on blood pressure, bone health, or sex

hormone levels. Small changes in thyroid hormone levels were observed but did not affect overall thyroid function (19).

Taken together with the regulatory approvals now obtained in USA and Europe, these results suggest that resmetirom offers important benefits for patients with liver fibrosis due to MASH, with a safety profile that is generally manageable and compares favourably to placebo. .

3h) Summary of key benefits of treatment for patients

Issues to consider in your response:

- Please outline what you feel are the key benefits of the treatment for patients, caregivers and their communities when compared with current treatments.
- Please include benefits related to the mode of action, effectiveness, safety and mode of administration

Resmetirom offers patients the first approved treatment option for MASH with liver fibrosis, a condition where there are currently no licensed medicines available. Until now, people with this disease have mainly been advised to rely on lifestyle changes such as diet and exercise, which can be difficult to maintain and often do not stop the disease from getting worse.

The key benefit of resmetirom is that it directly targets the underlying liver disease and has been shown to improve both liver inflammation and scarring. This means it has the potential to slow or even prevent the disease from progressing to end-stage liver disease, where patients may face serious complications or require a liver transplant. Having an effective treatment available provides hope for patients and reassurance for their families and caregivers.

Resmetirom is taken as a once-daily tablet, which is simple to use and less burdensome compared with more invasive treatments. Clinical studies show that it is generally well tolerated, with side effects that are mostly mild and manageable, which means many patients can stay on treatment long term (19).

At a community level, an effective treatment could reduce the need for advanced hospital care, prevent progression to liver failure and transplantation, help people remain healthier and more active, and ease the emotional and financial burden on families, caregivers, and the healthcare system.

3i) Summary of key disadvantages of treatment for patients

Issues to consider in your response:

- Please outline what you feel are the key disadvantages of the treatment for patients, caregivers and their communities when compared with current treatments. Which disadvantages are most important to patients and carers?
- Please include disadvantages related to the mode of action, effectiveness, side effects and mode of administration
- What is the impact of any disadvantages highlighted compared with current treatments

Resmetirom is generally well tolerated, and the disadvantages for patients are limited compared with the potential benefits. Some people may experience mild stomach-related side effects such as diarrhoea or nausea, particularly when starting treatment. These symptoms usually settle over time and can often be managed without stopping therapy. Only a small proportion of patients needed to discontinue because of side effects.

Another consideration is that resmetirom is not a cure, and patients may need to take it long term alongside lifestyle measures such as healthy eating and exercise. However, this is similar to the way many long-term conditions are managed, and the convenience of a once-daily tablet makes it far less burdensome than more invasive treatments.

Compared with the current situation where no licensed medicines exist, these disadvantages are relatively minor. For most patients, caregivers, and communities, the manageable side effects and need for ongoing use are greatly outweighed by the significant benefits resmetirom offers in slowing disease progression and reducing the risk of cirrhosis, end-stage liver disease, and the need for liver transplantation.

3i) Value and economic considerations

Introduction for patients:

Health services want to get the most value from their budget and therefore need to decide whether a new treatment provides good value compared with other treatments. To do this they consider the costs of treating patients and how patients' health will improve, from feeling better and/or living longer, compared with the treatments already in use. The drug manufacturer provides this information, often presented using a health economic model.

In completing your input to the NICE appraisal process for the medicine, you may wish to reflect on:

- The extent to which you agree/disagree with the value arguments presented below (e.g., whether you feel these are the relevant health outcomes, addressing the unmet needs and issues faced by patients; were any improvements that would be important to you missed out, not tested or not proven?)
- If you feel the benefits or side effects of the medicine, including how and when it is given or taken, would have positive or negative financial implications for patients or their families (e.g., travel costs, time-off work)?
- How the condition, taking the new treatment compared with current treatments affects your quality of life.

The economic model developed for resmetirom follows individual patients with MASH over time. It reflects that liver scarring (fibrosis) can improve or worsen, that some patients may relapse, and that others may progress to cirrhosis, liver cancer, or eventually need a transplant. The model also includes other health problems often linked with MASH, such as heart disease and diabetes, which add to the overall health burden and NHS costs.

Resmetirom is modelled to delay or prevent worsening of liver disease by improving inflammation and scarring. Clinical trial results over the first year provide the main data, and where long-term evidence is not yet available, cautious assumptions are used to project outcomes into the future. This allows the model to estimate how treatment might extend life and reduce the risk of serious complications.

In terms of QoL, resmetirom is expected to improve daily health by reducing active liver disease, while complications such as cirrhosis or stroke lower QoL. Standard measures (EQ-5D estimated

from SF-36) were used to capture these changes. However, these tools may not fully capture aspects that are important to patients, such as fatigue, emotional wellbeing, or anxiety about disease progression. This means the benefits of treatment could be underestimated.

On costs, resmetirom adds the price of the medicine and routine monitoring, but these are balanced against potential savings from avoiding expensive care such as hospital admissions, advanced cirrhosis treatment, liver cancer therapy, or a liver transplant. Because resmetirom is a once-daily tablet taken at home, there are no extra costs for infusion clinics or travel, and this is more convenient for patients and carers. The medicine may also improve cholesterol and blood pressure, which could help reduce the risk of heart attacks or strokes and the costs linked with these.

There are some uncertainties, mainly around how long the benefits of treatment last and the long-term course of the disease beyond the first year of trial data. These uncertainties were explored by testing different scenarios, such as shorter treatment duration or higher relapse rates, to make sure the results are robust. The model is anchored in clinical trial evidence and cross-checked against published research.

Not all benefits are fully captured in the modelling. For example, patients may experience less fatigue, improved day-to-day functioning, reduced anxiety, and greater confidence about avoiding end-stage liver disease or the need for transplant. These improvements can also reduce the burden on families and carers, even if they are not fully reflected in the numbers used for cost effectiveness.

3j) Innovation

NICE considers how innovative a new treatment is when making its recommendations. If the company considers the new treatment to be innovative please explain how it represents a 'step change' in treatment and/ or effectiveness compared with current treatments. Are there any QALY benefits that have not been captured in the economic model that also need to be considered (see section 3f)

Resmetirom represents a major step change in the treatment of MASH with liver fibrosis because it is the first licensed medicine for this condition. Until now, patients have only had access to lifestyle advice such as diet and exercise, which are difficult to maintain and often not enough to stop the disease from progressing. Having a targeted, effective medicine available is therefore a breakthrough for patients, caregivers, and the NHS.

Resmetirom works in a new way, by selectively activating thyroid hormone receptors in the liver. This reduces fat, inflammation, and scarring, directly addressing the underlying disease process rather than only managing associated conditions. Clinical trial results have shown meaningful improvements in liver health (19), which could prevent progression to cirrhosis, end-stage liver disease, and the need for a transplant.

The once-daily oral tablet also represents an innovation in ease of use. It avoids the burden of hospital-based treatments, supporting patient independence and reducing demands on NHS services.

Some benefits of resmetirom may not be fully captured in the economic model, including in the quality-adjusted life year (QALY) calculations. These include improvements in fatigue, emotional wellbeing, reduced anxiety about disease progression, and less disruption for families and carers.

By helping patients stay healthier for longer, resmetirom may also support people to remain active in work and community life.

3k) Equalities

Are there any potential equality issues that should be taken into account when considering this condition and this treatment? Please explain if you think any groups of people with this condition are particularly disadvantaged.

Equality legislation includes people of a particular age, disability, gender reassignment, marriage and civil partnership, pregnancy and maternity, race, religion or belief, sex, and sexual orientation or people with any other shared characteristics

More information on how NICE deals with equalities issues can be found in the NICE equality scheme
Find more general information about the Equality Act and equalities issues [here](#)

MASH with liver fibrosis affects a wide range of people, but certain groups may face particular disadvantages. The condition is closely linked with obesity, diabetes, and other metabolic conditions, which are more common in some ethnic minority groups and in people from lower socioeconomic backgrounds. These groups may therefore be at higher risk of developing MASH and its complications.

Women with a history of gestational diabetes or polycystic ovary syndrome (PCOS) may also be more likely to develop MASH. In addition, people living with disabilities or long-term conditions may find it harder to follow lifestyle-based management such as strict diet and exercise programmes, leaving them with few effective options.

Access to care may also be unequal. Patients in deprived areas or from minority ethnic backgrounds may be less likely to receive early diagnosis or specialist referral, meaning they are diagnosed later when the disease is more advanced. There is evidence that the rates of fatty liver-related death (not involving alcohol) are highest in English communities with high deprivation levels (22).

By providing the first targeted medicine for MASH with liver fibrosis, resmetirom has the potential to reduce these inequalities. It offers a treatment option to people who previously had none, including those for whom lifestyle change alone is not practical or effective. A once-daily oral tablet is simple to take and could help improve access and adherence across diverse patient groups.

SECTION 4: Further information, glossary and references

4a) Further information

Feedback suggests that patients would appreciate links to other information sources and tools that can help them easily locate relevant background information and facilitate their effective contribution to the NICE assessment process. Therefore, please provide links to any relevant online information that would be useful, for example, published clinical trial data, factual web content, educational materials etc.
Where possible, please provide open access materials or provide copies that patients can access.

About the medicine (plain facts, safety, interactions)

- **U.S. FDA Prescribing Information for resmetirom** – official label with indications, dosing, side effects, interactions, and patient counselling. [FDA Access Data](#)
- **European Medicines Agency (EMA) page for resmetirom (EU)** – European public assessment resources, including the European Public Assessment Report (EPAR) and regulatory updates. [European Medicines Agency \(EMA\)](#)
- **EMA news (June 20, 2025)** – summary that EU regulators recommended a conditional marketing authorisation for resmetirom. [European Medicines Agency \(EMA\)](#)

Key clinical evidence (what the trials show)

- **MAESTRO-NASH phase 3 publication (NEJM)** – biopsy-confirmed NASH with fibrosis; main 52-week results. (Abstract open access via PubMed.) [PubMed](#)
- **MAESTRO-NASH trial record (NCT03900429)** – full registry entry. [ClinicalTrials](#)
- **MAESTRO-NAFLD-1 safety study (NCT04197479)** – broader NAFLD/MASH population; safety and biomarker data. [ClinicalTrials](#)
- **MAESTRO-NASH OUTCOMES (NCT05500222)** – ongoing outcomes study tracking progression to cirrhosis, transplant, or death. [ClinicalTrials+1](#)

Understanding MASLD/MASH (condition background)

- **British Liver Trust** – MASLD/MASH overview – symptoms, risks, tests, and day-to-day guidance (UK-focused, plain language). [British Liver Trust](#)
- **EASL–EASD–EASO Clinical Practice Guidelines (2024)** – current, open-access European guidance and the updated MASLD/MASH terminology. [journal-of-hepatology.eu](#)

Tests and monitoring (non-invasive alternatives to biopsy)

- **FibroScan** (transient elastography) – British Liver Trust – what the test is and what results mean. [British Liver Trust](#)
- **NICE Diagnostics Guidance DG48** – FibroScan – when and where FibroScan can be used in the NHS. [NICE](#)

Further information on NICE and the role of patients:

- Public Involvement at NICE [Public involvement | NICE and the public | NICE Communities | About | NICE](#)
- NICE's guides and templates for patient involvement in HTAs [Guides to developing our guidance | Help us develop guidance | Support for voluntary and community sector \(VCS\) organisations | Public involvement | NICE and the public | NICE Communities | About | NICE](#)
- EUPATI guidance on patient involvement in NICE: <https://www.eupati.eu/guidance-patient-involvement/>
- EFPIA – Working together with patient groups: <https://www.efpia.eu/media/288492/working-together-with-patient-groups-23102017.pdf>
- National Health Council Value Initiative. <https://nationalhealthcouncil.org/issue/value/>
- INAHTA: <http://www.inahta.org/>
- European Observatory on Health Systems and Policies. Health technology assessment - an introduction to objectives, role of evidence, and structure in Europe: <http://www.inahta.org/wp->

4b) Glossary of terms

- **MASH (Metabolic dysfunction-associated steatohepatitis):** A serious type of fatty liver disease where fat builds up in the liver and causes inflammation and damage.
- **Fibrosis:** Scarring in the liver caused by long-term inflammation. It can range from mild (early stage) to severe (advanced stage).
- **Cirrhosis:** Severe scarring of the liver that makes it hard for the liver to work properly. Cirrhosis can lead to liver failure or liver cancer.
- **End-stage liver disease:** The most advanced stage of liver disease, where the liver can no longer function normally and a transplant may be needed.
- **Liver transplant:** An operation where a damaged liver is replaced with a healthy one from a donor.
- **Placebo:** A dummy treatment with no active medicine, used in clinical trials to compare against the real treatment.
- **Adverse event (side effect):** An unwanted effect that happens while taking a medicine. These can be mild, moderate, or serious.
- **QALY (Quality-Adjusted Life Year):** A way of measuring the benefit of a treatment by looking at both how long people live and how good their quality of life is.
- **Standard of Care (SoC):** The usual treatment currently offered to patients, which for MASH is mainly lifestyle advice such as diet and exercise.
- **NICE (National Institute for Health and Care Excellence):** The organisation that decides which treatments should be available on the NHS in England.

4c) References

Please provide a list of all references in the Vancouver style, numbered and ordered strictly in accordance with their numbering in the text:

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NATIONAL INSTITUTE FOR HEALTH AND CARE EXCELLENCE

Single technology appraisal

Resmetirom for treating moderate to advanced liver fibrosis (without cirrhosis) caused by metabolic dysfunction-associated steatohepatitis [ID6529]

Clarification questions

October 2025

File name	Version	Contains confidential information	Date
		Yes/no	

Clarification questions: Resmetirom for treating moderate to advanced liver fibrosis (without cirrhosis) (MASLD) ID6529

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Section A: Clarification on effectiveness data

Resmetirom therapy

A1. The eligibility criteria for MAESTRO-NASH include a criterion of ≥ 3 metabolic risk factors, and biopsy-confirmed MASH. This is more limited than the anticipated indication.

- a) Please provide evidence for your claim that this population is representative of the wider population of patients with MASH and moderate to advanced (F2-F3) liver fibrosis.
- b) Please explain whether resmetirom could be assumed to be equally effective in patients with one or two metabolic risk factors (in addition to MASH, F2-F3), compared to the trial population.
- c) Please comment on whether you think resmetirom could be offered to patients with fewer than 3 metabolic risk factors.
- d) Please comment on whether biopsy should be required before administering resmetirom, and if so, the practical implications given high cost and limited availability of biopsy in the NHS.

Company Response: To the Evidence Assessment Group's (EAG's) characterisation of the MAESTRO-NASH eligibility and screening criteria in question A1, it is important to add that patient selection also involved a pre-screening Controlled Attenuation Parameter (CAP) from Vibration Controlled Transient Elastography (VCTE) performed on patients' livers (or an equivalent biopsy performed within 6 months of randomisation). As summarised in Table 8 of the company submission (CS), the cardiometabolic risk factor (CMRF) count was considered together with target VCTE thresholds, or an accepted historical biopsy confirming MASH (in lieu of these tests). In MAESTRO-NASH, the question of how many CMRFs to count chiefly had relevance to the positive likelihood ratio (+LR) of the VCTE, i.e., if fewer CMRFs were accepted as a screening criterion, more patients would move forward to VCTE/CAP measurement, but their admission to

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study would still require assessed CAP and liver stiffness measurements (LSMs) above pre-defined thresholds in line with the study inclusion criteria.

At the time of the initiation of MAESTRO-NASH, the utilisation of non-invasive tests (NITs) to identify patients with metabolic dysfunction-associated steatohepatitis (MASH) was not as well specified as today. Trial designers were still working to the old non-alcoholic fatty liver disease/non-alcoholic steatohepatitis (NAFLD/NASH) definition (i.e., steatosis in the absence of any other cause) (1). However, in anticipation of future developments, Madrigal built a requirement for the presence of CMRFs to define the target disease entity into the MAESTRO-NASH selection criteria, which provides a basis for which to evaluate patients with NITs on the NHS who may be at risk of having MASH fibrosis stages F2 to F3.

Madrigal's proposal for patient selection within MAESTRO-NASH aligns with current international definitions of metabolic dysfunction-associated steatotic liver disease (MASLD)/MASH, supported by the American Association for the Study of Liver Diseases (AASLD), the British Society of Gastroenterology (BSG), and the British Association for the Study of the Liver (BASL), and adopted into routine practice. Since these guidelines all stipulate screening involving both presence of CMRFs (typically ≥ 1 as a threshold), as well as pre-defined cutoffs for NIT assessments (typically both FIB-4 blood tests as well as VCTE values), we expect that resmetirom can suitably be offered to eligible patient populations as defined by the Summary of Product Characteristics (SmPC) and consensus guidelines. This would, therefore, include patients who may have fewer than three risk factors as this is not an indicated requirement in the anticipated product label but rather will be defined based on fibrosis stages F2 and F3. As discussed in the CS and later in response to other clarification questions, we expect diagnosis of MASH with fibrosis stages F2 to F3 within the NHS to be defined by NITs.

The diagnosis of MASLD (CS section 1.3.1.8), requires evidence of hepatic steatosis ($\geq 5\%$ liver fat accumulation on imaging or histology) together with at least one CMRF, such as increased body mass index (BMI) or waist circumference, impaired glucose tolerance or type 2 diabetes mellitus (T2DM), elevated blood pressure or antihypertensive drug treatment, or dyslipidaemia (defined by elevated triglycerides,

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low high-density lipoprotein (HDL) cholesterol or treatment with lipid lowering medication) and the absence of other discernible causes such as excessive alcohol consumption (2,3). The liver-targeting mechanism of action of resmetirom is not dependent on number and type (or combination thereof) of CMRFs, which are prominent in MASH patients with fibrosis stages F2 to F3. In line with guidelines and our anticipated label, we believe that in the absence of robust phase III trial data in patients with fewer than three CMRFs, resmetirom could be assumed to be equally effective in combination with diet and exercise versus having no active pharmacotherapy. These international guidelines (further discussed in CQ A18) recommend resmetirom for use in MASH patients with fibrosis stages F2 to F3 based on NITs and do not distinguish based on number of CMRFs.

Biopsy is not expected to be required before administering resmetirom, which is in line with current recommended and anticipated MASH diagnosis guidelines. The utility of NITs has improved substantially in recent years and NITs are now under consideration as surrogate endpoints to replace biopsy in future regulatory drug trials for MASH (4). NITs already underpin published and forthcoming national guidelines around the identification of MASH and staging of liver fibrosis (5,6).

A2. Page 49 (CS) states that “throughout the trial participants received nutrition and exercise counselling according to current recommendations”. Please provide details on how this counselling was provided.

Company Response: Lifestyle counselling, which includes nutrition and exercise recommendations, was given by the Investigator at the beginning of each patient’s participation and was maintained throughout the study. Guidance was provided in Appendix 4 of the protocol (see below). The counselling focused on making changes and improvement in lifestyle habits since NASH progression can be controlled by changing the type and amount of foods eaten as well as incorporating regular moderate exercise as part of the routine.

The Investigator and research staff continue to reinforce with the patient at each visit the changes in nutrition and exercise habits that should be made. When possible, every effort should be made to ensure that the counselling approach taken with each patient is consistent from visit-to-visit and extreme changes to either nutrition or

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exercise should be avoided once the patient is following them as a part of his/her daily lifestyle.

An assessment of lifestyle compliance will occur at each visit by asking the patient questions to confirm if they have remained compliant to the lifestyle recommendations. A yes/no response will be recorded in the electronic case report form (eCRF).

In addition, randomised patients should avoid alcohol as much as possible. However, if alcohol is consumed, it should not go beyond the significant alcohol consumption, as defined in Exclusion Criterion #1.

Appendix 4 of the MAESTRO-NASH protocol – How to Manage NASH through Lifestyle Changes

NASH progression can be controlled through improvement in lifestyle habits: Lifestyle modification involves changing the foods you eat and the amount, as well as intensity and frequency of exercise.

Here are some tips to support you in managing your weight and helping your liver:

DIET and NUTRITION

- Cook your own meals, avoid processed foods
- Eat slowly, focus on what you are eating, let your brain understand that your stomach is full (it takes time)
- Control your portions: Use smaller plates and glasses
- Use oils rich in unsaturated fats (olive oil, flaxseed oil)
- Eat lots of vegetables and fruits
- Try not to eat the following foods: bread, tortillas, pasta, pizza, rice, potatoes
- Limit alcohol consumption
- Snack healthy: choose fruits, nuts
- Read food labels to know what you are eating: main ingredients come first (if butter or oil comes first then the product has a high fat content, same for sugar content if it comes at the top of the list)

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- Drink plenty of water: keep hydrated; you can add lemon, mint or cucumber if you don't like plain water, drink tea. Staying hydrated reduces the feeling of hunger
- Avoid drinks with high sugar and fructose (sodas)
- Choose skim dairy products
- Eat meals at regular times, do not skip a meal

EXERCISE and PHYSICAL ACTIVITY

- Exercise at your pace and intensity
- Exercise should include walking at a brisk pace, biking, rowing, jogging or spending time on an elliptical machine for about 30 minutes, 4-5x per week. Ideally, you should be sweating by the time you are done, but not short of breath at any time in the workout
- Work out with a friend or group: you may enjoy it more if it becomes a social activity
- Build it into your day: Find ways to include exercise in your daily routine, for example taking stairs instead of elevators
- Try something new, to add fun in your exercise routine
- Low impact activity like walking or gardening is still exercise

A3. Do you expect resmetirom and counselling to be more effective in combination than in isolation? In other words, do you expect an interaction in relation to improvement in fibrosis or other outcomes?

Company Response: As per the European guidance, lifestyle counselling (diet + exercise) is part of standard care and should accompany any MASH-targeted drug (3). Trials that omit lifestyle counselling would withhold a strongly recommended intervention, so the resmetirom MAESTRO-NASH study has an appropriate design. Our anticipated label is not in isolation but as noted in CS and the SmPC provided, is expected to be indicated in conjunction with diet and exercise. The MAESTRO-NASH study did not evaluate resmetirom without underlying SoC including this, and

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we cannot comment on the effectiveness of resmetirom in absence of this as it is not in line with our study or anticipated label.

EASL–EASD–EASO make strong, level-1/2 recommendations to deliver dietary/behavioural weight-loss therapy and to prescribe physical activity to all adults with MASLD/MASH (≥ 150 min/week moderate or 75 min/week vigorous), aiming for $> 5\%$ weight loss for steatosis, 7–10% for inflammation, and $> 10\%$ for fibrosis (3). These are presented as core care, not optional add-ons for patients with MASLD/MASH underscoring that counselling is a standard component to be delivered alongside other treatments. Given this, a drug-only arm would be ethically and scientifically problematic. The fair, guideline-concordant comparison is resmetirom + counselling vs. counselling alone.

For non-cirrhotic MASH with significant fibrosis (fibrosis stages F2 to F3), resmetirom is recommended based on phase III histological efficacy on steatohepatitis and fibrosis, with acceptable safety. This recommendation sits in addition to (not instead of) lifestyle therapy in the same guidance set. The guideline acknowledges that while exercise and diet improve steatosis and inflammation, evidence for histological fibrosis effects from lifestyle alone is less robust; thus a positive interaction is clinically plausible but remains untested in a robust phase III setting.

A4. GLP-1 receptor antagonists were used 13.1-16.8% of patients per trial arm (Table 10).

- a) Does this refer to previous or current use of GLP-1 RAs?
- b) How does this proportion relate to current NHS practice?
- c) Would patients who are using GLP-1 RAs be eligible for resmetirom?

a) Table 10 in the CS noted that 13.1-16.8% of patients per trial arm were receiving GLP-1 RAs – this referred to current use. The group using GLP-1 RAs at baseline had already been screened to ensure their GLP-1 medication complied with exclusion/inclusion criteria. As noted in CS section 2.3.1.3, the MAESTRO-NASH design stipulated that patients must have had a stable dose of GLP-1 RA for 24 weeks prior to biopsy, and that GLP-1 RA therapy could not be initiated or up-titrated

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during the first 52 weeks of the study. Patients receiving GLP-1 who were not dose-stabilised for 24 weeks prior to study were excluded.

b) The observed proportions are comparable to current practice in the UK. Access to GLP-1 therapies among people living with diabetes is growing but in the most recent National Diabetes Audit covering 2023-2024, 9.02% of people with T2DM in England were on a GLP-1 RA (7). A much smaller proportion of people with obesity have access to semaglutide or tirzepatide in the absence of multiple complications of obesity (MASLD is not one of these).

c) Patients on GLP-1 RAs included in MAESTRO-NASH met the inclusion criterion of histological evidence at baseline of MASH and fibrosis. The majority of people on GLP-1 are not on a dose known to impact MASH and fibrosis. Where NHS patients have a diagnosis of MASH with F2 or F3 fibrosis stage, they should be eligible for resmetirom, a liver-targeted therapy, to treat their liver fibrosis on the NHS irrespective of whether they are indicated for a GLP-1 RA to treat an underlying comorbid condition as shown in the MAESTRO-NASH design and study results.

MAESTRO-NASH trial data

A5. Priority question: Section 2.6 of the company submission (CS) currently reports results for the mITT-LB-W52 population but does not include results for the modelled population (i.e., the PLB-W52 population excluding F1 and F1/B patients). Please provide all results presented in Section 2.6 for the PLB-W52 population, excluding F1 and F1/B patients.

Company Response: We can confirm that the requested results for the PLB-W52 population (excluding F1 and F1/B patients) have been provided in Appendix A-A. These results tables correspond directly to those in Section 2.6 of the CS but are restricted to the PLB-W52 population which we used to inform our microsimulation model (MSM).

We would also like to take this opportunity to provide the EAG with some further explanation about the data sources and methods used to derive transition

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probabilities for NASH resolution and fibrosis changes in the model using this PLB-W52 population, as some detail was lacking in the original CS:

[REDACTED]

- 2- Our model's transition probabilities for **NASH resolution** were estimated using the consensus (ADCNF) results, which reflected adjudicated pathologist assessments after alignment of independent reads. This dataset provides a single, unambiguous determination of NASH resolution and therefore represents the most reliable estimate for modelling purposes.
- 3- Probabilities of **fibrosis progression or improvement** had to be derived by directly comparing each patient's fibrosis stage at Week 52 with their baseline fibrosis stage. This calculation differed slightly from the MAESTRO-NASH trial's definition of "fibrosis improvement" (the trial's assessment was in fact a composite measure defined as "≥ 1-stage improvement without worsening of NAFLD Activity Score (NAS)"). A new calculation was necessary for our model since we required explicit categorisation of directional fibrosis shifts (improvement, no change, or worsening) to populate transition matrices.
- 4- Since individual fibrosis transition values at Week 52 could still record residual pathologist disagreements even in the PLB-W52 dataset after the remedial "consensus" process ("consensus" was done to achieve agreement on a composite measure rather than each of its sub-components - see answer to A10 for further details), we implemented a statistical adjustment in line with

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the statistical analysis plan (SAP) to derive directional fibrosis transitions for the microsimulation. Further details are available on request and can also be found in the annotations of the R code.

A6. Priority question: The NICE scope includes progression to cirrhosis and other hepatic events, but these do not appear to have been reported in Section 2 of the submission. Please supply outcome data from MAESTRO-NASH for all hepatic outcomes in the scope (i.e. progression to cirrhosis, both compensated and decompensated; all hepatic decompensation events, including development of ascites, hepatic encephalopathy, variceal bleeding; liver transplant; HCC; mortality and overall survival). Please supply all relevant data, even if numbers are small or zero.

Company Response: The MAESTRO-NASH study (NCT03900429) continues under blinded follow-up to assess long-term clinical outcomes, including progression to cirrhosis, hepatic decompensation, and mortality. Study publications may report these outcomes only at pre-specified times, at pre-agreed levels of detail in terms of study arm and subpopulation, and when sharing data with external agencies such as NICE or their overseas equivalents, Madrigal must observe strict conditions regardless of local confidentiality agreements or public redaction. Counts of cirrhosis, hepatic decompensation outcomes, liver transplant, or death cannot be disclosed externally outside pre-specified and pre-agreed timepoints as it risks exposure of individual patient randomisation status; the regulator could mandate termination of the study if this information were shared with NICE, even in confidence.

A7. Were metabolic and cardiovascular outcome data collected in the trial?

- a) If so, please supply this data, even if numbers are small or zero. Specifically, please supply data for: BMI, other obesity measures, blood pressure, MI, stroke, TIA, and mortality due to CVD events.
- b) If they were not collected, please explain why.

Company Response: Patients in MAESTRO-NASH were pre-screened on the basis of CMRFs as previously described in A1. CVD events and other cardiometabolic statistics are presented as counts or mean change from baseline at Week 52 for the

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full mITT (n = 966) population (Table 1, Table 2). They cannot be separated by study arm due to the rarity of events and blinding obligations.

Table 1. Cardiometabolic measurements in MAESTRO-NASH - change from baseline to Week 52 (mITT-W52 population, n = 966)

Parameter	n	n_missing	Mean	SD	Median	Min
Weight (kg)	966	0	78.5	15.5	75.0	55.0
Weight (mm)	966	0	78.5	15.5	75.0	55.0
Weight (mm)	966	0	78.5	15.5	75.0	55.0
Weight (mm)	966	0	78.5	15.5	75.0	55.0
Weight (mm)	966	0	78.5	15.5	75.0	55.0
Weight (mm)	966	0	78.5	15.5	75.0	55.0
Weight (mm)	966	0	78.5	15.5	75.0	55.0
Weight (mm)	966	0	78.5	15.5	75.0	55.0
Weight (mm)	966	0	78.5	15.5	75.0	55.0
Weight (mm)	966	0	78.5	15.5	75.0	55.0

Abbreviations: cm, centimetres; kg, kilograms; mm, millimetres.

Table 2. CV events captured at Week 52 in MAESTRO-NASH (mITT-W52 population, n = 966)

Event	n	n_missing	Events	%
Cardiovascular death	966	0	1	0.1
Non-fatal CV death	966	0	1	0.1
Fatal CV death	966	0	1	0.1
CV death	966	0	1	0.1

Abbreviations: CV, cardiovascular.

A8. Please provide data on rates of pioglitazone and Vitamin E use in the MAESTRO-NASH trial, both at baseline and subsequent uptake.

Company Response: We would like to reiterate, per our prior Scoping and Decision Problem consultation responses as well as CS Section 1.1 (Table 1 and text on page 20), these medications are neither well-established nor routinely recommended for MASH treatment in the NHS setting. They were permitted within MAESTRO-NASH as part of the background standard of care (SoC) to which resmetirom would be added and were not evaluated as comparators in their own right.

As cited in CS Section 1.3.1 (page 35), a recently published analysis of Clinical Practice Research Datalink (CPRD) data (8) found that only around 3%-5% of MASH

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patients had been exposed to these agents. The scarcity of use seen in clinical practice [REDACTED]

[REDACTED] summarised in Table 3 for our model population (**PLB-W52**).

Table 3. Usage of pioglitazone and vitamin E at baseline and post-baseline in resmetirom model population (MAESTRO-NASH PLB-W52 population)

Parameter	n	%
Pioglitazone at Baseline	[REDACTED]	[REDACTED]
Pioglitazone post Baseline	[REDACTED]	[REDACTED]
Vitamin E at Baseline	[REDACTED]	[REDACTED]
Vitamin E post Baseline	[REDACTED]	[REDACTED]

A9. In the decision problem section, it is stated that subgroup data by fibrosis stage will not be presented. The EAG notes that the request is for subgroup analysis by fibrosis stage at randomisation only, so potential unblinding should not be a concern. We note, however, that Appendix C does report some outcomes by fibrosis stage at baseline. Please therefore:

- Supply all trial outcomes categorised by fibrosis stage at randomisation.
- Clarify whether the analyses in Appendix C are subgroup analyses by fibrosis stage at randomisation

Company Response: As stated in the decision problem section of the CS, “the economic model does not estimate cost-effectiveness in subpopulations by fibrosis stage. This is because the study remains protocol-blinded through Month 54, and to preserve the integrity of the confirmatory clinical outcomes analyses, detailed arm-level data on fibrosis stage progression cannot be disclosed.”

The MAESTRO-NASH study (NCT03900429) continues under blinded follow-up to assess long-term clinical outcomes, including progression to cirrhosis, hepatic decompensation, and mortality. Releasing detailed trial outcomes disaggregated by fibrosis stage at randomisation—even in summary form—would risk unblinding the protocol-blinded 54-month phase by enabling reverse calculation of the number of F2 and F3 patients progressing to compensated cirrhosis (F4). Such disclosure could compromise the pre-specified confirmatory analyses under the FDA Subpart H

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and European Medicines Agency (EMA) conditional approval frameworks, which depend on the blinded conduct of the ongoing outcome period.

Therefore, in line with regulatory and trial governance requirements, no further arm-level or subgroup-level outcomes by baseline fibrosis stage can be provided at this time. All available clinical efficacy results already capture the overall F2–F3 population defined in the decision problem, which remains consistent with the licensed indication for resmetirom.

Appendix C of the CS presents the pre-specified and post-hoc subgroup analyses from Harrison et al. 2024 (9) stratification by baseline fibrosis stage (F1B, F2, F3) as per randomisation strata; however, the analyses are expressed as relative differences versus placebo within the **combined** mITT-LB-W52 population and the paired-biopsy (PLB-W52) subset, rather than absolute cell counts.

The analyses in Appendix C of the CS therefore:

- stratify evaluations by fibrosis stage at randomisation, consistent with the pre-specified stratification factors in the SAP;
- but do not constitute independent arm-level subgroup analyses (i.e., they do not disclose per-arm data by baseline fibrosis stage) that could reveal interim unblinded information;
- and are limited to the dual primary endpoints (NASH resolution and fibrosis improvement) for the Week 52 biopsy population.

These results demonstrate that treatment effects were directionally consistent across fibrosis stages, supporting the robustness of overall efficacy, while maintaining the confidentiality of the blinded data.

A10. Could you provide more details to explain how disagreements between clinicians on NASH status and fibrosis stage were handled in the efficacy results?

- a) Please comment on why physicians disagree on NASH status of fibrosis stage and how common disagreement is.
- b) Were all digitised images of biopsies for which there was disagreement reviewed in the consensus read, or a subset?
- c) How were disagreements handled for the data presented in the 'primary' row of Table 13, p. 65?

Company Response: a) In order to assess histological endpoints, the pathologists need to rate multiple characteristics of the biopsy, which introduces subjectivity and variability to the assessment. The items needing assessment and how they are scored are:

- Fibrosis Stage (0,1a,1c,1b, 2,3,4)
- Steatosis Stage (0 = < 5%, 1 = 5-33%, 2 = 34-66%, 3 => 66%)
- Ballooning (0 = none, 1 = rare, 2 = many)
- Lobular Inflammation (0 = none, 1 = < 2 foci, 2 = 2-4, 3 => 4)

Each of these items requires interpretation and a subsequent decision. For example, one pathologist may interpret "many" for ballooning differently from another pathologist. For these reasons, the U.S. Food and Drug Administration (FDA), in its guidance on developing treatments for NASH, has encouraged the use of multiple pathologists and for trials to establish an approach to appropriately integrate their responses (e.g., consensus).

Consensus reads of digitised images of glass slides by the two central pathologists were conducted in cases where the two pathologists scores disagreed as to whether there was a response for either NASH resolution (ballooning 0,1; 2-point NAS reduction and no worsening of fibrosis) OR ≥ 1 stage fibrosis reduction with no worsening of NAS (primary endpoints) OR a 2-stage reduction in fibrosis with no worsening of NAS.

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The study pathologists remained blinded to all clinical data, patient ID, and slide/image identity or time of biopsy. Study personnel remain blinded to patient-level data and detailed group analyses. In total, 387 total assessments took place requiring four Zoom meetings between the pathologists. The consensus meetings were conducted by an unblinded reviewer who showed the pathologists the initial scores on a spreadsheet, and then the pathologists decided on the consensus score for the disagreed component.

b) All slides on which there was disagreement were reviewed. The only time a consensus review was performed was when the two central pathologists disagreed on the determination of NASH resolution, fibrosis improvement or 2-stage reduction in fibrosis based on their primary reading of glass slides.

No review utilising digitised slides were performed, when the two pathologists were already in agreement based on their primary reads.

A total of 139 patients required a consensus review for NASH resolution and 151 patients for fibrosis improvement.

c) Disagreements in assessment in the 'primary' analysis dataset were accounted for using a statistical adjustment method set out in our answer to Question A11 part a. This methodology was summarised in CS part 2.4.1 (page 59) and is also described in the online supplementary appendix to the main Harrison et al. 2024 publication for MAESTRO-NASH (9) (on page 21).

A11. CS Table 13 distinguishes between “primary” and “consensus” assessment of outcomes. Could you please:

- a) Explain what constitutes a “primary” and “consensus” definition and why they are different.
- b) Supply the number of patients in each arm for each outcome where patients had uncertain results requiring a consensus assessment.
- c) Please explain the difference between the “consensus” sensitivity analysis (Table 13) and the “multiple imputation” sensitivity analysis (Table 14)

Company Response: a) The primary review was performed independently by each pathologist reading glass slides through a high-powered microscope. These readings were used to derive the dual primary endpoints and conduct the primary analysis of NASH resolution and fibrosis improvement. Details of the primary analysis are described within the study’s SAP (available in the online supplement to primary study publication Harrison et al. 2024 (10)). The consensus review was done subsequently, to support a post-hoc analysis at the request of the U.S. FDA. For this analysis, when the two pathologists had disagreed on a patient’s outcome, results from the consensus review were used. Otherwise, results from the primary read were used.

The primary analysis does not use any results from the consensus review. Instead, it takes into account when pathologists disagreed by using a scoring system. The scoring assigned the following value to a patient:

- 1 = both pathologists agreed the patient met response criteria;
- 0.5 = only a single pathologist determined response criteria were met;
- 0 = both pathologists agreed the patient did not meet response criteria.

Detailed description of the methods for the primary analysis is described in the study’s SAP.

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b) Numbers of patients requiring a consensus review for each outcome are summarised below:

[REDACTED]

[REDACTED]

c) As previously described, the consensus analysis incorporated the determination of the two central pathologists after meetings to resolve differences in their primary reads. For patients who did not have a Week 52 biopsy, their outcome for NASH resolution and fibrosis improvement was imputed to be “no response”. The analysis using multiple imputation is also a secondary analysis but differs in several ways. Firstly, this analysis does not use the consensus results but does use the primary readings as determined by the two pathologists, employing the SAP-defined approach to combining data from the two pathologists in the event of disagreement.

In addition, this analysis handles missing data quite differently. Missing data are imputed based upon a modelling and simulation approach, which assumes that patients, regardless of treatment, behave like placebo-treated patients once treatment is discontinued. The statistical model simulated the missing outcome for each patient 100 times. This results in 100 different statistical analyses that are then combined to assess statistical significance. Multiple imputation is a common approach for dealing with missing data.

A12. Primary outcomes are reported for a “Liver biopsy mITT” population, who appear to have had a liver biopsy at 52 weeks. However, analyses are described as requiring imputation for missing data. Please clarify:

- a) How observations could be judged to be missing if a liver biopsy had been performed.
- b) If no liver biopsy data at follow-up were available for a subset of patients, why was it necessary to exclude 11 patients without biopsy entirely?
- c) How many observations were missing, for each arm and each outcome
- d) Whether any imputations were based on physician opinion, where this differed between physicians

Company Response: a) & b) Data are reported for the primary analysis population (n = 955, after removal of COVID-impacted biopsies outside the Week 60 window). Eleven patients (3 in placebo arm, 6 in resmetirom 80 mg arm, and 2 in resmetirom 100 mg arm) had a delay in their Week 52 biopsies due to COVID-19-related site closures or related reasons and were removed from the analysis. The resulting Liver Biopsy mITT Population (mITT-LB-W52, n = 955) were a group who continued in the trial until Week 52 and had completed a screening biopsy at baseline. They were the population used to estimate all biopsy-related outcomes – however, this does not mean they all had Week 52 biopsies done. Missing biopsy data were recorded for a number of reasons, for example biopsy refused/not done or biopsy unreadable.

c) The mITT-w52 population (n = 966) is summarised in terms of its biopsy data collection in Table 4. [REDACTED]

Table 4. Summary of biopsy collection in mITT-LB-W52 population (n = 966)

Patient characteristic, n (%)	Resmetirom 80 mg	Resmetirom 100 mg	Placebo	Overall
	(n = 322)	(n = 323)	(n = 321)	(n = 966)
Liver biopsy at Week 52				

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This trial was conducted during the COVID pandemic. We observed signs that discontinuations were more frequent during this period. Furthermore, some patients may have refused a serial biopsy at Week 52, due to their experience with the screening biopsy. Some biopsy samples may also have been inadequate for pathologists to read. These reasons would likely support a MAR assumption.

The main conclusion is all methods for treating missing data resulted in the same interpretation and statistical conclusions.

A14. In the trial a movement from F1B to F2 was not considered a 1-stage worsening (Page 54). Please justify the applicability of this to general clinical practice.

Company Response: Per the study protocol, a change to F2 from F1B was not considered a 1-stage worsening in fibrosis in the context of part 1 from MAESTRO-NASH's **dual primary objective**, which was:

“1. The resolution of NASH associated with an at least 2-point reduction in NAS and without worsening of fibrosis by liver biopsy after 52 weeks of treatment. Resolution includes:

- The total absence of ballooning (score = 0) and absent or mild inflammation (score 0 to 1) (associated with an at least 2-point reduction in NAS).
- No worsening of fibrosis, defined as any progression ≥ 1 stage.”

In the above context, a change from F2 to F1B fibrosis, if observed in combination with histology results consistent with MASH resolution, may reflect minor histological fluctuation rather than a failure to meet the endpoint of NASH resolution.

However, this point is of limited relevance to the decision problem and future NHS clinical practice around resmetirom, as the license does not include F1B patients and as such, we have not included them in our economic analyses. F1B patients are not considered in current MASH treatment guidelines relating to resmetirom, which focus on how to reliably detect the indicated population of non-cirrhotic MASH patients with moderate to advanced liver fibrosis (fibrosis stages F2 and F3).

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A15. Nouredin (2024) [<https://doi.org/10.1016/j.cgh.2024.07.003>] outlines selection criteria that could be used to evaluate patient suitability to receive resmetirom (Figure 1). Please provide details on the proportion of the population meeting these eligibility criteria in the MAESTRO-NASH trial.

Company Response: At present there are no published UK guidelines regarding the management of MASH patients with resmetirom, although a draft consensus document from the BASL Special Interest Group (SIG) in MASLD has set out a recommended NIT framework for the identification of patients who would be eligible for resmetirom (please see section below table).

By mapping baseline NIT data from the MAESTRO-NASH F2/F3 population to the patient suitability criteria outlined in Nouredin et al. 2024 (6), we were able to calculate proportions of the MAESTRO-NASH population for each category as shown in Table 5. An additional category, titled 'no recommendation provided' for trial participants with baseline NITs below the Nouredin et al. 2024 'Treat' thresholds is presented for a more complete picture. All MAESTRO-NASH participants lacked histological evidence of cirrhosis and, therefore, platelet count **and** evidence of portal hypertension have not been included in the analysis.

The proportion of MAESTRO-NASH participants meeting the eligibility criteria ('treat' and 'consider treatment') is approximately [REDACTED]% for VCTE and [REDACTED]% for Enhanced Liver Fibrosis (ELF) test on average across arms (in trials participants with available data). Approximately [REDACTED]% of participants meet the 'treat' eligibility criteria in one of available NITs (VCTE or MRE or ELF). It is worth noting that MAESTRO NASH had an inclusion criterion of a VCTE LSM ≥ 8.5 kPa, with participants with LSM ≥ 8.5 kPa but ≤ 9.9 kPa attributed to the 'no recommendation provided' category in Table 5 and representing approximately [REDACTED]% of the trial population.

The analysis of applying the Nouredin et al. 2024 (6) suitability criteria on the MAESTRO-NASH population [REDACTED]. The patients enrolled in MAESTRO-NASH were an enriched population with a likely history of multiple non-invasive diagnostics. MAESTRO-NASH is a histopathological confirmatory phase III study and not designed as a NIT-driven clinical trial (randomisation and primary endpoints).

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Table 5. Noureddin thresholds and M-NASH baseline NITs (VCTE, ELF, Magnetic Resonance Elastography (MRE)) (n = 966)

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

Abbreviations: ELF, Enhanced Liver Fibrosis; kPa, Kilopascal; MRE, magnetic resonance elastography; NIT, non-invasive test; VCTE, Vibration-Controlled Transient Elastography.

Note: The percentages presented for categories (Treat, Consider, Do Not Treat and No recommendation provided) exclude participants where NIT data was not available (NA, cells shaded grey, % from all participants).

The BASL MASLD SIG recently shared UK consensus recommendations on Pharmacotherapy in MASLD/MASH, which were presented at their Oxford meeting in September 2025 (manuscript in submission) (11). The recommendations were developed from a Delphi process and assumed that drugs would be available for the treatment of MASH and fibrosis using U.S. licensing as a guide. Treatment should be considered where the VCTE LSM $\geq$ 10kPa and there is no clinical evidence of cirrhosis. Similar to the data provided for Noureddin et al. 2024 (6) above, approximately █████% of the MAESTRO-NASH trial population across resmetirom and placebo arms would meet these BASL criteria according to baseline LSM.

The AASLD updated the practice guidance on the clinical assessment and management of NAFLD in 2024 following the FDA approval of resmetirom (12). The update outlines the selection of patients for resmetirom in Figure 1 of the paper.

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There is no recommendation for use in cirrhosis with similar LSM thresholds to other guidance (VCTE > 20 kPa, MRE > 5 kPa). Resmetirom is 'recommended' with a VCTE LSM from 8-15 kPa and 'may be used' with LSM values outside this range or other non-invasive liver disease assessment (NILDA) consistent with F2/3 in individualised decisions by specialists. MAESTRO-NASH participants with LSM ≥ 8.5 kPa but ≤ 9.9 kPa would be attributed to the AASLD 'recommended' category by VCTE criteria. Therefore, 89.7% of MAESTRO-NASH population would achieve the AASLD VCTE eligibility criteria for treatment, being categorised as 'recommended' or 'may be used'.

A16. Please comment on the adequacy of the 12-month follow-up period in the MAESTRO-NASH trial to assess: i) NASH/MASH resolution, ii) improvements in fibrosis stage.

Company Response: The dual histological endpoints captured during a 12-month follow-up period were accepted by regulators as surrogate measures reasonably likely to predict longer-term clinical benefit in phase III MASH programs, and MAESTRO-NASH met both at Week 52. This satisfies the near-term evidentiary standard for efficacy while the longer-term outcomes mature.

The follow-up period was informed by the pharmacodynamic observation of relative liver fat reductions after 16 weeks of resmetirom treatment, which is maintained through week 52. Stine et al. 2021 have observed that relative liver fat reduction of $\geq 30\%$ are predictive of histological improvements at 52 weeks (13).

The MAESTRO-NASH phase III trial was explicitly designed with MASH resolution without worsening of fibrosis at Week 52 as one of its two pre-specified dual primary histological endpoints, with clear, standard definitions (ballooning = 0; inflammation = 0–1; ≥ 2 -point NAS reduction; no fibrosis worsening) read by independent central pathologists. These endpoint definitions and the Week-52 window were prospectively specified in the protocol for the primary analysis population (mITT-LB-W52).

As indicated in CS 2.6.1 and 2.6.2, positive efficacy findings for resmetirom were demonstrated for a large range of endpoints and supported across multiple

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sensitivity analyses. The findings demonstrate that 12 months is sufficient to detect clinically meaningful histological remission of steatohepatitis under blinded, controlled conditions.

Other trials

A17. Please supply all relevant publications, the CSRs and protocols for the Phase II trial and the MAESTRO-NAFLD trial.

Company Response: We have provided the CSR for MAESTRO-NAFLD-1 (**Appendix A-B**) and Phase II (NCT02912260) (**Appendix A-C**) as separate attachments.

The Phase II study (NCT02912260) differs substantially from MAESTRO-NASH. It randomised patients (2:1) to receive 80 mg resmetirom or placebo, whereas MAESTRO-NASH evaluated 80 mg or 100 mg resmetirom versus placebo. The Phase II study was powered to assess a primary efficacy objective of the percent change in hepatic fat fraction by (magnetic resonance imaging-based proton density fat fraction (MRI-PDFF)) from baseline to Week 12. However, in this study, patients were assessed for pharmacokinetics (PK) at week 2 and study drug dose was revised (up to 100 mg, down-titrated to 60 mg, or steady at 80 mg) after week 4 based drug exposure. Of those with assessments at 36 weeks of the Phase II study, [REDACTED] after week 4 adjustment versus [REDACTED] receiving 80 mg, [REDACTED].

Inclusion criteria were similar in the Phase II study to MAESTRO-NASH; therefore, we have supplied the materials requested for the Phase II study. However, we do not believe that the Phase II study is of relevance to this decision problem other than to reinforce the safety and efficacy of resmetirom versus placebo, even at a different dose than that studied in MAESTRO-NASH.

The Phase III MAESTRO-NAFLD-1 trial (NCT04197479) was primarily a safety study involving a significantly broader range of patients than those to whom the decision problem for TA ID6529 (i.e., patients with non-cirrhotic MASH and moderate to advanced liver fibrosis, stages F2 and F3) applies. It was not powered to inform a

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comparison of resmetirom to placebo on the primary endpoints of MAESTRO-NASH in the indicated population. [REDACTED]

The MAESTRO-NAFLD-1 study included patients with **any non-cirrhotic fibrosis stage**, as presented in the inclusion criteria. The core diagnosis for the study was suspected NASH/NAFLD based on NITs or confirmed NASH/NAFLD via biopsy. Inclusion criteria for **patients without a biopsy** were Fibroscan values of kPa ≥ 5.5 and < 8.5 ; CAP ≥ 280 dB.m⁻¹ OR MRE ≥ 2 and < 4.0 ; MRI-PDFF $\geq 8\%$ liver fat consistent with steatosis and fibrosis stage ≥ 1 and < 4 . For **patients with a biopsy within two years documenting NASH/NAFLD with steatosis**, patients with biopsy-confirmed fibrosis stage F0-F3 met the inclusion criteria. As noted in clarification question A15, F2 and F3 patients are broadly accepted as having 10-19.9 kPa scores as measured via Fibroscan and Nouredin et al. 2024 (6) note that only MRE ≥ 3.3 and < 5 is sufficient for treatment with resmetirom, aligning with F2 and F3 stage fibrosis.

We do not believe that MAESTRO-NAFLD-1 has direct relevance to the decision problem in terms of population nor methodology. However, its long-term extension data do provide some potential insight into the duration of resmetirom effect, which might help to address the EAG question raised in B6.

A18. Clinical advice to the EAG suggested that resmetirom might be used without a biopsy to confirm MASH. Consequently, the EAG thinks the MAESTRO-NAFLD trial

may be relevant to this assessment as it includes patients likely to be offered resmetirom. Please therefore supply:

- a) A full summary of the MAESTRO-NAFLD-1 trial.
- b) Tabulations of demographics and patient characteristics for the trial.
- c) Tabulations of results for all outcomes listed in the scope for this assessment that were evaluated in the MAESTRO-NAFLD-1 trial.

Company Response: As stated in Table 2 (Section 1.2 of CS), liver biopsy is not routinely required for diagnosis or monitoring of non-cirrhotic MASH with moderate to advanced liver fibrosis (F2-F3) and we anticipate patients will undergo NITs such as transient elastography (TE) (FibroScan®) to assess liver stiffness, TE used to assess CAP, ultrasound, MRI-PDFF, MRE, shear-wave elastography, and ELF test to assess steatosis or fibrosis. A liver biopsy is not required for clinical management of individuals with MASLD, unless NITs are indeterminant (3). Changes in fibrosis and steatosis can be tracked using imaging-based NITs, which may serve as indicators of therapeutic response. The clinical community (e.g. BASL MASLD Special Interest Group [SIG], Nouredin et al. 2024 (6), European Association for the Study of the Liver (EASL)) has expressed unanimous support for identifying MASH patients with moderate to severe fibrosis (fibrosis stages F2 to F3) using NITs without biopsy, and several publications specify a detailed pathway for assessing the presence of non-cirrhotic MASH with advanced fibrosis (fibrosis stages F2 and F3). An emerging common recommendation is that fibrosis stages F2 and F3 should be assumed with TE measures via Fibroscan of 10-19.9 kPa, as presented in prior clarification question A15.

As stated in our answer to A17, we do not believe that MAESTRO-NAFLD-1 is of direct relevance to this decision problem. The study recruited a broader patient population than the one being considered for the NHS and differs in its clinical methodology and endpoints. The study includes NITs for determining trial eligibility and fibrosis stage, [REDACTED]

[REDACTED] we fully anticipate NITs to be sufficient to diagnose fibrosis

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stages, at thresholds determined by the clinical expert community, and do not expect biopsy to be required for treatment with resmetirom. Therefore, we are happy to provide the CSR for reference but will not be developing a separate information summary as requested by the EAG from MAESTRO-NAFLD-1. We believe all key information requested, if required by EAG, can be readily found in the uploaded CSR sub-document “” in **Appendix A-B**.

Section B: Clarification on cost-effectiveness data

Where questions request or require changes to the model, please clearly indicate these changes in the R model labelling, specifying which question they relate to. In addition, please provide a Word document summarising all modifications made to the economic model.

Company Response: We confirm that all requested changes to the R model have been implemented and clearly labelled in the code. Each modification is marked with identifiable flags placed at the beginning and end of the relevant code sections, specifying the question to which the change relates.

In line with the EAG's instructions, we have also prepared and uploaded a Word document summarising all modifications made to the economic model.

In addition, we have provided a separate user guide describing how to adjust input parameters and execute scenario analyses, including those specified in the CS and additional scenarios requested in the clarification document.

B1. Priority Question: The EAG noted several discrepancies between the input parameter values used in the model and those reported in the company submission (CS). Please clarify which values are appropriate for use in the model. If the model inputs are incorrect, please update the model accordingly and provide updated base case and scenario analyses results.

- a) **The mean value reported in Table 28 of the CS for the joint transition probabilities of MASH resolution and fibrosis worsening in the placebo arm of MAESTRO-NASH is [REDACTED], whereas the corresponding value used in the model is [REDACTED]**
- b) **The mean values reported in Table 29 of the CS for the joint transition probabilities in the T2DM subpopulation do not correspond to those used in the model. Specifically:**
 - **The values reported under the columns for fibrosis improvement (for both MASH resolution “Yes” and “No”) correspond to “stable” fibrosis in the model inputs, rather than “improvement.”**

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- The values reported under the column for fibrosis worsening with MASH resolution correspond to “improvement” in the model inputs, rather than “worsening.”
 - The mean value reported under the column for fibrosis worsening without MASH resolution in the placebo arm is [REDACTED], while the corresponding value used in the model is [REDACTED].
 - Similarly, the mean value reported for the resmetirom 100mg arm in this column is [REDACTED], while the corresponding value used in the model is [REDACTED].
- c) The mean annual transition probability from DCC to liver transplant from year 2 onwards is reported in Table 32 of the CS as 43%, whereas the corresponding value used in the model is 0.8%.
- d) The mean annual transition probability from HCC to liver transplant from year 2 onwards is reported in Table 32 of the CS as 55.7%, whereas the corresponding value used in the model is 1.7%.
- e) Please confirm that the relative risk multiplier for health states F0 to F2 is fixed at a value of 1.0 in the PSA (Table 35), as the input parameters sheet suggests that a lognormal distribution is applied to this fixed parameter.
- f) The mean annual probability of death from DCC is reported as 1.3% in Table 36 of the CS, whereas the corresponding value used in the model is 13%.
- g) The mean utility value for health state F3 without MASH is reported in Table 37 of the CS as 0.870, whereas the corresponding value used in the model is 0.750. Similarly, the mean utility value for health state F3 with MASH is reported as 0.840, whereas the corresponding value used in the model is 0.720.

Company Response: We acknowledge the EAG’s observation and apologise for the inconsistencies noted. We appreciate the opportunity to clarify these points.

- a) The value of [REDACTED] used in the model is correct. Please refer to the updated table below (Table 6) for confirmation and clarity.

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Table 6. (Year 1) Joint transition probabilities (mean (95% CI)); (MAESTRO-NASH, paired-biopsy population; base case) [Updated Table 28 in CS]

	MASH resolution	MASH Resolution: YES		MASH Resolution: NO	
		Fibrosis improvement	Fibrosis worsening	Fibrosis improvement	Fibrosis worsening
Placebo	██████████	██████████	██████████	██████████	██████████
Resmetirom 100 mg	██████████	██████████	██████████	██████████	██████████
Resmetirom 80 mg	██████████	██████████	██████████	██████████	██████████

b) We confirm that the labels of the transition probabilities in the CS were inadvertently swapped and some TPs were delivered in the CS using a wrong sheet in the “Transition probabilities.xlsx” in folder 01_data_raw. However, the parameters applied within the model are accurate and correctly implemented. The corrected figures are presented in the updated Table 7.

Table 7. (Year 1) Joint transition probabilities (mean (95% CI)); (MAESTRO-NASH, T2DM subpopulation) [Updated Table 29 in CS]

	MASH resolution	MASH Resolution: YES		MASH Resolution: NO	
		Fibrosis improvement	Fibrosis worsening	Fibrosis improvement	Fibrosis worsening
Placebo	██████████	██████████	██████████	██████████	██████████
Resmetirom 100 mg	██████████	██████████	██████████	██████████	██████████
Resmetirom 80 mg	██████████	██████████	██████████	██████████	██████████

c) And d) The transition probabilities for DCC → LT (0.8%) and HCC → LT (1.7%) from year 2 onwards were derived from the long-term (Year 5+) values reported in ICER 2023 (Table E.8) (14) to represent a steady-state probability of liver transplantation among patients who remain on the waiting list beyond the first year.

The higher rates observed in the first year (43% and 55.7%) reflect an early surge in transplants among newly listed, eligible patients and are not sustainable over time, as most will have either undergone transplantation, been delisted, or died due to disease progression. Consistent with ICER’s

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approach, and given that the undiscounted life expectancy for NASH-related cirrhosis is approximately 20 years, the 5-year steady-state rates were conservatively applied from year 2 onwards to ensure realistic long-term modelling of transplant dynamics in stable cohorts.

e) Yes, we confirm that relative risk multipliers for health states F0 to F2 are fixed in the sensitivity analyses.

f) We have incorporated the correct value into the model. The updated version of Table 36 from the CS is provided below (Table 8):

Table 8. Liver-related mortality probabilities [updated Table 36 in CS]

Health state transition	Mean annual probability	Low value; High value	Source
F4 to death	0.021	0.0168 – 0.0252	Pearson et al. 2016 (15) - Ascha et al. 2010 (16)
DCC to death	0.130	0.1040 – 0.1560	Pearson et al. 2016 (15)- Ascha et al. 2010 (16)
HCC to death year 1	0.144	0.1152 – 0.1728	Thuluvath et al. 2019 (17)
HCC to death year 2	0.044	0.0352 – 0.0528	Thuluvath et al. 2019 (17)
HCC to death year 3	0.012	0.096 – 0.144	Thuluvath et al. 2019 (17)
HCC to death year 4	0.009	0.072 – 0.108	Thuluvath et al. 2019 (17)
HCC to death year 5+	0.008	0.064 – 0.096	Thuluvath et al. 2019 (17)
LT to death	0.098	0.0784 – 0.118	Lidgren et al. 2007 (18)
PLT to death	0.057	0.0456 – 0.0684	Lidgren et al. 2007 (18)

Abbreviations: CS, company submission; DCC, decompensated cirrhosis; HCC, hepatocellular carcinoma; LT, liver transplantation; PLT, post-liver transplantation.

g) We confirm that the values used in the economic model are correct. The discrepancy arises from a typographical error in Table 37 of CS. The model correctly applies the following mean utility values shown in Table 9.

Table 9. Summary of utility values for CEA – Base-case analysis [updated Table 37 in CS]

State	Utility value: mean (standard error)	95% CI	Reference in submission (section and page number)	Justification
F0 without MASH (NAFL)	0.870	0.705 – 1.000	NG49 – 611 (19)	Applied in prior NICE evaluations We used NASH (F012) - treated data in NG49 for fibrosis state with MASH resolution
F0 + MASH	0.840	0.680 – 1.000	NG49 – 611 (19)	
F1 without MASH	0.870	0.705 – 1.000	NG49 – 611 (19)	
F1 + MASH	0.840	0.680 – 1.000	NG49 – 611 (19)	
F2 without MASH	0.870	0.705 – 1.000	NG49 – 611 (19)	
F2 + MASH	0.840	0.680 – 1.000	NG49 – 611 (19)	
F3 without MASH	0.750 *	0.705 – 1.000	NG49 – 611 (19)	
F3 + MASH	0.720	0.680 – 1.000	NG49 – 611 (19)	
F4 (Cirrhosis)	0.600	0.483 – 0.717	NG49 – 611 (19)	
DCC	0.540	0.435 – 0.645	NG49 – 612 (19)	
HCC	0.540	0.435 – 0.645	NG49 – 612 (19)	
PLT First year	0.800	0.646 – 0.954	NG49 – 612 (19)	
PLT subsequent years	0.850	0.688 – 1.000	NG49 – 612 (19)	

Abbreviations: CI, confidence interval; CS, company submission; DCC, decompensated cirrhosis; F0-F4, fibrosis stages F0-F4; HCC, hepatocellular carcinoma; MASH, metabolic dysfunction-associated steatohepatitis; NAFL, non-alcoholic fatty liver; PLT, post-liver transplantation.

* It was assumed that the **difference between treated and untreated patients in fibrosis stages F0–F2** was representative of the expected treatment effect in **F3 without MASH**. In other words, the **relative treatment effect** observed in earlier disease stages was applied to estimate outcomes for the **F3 non-MASH** subgroup, in the absence of direct evidence for this population.

B2. The cost-effectiveness review identified several previous economic evaluations of resmetirom: Le (2025), Kim (2024), Tice (2023), and Javanbakht (2023). Please provide a concise summary and critique of each of these models, focusing on the following key aspects:

- i) model structure,
- ii) natural history and modelled treatment effect,

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- iii) utility values, and
- iv) stopping rules.

In addition, please provide a comparative commentary that contrasts the results of these evaluations with those generated by the *de novo* model, highlighting potential reasons for any differences in predicted outcomes.

Company Response: We provide below concise summaries and critiques requested for each prior economic evaluation, followed by a short comparative commentary to contrast them with our *de novo* model (Table 10).

Table 10. Summary and critiques requested for each prior economic evaluation

Study (year)	Model structure	Natural history & treatment effect	Utility values	Stopping / discontinuation rules	Key results (context)	Critique / comments	Comparison with company de novo model
Le (2025) – <i>JAMA Netw Open</i> (20)	Agent-based microsimulation with 14 fibrosis/clinical states (F0–F4 ± MASH, DC, HCC, LT, death); lifetime horizon.	Natural history from meta-analysis of paired biopsies; treatment effects from MAESTRO-NASH (RRs for fibrosis improvement / MASH resolution). No cardiometabolic module.	Early stages mapped from SF-36 → HUI; advanced stages from hepatitis C sources; age/sex adjustments.	Stop at F4/DC/HCC; restart if F4 → F3; 21.3 % annual discontinuation; no treatment disutility.	+0.26 QALYs; +\$36 k; ICER ≈ \$140 k/QALY.	Heterogeneous natural-history inputs and no CV effects; results sensitive to utilities. For more detailed, please see our explanations in section 3.3.2 CS	CS model uses MAESTRO-NASH patient-level transitions with separate resolution and fibrosis effects, and an explicit CV risk module → more biologically realistic captures total QALY gain.
Kim (2024) – <i>ISPOR Europe poster presentation</i> (21)	Cohort state-transition Markov model for adults (F2–F3) over 50 years; 1-year cycles; US private-payer perspective.	Non-cirrhotic transition probabilities from MAESTRO-NASH placebo arm + literature; resmetirom effects on progression,	Non-cirrhotic utilities from MAESTRO-NASH; advanced states from published sources	Discontinuation and AE rates from MAESTRO-NASH; permanent stop at cirrhosis.	11.91 vs 10.02 QALYs; +\$213,948; ICER \$113,391/QALY; cost-effective at ≤\$110 k/QALY.	Well-calibrated US CEA using phase III data; excluded CV effects and assumed US costs only.	CS model builds on this foundation but adds dual-endpoint microsimulation, UK NHS costs, empiric relapse logic, and label-aligned on/off rules , capturing the dynamic

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		regression and NASH resolution from MAESTRO-NASH. Excluded lipid benefits.					interaction of fibrosis improvement and MASH resolution more precisely.
Tice (2023) – ICER Final Evidence Report (14)	Cohort Markov model (no / prior CV event sub-models); fibrosis ladder F0–F4 → DC, HCC, LT, death; annual cycles; lifetime horizon.	Natural history from NAFLD/NASH meta-analyses; treatment effects from top-line MAESTRO-NASH applied uniformly across stages; includes CV event module (Framingham).	Disease-stage utilities from GAIN EQ-5D-5L; AE disutilities applied.	Stop at F4; base case AE + all-cause discontinuation ≈ 16 %/yr	Resmetirom cost-saving or ≤ \$30 k/QALY at placeholder prices.	Mature framework with CV module; relied on early efficacy and placeholder price.	Company model refines with full phase III patient-level data and UK resource costs, ensuring relevance for NICE while retaining CV effects.
Javanbakht (2023) – <i>Pharmacoecon Open</i> (22)	Cohort Markov with parallel CV sub-model (no / prior CV event); lifetime horizon.	Transition rates from phase II trial mapped to fibrosis states; long-term extrapolation to 30 yrs.	Early NAFLD/NASH utilities; advanced stages from hepatitis C studies; sensitivity noted.	Fixed treatment duration (95 % adherence); discontinuation not parameterised.	\$53,929 /QALY (2021 USD); price threshold ≈ \$50–94/day.	First formal CEA; transparent thresholds; limited by phase II data.	De novo model uses phase III biopsy-based transitions, UK utility sources, and explicit relapse / re-initiation rules.

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Company de novo model (2025)	Patient-level microsimulation calibrated to MAESTRO-NASH paired-biopsy transitions; lifetime horizon.	Dual-endpoint (MASH resolution and $\geq$ 1-stage fibrosis improvement) includes CV and T2DM event risk modifiers.	Contemporary HRQoL data for MASLD/MASH and advanced states; mutually exclusive utility gains for resolution vs fibrosis improvement.	Permanent stop at F4/DCC/HCC; temporary stop if < F2 with re-start at F2–F3; dose-specific discontinuation from MAESTRO-NASH.	Incremental QALY gain > literature; ICER well below NICE thresholds.	Strengths: trial-anchored, UK inputs, explicit relapse logic; Limitations: long-term effect extrapolated beyond 52 wks.	Integrates regulatory-accepted endpoints, label-consistent eligibility, and NHS costs—addressing key gaps in prior models.

Abbreviations: AE, adverse event; CEA, cost-effectiveness analysis; CS, company submission; CV, cardiovascular; DCC, decompensated cirrhosis; EQ-5D, Euroqol-5 Dimensions; F0-F4, fibrosis stages F0-F4; HCC, hepatocellular carcinoma; HRQoL, health-related quality of life; HUI, Health Utilities Index; ICER, incremental cost-effectiveness ratio; LT, liver transplantation; MASH, metabolic dysfunction-associated steatohepatitis; MASLD, metabolic dysfunction–associated steatotic liver disease; NAFLD, non-alcoholic fatty liver disease; NASH, non-alcoholic steatohepatitis; QALY, quality-adjusted life year; RR, risk ratio; SF-36, Short Form-36.

B3. Priority Question: Validate the predicted outcomes of the economic model against the published literature reporting the natural history of NAFLD.

Specifically compare: (i) cause-specific mortality (background, cardiovascular, and liver-related), (ii) timing of hepatic events (onset of compensated cirrhosis, first decompensation events, and HCC), and (iii) progression times between fibrosis stages.

Company response: Our economic model is primarily informed by paired-biopsy results from weeks 0–52 of MAESTRO-NASH, which provide data on fibrosis improvement/worsening and MASH resolution. Differences in health state transition probabilities between resmetirom and SoC patients are limited to the period when patients are at fibrosis stages F2 or F3, consistent with the anticipated label. Beyond this window, transitions in fibrosis stage and MASH resolution are modelled as identical for both arms. Mortality, hepatic events, and decompensation risks are based on published NICE guidance for NAFLD (NG49) (19), are applied equally to all patients.

The MAESTRO-NASH study currently provides the most comprehensive evidence on disease progression and outcomes in MASH and thus serves as the key source for informing fibrosis progression within the model. Outside this trial, publicly available natural history data for MASH and NAFLD/MASLD remain limited and heterogeneous. We reached out to the British Liver Trust (BLT) charity early in our model development to establish whether there were sources or registries that could be used in high-risk MASH with CMRFs moderate-to-advanced liver fibrosis. Unfortunately, we determined that while the BLT was involved with general cross-sectional research into the screening and provision of care for liver disease (23), there were no UK-specific registry data available for MASH patients. We considered international publications relating to the natural history of NAFLD/MASLD + NASH/MASH (24,25). While these did feed into our general understanding about disease progression, they were unsuitable for use as validation sources, since they were either model-based estimations based on T2DM prevalence, or cross-sectional prevalence estimates of NASH populations. Neither obtained data from registries or real observations of NAFLD progression – instead relying on physician consensus.

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While direct validation of the model's predicted outcomes against real-world natural history data is not currently feasible, given the absence of robust, longitudinal MASH registries comparable to those available in other liver diseases (e.g., Global PBC, UK-PBC), the model has been designed to align as closely as possible with the best available clinical and epidemiological evidence. We remain open to incorporating additional real-world or longitudinal data sources as they become available to further strengthen the model's external validity.

Population

B4. Priority Question: The modelled population is based on the paired liver biopsy (PLB-W52) trial population, excluding patients at fibrosis stage F1/F1B. The EAG agrees with the exclusion of F1/F1B patients but is concerned about the reliance on the PLB-W52 subpopulation, as this represents a post-hoc subgroup of the MAESTRO-NASH trial.

- a) Please provide further justification for modelling the PLB-W52 population. The EAG's understanding is that this approach was adopted because assessment of NASH/MASH resolution and fibrosis improvement relied on independent histological review, and transition probabilities could not be generated where assessors disagreed.
- b) Please provide a breakdown of patients excluded from the PLB-W52 analysis set, including reasons for ineligibility.
- c) To better align the modelled treatment effect with the mITT-LB52 population, please conduct a scenario analysis in which odds ratios from the primary analysis are used to estimate the probability of NASH/MASH resolution (the reference arm should use the probabilities calculated for the PLB-W52 population).

Company Response: a) We appreciate the EAG's concern regarding the choice of analysis population. The company's base-case model uses the paired liver biopsy (PLB-W52) dataset from MAESTRO-NASH (n = 782), comprising patients who had a centrally read liver biopsy at both baseline and Week 52. This dataset provides the

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most robust evidence of true histological response and progression, as it is based solely on biopsies verified by independent pathologists under blinded conditions. We have selected the PLB-W52 due to:

- **Direct evidence of biological change**

Transition probabilities in the MSM are based on observed, paired histologic data (fibrosis improvement and MASH resolution). This is only possible when both baseline and Week-52 biopsies are available and centrally adjudicated. The PLB-W52 set thus avoids reliance on imputation or on “missing = non-responder” conventions that are appropriate for regulatory trials but unsuitable for modelling long-term patient trajectories. (CS Section 3.3.2.1 – Derivation of treatment-effect parameters).

- **Pre-specified analytic population**

The paired biopsy population was pre-defined in the SAP as the evaluable set for histological endpoints, not a post-hoc subgroup. Patients were included if their biopsy quality met central review criteria for fibrosis and ballooning scores at both timepoints. Thus, PLB-W52 represents a methodologically required analytic subset, not an exploratory subgroup.

- **Statistical validity and unbiased representation**

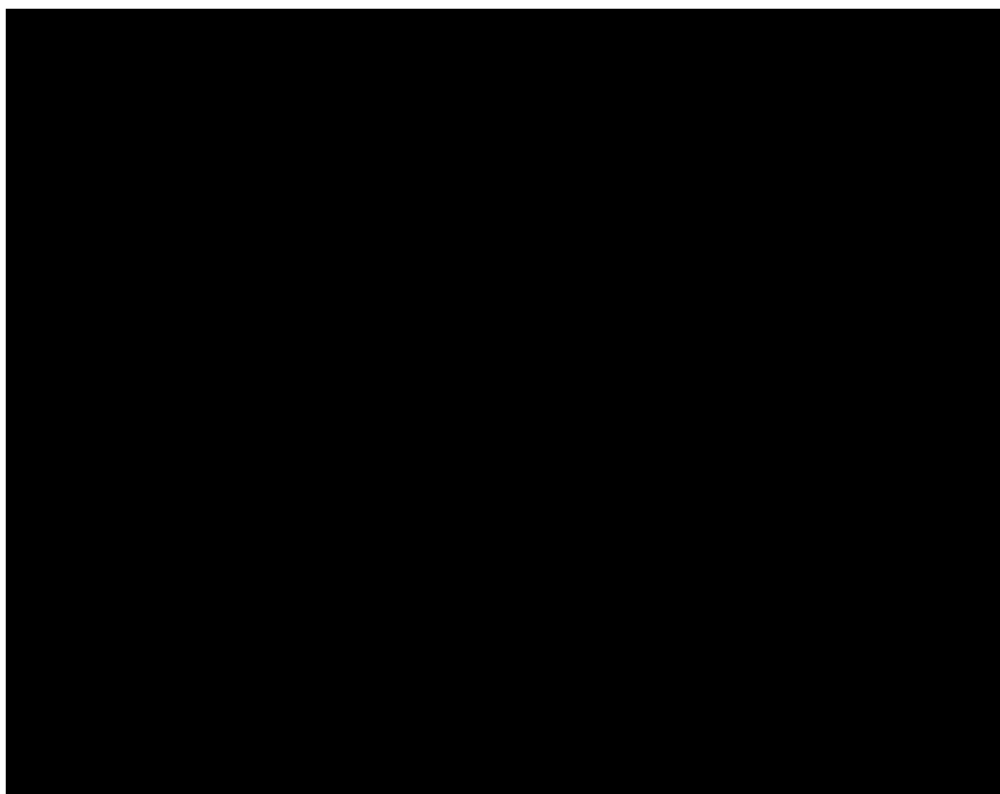
To address potential selection bias, the company compared baseline characteristics between the PLB-W52 and mITT-LB-W52 populations for the key covariates most likely to influence treatment effect—specifically age, sex, BMI, baseline fibrosis stage, and presence of T2DM. These factors were selected because they are known modifiers of histological progression and/or metabolic response in NASH.

All tested covariates demonstrated standardised mean differences (SMDs)

[REDACTED]

[REDACTED], confirming excellent baseline comparability between PLB and mITT populations with respect to these clinically relevant characteristics.

Figure 1. Standardised mean differences between mITT population (n = 966) and PLB-W52 (n = 871)



Although other baseline variables were not formally assessed, there is no mechanistic or clinical rationale to expect material differences in unmeasured covariates, given the randomised trial design and the technical nature of most exclusions (e.g., missing or unevaluable biopsy samples rather than biological factors). Consequently, the PLB-W52 dataset can be considered representative of the randomised MAESTRO-NASH population for the purposes of modelling treatment effects.

- **Conceptual justification**

For economic modelling, we aimed to represent **biological movement between disease states** and minimise administrative assumptions about missing data. The “missing = non-responder” rule used in regulatory analyses introduces artificial downgrades that would systematically underestimate efficacy in the long-term simulation.

The PLB-W52 dataset represents the best-available, biopsy-verified evidence suitable for estimating transition probabilities. It is pre-specified in the SAP, representative of the overall trial population, and methodologically relevant for use in health-economic modelling.

b) The PLB-W52 analysis set was derived from the 966 patients enrolled in the MAESTRO-NASH trial. Stepwise exclusions were applied to identify those with paired, centrally read, and **evaluable** liver biopsies at both baseline and Week 52.

A total of 234 patients were excluded from the paired liver biopsy (PLB-W52) analysis set for the reasons summarised in Table 11. The most frequent reason for exclusion was absence of a Week 52 biopsy (n = 161), primarily due to withdrawal of consent, scheduling difficulties, or adverse events. A further 11 patients experienced COVID-19–related site closures that prevented timely biopsies.

Additional exclusions were due to technical or procedural issues: biopsies outside the protocol window (n = 7), non-evaluable baseline or Week 52 slides because of poor quality or incomplete data (n = 5 in total), and one patient later excluded when the baseline physical slide could not be re-read centrally. Finally, 49 patients with fibrosis stages outside the target indication (F1B) were excluded, resulting in a final PLB-W52 population of 732 patients.

Table 11. Stepwise exclusions from the paired liver biopsy dataset to derive the F2–F3 population used in the economic model (starting population n = 966)

Reason for exclusion	Description	Number excluded	Remaining population (n)
Delay in Week 52 biopsy due to COVID-19	Week 52 biopsy delayed because of COVID-19–related site closures or restrictions	-11	955
No Week 52 biopsy obtained	Biopsy not performed due to withdrawal of consent, scheduling constraints, or adverse events	████	████

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Week 52 biopsy not evaluable by central reviewers	Slide of insufficient quality, poor orientation, or incomplete data for CRN scoring	■	■
Week 52 biopsy outside protocol window	Biopsy performed outside the acceptable timing window for Week 52	■	■
Baseline biopsy not evaluable or missing key components	Technical failure or inadequate tissue at baseline	■	■
Later excluded from paired-biopsy dataset	Baseline physical slide could not be retrieved or read by central pathologist	■	■
Excluded fibrosis stage F1B	Patients outside the target fibrosis stage for modelling (not within F2–F3)	■	732

Abbreviations: CRN, Central Reader Network; F1-F3, fibrosis stages F1-F3.

c) To implement the requested scenario, we referred to CS Table 13, which presents the two primary histological endpoints:

- NASH resolution with no worsening of fibrosis, and
- Fibrosis improvement with no worsening of NAS.

Because the table does not report the proportion of patients who experienced fibrosis worsening, several transparent assumptions were required to operationalise the EAG's request:

1. The probability of NASH resolution with no worsening of fibrosis reported in CS Table 13 was assumed to correspond directly to the probability of NASH resolution used in the model for the PLB-W52 population (placebo reference arm).
2. The probability of fibrosis improvement was assumed to be the same for patients with and without NASH resolution, as no subgroup-specific data were available.
3. For the remaining patients (i.e., those without fibrosis improvement), the proportions assigned to fibrosis no change and fibrosis worsening were distributed proportionally based on the placebo arm in the PLB-W52 dataset.

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Table 12 summarises the treatment effect estimates (odds ratios) from the mITT-LB52 primary analysis for the two key histological endpoints: NASH resolution with no worsening of fibrosis and fibrosis improvement with no worsening of NAS against placebo arm in the PLB-W52 population.

Table 12. Estimated odds ratios (95% confidence intervals) from the primary analysis used in the scenario alignment with the mITT-PLB52 population

NASH resolution	OR	SE	LL	UL
Resmetirom 80 mg vs placebo				
Resmetirom 100 mg vs placebo				
Fibrosis improvement	OR	SE	LL	UL
Resmetirom 80 mg vs placebo				
Resmetirom 100 mg vs placebo				

Abbreviations: LL, lower limit; OR, odds ratio; SE, standard error; UL, upper limit.

Table 13 presents the estimated transition probabilities used in the scenario aligning treatment effects with the mITT-LB52 primary analysis. These probabilities reflect the likelihood of fibrosis improvement or worsening, conditional on MASH resolution status, for each treatment arm (placebo, resmetirom 80 mg, and resmetirom 100 mg).

The estimates were derived by applying the odds ratios from the mITT-LB52 primary analysis (see Table 12) to the placebo probabilities from the PLB-W52 dataset. This approach preserves the absolute event rates observed in the PLB population while adjusting the treatment arms according to the relative effects observed in the broader mITT analysis.

Table 13. Estimated transition probabilities for fibrosis and MASH resolution by treatment arm, based on odds ratios from the mITT-LB52 primary analysis and applied to the PLB-W52 reference population

	MASH Resolution	MASH Resolution: YES		MASH Resolution: NO	
		Fibrosis improvement	Fibrosis worsening	Fibrosis improvement	Fibrosis worsening
Placebo					
Resmetirom 100 mg					
Resmetirom 80 mg					

Abbreviations: MASH, metabolic dysfunction-associated steatohepatitis.

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Table 14 presents the results of the probabilistic sensitivity analysis (PSA) conducted to assess the robustness of the cost-effectiveness results for resmetirom compared with SoC. The PSA was based on 1,000 simulated patients and 2,000 model iterations. The resulting incremental cost was [REDACTED], with an incremental quality-adjusted life year (QALY) gain of [REDACTED], yielding an incremental cost-effectiveness ratio (ICER) of £16,550 per QALY gained.

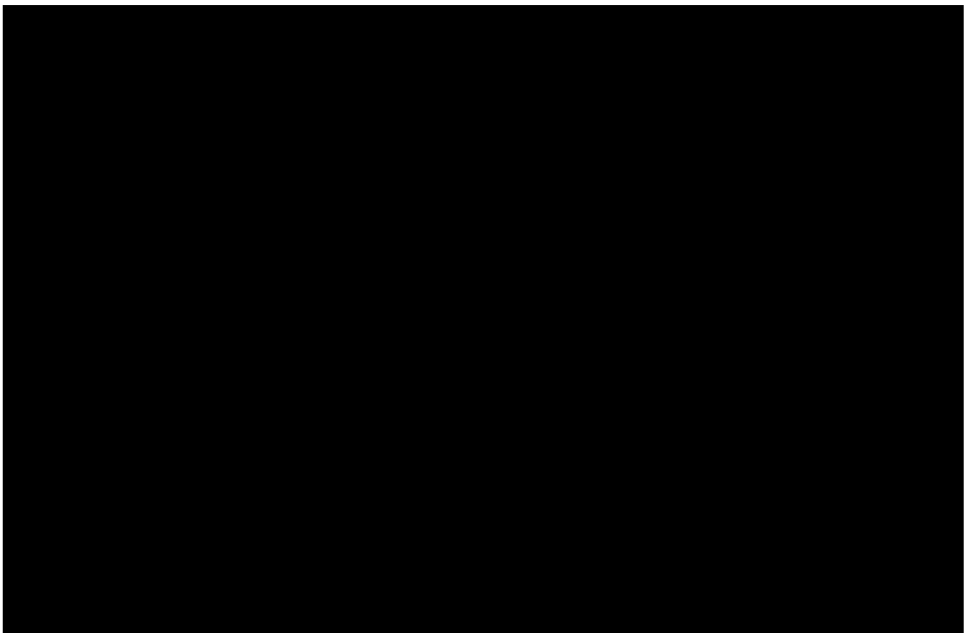
Table 14. Results of probabilistic sensitivity analysis with 1,000 sampled patients and 2,000 iterations

Technologies	Total costs (£)	Total QALYs	Incremental costs (£)	Incremental QALYs	ICER (£/QALY)
SoC	[REDACTED]	[REDACTED]	[REDACTED]	-	-
Resmetirom	[REDACTED]	[REDACTED]	[REDACTED]	[REDACTED]	16,550

Abbreviations: ICER, incremental cost-effectiveness ratio; QALY, quality-adjusted life year; SoC, standard of care.

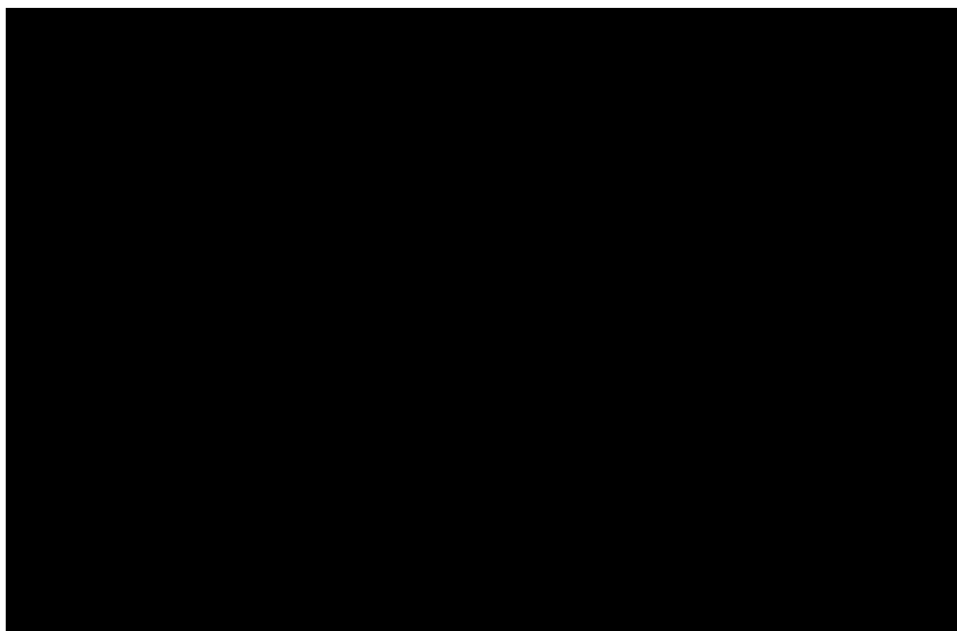
The PSA (Figure 2 and Figure 3) demonstrates that resmetirom consistently dominates SoC across simulations, with the majority of iterations falling within the northeast quadrant of the cost-effectiveness plane and an average ICER of approximately £16,550/QALY.

Figure 2. Cost-effectiveness plane for resmetirom versus SoC- Scenario using mITT-LB52 odds ratios applied to PLB-W52 placebo data



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Figure 3. Cost-effectiveness acceptability curve for resmetirom versus SOC - Scenario using mITT-LB52 odds ratios applied to PLB-W52 placebo data



B5. Please clarify how the modelled baseline characteristics were generated.

- a) Are the values in the MGL-3196-11_HEcon_Baseline_Listing.xlsx file those of the actual patients recruited the MAESTRO-NASH trial, or are they a simulated cohort?
- b) If they are a simulated cohort, please explain the process used to generate these values.

Company Response: The file MGL-3196-11_HEcon_Baseline_Listing.xlsx contains the individual patient-level data exported directly from the MAESTRO-NASH clinical trial database. This dataset includes baseline demographic and clinical characteristics for 966 randomised patients who formed the mITT-LB-W52 population (i.e., all participants with an evaluable baseline liver biopsy).

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Treatment Effectiveness

B6. Priority Question: A core assumption of the economic model is that improvements in fibrosis stage led to downstream reductions in liver decompensation, HCC, and mortality. These downstream benefits were not directly observed in the MAESTRO-NASH trial. Please conduct a critical review of the peer-reviewed literature assessing:

- **The association between fibrosis stage and subsequent risk of liver decompensation, HCC, and all-cause and cause-specific mortality.**
- **Evidence that changes or improvements in fibrosis stage (e.g., regression by ≥ 1 stage on biopsy or non-invasive measures) are followed by reduced rates of these downstream outcomes.**

Company Response: The work of Angulo et al. 2015 (26) and Dulai et al. 2017 (27) (as well as by Sanyal et al. 2021 (28) and Taylor et al. 2020 (29)) highlight the relationship between fibrosis stage and the risk of progression to major adverse liver events. These works form the basis of the regulatory guidance that fibrosis change is most reasonably likely to predict liver related outcomes (30). However, to date, there is no double-blinded, RCT-derived evidence showing the association of pharmacotherapy-induced (nor indeed any intervention) fibrosis regression with long-term hepatological outcomes risk. This is why the MAESTRO-NASH-OUTCOMES extension phase continues double-blinded, supported by the conditional marketing authorisation based on fibrosis and MASH resolution outcomes at Week 52.

What we were able to identify (see CS section 1.3.1, Disease overview; and CS section 1.3.1.2, Disease Progression) from the UK-based Davidson et al. 2025 (using CPRD data linked to HES data) analysis (8), was that the rate of progression toward end-stage liver disease (ESLD) is greater at more severe levels of fibrosis, and is highest at stage F4.

Our model does not explicitly apply transitions or risks reflecting a link between fibrosis stage improvement and the risks of liver decompensation, HCC, or mortality. However, in its simulation of progression through different grades of fibrosis, which

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can develop into cirrhosis of worse health states linked thereto, it reflects the established relationship between fibrosis stage and long-term outcomes as reported in the published NAFLD literature and incorporated within NICE guidance (NG49) (19).

Our model uses the same transition probabilities regardless of treatment arm for transitions between health states that could not be informed by the MAESTRO-NASH data, as detailed in Table 30 in CS section 3.3.2.1 and Table 32 in CS section 3.3.2.5. Treatment could influence transition to cirrhosis and beyond, but **only by preventing or delaying entry into advanced fibrosis**. Reliable arm-level data on F4 and subsequent outcomes were not available from MAESTRO-NASH due to the agreed blinding conditions.

As noted in the CS, delay to entering the cirrhotic stage (health state F4) may have had between-arm differences, but prior regression does not impact later transitions. Considering the higher proportion of patients in MAESTRO-NASH who experienced resolution of fibrosis ≥ 1 stage in the resmetirom arm versus the placebo arm (as shown in CS section 2.13.1), there will naturally be a delay to experiencing downstream effects and worsening of disease purely from a model transition and individual patient pathway through the economic model based on probabilities experienced at each health state.

A further review of the literature could be undertaken to summarise the available evidence linking fibrosis regression with subsequent clinical outcomes. We note, however, that published data in MASH remain limited and largely indirect. In this context, input from clinical experts will be particularly valuable in assessing whether a patient with MASH who experiences regression of ≥ 1 fibrosis stage might reasonably be expected to predict a longer time to developing advanced liver disease compared with a patient who does not experience such regression.

B7. Priority Question: The economic model distinguishes between patients receiving 80 mg and 100 mg of resmetirom, aligning this with the weight-based dosing specified in the SmPC. This involves modelling separate treatment effects for the 80 mg and 100 mg groups. The EAG is concerned that this

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approach misrepresents the trial design, as dosing in the trial was not determined by patient weight; instead, the 80 mg and 100 mg doses were evaluated as separate trial arms.

- a) Please outline the rationale for the weight-based dosing specified in the SmPC.
- b) Report subgroup analyses for the dual primary outcome, stratifying patients into two groups: those weighing 100 kg or more and those weighing less than 100 kg. Please provide this for both the mITT-LB52 and PLB-W52 trial populations.
- c) Present transition probabilities derived from the subgroup analyses requested in part b (PLB-W52 trial population only).

Company Response: In the population PK analysis, bodyweight (BW) was identified as a significant covariate impacting the clearance and volume of distribution of resmetirom. Additional analyses were conducted during the NDA review process with the U.S. FDA to understand recommended dosing. Madrigal performed a thorough evaluation of weight, since Population PK modelling had indicated an effect of BW on resmetirom's plasma concentrations.

The following measures were assessed at 52 weeks with regards to baseline BW (categorised in 10kg increments):

- Change in MRI-PDFF, a measure of liver fat reduction
- Histological endpoints of NASH resolution and fibrosis improvement (dual primary endpoints)
- Sex hormone-binding globulin (SHBG) as a marker of resmetirom's drug concentration in the liver
- Number of patients discontinued for adverse events

Based on these analyses, several observations were made:

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- SHBG levels were lower in patients with higher BWs (> 100kg) for those treated with 80 mg versus 100 mg.
- For MRI-PDFF, NASH resolution and fibrosis improvement, patients treated with 100 mg, a consistent response was seen in the heaviest patients (> 100kg) when compared with response in patients with lower body weights. However, for the 80 mg group, a decrease in effect was observed for the heaviest patients (> 100kg) when compared to lower body weight patients treated at that dose.
- An increase in discontinuations was observed for patients treated with 100 mg for patients weighing < 100kg compared to those weighing > 100kg. With regards to the 80 mg dose, discontinuations for adverse events was not impacted by body weight.

These findings led to adoption of the weight-based dosing labelling agreed to by both the U.S. FDA and EMA.

Please find the requested analyses in **Appendix A-D**.

c) Transition probabilities derived for the weight-based subgroup analyses (PLB-W52 trial population only) are shown in Table 15.

Table 15. Transition probabilities for weight-based subpopulation (PLB-W52)

		MASH Resolution: YES		MASH Resolution: NO	
	MASH Resolution	Fibrosis improvement	Fibrosis worsening	Fibrosis improvement	Fibrosis worsening
Placebo					
Resmetirom 100 mg					
Resmetirom 80 mg					

Abbreviations: MASH, metabolic dysfunction-associated steatohepatitis.

B8. Priority Question: The economic model draws on Singh et al. (2015) to estimate the magnitude of changes in fibrosis stage. The EAG is concerned that this approach misinterprets the data: Singh et al. does not report annual transitions in fibrosis stage but instead synthesises evidence on changes in

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patients over variable follow-up periods, often considerably longer than one year

- a) Please clarify how Singh et al. (2015) was identified and whether alternative evidence sources were considered.
- b) Please justify the use of Singh et al. (2015) to inform the magnitude of fibrosis stage changes, taking into account the EAG's concern that the study does not provide annualised transition rates.
- c) Please comment on the biological plausibility of patients progressing by more than one fibrosis stage within a year, given that Singh et al. report an average time of ■■■ years to progress by one stage in patients with MASH, and ■■■ years in those with MAFL.
- d) Please provide scenario analyses in which fibrosis progression (not improvement) is constrained to a maximum of one stage per year.

Company Response: a) Singh et al. 2015 (31) was selected because it is a PRISMA-based systematic review/meta-analysis of paired-biopsy studies (minimum 1-year interval) that reports fibrosis progression as stages moved stratified by baseline stage, the construct we need to apportion the directional fibrosis changes we observe in MAESTRO-NASH across destination stages in a 1-year cycle. RCTs with only 12-month paired biopsies and no stage-specific detail were explicitly excluded from Singh's stage-specific pooling, underscoring its methodological fit for baseline-stage splits rather than absolute annual rates.

Alternative natural-history sources were reviewed (e.g., Le et al. 2023 (32)). These pooled heterogeneous populations and produced clinically unintuitive stage-to-stage times (e.g., 11.9 years F2→F3; 19.6 years F3→F4), which we judged unsuitable for an F2–F3, high-risk MAESTRO-NASH-like population and for a 1-year model cycle.

b) Singh et al. 2015 (31) uses only RCTs with paired biopsy data. It does report estimated mean single-stage fibrosis progression rates of ■■■ years for MASH and MAFL respectively although these values come from a pooled analysis which is described in the answer to sub-question c below. However, our model does not use

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Singh to annualise transitions. Year-1 joint probabilities of (i) NASH resolution, (ii) fibrosis improvement/worsening, and (iii) having stable fibrosis, come directly from the MAESTRO-NASH paired-biopsy population (base case and T2DM subgroup). Singh et al. 2015 (31) was used only to determine how many stages of fibrosis progression/regression we should associate with ‘worsening’ or ‘improvement’ at each cycle, for each fibrosis category. This preserves the trial-observed rate of worsening/improvement while supplying biologically grounded directional splits where the trial could not disclose detailed movements (e.g., to F4) due to protocol blinding through Month 54. The implementation (Table 30 in our submission) shows precisely these Singh et al.-based splits by baseline stage, parameterised with Dirichlet/Beta distributions for uncertainty.

Regarding the EAG’s comment about the rates in Singh et al. 2015 not being annualised – proportions shown in Table 30 of our submission are derived from patient counts in the “Non-Alcoholic Steatohepatitis (NASH)” section of Table 3 of Singh et al. 2015 (31). These counts were collected across multiple patient-years and we did not attempt to adjust the counts for these time-frames as we wished to anchor the rates of fibrosis worsening in MAESTRO-NASH. We noted that Singh et al. 2015 found around 20% of the studied MASH patients were “Rapid Progressors”, whose fibrosis progressed from stage 0 to bridging/cirrhosis between baseline and follow-up biopsy, demonstrating that multi-stage movements, while uncommon, are biologically plausible in a subset of patients. Although there is insufficient disaggregated data in the publication to inform the timeframe for such rapid progression, we consider the application of the proportions in the paper (noting that single-stage fibrosis progression is still the predominant transition) to our ‘worsening’ and ‘improvement’ rates to be relevant to the modelled population, especially when considering that the modelled population was enriched for patients at high risk of fibrosis progression.

c) The EAG’s cited average times from Singh et al. 2015 (31) (e.g., “■ years per stage”) are derived from pooled, variable-follow-up natural-history cohorts and are mainly anchored in earlier-stage disease; Singh authors themselves emphasise heterogeneity and excluded short 12-month RCT data from stage-specific pooling,

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consistent with our choice to anchor rates in the trial and use Singh only for allocation of worsening/improvement magnitudes by baseline stage.

We used Table 3 in Singh et al. 2015 (31) as a means to reflect the anticipated dynamic that while most patients would progress one fibrosis stage upon ‘worsening’, a smaller but still important proportion of patients might be expected to progress more than one stage. In response to the EAG’s question we have sought further external clinical opinion on our methodology. Although we understand the EAG’s concern regarding the nature of the data and how they are used, we have been told by clinicians that the assumed proportions of MASH patients whose fibrosis may worsen/improve by more than one stage are reasonable and in line with what might be expected when considering MASH patients eligible for resmetirom.

d) As requested, the model was re-run constraining fibrosis progression (but not improvement) to a maximum of one stage per annual cycle. The results are summarised in Table 16 and indicate that constraining fibrosis progression to this clinically conservative approach of one stage per year has only a modest effect on overall cost-effectiveness outcomes, and the model conclusions remain consistent with the base case—resmetirom continues to represent a cost-effective treatment option for patients with NASH at WTP threshold of £30,000 per QALY gained.

Table 16. Results for scenario constraining fibrosis progression to a maximum of one stage per year

Technologies	Total costs (£)	Total QALYs	Incremental costs (£)	Incremental QALYs	ICER (£/QALY)
SoC	██████	██████	-	-	-
Resmetirom	██████	██████	██████	██████	28,627

Abbreviations: ICER, incremental cost-effectiveness ratio; QALY, quality-adjusted life year; SoC, standard of care.

B9. Priority Question: The EAG is concerned by the repeated application of year 1 transition probabilities to subsequent years. Specifically, the EAG is concerned that this implies that an increasing proportion of patients will

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achieve MASH/NASH resolution. The EAG considers this clinically implausible and unjustified, given the limited follow-up in the MAESTRO-NASH trial.

- a) Please comment on the plausibility of patients achieving NASH/MASH resolution after 12 months and the clinical validity of the Markov trace. This suggests that patients on resmetirom will spend 55% of their time in health states where MASH is resolved.
- b) Please conduct scenario analysis in which the year 2+ transition probabilities for NASH/MASH resolution are set to zero, i.e. patients can only achieve NASH/MASH resolution in year 1 (in patients restarting treatment, year 1 transitions should be applied again for one cycle).

Company Response: a) The EAG correctly identifies that no explicit on-treatment waning is modelled for resmetirom + SoC nor SoC alone arms. Among the group of patients that continued therapy in MAESTRO-NASH for 52 weeks, there were insufficient data collection timepoints to form an empirical basis for on-treatment decay curves. Instead, treatment discontinuation, estimated directly from MAESTRO-NASH up to Week 52, was used as the evidence-based proxy for waning and is varied in scenario analyses.

Waning occurs endogenously in the model. In the microsimulation, discontinuation and MASH relapse jointly limit the accumulation of patients in “resolved” states. Permanent and temporary discontinuation rules (F4/DCC/HCC stop; < F2 stop with re-start at F2–F3) remove 5–8 % of treated patients per year, while a 5% annual relapse of MASH is applied symmetrically in both arms. Together these mechanisms produce a bounded, steady-state proportion of person-time in ‘MASH-resolved’ states (~40–55 %), rather than indefinite growth. This dynamic is fully consistent with Section 3.3.2.2 of the CS and ensures clinical plausibility of the Markov trace.

Per-patient transition matrices are fixed (anchored to observed 0–52 week biopsy outcomes), but the cohort-average transition matrix naturally converges to SoC over time as the on-treatment share falls with discontinuation. Formally, the cohort matrix each cycle is a mixture of on-treatment and SoC matrices $P_t = \text{pon}(t) P_{\text{on}} + [1 - \text{pon}(t)] P_{\text{SoC}}$

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pon(t)] PSoC , so as pon(t) declines monotonically overtime, Pt naturally converges to PSoC, effective treatment impact wanes. This is the mechanism driving the Markov trace.

The Markov trace of person-time in “MASH resolved” states is clinically plausible. The model explicitly represents MASH resolution as a trial-validated outcome at 12 months and allows relapse thereafter (i.e., patients can move back from “resolved” to active MASH). Resolution and fibrosis-change are modelled jointly from patient-level MAESTRO-NASH biopsy data, preserving observed correlations and enabling post-Year-1 relapse dynamics. Thus, time spent in resolved states accumulates because some patients resolve and then remain resolved for a period, not because probabilities escalate over time.

Evidence base for transitions. Year-1 joint transitions for MASH resolution and fibrosis change are taken directly from paired-biopsy individual patient data and applied consistently in later cycles, reflecting the most relevant empirical anchor available in a setting with no robust longitudinal, multi-year biopsy data. Parameterisation uses multinomial/Dirichlet methods that preserve internal dependencies and are explored in sensitivity analysis.

On the EAG’s interpretation that 55% of time is spent in health states where MASH is resolved. This interpretation depends on reading an aggregated Markov trace without taking into account the model’s relapse and discontinuation mechanisms. Because (i) patients who regress below F2 stop therapy and follow SoC transitions until they re-qualify (eligibility gating), (ii) relapse is explicit, and (iii) the on-treatment share declines over time, the model does not imply an ever-increasing fraction newly achieving resolution. Rather, it reflects an evidence-anchored stock-and-flow of resolution and relapse under dynamic treatment eligibility.

b) On the proposed scenario “set Year 2+ resolution probabilities to zero”.

While this scenario may be of interest, we would reason that there is no biologically plausible reason to assume that resmetirom will cease to have a differential impact on the chances of MASH resolution after 52 weeks. Although we do not have the Clarification questions: Resmetirom for treating moderate to advanced liver fibrosis (without cirrhosis) (MASLD) ID6529

biopsy data from MAESTRO-NASH to evidence this yet, we can use discontinuation as a reasonable proxy of effect waning and confirm that there has been no change in this rate as the study has progressed. Such a scenario would also assume that a patient who had experienced some degree of improvement and changes in his or her liver by week 52 (i.e., toward MASH resolution), but not enough change to be classed as MASH resolved would cease to have further benefit and could never achieve any potential MASH resolution.

Of potential interest, although collected in a different population, we would also reference published evidence from the 2-year follow-up of the MAESTRO-NAFLD-1 study and its open-label continuation. This evidence, presented orally at the EASL Congress in May 2025 (33), found that NIT scores indicated a sustained effect of resmetirom at 2 years on liver fat and liver stiffness, ALT and GGT readings, as well as fibrosis and liver injury biomarkers, showing that resmetirom does continue to impact these outcomes after 52 weeks in the studied patient population.

If the model were constrained as suggested by EAG, we consider that the following contradictions would be introduced:

1. Contradicts trial-anchored transitions

All resolution/fibrosis transitions are anchored to observed MAESTRO-NASH biopsy outcomes at 52 weeks and then applied consistently when patients remain on treatment, with waning captured via discontinuation. Forcing zero probability of resolution beyond Year 1 would sever the link to the only biopsy-confirmed evidence available and create a discontinuity not supported by data.

2. Inconsistent with model structure and clinical logic

Patients can relapse from resolved to active MASH and later re-resolve while eligible and on treatment; eligibility itself being label-consistent (F2–F3 fibrosis stages only). A zero-after-Year-1 constraint would eliminate clinically plausible re-resolution in patients who remain or become eligible and continue therapy but would still incur cost of treatment, biasing the evaluation.

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3. Exceeds what is warranted in context of uncertainty handling already provided

Uncertainty about long-term durability is already addressed through scenario analyses (e.g., finite treatment duration after 2 years; alternative discontinuation rates) and deterministic/probabilistic sensitivity analyses. These approaches test waning without inserting a zero-probability transition for the remainder of modelled time.

4. Conservative assumptions already applied elsewhere

The model assumes no legacy effect after discontinuation (i.e., immediate reversion to SoC transitions).

For these reasons, we do not support a “Year 2+ = SoC resolution rate” scenario for resmetirom.

B10. Please provide further details on how the clinical risk factors BMI, LDL-C, HDL-C, and triglycerides are updated over time. This should include an explanation of any assumptions made regarding the persistence of treatment effects on these factors.

- a) Please also outline the assumptions and sources used to model the trajectories of other risk factors included in the risk equations, that is, those other than BMI, LDL-C, HDL-C, and triglycerides.

Company Response: The model was explicitly designed to capture both short-term treatment effects (as observed in the MAESTRO-NASH trial) and long-term physiological trends based on external epidemiological data. This ensures consistency between trial evidence and long-run natural history projections.

As shown in Table 17, BMI, LDL-C, HDL-C, and triglycerides are all updated annually within the “Updating Variables” module of the simulation (see code section starting at `## | BEGIN UPDATING VARIABLES MODULE |`). Each variable follows a clearly defined update rule, implemented through the functions `n_BMI_update`, `n_LDL_C_update`, `n_HDL_C_update`, and `n_trigl_update`. These updates incorporate both a background trend and a treatment effect, depending on whether patients remain on active therapy.

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Table 17. Annual updating of metabolic risk factors in the microsimulation

Risk factor	Function (in code)	Mechanism / formula	Data source or calibration	Units used	Persistence assumption	Notes / relevant parameters
Body Mass Index (BMI)	<code>n_BMI_update(male, age, dosage, bmi)</code>	Applies absolute population Δ BMI from NHS Digital trends (<code>l_BMI_change</code>) + arm-specific % effect from MAESTRO-NASH (<code>l_BMI_effect</code>); capped at <code>n_BMI_max</code> .	NHS Digital (UK population trends); MAESTRO-NASH trial	kg/m ²	Treatment % effect applied annually while on therapy; background age–sex trend continues each year.	Used to update Weight, obesity flags, and cancer risks.
Weight	Derived ($\text{BMI} \times \text{Height}^2$)	Deterministic update after BMI	Derived from BMI	kg	Same as BMI	Height fixed at baseline.
LDL-C	<code>n_LDL_C_update(ldl, age, dosage)</code>	Year 1: trial-based % change (<code>n_LDL_C_effect</code>) from MAESTRO-NASH. Year 2+: adds drift +0.1 mg/dL/year (<code>n_LDL_C_incr</code>).	MAESTRO-NASH; Domanski et al. 2020 (34)	mg/dL (converted to mmol/L for UKPDS: $\times 0.0259$)	Year 1 % effect persistent for 1 cycle; after Year 1, natural upward drift.	<code>n_cycles_risk_factor_effect=1</code> ; drift from Year 2 onward.
HDL-C	<code>n_HDL_C_update(hdl, age, dosage)</code>	Year 1: trial-based % change (<code>n_HDL_C_effect</code>) from MAESTRO-NASH. Year 2+: -0.1 mg/dL/year (<code>n_HDL_C_decr</code>).	MAESTRO-NASH; Domanski et al. 2020 (34)	mg/dL (converted to mmol/L $\times 0.0259$)	Year 1 % effect persistent for 1 cycle; thereafter gradual decline.	Matches Year-1 TE persistence; then background drift.
Triglycerides	<code>n_trigl_update(trigl, age, dosage)</code>	Year 1: trial-based % change (<code>n_trigl_effect</code>) from MAESTRO-NASH. Year 2+: reverts to baseline.	MAESTRO-NASH	mg/dL	Trial % effect for Year 1 only; returns to baseline from Year 2 onward.	Conservative assumption in the absence of other data; no persistence beyond first year. If sustained benefit occurred, this assumption would underestimate long-term cardiovascular benefit
Total cholesterol (TC)	Recalculated: $\text{LDL} + \text{HDL} + (\text{TG} / 5)$	Friedewald formula recomputed annually.	Derived	mg/dL	Updated each year with current LDL, HDL, TG	Used in TC/HDL ratio and QRISK3 equation.

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Risk factor	Function (in code)	Mechanism / formula	Data source or calibration	Units used	Persistence assumption	Notes / relevant parameters
TC/HDL ratio	Recalculated: <code>TC / HDL</code>	Derived from updated TC and HDL	Derived	Unitless	Updated annually	Used in QRISK3 and Framingham risk equations.

Abbreviations: BMI, body mass index; HDL, high-density lipoprotein; KG, kilogram; LDL, low-density lipoprotein; mg, milligram; TC, total cholesterol.

Specifically, BMI evolves according to age- and sex-specific absolute annual changes taken from NHS Digital population data, combined with percentage treatment effects derived from the MAESTRO-NASH trial. Weight and obesity status are recalculated deterministically from BMI each cycle. For lipids, the trial-based percentage changes are applied during the first year of treatment (`n_cycles_risk_factor_effect = 1`), after which long-term drifts are introduced: LDL-C increases by +0.1 mg/dL per year and HDL-C decreases by -0.1 mg/dL per year, consistent with Domanski et al. 2020 (34). Triglycerides are conservatively assumed to revert to baseline values after the first year, reflecting the absence of robust long-term evidence on sustained changes. All lipid variables are stored in mg/dL for internal consistency, with conversion to mmol/L ($\times 0.0259$) where required by UKPDS cardiovascular equations.

A summary of these dynamic updates, including units, data sources, and persistence assumptions, is provided in Table 17 (metabolic factors) and Table 18 (other time-dependent risk factors). These tables show how each factor is recalculated annually and how persistence is controlled through a small set of model parameters (e.g., `n_cycles_risk_factor_effect`, `n_LDL_C_incr`, `n_HDL_C_decr`).

Age and age group are incremented deterministically each year; smoking status and ethnicity remain fixed, consistent with trial data. Diabetes onset is modelled dynamically using the QDiabetes-2018 algorithm, which depends on updated BMI, HbA1c, age, and other clinical factors. Duration of diabetes is incremented annually once the condition is established. CVD history is tracked continuously, with first events estimated using QRISK3 and recurrent events using Framingham equations. Cancer incidence for colorectal, breast, and endometrial cancers is updated each year as a function of age and BMI, ensuring consistency between obesity progression and cancer risk.

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Table 18. Updating of other time-dependent risk factors

Variable	Mechanism / Function	Change per year	Used in	Persistence / dynamics	Source / note
Age / age group	Age[t+1] = Age[t] + 1; recoded via recode_age_categories()	+1 year per cycle	All risk equations (QRISK3, UKPDS, cancer incidence)	Increases each cycle	Deterministic
Smoking status	recode_smoking_status()	None	QRISK3, QDiabetes	Fixed at baseline	MAESTRO-NASH
Ethnicity	recode_ethnicity()	None	QRISK3, QDiabetes	Fixed	MAESTRO-NASH
Diabetes onset	QDR2018C_optim() (QDiabetes 2018)	Probability depends on BMI, age, HbA1c, ethnicity, smoking, FH, CVD, meds	Determines Diabetes=1 and Diabetes_dur=1	Updated annually for non-diabetics	Hippisley-Cox et al. 2018 (35)
Diabetes duration	Diabetes_dur[t+1] = Diabetes_dur[t] + 1	+1 per year	UKPDS macro/microvascular risk	Continuous	Derived
ASCVD history	QRISK3 for first event, Framingham for subsequent	Updated by event occurrence	CVD recurrence risk, mortality	Cumulative	QRISK3 (36)/ Framingham equations (37)
Non-liver mortality (MI, stroke, cancer)	Cause-specific probabilities applied (p_D_MI1, p_D_STR1, p_D_CRC_Y1, etc.)	Per event occurrence	Death attribution	Applied dynamically each cycle	Smolina et al. 2012 (38); Lee et al. 2011 (39)

Abbreviations: ASCVD, atherosclerotic cardiovascular disease; BMI, body mass index; CVD, cardiovascular disease; MI, myocardial infarction; UKPDS, UK Prospective Diabetes Study.

The assumptions regarding persistence of treatment effects are presented in Table 19. The parameter `n_cycles_risk_factor_effect` controls the duration for which MAESTRO-NASH treatment effects are applied. In the base case, trial-based percentage reductions in LDL-C, HDL-C, and triglycerides are assumed to persist for **one year only**, after which the model transitions to long-term background trends informed by Domanski et al. 2020 (34).

From Year 2 onwards, LDL-C increases by +0.1 mg/dL per year, HDL-C decreases by −0.1 mg/dL per year, and triglycerides revert fully to baseline—representing a conservative assumption that avoids overstating long-term metabolic benefit.

In contrast, BMI continues to evolve annually, reflecting both background population changes and persistent modest treatment effects while patients remain on therapy. These persistence assumptions are parameterised, allowing sensitivity analyses to test alternative durations or magnitudes of sustained effect.

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Table 19. Persistence assumptions for metabolic risk factor effects

Parameter	Cycle(s) applied	Mechanism	Persistence beyond first year	Rationale / Source
n_LDL_C_incr = +0.1 mg/dL/year	≥ Year 2	LDL gradual increase	Yes	Domanski et al. 2020 (34) population trend
n_HDL_C_decr = -0.1 mg/dL/year	≥ Year 2	HDL gradual decline	Yes	Domanski et al. 2020 (34)
Triglycerides	Year 1	Trial-based % change	No persistence	Conservative (reverts to baseline)
BMI	All years	Adds population ΔBMI + trial % change	Yes, annual	NHS Digital trend + ongoing treatment effect

Abbreviations: BMI, body mass index; HDL, high-density lipoprotein; LDL, low-density lipoprotein.

Finally, Table 20 summarises how these evolving variables feed directly into the relevant risk equations used in the microsimulation. Each risk equation (QRISK3, UKPDS, Framingham, and QDiabetes) uses the *most recent simulated values in each cycle* for BMI, lipids, and other predictors to calculate the annual probabilities of cardiovascular, microvascular, and metabolic events. This dynamic linkage ensures that improvements in metabolic profile translate into lower event risks during active treatment and that risks gradually return toward baseline levels after treatment discontinuation or as physiological parameters drift with age. Non-liver mortality risks—including those from myocardial infarction, stroke, and obesity-related cancers—are also updated annually based on current health states and comorbidity status.

Table 20. Risk equation mapping and required inputs

Equation / Module	Population	Inputs (updated each cycle)	Outputs	Used for
QRISK3_2017_optim	Non-diabetic	Age, sex, SBP, BMI, TC/HDL ratio, smoking, ethnicity, deprivation, comorbidities	10-year CVD risk → annualized	First MI/stroke event
compute_framingham_new	Non-diabetic (with prior ASCVD)	Age, sex, TC/HDL, smoking, BP	10-year risk → annualized	Subsequent MI/stroke
p_weibull_UKPDS	Diabetic	Age, sex, BMI, LDL, HDL, SBP, duration of diabetes	Annual probability	MI, stroke, blindness, CKD
QDR2018C_optim	Non-diabetic	Age, sex, BMI, HbA1c, smoking, family history, meds	10-year diabetes risk → annualized	New diabetes onset
Mortality module	All	MI/stroke/cancer events	Cause-specific annual death probability	Non-liver mortality attribution

Abbreviations: ASCVD, atherosclerotic cardiovascular disease; BMI, body mass index; BP, blood pressure; CVD, cardiovascular disease; HbA1c, glycated haemoglobin; HDL, high-density lipoprotein; LDL, low-density lipoprotein; SBP, systolic blood pressure; TC, total cholesterol.

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B11. The model predicts that patients in both arms experience continuous weight loss over their lifetime. This seems to result from the assumption that the initial 12-month weight change is applied repeatedly across the entire time horizon.

- a) Please comment on the clinical plausibility of sustained lifetime weight loss. Where possible, provide references to published literature that support (or contradict) this assumption.
- b) Please justify why patients initiating resmetirom are assumed to continue losing weight at a faster rate than those receiving SoC, even after treatment discontinuation.
- c) Please conduct a scenario analysis in which weight reductions are applied only in the first cycle, rather than being perpetuated over the full model horizon.

Company Response: When a pharmaceutical product alongside of lifestyle management is evaluated against lifestyle management alone (SoC), the SoC regimen—dietary counselling, physical-activity guidance, and behaviour change support—is the ongoing SoC. In a lifetime cost-effectiveness comparison, SoC must operate continuously in both arms. The drug’s impact is incremental while on therapy and absent after stopping, but the lifestyle effect never “turns off.”

In this context, SoC operates in both arms of the model. The pharmacological intervention (resmetirom) provides an incremental benefit in addition to the SoC effect while patients remain on therapy. Once treatment is discontinued, the incremental effect of resmetirom ceases, but the underlying SoC effect continues, as patients are expected to maintain ongoing lifestyle management.

The SoC arm therefore captures the gradual and sustained weight reduction achievable through lifestyle and behavioural modifications. Following treatment discontinuation, patients’ weight trajectories are assumed to align with those observed in the SoC group, reflecting the influence of continued lifestyle management rather than a persistent pharmacologic effect.

The approach used to model weight changes over time is described in detail below:

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- Baseline BMI values were **directly drawn from individual-patient data (IPD) in MAESTRO-NASH**, and each patient's height is calculated and held constant throughout the simulation.
- BMI updates annually using the following algorithm:
 - Apply the absolute annual BMI change from Health Survey for England (HSE) 2021 Overweight and Obesity tables, which represent age- and sex-specific natural-history trends for the UK population [<https://files.digital.nhs.uk/03/D7F19D/HSE-2021-Overweight-and-obesity-tables.xlsx>] (40).
 - Apply, the 52-week percentage BMI change from MAESTRO-NASH:
 - For resmetirom (80 mg, 100 mg), this effect is applied each year only while patients remain on treatment and eligible (F2–F3).
 - For SoC, the placebo effect from MAESTRO-NASH is applied each year.
 - When patients discontinue, their BMI effect is switched to the placebo one.
 - Weight is recalculated from BMI using the fixed height, so all weight changes derive mathematically from BMI changes.
- b) In our model, patients actively receiving resmetirom experience additional weight reduction attributable to the pharmacologic effect of the treatment. Once resmetirom is discontinued, this specific treatment effect ceases, and subsequent weight changes are aligned with those observed in the SoC group. However, we haven't seen the reported effect by the EAG that losing weight at a faster rate in resmetirom arm than those receiving SoC, even after treatment discontinuation.
- c) We implemented the requested scenario using the following approach:

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- i. In the first year, we applied the effects of both SoC and resmetirom on weight changes across all age groups. As illustrated in Figure 4, both groups experienced an initial reduction in mean body weight, with the resmetirom group showing a slightly greater decrease compared to SoC.
- ii. From the second year onward, weight changes were modelled using data from the Health Survey for England to reflect typical long-term weight trends in the UK population.

The results of this scenario are summarised in Table 21, which presents the projected weight trajectories over time under these assumptions.

Figure 4. Mean weight changes over time: Resmetirom vs. SoC when treatment effect on weight reduction limited to one year

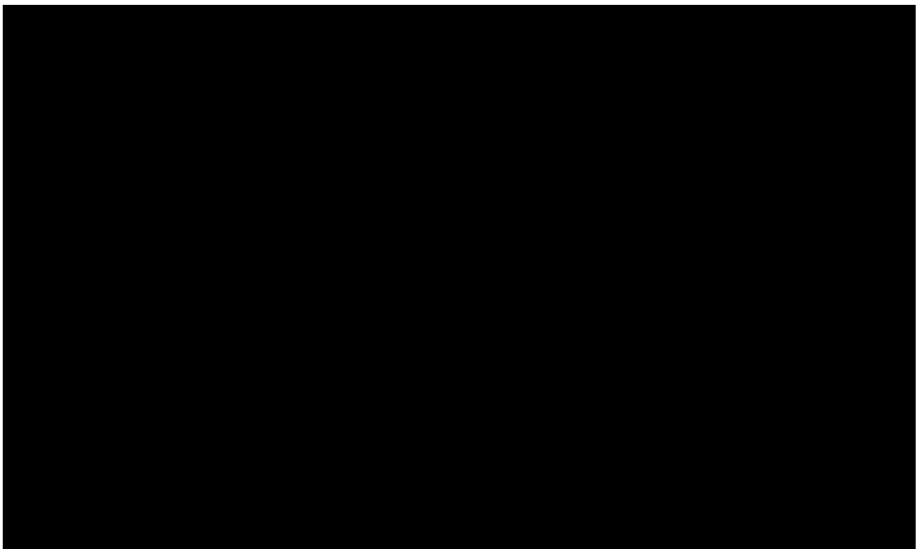


Table 21. Scenario analysis: weight reductions were applied only in the first cycle

Technologies	Total costs (£)	Total QALYs	Incremental costs (£)	Incremental QALYs	ICER (£/QALY)
SoC	██████	██████	-	-	-
Resmetirom	██████	██████	██████	██████	19,906

Abbreviations: ICER, incremental cost-effectiveness ratio; QALY, quality-adjusted life year; SoC, standard of care.

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Stopping rules

B12. Nouredin (2024) outlines criteria for stopping treatment based on response to treatment at 12 months. Does the company consider the proposed stopping rules reasonable? Why was a response based stopping rule does not considered in the company base case?

Company Response: Nouredin's expert panel proposes assessing response at 12 months (not earlier) using a totality-of-NITs approach (e.g., $\geq 30\%$ MRI-PDFF reduction; alanine aminotransferase (ALT) improvement; and liver stiffness trends), with discontinuation considered when no response is seen by 12 months or when ≥ 2 NITs worsen. We consider the soon-to-be-published BASL MASLD SIG consensus recommendations (presented in September 2025) to be more appropriate for UK clinical practice, as they define all criteria in terms of NITs available and in routine use within the NHS. BASL MASLD SIG recommends assessing hepatological response after a minimum of 12 months (11). A 'verified or repeated' $> 30\%$ decrease in liver stiffness indicates response to therapy. Non-response is a 'verified or repeated' $> 30\%$ increase in LSM or if there is clinical evidence of cirrhosis (lab, imaging), where discontinuation should be considered or an alternative pharmacotherapy. Those with an indeterminate change in LSM should continue treatment and should be reassessed at a further 12-month interval.

We considered there was insufficient empirical evidence in MAESTRO-NASH to inform a response-based discontinuation rule in our economic model. MAESTRO-NASH was primarily designed and powered for histological primary endpoints, and not for NIT primary endpoints. The available NIT data should be reviewed with a degree of caution if NIT patient selection and response are to be inferred as mentioned in A15. Instead, the observed annual all-cause discontinuation rates from that trial, as described in our methodology, acted as a proxy for multiple potential discontinuation reasons including loss of response. We felt that introducing an additional performance-linked stopping rule to this framework would have risked double-counting and may have generated further structural uncertainty. However, should NICE or the EAG wish to further explore response/performance based

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stopping rules for resmetirom, we would appreciate being advised as to the rules being considered to ensure they are realistic and within license.

B13. Priority Question: Please provide further justification for the assumption that patients stop treatment on entry to the F4 compensated cirrhosis health state.

- a) Please comment on whether this is required by the SmPC.
- b) Please comment on whether this was a protocol-mandated stopping rule in the MAESTRO-NASH trial and report how many patients stopped treatment due to progression to F4 compensated cirrhosis.
- c) Please comment on the clinical factors that might determine whether patients continue or discontinue treatment on progression to F4 compensated cirrhosis.
- d) Please provide scenario analysis in which:
 - i. 50% of patients continue on treatment in F4 compensated cirrhosis,
 - ii. 100% of patients continue on treatment in F4 compensated cirrhosis.

Company Response: The anticipated label wording is “Rezdiffra is indicated in conjunction with diet and exercise for the treatment of adults with noncirrhotic metabolic dysfunction-associated steatohepatitis (MASH) with moderate to advanced liver fibrosis (fibrosis stages F2 to F3).” Cirrhotic patients with fibrosis stage F4 are expected to be excluded in the indication as ‘the safety and effectiveness of resmetirom have not been established in patients with MASH cirrhosis’ (statement from European SmPC for Rezdiffra). Our submission and economic model were developed to demonstrate the cost-effectiveness of resmetirom within the anticipated SmPC indication.

Based on existing guidelines and the SmPC, we do not assume that treatment with resmetirom would continue in F4 CC patients. We cannot support off-label use even through speculative models and, at present, are not able to comment on clinical

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factors that might determine whether patients continue or discontinue treatment on progression to F4. Our model cycle length of one year is well-aligned with an anticipated schedule of annual clinical review in MASH; at each such review we would expect that a patient would be tested for presence for cirrhosis and have their eligibility for pharmacotherapies re-evaluated. This view has been supported by recently elicited expert clinical opinion directly regarding this EAG question.

The paper by Nouredin et al. 2024 (6) - previously highlighted by the EAG in Clarification Questions A15 and B12 - states that “patients with confirmed or suspected cirrhosis” falls under the classification of **“Patients who should not be treated with resmetirom”**. The only other population included under this subheading is “patients with early stage MASLD (no or early fibrosis [eg, stage 0 or 1]) because they are at very low risk for adverse liver-related outcomes”. Regarding cirrhotic patients, Nouredin et al. 2024 write, “we suggest erring on the side of not treating patients on the earlier side of the spectrum and avoiding patients who are likely to have established cirrhosis, because the benefit of resmetirom in this population is still being assessed in a phase 3 cirrhosis trial and this patient population may require different dosing and assessment”. The expert panel felt that resmetirom should not be recommended for use in this population “until efficacy and safety data in patient with cirrhosis are published”. The authors later note that the “MAESTRO OUTCOMES trial (NCT05500222), which is near full enrollment, will provide full efficacy and safety data in patients with compensated cirrhosis, which will guide dosing and future treatment decisions in this population (41).” The authors conclude that, “At this point, patients with cirrhosis and those with early (F0-1) fibrosis should not be treated with resmetirom.” The recently presented BASL MASLD SIG recommendations state that at follow up review at 12 monthly intervals, treatment should be stopped if there is evidence of progression to cirrhosis (11).

Considering the above, we consider that in response to this question and the next, Madrigal should not create or supply economic analyses for subpopulations currently falling outside of the anticipated regulatory license, the current decision problem, and the final scope issued by NICE. We have discussed with the EAG the challenges of modelling populations outside the scope of our trial data – for example, what to

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assume about the efficacy of resmetirom in such scenarios. We conclude that if the EAG were to independently consider analyses outside the F2/F3 population for any reason, these could at best serve as cost sensitivity analyses designed to assess operational or financial impacts of delayed or missed diagnostic updates, rather than conscious clinical decisions to maintain patients on therapy outside the licensed indication and inconsistent with consensus clinical recommendations.

B14. Priority Question: Please provide further justification for the assumption that patients stop treatment upon entering the F0 and F1 health states.

- a) **Please comment on whether this is required by the SmPC?**
- b) **Please comment on whether this was a protocol-mandated stopping rule in the MAESTRO-NASH trial and report how many patients stopped treatment due to regression to stage F0/F1 liver fibrosis.**
- c) **Please comment on the clinical factors that might determine whether patients continue or discontinue treatment on regression to stage F0/F1 liver fibrosis.**
- d) **Please comment on whether a similar stopping rule is used in practice within other locations. For example, is this stopping rule applied in the United States?**
- e) **Please comment on how you envisage regression to fibrosis stage F0/F1 would be assessed in practice and the suitability of non-invasive tests? The EAG is concerned that this may require regular liver biopsies (which are highly undesirable) due to the limitations of NITs in evaluating the fibrosis stage.**
- f) **Please conduct scenario analysis in which this stopping rule is removed from the model.**
- g) **Our clinical advisors suggested that this stopping rule could be operationalised by repeating NITs six months after the regular testing schedule, to confirm whether there has been regression in fibrosis**

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stage. Please conduct a scenario analysis in which the following costs are applied at treatment discontinuation under this stopping rule: i) six months of resmetirom acquisition and administration costs, ii) one additional outpatient consultation, and iii) additional NIT testing costs.

Company Response: a, b, and c) Please note our response to Clarification Question B13 above. We intend to present only analyses involving on-label treatment of MASH and have presented our main justifications. However, we acknowledge that the SmPC and MAESTRO-NASH study do not stipulate stopping rules related to fibrosis level or attainment/ of a particular clinical response. We also recognise that the EAG's questions in B14 also pertain to operationalisation of guidance.

Our economic model simulates a one-year cycle of annual review and health state updates, which align well with published guidance already cited (particularly recent BASL SIG recommendations). The paper by Nouredin et al. 2024 (6) was informed by an expert panel, which stated that “patients with early stage disease” falls under the classification of “**Patients who should not be treated with resmetirom**”. The authors state “Patients with early stage MASLD (no or early fibrosis [eg, stage 0 or 1]) should not be considered for resmetirom treatment because they are at very low risk for adverse liver-related outcomes”. The expert panel believes that such patients should be managed “with lifestyle intervention and optimization of cardiometabolic disease as outlined in the AASLD practice guidance.” The authors later conclude that, “At this point, patients with cirrhosis and those with early (F0-1) fibrosis should not be treated with resmetirom.” Nouredin et al. 2024 is a U.S.-focused publication informing U.S. clinical practice (6), whereas the FDA label is for patients with fibrosis stages F2 to F3, as stated in CS section 1.1. We do not consider the recommendations by Nouredin et al. 2024 and the U.S. Prescribing Information to constitute “stopping rules” around the F0/F1 or F4 populations, but rather as prerequisites for receiving treatment.

d) Regarding current U.S. clinical practice, resmetirom has had a U.S. license since April 2024. We cannot promote active off-label use and cannot comment on

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applications of stopping rules outside license, save to again cite the US-based Nouredin et al. 2024 paper (6).

e) As stated in the CS, we do not anticipate patients will be monitored using liver biopsy in the NHS. We anticipate that patients likely to receive resmetirom (fibrosis stages F2 to F3) are already being monitored within secondary care NHS services, having been identified by NITs. In CS section 1.3.1.8, we describe the current approach in NHS clinical practice for monitoring patients with NASH at fibrosis stages F2 and F3. The recent BASL SIG panel recommendations unanimously exclude biopsy as a required means to assess and stage MASH patients.

We further describe service provision of resmetirom and monitoring in CS section 2.13.3.3 and did not include liver biopsy as a method of monitoring patients in either treatment arm within the cost-effectiveness model.

g) We note that clinical expert opinion provided to the EAG suggested that a stopping rule should be implemented by means of an additional NIT midway through the current model cycle length. Having sought independent clinical advice from two NHS hepatologists on this suggestion, we believe this additional assessment timepoint would not be implemented in the NHS due to its burden on clinics and patients. More importantly, the clinicians noted that changes in NITs need to be assessed within a biologically plausible timeframe. Changes observed after only 6 months would likely be too subtle to facilitate a clinical decision; a suggested threshold for discriminating a real directional change in NIT value was a magnitude of > 25% in either direction in VCTE liver stiffness, which is unlikely to manifest over periods as short as six months. Moreover, BASL MASLD SIG consensus recommendations outline 12 monthly assessment intervals and NIT evaluation (11).

We do appreciate that in this sub-question the EAG is considering whether an additional financial impact should be modelled in the implementation of a stopping rule around transition to F1/F0. We would assert that this penalty is already sufficiently applied via the clinically most plausible one-year cycle length and considerable uncertainty distribution around patient fibrosis transitions to F0/F1. Therefore, we have not provided the analysis. The economic model documentation

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provided shows which parts of the R code handle costings around stopping rules, in case further sensitivity analysis is required.

Health-related quality of life

B15. Priority Question: The following questions relate to the HRQoL data that was collected in the MAESTRO-NASH trial.

- a) Please provide details on what population from the trial that the HRQoL values in the economic model are derived from; i.e, the mITT population (n=966) or the F2-F3 paired-biopsy population (PLB-W52, n=739) as described in Appendix K, Table 1.
- b) For each time point (baseline, week 24 and week 52) that the HRQoL (SF-36v2) questionnaire was administered in MAESTRO-NASH trial, please provide a summary, stratified by treatment arm, of the total patients available and the number of completed questionnaires.
- c) Please provide information on the number of missing observations in the HRQoL analyses at each time point. Provide details on how these were handled in subsequent regression analysis (e.g. complete case analysis or multiple imputation).

Company Response: We confirm that the health-related quality of life (HRQoL) values used in the economic model are derived from the mITT population (n = 966).

We have provided the following summary results, stratified by treatment arm, for each timepoint (baseline, week 24, and week 52) at which the SF-36v2 questionnaire was administered in the MAESTRO-NASH trial. Table 22 to Table 27 include the total number of patients available and the number of completed questionnaires at each timepoint for both treatment and placebo arms in both requested populations.

Table 22. EQ-5D-3L baseline utility outcome by treatment arm (miTT n = 966)

Treatment	Fibrosis Stage	MASH Resolution	Mean	n	Number missing	95% CI-LL	95% CI-UL
Placebo	1b	Yes					

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Placebo	1b	No					
Placebo	2	Yes					
Placebo	2	No					
Placebo	3	Yes					
Placebo	3	No					
Resmetirom 100 mg	1b	Yes					
Resmetirom 100 mg	1b	No					
Resmetirom 100 mg	2	Yes					
Resmetirom 100 mg	2	No					
Resmetirom 100 mg	3	Yes					
Resmetirom 100 mg	3	No					
Resmetirom 80 mg	1b	Yes					
Resmetirom 80 mg	1b	No					
Resmetirom 80 mg	2	Yes					
Resmetirom 80 mg	2	No					
Resmetirom 80 mg	3	Yes					
Resmetirom 80 mg	3	No					

Abbreviations: CI, confidence interval; F1-F3, fibrosis stages F1-F3; LL, lower limit; MASH, metabolic dysfunction-associated steatohepatitis; UL, upper limit.

Table 23. EQ-5D-3L 52-week utility outcome by treatment arm (miTT n = 966)

Treatment	Fibrosis Stage	MASH Resolution	Mean	n	Number missing	95% CI-LL	95% CI-UL
Placebo	1	no					
Placebo	2	no					
Placebo	3	no					
Placebo	1	yes					
Placebo	2	yes					
Placebo	3	yes					
Resmetirom 100 mg	1	no					
Resmetirom 100 mg	2	no					
Resmetirom 100 mg	3	no					
Resmetirom 100 mg	1	yes					
Resmetirom 100 mg	2	yes					
Resmetirom 100 mg	3	yes					
Resmetirom 80 mg	1	no					

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Resmetirom 80 mg	2	no					
Resmetirom 80 mg	3	no					
Resmetirom 80 mg	1	yes					
Resmetirom 80 mg	2	yes					
Resmetirom 80 mg	3	yes					

Abbreviations: CI, confidence interval; F1-F3, fibrosis stages F1-F3; LL, lower limit; MASH, metabolic dysfunction-associated steatohepatitis; UL, upper limit.

Table 24. EQ-5D-3L 24-week utility outcome by treatment arm (miTT n = 966)

Treatment	Fibrosis Stage	MASH Resolution	Mean	n	Number missing	95% CI-LL	95% CI-UL
Placebo	1	no					
Placebo	2	no					
Placebo	3	no					
Placebo	1	yes					
Placebo	2	yes					
Placebo	3	yes					
Resmetirom 100 mg	1	no					
Resmetirom 100 mg	2	no					
Resmetirom 100 mg	3	no					
Resmetirom 100 mg	1	yes					
Resmetirom 100 mg	2	yes					
Resmetirom 100 mg	3	yes					
Resmetirom 80 mg	1	no					
Resmetirom 80 mg	2	no					
Resmetirom 80 mg	3	no					
Resmetirom 80 mg	1	yes					
Resmetirom 80 mg	2	yes					
Resmetirom 80 mg	3	yes					

Abbreviations: CI, confidence interval; F1-F3, fibrosis stages F1-F3; LL, lower limit; MASH, metabolic dysfunction-associated steatohepatitis; UL, upper limit.

Table 25. EQ-5D-3L baseline utility outcome by treatment arm (PLB n = 739)

Treatment	Fibrosis Stage	MASH Resolution	Mean	n	Number missing	95% CI-LL	95% CI-UL
Placebo	2	No					
Placebo	2	Yes					

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Placebo	3	No					
Placebo	3	Yes					
Resmetirom 100 mg	2	No					
Resmetirom 100 mg	2	Yes					
Resmetirom 100 mg	3	No					
Resmetirom 100 mg	3	Yes					
Resmetirom 80 mg	2	No					
Resmetirom 80 mg	2	Yes					
Resmetirom 80 mg	3	No					
Resmetirom 80 mg	3	Yes					

Abbreviations: CI, confidence interval; F2-F3, fibrosis stages F2-F3; LL, lower limit; MASH, metabolic dysfunction-associated steatohepatitis; UL, upper limit.

Table 26. EQ-5D-3L 24-week utility outcome by treatment arm (PLB n = 739)

Treatment	Fibrosis Stage	MASH Resolution	Mean	n	Number missing	95% CI-LL	95% CI-UL
Placebo	2	No					
Placebo	2	Yes					
Placebo	3	No					
Placebo	3	Yes					
Resmetirom 100 mg	2	No					
Resmetirom 100 mg	2	Yes					
Resmetirom 100 mg	3	No					
Resmetirom 100 mg	3	Yes					
Resmetirom 80 mg	2	No					
Resmetirom 80 mg	2	Yes					
Resmetirom 80 mg	3	No					
Resmetirom 80 mg	3	Yes					

Abbreviations: CI, confidence interval; F2-F3, fibrosis stages F2-F3; LL, lower limit; MASH, metabolic dysfunction-associated steatohepatitis; UL, upper limit.

Table 27. EQ-5D-3L 52-week utility outcome by treatment arm (PLB n = 739)

Treatment	Fibrosis Stage	MASH Resolution	Mean	n	Number missing	95% CI-LL	95% CI-UL
Placebo	2	No					
Placebo	2	Yes					
Placebo	3	No					
Placebo	3	Yes					

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Resmetirom 100 mg	2	No	■	■	■	■	■
Resmetirom 100 mg	2	Yes	■	■	■	■	■
Resmetirom 100 mg	3	No	■	■	■	■	■
Resmetirom 100 mg	3	Yes	■	■	■	■	■
Resmetirom 80 mg	2	No	■	■	■	■	■
Resmetirom 80 mg	2	Yes	■	■	■	■	■
Resmetirom 80 mg	3	No	■	■	■	■	■
Resmetirom 80 mg	3	Yes	■	■	■	■	■

Abbreviations: CI, confidence interval; F2-F3, fibrosis stages F2-F3; LL, lower limit; MASH, metabolic dysfunction-associated steatohepatitis; UL, upper limit.

The number of missing utility observations at each timepoint are provided in the tables above. To assess whether utility scores differed by treatment arm, we performed regression analyses adjusting for fibrosis stage, NASH resolution status, treatment assignment, age, and sex, thereby capturing heterogeneity and controlling for confounding. The dependent variable was the EQ-5D utility score, and independent variables included fibrosis stage, NASH resolution status, treatment assignment, age, and sex. Given that health-utility data are bounded and often have skewed distributions with non-normal residuals, we judged standard linear regression inappropriate. Instead, we explored alternative functional and link specifications for the generalised linear model and selected the best-fitting one. No imputation was performed for missing data; all regression analyses were based on complete-case data only.

B16. Priority Question: The following queries concern the mapping of SF-36v2 data collected in the MAESTRO-NASH trial to EQ-5D-3L utilities.

- a) Please provide a detailed, step-by-step description of how SF-36v2 trial data were converted to the utility values reported in Table 38. This should include: (i) tables of results for each health state, (ii) the equations and calculations used, (iii) any assumptions applied, and (iv) clarification of the “best-performing published regression model from Rowen et al. (2009)” referred to in the CS (CS, p.129).

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- b) Please specify the trial population from which these values were derived [e.g. the mITT population (n=966) or the F2–F3 paired-biopsy population (PLB-W52, n=739; Appendix K, Table 1, p.1)]. Please re-run the HRQoL analyses for both populations and highlight any differences in results.**
- c) Please report in full the regression analysis used to estimate the health state utility values from the trial.**
- d) Please conduct an additional analysis of trial data to investigate the impact of MASH resolution on utility scores. This model should not include fibrosis state as a covariate.**
- e) Please provide analysis evaluating the impact of treatment arm on HRQoL.**
- f) If available, please provide HRQoL data and mapped EQ-5D-3L utility values for patients with stage F4 fibrosis.**

Company Response: a) To generate preference-based utility values suitable for cost-effectiveness modelling, SF-36v2 domain scores from the MAESTRO-NASH trial were converted into EQ-5D-3L utility values using the regression-based mapping algorithm developed by Rowen and colleagues in 2009 (42). This approach is widely used and accepted by NICE for health-economic evaluations when EQ-5D data are not directly available, as it has been validated across a wide range of UK patient populations. Among the models proposed by Rowen et al. 2009, Model 3 – a random-effects generalised least-squares (GLS) model including squared and interaction terms – was selected for this analysis because it demonstrated the best overall predictive accuracy.

The eight SF-36 domains – Physical Functioning (PF), Role Physical (RP), Bodily Pain (BP), General Health (GH), Vitality (VT), Social Functioning (SF), Role Emotional (RE), and Mental Health (MH) – were used as predictors in the regression equation. In addition to these main effects, squared terms for each domain and several significant interaction terms were included to capture non-linear and cross-dimensional health relationships. The model equation can be expressed generally as

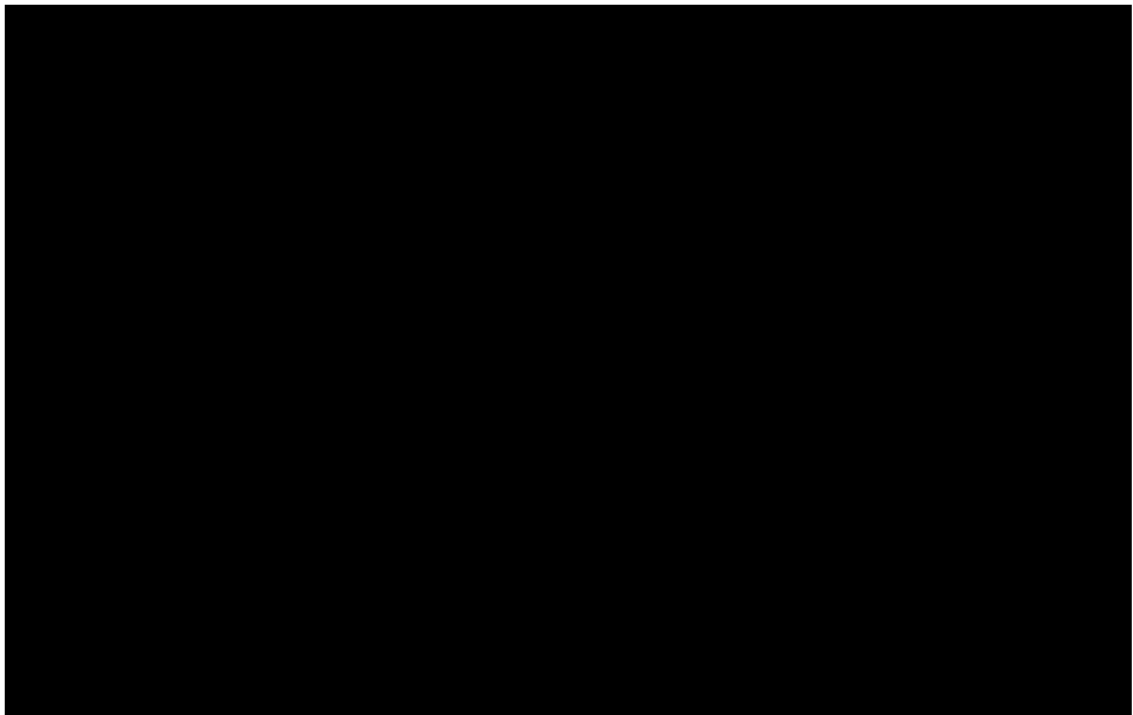
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the sum of a constant, each domain weighted by its coefficient, plus the squared and interaction terms. Mathematically, EQ-5D utility equals β_0 plus the weighted contributions of the eight domains, their squares, and the selected interactions, plus a residual error term.

In this analysis, the coefficient values reported by Rowen et al. 2009 for Model 3 were applied directly. The constant was -0.256 . The domain coefficients were 0.559 for PF, -0.146 for RP, 0.715 for BP, 0.407 for GH, 0.017 for VT, 0.293 for SF, 0.067 for RE, and 0.483 for MH. Corresponding squared-term coefficients were -0.227 for PF^2 , 0.001 for RP^2 , -0.303 for BP^2 , 0.032 for GH^2 , -0.012 for VT^2 , -0.163 for SF^2 , 0.034 for RE^2 , and -0.242 for MH^2 . Significant interaction terms included PF $\times$ BP (-0.031), PF $\times$ SF (-0.023), PF $\times$ MH ($+0.014$), RP $\times$ SF ($+0.049$), BP $\times$ MH (-0.113), GH $\times$ MH (-0.066), and VT $\times$ MH ($+0.148$). These interaction effects were incorporated for all patients and timepoints, as they improved the model's fit and captured relationships between mental and physical components of health.

b) The HRQoL values were derived from the mITT population ($n = 966$). We have re-run the analyses using both the mITT and the F2–F3 paired-biopsy (PLB-W52, $n = 781$ (including F1B)) populations. The results are consistent across both groups, with only minor numerical differences that do not change the overall interpretation of treatment effects.

Figure 5. Comparison of 52-week EQ-5D utility scores by fibrosis stage and NASH resolution status (miTT vs. PLB)



- c) We did not use regression modelling to estimate the health state utility values. Instead, descriptive statistics were used to calculate the mean EQ-5D utility scores at each assessment point. It worth noting that the regression-based estimates yielded comparable results and did not materially alter the conclusions.
- d) The GLM regression results for EQ-5D utility at 52 weeks (miTT population), using Gaussian and Beta distributions with identity link functions, are in Table 28 to Table 30.

Table 28. GLM regression results for EQ-5D utility at 52 weeks (miTT population), using Beta dist. and identity link function

term	Coefficient	std.error	Statistic	p-value
(Intercept)				
Resmetirom 100 mg				
Resmetirom 80 mg				
AGE				
SEXM				
NASH resolution				
(phi)				

Abbreviations: NASH, non-alcoholic steatohepatitis.

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Table 29. GLM regression results for EQ-5D utility at 52 weeks (miTT population), using Gaussian dist. and identity link function

term	Coefficient	std.error	Statistic	p-value
(Intercept)				
Resmetirom 100 mg				
Resmetirom 80 mg				
AGE				
SEX				
NASH resolution				

Abbreviations: NASH, non-alcoholic steatohepatitis.

Table 30. GLM regression results for EQ-5D utility at 52 weeks (miTT population), using Beta dist. and identity link function

term	Coefficient	std.error	Statistic	p-value
(Intercept)				
Resmetirom 100 mg				
Resmetirom 80 mg				
AGE				
SEX				
NASH resolution				

Abbreviations: NASH, non-alcoholic steatohepatitis.

- d) Please note that MAESTRO-NASH is an ongoing study collecting long-term outcomes. At this stage we are blinded to the F4 (cirrhosis) subgroup in the trial dataset; therefore, we are unable to provide HRQoL data or mapped EQ-5D-3L utility values specifically for patients with stage F4 fibrosis.

B17. The following questions relate to Appendix F: Health-related quality-of-life studies SLR

- a) The PRISMA flow diagram (Figure 1, p7) has excluded full-text publications (n=144). Can the company please provide rationale for excluding each of these studies?
- b) The EAG has identified the following study which may be relevant source of utility values Paptheodoridi et al. 2023 (doi: 10.1016/j.cgh.2023.04.018). Was this identified in the systematic review searches? If so, why was it excluded?

Company Response: (a) A table listing the studies excluded at the full-text screening stage, along with the corresponding reasons for exclusion, has now been provided for the review of HRQoL studies (Appendix A-E).

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(b) Yes, Paptheodoridi et al. 2023 (43) was identified during the systematic review of HRQoL data. However, as described in Appendix F of the CS, the population inclusion criteria for the HRQoL review were restricted to adult patients (≥ 18 years) with a diagnosis of MASH and liver fibrosis, or to patients with MASLD and presumed or suspected MASH.

The Paptheodoridi et al. 2023 study (43) did not meet these criteria, as it focused on a broader NAFLD cohort rather than patients with clinically defined MASH/NASH. To maintain alignment with the indication of interest—MASH with moderate to advanced fibrosis (F2–F3, non-cirrhotic)—and to ensure that derived utility values reflected the appropriate disease severity and pathophysiology, studies in broader NAFLD populations were excluded.

B18. The following questions relate to the NG49 utility values used in the company base case.

- a) The company state that the most relevant published source of utility values is from NICE Guidelines (NG49) published in 2016. The company state that these values have been used in prior health technology evaluations in fatty liver disease. Other than NG49, can you please provide the reference (s) for the other prior health technology evaluations?
- b) Can the company please explain the original source of the utility values used in NG49 for all health states and to report exactly how they were derived (e.g. the patients/population from, where the study was conducted)?

Company Response: (a) NICE's NG49 (2016) utility values for NAFLD/NASH (19) have become a de facto reference standard. They have been explicitly used in a previous Health Technology Wales report (44). Major HTA bodies globally have acknowledged NG49's findings (for instance, ICER 2023 cited NICE's guideline recommendations and modeled similar utility decrements (14)).

b) In NG49 (19), the Guideline Development Group (GDG) first undertook a systematic review and found very limited, state-specific EQ-5D evidence for NAFLD/NASH—most studies did not report utilities by fibrosis or cirrhosis stage, and

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several used instruments without validated mappings to EQ-5D—so direct use of trial-based utilities was not feasible; one study (David et al., 2009 (45)) did report a mean utility of 0.52 for non-NASH NAFLD, but the GDG considered this implausibly low for baseline modelling. Consequently, the GDG derived utilities by (i) setting the baseline utility for non-NASH NAFLD equal to the obesity utility estimated in NICE PH53 (46), which modelled the BMI–EQ-5D relationship using UK population data (thereby providing a UK-relevant EQ-5D-3L baseline consistent with the NICE reference case), and then (ii) obtaining utilities for progressive liver health states (NASH/fibrosis stages, compensated cirrhosis, decompensated cirrhosis, hepatocellular carcinoma) by applying proportional decrements taken from a published hepatitis B utility set previously used in NICE hepatitis B economic modelling (drawn from published patient cohorts), i.e., each NAFLD/NASH state utility was calculated as the obesity baseline multiplied by the ratio of the hepatitis B state utility to the hepatitis B baseline utility. All values were anchored to EQ-5D-3L with the UK tariff, reflecting UK preferences and ensuring consistency with NICE methods. This approach—grounded in UK data for the baseline (PH53) and disease-progression decrements from a clinically analogous liver disease (hepatitis B)—produced a coherent, UK-relevant set of utilities spanning mild NAFLD through cirrhosis and HCC, while avoiding reliance on a single outlying estimate and addressing the absence of robust, state-specific EQ-5D data in NAFLD at the time.

B19. Priority Question: The following queries relate to Paptheodoridi et al. (2023) and the clinical validity of the utility values in the base case analysis.

- a) Paptheodoridi et al. (2023) reported that HRQoL was significantly lower in patients with NAFLD compared with matched controls from the general population. This contrasts with the company’s base-case analysis, in which utility values are higher than those of age- and sex-matched general population values. Please justify why the base-case utility values exceed those of the general population.**
- b) Paptheodoridi et al. (2023) found no statistically significant difference in HRQoL between patients with advanced fibrosis (F3) and those without advanced fibrosis. Does the company consider that patients with**

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moderate fibrosis (F2) have equivalent utility values to those with advanced fibrosis (F3)?

- c) Paptheodoridi et al. (2023) reported a statistically significant difference in HRQoL of 0.062 between patients with cirrhosis (F4) and those without cirrhosis (Supplementary Table 2). This decrement is substantially smaller than the 0.24 decrement applied in the company's base case. Please justify why the utility value for compensated cirrhosis (F4) in the model is so low, and comment on the inconsistency between the modelled utility values and those reported by Paptheodoridi et al. (2023).**
- d) Clinical advice to the EAG suggests that the largest decrement in HRQoL occurs between compensated cirrhosis (F4) and decompensated cirrhosis (DCC). Does the company agree with this assessment?**

Company Response: (a) We agree with Papatheodoridi et al. 2023 (43) that NAFLD is associated with lower HRQoL than the general population. Their cohort is older (mean ≈59 years), has a heavier metabolic burden, and includes ~one-third with cirrhosis—all factors that depress EQ-5D; it is also a tertiary-centre sample, which tends to concentrate sicker patients. It should be mentioned that the HRQoL instrument used in the study by Paptheodoridi et al. 2023 is EQ-5D-5L, not the 3L. By contrast, our base case uses data from a screened population with active follow-up; F4 is not included in the trial-based utility estimates, and for advanced states we apply conservative NG49 utilities (e.g., F3 with NASH = 0.72, F3 without NASH = 0.75, F4 = 0.600), which are well below UK general-population EQ-5D-3L norms (Kind, Hardman & Macran, 1999 (47)). Please note: the utility values in CS Table 37 should be amended to 0.75 for F3 without NASH and 0.72 for F3 with NASH. We confirm the model already uses these correct values; the discrepancy is a typographical error in the CS.

b) We do not assume equivalence between F2 and F3. In the base case, we apply lower utilities for F3 than for F2 to remain consistent with NICE NG49 and to avoid overstating HRQoL in more advanced disease:

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F2: 0.870 (without MASH), 0.840 (with MASH)

F3: 0.750 (without MASH), 0.720 (with MASH)

This approach maintains alignment with NICE precedent and ensures a conservative representation of more advanced (non-cirrhotic) disease. In our scenario analysis, we used utility data from the MAESTRO-NASH clinical trial, which provides direct EQ-5D values for fibrosis stages. The trial data show very similar utilities for F2 and F3, consistent with the findings reported by Papatheodoridi et al. 2023 (43).

Importantly, when these trial-based utilities are applied, the impact on model outcomes is minimal, and the overall cost-effectiveness results remain unchanged.

c) The utility value for compensated cirrhosis (F4) in our model was taken from NICE Guideline NG49, in line with the approach used for all other health states. The values in NG49 are based on UK-relevant data and expert consensus, providing utilities applicable to the UK setting and consistent across chronic liver disease models (19).

The methodology and population used by Paptheodoridi et al. 2023 differ substantially from those informing NG49. Specifically, Paptheodoridi et al. 2023 employed EQ-5D-5L data and NAFLD cohort not NASH whereas NG49 utilities were developed for progressive chronic liver diseases. Therefore, the two sources are not directly comparable in terms of instruments, populations, or valuation methods.

d) There is limited direct evidence in the published literature quantifying health-related quality of life (HRQoL) decrements between specific stages of liver disease, particularly for the transition from compensated cirrhosis (F4) to decompensated cirrhosis (DCC). However, findings from our systematic review indicate a consistent and clinically meaningful additional loss in HRQoL associated with decompensation. Studies such as Aggio et al. 2024 (48) demonstrated a clear decline in EQ-5D-5L utility values from F3 to compensated and decompensated stages, while the NASH-CHECK studies (O'Connor et al., 2024/2025 (49)) reported statistically significant deterioration in activity limitation and social impact domains in patients with decompensated disease compared to those with compensated cirrhosis.

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B20. In the CS (p.131), acute event decrements (for example, CVD events) were applied to those state utilities for the duration specified in the model (**Error! Reference source not found.**). Please clarify and tabulate the duration given the mean number of cycles that the decrements were applied for.

Company Response: We confirm that for myocardial infarction (MI) and stroke, the acute disutility (–0.04 and –0.05, respectively) is applied for the first year following the event, after which a chronic post-event disutility (–0.03) is applied for the remainder of the patient’s life. For T2DM, a constant lifetime disutility (–0.037) is applied to reflect its chronic impact on HRQoL.

B21. Priority question: In the CS (p.131), it states: “...explored age-adjusted utilities using HSE 2014 norms”. Please clarify the reference upon which the age-adjustment is based and explain how these values were applied (programmed) in the economic model.

- a. The results of this scenario analysis (Table 48, Scenario 6: Applying age- and sex-specific utility decrements) seem odd to the EAG. The result is the exact same as the base-case. Can the company check this analysis has been implemented and reported correctly.

Company Response: The age-adjusted utilities were derived using methods outlined in the NICE Decision Support Unit (DSU) report: “Estimating EQ-5D by Age and Sex for the UK” (Hernández Alava, Pudney, & Wailoo, 2022, University of Sheffield (50)). This approach uses EQ-5D-3L norms from the Health Survey for England (HSE 2014) dataset to estimate expected utility values by age and sex for the UK general population. In line with the DSU methodology, utilities decline progressively with age to reflect natural deterioration in HRQoL. Within the economic model, this adjustment was programmed by applying the age- and sex-specific EQ-5D values as multiplicative age-weighting factors to each health-state utility. At every cycle, the mean age was updated, and the corresponding utility adjustment was automatically applied based on the DSU-derived age–utility function.

a) We have reviewed the model and realised that age-adjusted utilities were used in all base cases and scenario analyses. This issue relates to a switch within the MSM

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that controls the application of age-adjusted utility values. The switch was defined to turn on only for the scenario analysis testing the impact of age-adjusted utilities. However, it remained on across all analyses, including the base case. As a result, the results for Scenario 6 (Applying age- and sex-specific utility decrements) in Table 48 are identical to those in the base case. Moreover, we realised that these age-adjusted utilities were not used in the PSA. Therefore, we would like to provide some updates to the CS.

1- Modification in page 129 and 130

[started from: In the base-case analysis, time-varying age or sex adjustments are not applied to: we explored age-adjusted utilities using HSE 2014 norms in a scenario analysis]:

In the base-case analysis and all scenario analyses, time-varying age- and sex-specific adjustments are applied to health-state utility values. This approach aligns with the NICE reference case, which recommends using UK population norms to ensure that quality-of-life trajectories reflect age-related changes over time.

2- In Table 43, the following row should be removed:

Utilities (age/sex adjustment)	No time-varying age- or sex-specific decrements applied to base-case health-state utilities; scenario analysis applies HSE 2014 norms.	Base case avoids double-counting ageing effects already captured via comorbidities; prevents methodological bias against survival gains; DSU evidence shows limited impact of alternative age-adjustments on severity metrics and variability across data sources. Maintains consistency with trial-derived utilities; scenario with HSE 2014 norms explores uncertainty.

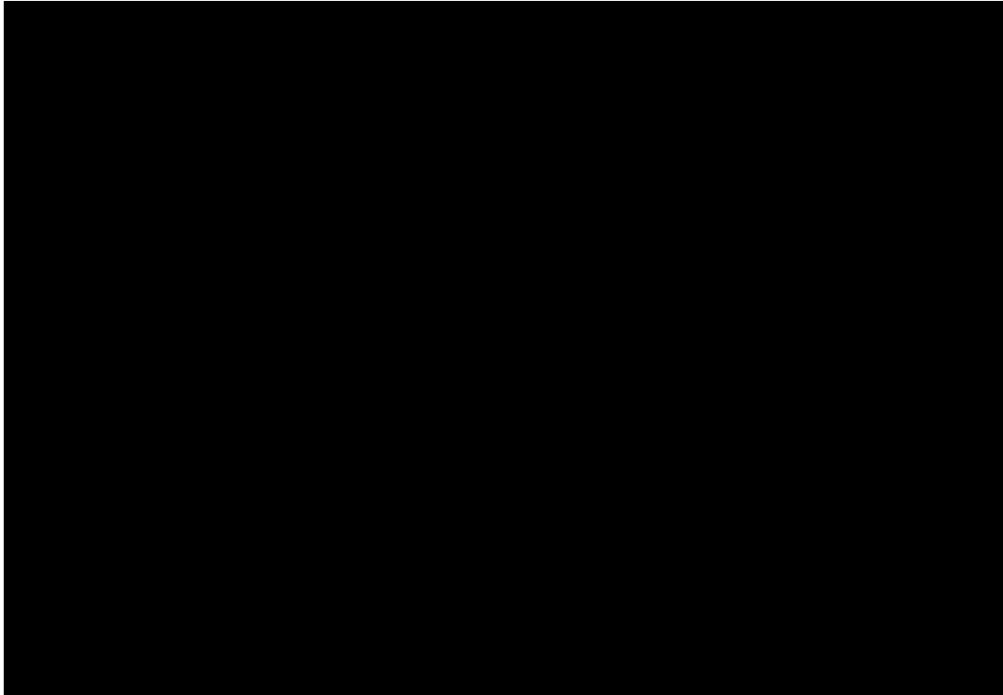
3- Table 46

Technologies	Total costs (£)	Total LYG	Total QALYs	Incremental costs (£)	Incremental LYG	Incremental QALYs	ICER versus baseline (£/QALY)
SoC							
Resmetirom							22,125

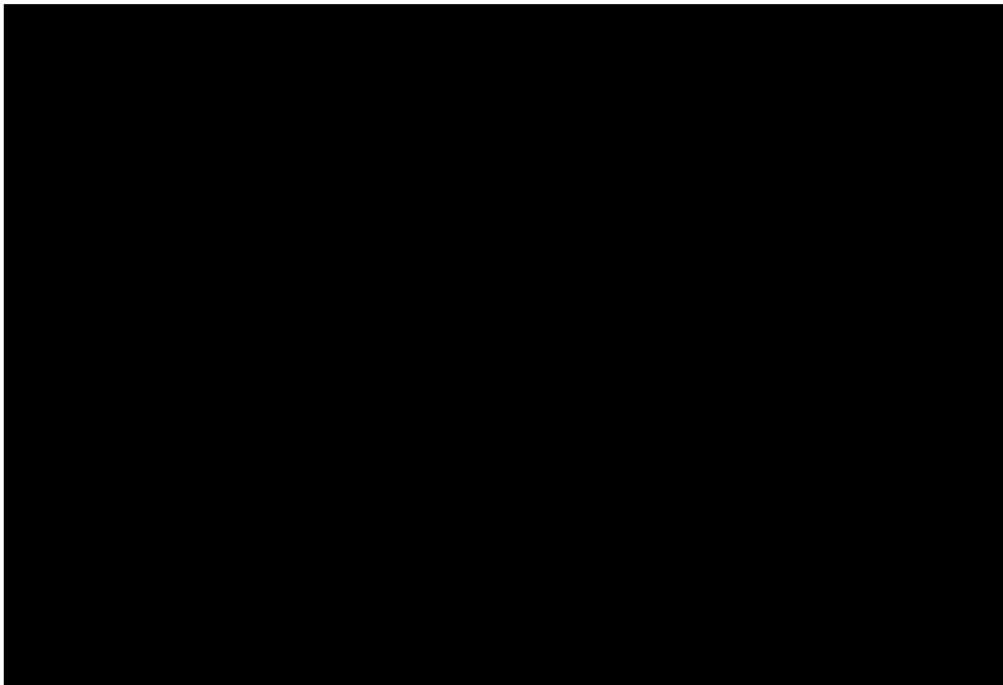
Abbreviations: ICER, incremental cost-effectiveness ratio; LYF, life years gained; QALY, quality-adjusted life year; SoC, standard of care.

4- Figure 16

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5- Figure 17



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6- In Table 48, Scenario 6 should be updated so that age- and sex-specific utility decrements are not applied.

Technologies	Total costs (£)	Total QALYs	Incremental costs (£)	Incremental QALYs	ICER (£/QALY)
Scenario 6: Exclude the application of age- and sex-specific utility decrements					
SoC	████	████			
Resmetirom	████	████	████	████	19,487

7. The results for the diabetes subpopulation have been updated and incorporated into the revised company submission. The revised submission can be found in **Appendix A–F**. The table 49 in the main CS should be updated as below.

Technologies	Total costs (£)	Total LYG	Total QALYs	Incremental costs (£)	Incremental LYG	Incremental QALYs	ICER versus baseline (£/QALY)
SoC	████	████	████				
Resmetirom	████	████	████	████	████	████	26,671

8. The table 51 in the main CS should be updated as below.

Technologies	Total costs (£)	Total QALYs	Incremental costs (£)	Incremental QALYs	ICER versus baseline (£/QALY)
SoC	████	████			
Resmetirom	████	████	████	████	29,789

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Resource use and costs

B22. Priority Question: The CS states sources from which health state costs were derived (Table 40 of CS). However, the corresponding mean values reported in the ‘cost_inputs.xlsx.’ file, before inflation, differ from those in the cited sources. Please clarify:

- a. Which specific values from Davidson et al. 2025 were used for the following health states: DCC year 1, DCC year 2+, HCC year 1 and HCC year 2+? Clarify any adjustments or alternative data sources applied in deriving the costs presented in the submission.
- b. Which specific values for liver transplantation costs: LT (procedure), LT (year 1 follow-up), LT (year 2+ follow-up), from NICE NG49 were used? Clarify any adjustments or alternative data sources applied in deriving the costs presented in the submission.

Company Response: a) Thank you very much for your observation. The data for the costs of DCC and HCC were obtained from an unpublished part of the data analysis conducted by Davidson et al. 2025 (8). These data were not included in the published version of the study but were made available to us by the authors as additional internal communication (Table 31). We used this unpublished dataset because it reflects more real-world resource use and provides more conservative cost estimates compared with those reported in NG49 (19).

Please note that the values used in the model for DCC (Year 1 and Year 2+) and HCC (Year 1 and Year 2+) correspond to this unpublished dataset after inflation adjustment.

Table 31. Unpublished costs of DCC and HCC (Year 1 and Year 2+) from Davidson et al. (2025), reported in 2022 costs

		DCC	HCC
N patient Year 1	N		
	N (%) with cost		
	Total		
	Mean (SD)		
	Median (IQR)		

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	Range (min - max)		
Year 2+	N (%) with cost		
	Total		
	Mean (SD)		
	Median (IQR)		
	Range (min - max)		

Abbreviations: DCC, decompensated cirrhosis; HCC, hepatocellular carcinoma; IQR, interquartile range; SD, standard deviation.

c) The first-year cost of liver transplantation was obtained from the average estimate reported in NICE Guideline NG49 (19), which was originally based on 2013–2014 price levels and reflected a 6-month period. Given that the model uses an annual cycle length, the cost was first annualised and subsequently inflated to 2024 prices using the PSSRU inflation indices. This resulted in an updated cost of £76,762. For context, the National Schedule of NHS Costs (2022/23) indicates that the HRG code GA15A – Liver Transplant, 18 years and over has a unit cost of £35,595, which, when inflated to 2024, equates to approximately £38,123. However, this HRG cost reflects only the procedural component and does not account for additional expenses related to organ procurement, preservation, and the high rate of post-transplant complications that the NHS incurs. Post-transplant complication includes early allograft dysfunction, renal replacement therapy, primary non-function, hepatic artery thrombosis, biliary complications, and re-transplantation following graft failure. These complications substantially increase NHS resource utilisation beyond the base HRG tariff. The estimated cost also aligns with the findings reported in Table 4 of the study by Morgan et al 2021 (51). It is important to note that the study by Singh et al. 2017 (52) has estimated much higher overall costs when combining contemporary NHS Blood and Transplant data with expert elicitation, reporting a best estimate of £121,211.

B23. The CS states (Table 2, p.24): Patients should be monitored during treatment with resmetirom for elevations in liver tests and for the development of liver-related adverse reactions. Monitor for symptoms and signs of hepatotoxicity (e.g., fatigue, nausea, vomiting, right upper quadrant pain or tenderness, jaundice, fever, rash,

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and/or eosinophilia [$> 5\%$]. Please justify why no monitoring costs are applied in the economic model?

Company Response: The monitoring described in CS Table 2 pertains to routine safety surveillance (liver function tests (LFTs) and clinical assessment for hepatotoxicity symptoms). These activities are part of standard NASH care and occur in both comparator and intervention arms; as such, they do not generate incremental costs attributable to resmetirom.

Severity Modifier

B24. Priority Question: The company's submission does not include a calculation of the disease severity modifier criteria. Please provide in table format in line with the NICE methods manual.

Company Response: In line with the NICE Health Technology Evaluations Manual (Sections 6.2.12–6.2.22) (53), the company has conducted a disease severity assessment based on both absolute and proportional QALY shortfall calculations. The results are summarised in Table 32.

Table 32. Severity modifier calculation based on NICE proportional shortfall methodology

Parameter	Description / Source	Value / Rationale
Mean age of modelled population	As per base-case model	56.2 years
Total QALYs – Standard of Care (SoC)	Lifetime QALYs under current NHS practice	■
Total QALYs – Resmetirom	Lifetime QALYs with resmetirom	■
Incremental QALY gain (Δ QALY)	Resmetirom – SoC	■
Total QALYs – General population (age 56)	Expected remaining lifetime QALYs for a general population of the same mean age (discounted, EQ-5D-based) calculated based on the following tool https://shiny.york.ac.uk/shortfall/	14.04
Absolute QALY shortfall	General population – SoC	$14.04 - \text{■} = \text{■}$
Proportional QALY shortfall	(General population – SoC) $\div$ General population	$\text{■} = \text{■}$
Severity level	Based on NICE thresholds (Section 6.2.18, PMG36 2025)	Below 0.32 $\rightarrow$ Low severity

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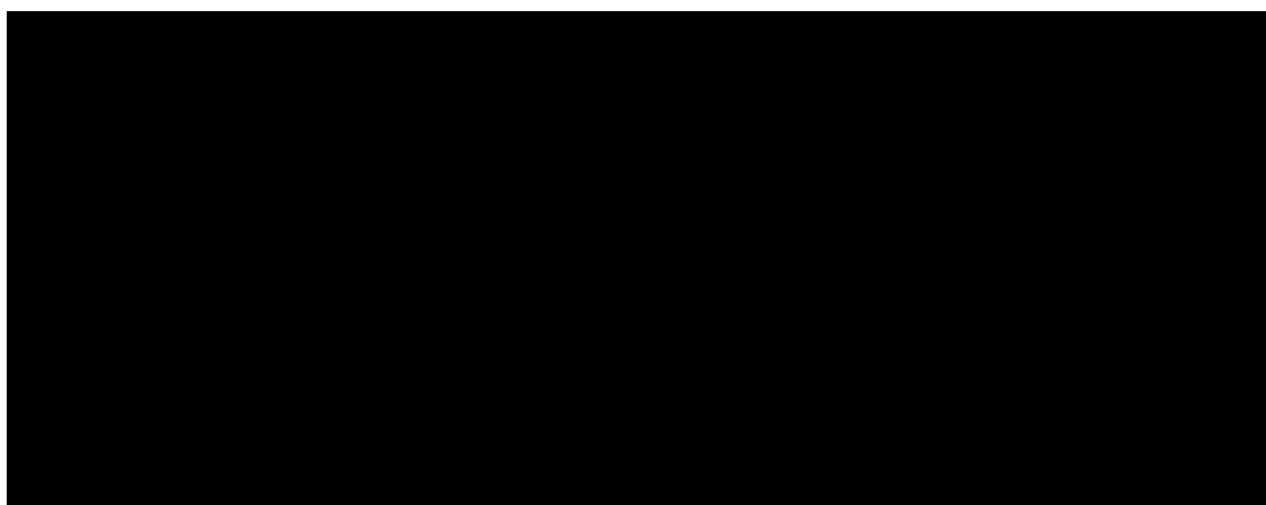
Applicable weighting	NICE severity weight (maximum of proportional or absolute shortfall)	1.0 (no modifier applied)
Adjusted ICER	$\text{ICER} \times (1 \div \text{modifier})$	No adjustment required

Abbreviations: EQ-5D, Euroqol 5-Dimensions; ICER, incremental cost-effectiveness ratio; QALY, quality-adjusted life year; SoC, standard of care.

The analysis was undertaken using the NICE-endorsed QALY Shortfall Calculator developed by the University of York (Hernández-Alava et al., 2022 (50)). Inputs were aligned with the modelled population in the base case, reflecting a mean age of 56.2 years and lifetime QALYs under SoC and resmetirom treatment.

Based on this calculation, the absolute shortfall in QALYs for untreated patients (SoC) is [REDACTED], and the proportional shortfall is 0.32 (32%), as shown in Figure 6. According to the severity thresholds in the NICE manual, this corresponds to a “low severity” condition (proportional shortfall < 0.32). Therefore, a severity weight of 1.0 applies, and no adjustment to the ICER is required.

Figure 6. QALY shortfall calculation using the NICE-endorsed QALY shortfall calculator (University of York, Hernández-Alava et al., 2022)



This confirms that the base-case ICER for resmetirom remains valid without modification for disease severity

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Section C: Textual clarification and additional points

Clarifications

C1. In Table 36 (p.126 - Liver-related mortality probabilities) of the CS, it appears that there is an error/typo in the mean annual probability of DCC to death. The EAG thinks this should be 0.130 and not 0.0130 as reported.

Company Response: Please refer to our detailed response in Section B1 (page 31) of this document.

C2. The company states in section 3.3.1 of the CS that “Dose adjustments are required for resmetirom in patients receiving concomitant therapy with moderate or strong CYP2C8 inhibitors” This contradicts the method of administration in Table 2 of the CS that states “Concomitant use of resmetirom with strong CYP2C8 inhibitors (e.g., gemfibrozil) is not recommended.” Please clarify if there is an expectation that doses will be adjusted in these cases.

Company Response: We thank the EAG for identifying this point and appreciate the opportunity to clarify.

According to the resmetirom SmPC, concomitant use with strong CYP2C8 inhibitors (such as gemfibrozil) is not recommended. Therefore, co-administration should be avoided altogether.

For moderate CYP2C8 inhibitors (such as clopidogrel), dose adjustment is recommended in line with the SmPC guidance — typically a reduction from 100 mg to 80 mg once daily.

The text in Section 3.3.1 of the CS refers to this latter situation (moderate inhibitors), whereas Table 2 refers specifically to strong inhibitors. The apparent contradiction reflects the distinction between dose adjustment (moderate inhibitors) and avoidance (strong inhibitors), both consistent with the SmPC.

C3. Table 7 of Appendix K includes a cost of liver enzyme test referenced to NICE NG49. The same value is included in the ‘cost_inputs.xlsx’ file (‘Dx costs’ sheet),

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however with a different reference source, Srivastava et al. 2019. Please update the relevant value or reference to the appropriate source.

Company Response: We thank the EAG for noting this inconsistency and confirm that Srivastava et al. 2019 (54) is the correct reference source for the unit cost of the liver enzyme test used in the model. The citation in Table 7 of Appendix K of the CS will be updated accordingly to ensure consistency with the value reported in the cost_inputs.xlsx file (sheet “Dx costs”) (Appendix A-F).

Data availability and sources

C4. For the MAESTRO-NASH trial, please supply its protocol, statistical analysis plan, and all appendices of the CSR.

Company Response: The redacted version of the CSR previously provided to EAG is an internally-approved document which Madrigal was able to prepare for sharing in confidence with external agencies, without jeopardising the continuation of MAESTRO-NASH by violating conditions agreed with FDA and EMA (please see our answers to Questions A6 and A9). Appendices to the CSR, which include thousands of pages and hundreds of tables, many containing unblinded data, have not yet been through this process of review and redaction and so cannot be shared at this time.

We can, however, point the EAG to the primary study publication Harrison et al. 2024 in NEJM, which contains the MAESTRO-NASH study protocol and SAP in its online Supplementary Appendices (10).

C5. Please supply the documentation of consultation with clinicians (CS p. 90).

Company Response: In CS section 2.13.3.1, page 90, it is stated that a clinical advisory board was held on 9 December 2024. This meeting’s objectives were to gain insights on the understanding and interpretation of key sections of the potential SmPC for resmetirom; to understand potential UK clinical care pathway implications for resmetirom, and discuss related implications for patient identification, treatment and monitoring. However, the CS erroneously attributes this meeting’s findings to our observation regarding patient baseline characteristics in MAESTRO-NASH and their applicability to UK clinical practice. In fact, this finding was made during a second

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health economic advisory board held on 28 May 2025. This meeting was attended by the following external advisors:

Table 33. Clinicians attending Madrigal UK health economic advisory board meeting 28 May 2025, 8:00-16:00 GMT

[illegible]

Clinician consensus at this meeting regarding the MAESTRO-NASH study population was that it was broadly similar to the UK MASH population expected to be eligible for resmetirom. However, it was noted that the UK has a higher proportion of South Asian patients, whose MASH risk level is not always accompanied by the otherwise commonly observed risk factor of high BMI.

C6. Please provide the source of data for Table 4 in the CS (p. 30).

Company Response: The source of the data is as referenced at the end of the sentence in the section accompanying Table 4, namely reference (59): Simon TG, Roelstraete B, Khalili H, Hagström H, Ludvigsson JF. Mortality in biopsy-confirmed nonalcoholic fatty liver disease: results from a nationwide cohort. *Gut*. 2021;70(7):1375–1382 (55).

C7. Could you provide an estimate for when data from the 54-month data-cut from MAESTRO-NASH will become available?

Company Response: The final Month 54 visit is expected in [REDACTED]. Subsequent to that will be time allocated to locking the database and performing statistical analysis. A complete timeline has not yet been established.

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Literature searching

C8. For the clinical searches in Appendix B, the search terms are not adequately provided for the individual clinical trials registries searched. Please can the company provide the exact search terms used for each individual source?

Company Response: Separate searches were conducted across the clinical trial registries to account for the change in disease nomenclature from NASH to MASH. The total number of identified studies was based on the combined results from searches using both terms.

The search parameters were as follows:

Condition/Disease: NASH – Nonalcoholic Steatohepatitis OR MASH – Metabolic Dysfunction–Associated Steatohepatitis

Intervention: Resmetirom, Pioglitazone, Vitamin E, Semaglutide, Lifestyle (separate searches performed for each intervention)

Sex: All

Age group: Adult (18–64 years) and Older adult (≥65 years)

Study phase: Phase II, III, or IV

Study type: Interventional

Study results: With results available

Other search fields: Not specified

These parameters were applied consistently across each trial registry searched.

C9. In the main submission document, page 129 notes the following on the health-related quality of life searches: ‘[a]dditional searches outside of the boundaries of the SLR were also conducted’. Please can the company provide these strategies?

Company Response: We acknowledge the statement in the submission noting that “additional searches outside of the boundaries of the SLR were also conducted.” To

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clarify, no separate formal systematic literature searches were undertaken beyond those reported as part of the HRQoL SLR.

Following completion of the SLR, the company identified important limitations in the available utility evidence specific to MASH/NASH populations, including heterogeneity in instruments used and limited mapping to preference-based measures suitable for use in a NICE cost-effectiveness model. In order to ensure that utility values applied in the model were aligned with both NICE reference case requirements and existing precedent in relevant appraisals, the company considered supplementary sources.

These supplementary sources were not identified via a formal structured database search, and therefore no additional search strategies exist beyond those already submitted. Instead, they were identified through expert consultation and reference checking of highly relevant NICE guidance and economic literature to address gaps in the direct SLR evidence base.

C10. For the clinical searches in Appendix B, no dedicated health technology assessment databases were searched (e.g. INAHTA). Please can the company clarify if any relevant was missed as a result?

Company Response: We note the EAG's comment; however, dedicated health technology assessment (HTA) database searches were performed.

As outlined in the 'Other sources' section of the 'Data sources' description in Appendix B of the CS, supplementary searches were undertaken to identify relevant appraisal data (e.g., manufacturer submissions and evidence review group reports) from previous NICE HTAs. In addition, the International HTA Database (<https://database.inahta.org/>) was searched separately for each pharmacological intervention of interest assessed in a population meeting the inclusion criteria (e.g., resmetirom, pioglitazone, vitamin E, semaglutide).

These searches were considered supplementary, and therefore detailed strategies are not presented in Appendix B of the CS. No additional relevant clinical effectiveness evidence was identified from the HTA database searches beyond that

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already captured through the main bibliographic databases (MEDLINE, Embase, and the Cochrane Library).

Accordingly, based on the supplementary HTA searches conducted and the overlap between HTA sources and bibliographic databases, it is considered unlikely that any relevant clinical effectiveness evidence was missed.

C11. For the clinical searches in Appendix B, the economic searches in Appendix E, and the health-related quality of life searches in Appendix F, the search terms for the condition could have been more sensitive. For instance, including some of the following examples (which are not exhaustive): nonalcohol steato-hepatitis, nonalcoholic fatty liver inflammation, nonalcoholic steatosis hepatitis, or nonalcoholic steatotic hepatitis. Moreover, the use of the proximity operator on Embase, Medline and Cochrane for line 2, was quite narrow and could have been wider. Please can the company clarify if any relevant evidence was missed as a result?

Company Response: We acknowledge the EAG's observation regarding the sensitivity of the condition-related search terms and the proximity operators used in the clinical (Appendix B of the CS), economic (Appendix E of the CS), and HRQoL (Appendix F of the CS) searches.

The search strategies were developed iteratively and informed by scoping searches, with the aim of achieving an appropriate balance between comprehensiveness (sensitivity) and precision (specificity). The chosen approach was intended to capture studies relevant to MASH or NASH populations, while limiting the retrieval of large volumes of literature related to broader non-alcoholic fatty liver disease (NAFLD) populations or unrelated hepatic conditions.

The search strategies combined controlled vocabulary (e.g., MeSH/Emtree terms for nonalcoholic steatohepatitis and nonalcoholic fatty liver disease) with free-text terms (e.g., NASH, non-alcoholic steatohepatitis) in titles, abstracts, and keywords to ensure comprehensive coverage. While certain additional variants of the condition term (e.g., "nonalcohol steato-hepatitis," "nonalcoholic steatosis hepatitis") were not explicitly included, these represent uncommon or overlapping descriptors. Given the overlap with established controlled vocabulary and main free-text terms, and the

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supplementary validation steps undertaken, it is considered unlikely that omission of these variants resulted in missed evidence.

To verify completeness, search outputs were cross-checked against known pivotal clinical trials and the reference lists of included studies and relevant systematic reviews. No additional eligible studies were identified through these checks, supporting the conclusion that no relevant evidence was missed due to the search structure or proximity operators used.

C12. For the clinical searches in Appendix B, the search terms for some of the interventions could have been more sensitive such as including some of the following examples, (which are not exhaustive). Pioglitazone is also referred to as pioglit, piozone, pioglu – in this respect a wider range of drug names could have been searched for various relevant interventions. The standard of care terms could have been more sensitive in various respects, such as through truncation; a more sensitive use of truncation (e.g. modif* instead of modification*); and a wider range of synonyms, etc. Please can the company clarify if any relevant evidence was missed as a result?

Company Response: We acknowledge the EAG's observation regarding the sensitivity of the intervention-related search terms used in the clinical searches (Appendix B of the CS).

The search strategies were developed iteratively to achieve an appropriate balance between comprehensiveness and precision, ensuring that all relevant interventions for the treatment of MASH or NASH were captured, while minimising retrieval of irrelevant records from other liver- or metabolic-related indications.

For pharmacological interventions, including pioglitazone, searches incorporated controlled vocabulary (e.g., MeSH/Emtree terms for individual drugs and drug classes) together with free-text synonyms and common brand or generic names (e.g., actos, duetact, etc.). While additional name variants such as pioglit, piozone, or pioglu were not explicitly included, these abbreviations are not commonly used as indexing terms or publication keywords in bibliographic databases. The inclusion of both controlled vocabulary (e.g., MeSH/Emtree headings for pioglitazone) and full

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free-text terms (e.g., pioglitazone, actos) was therefore considered sufficient to capture all relevant records.

For lifestyle and SoC interventions, the strategies included both controlled vocabulary (e.g., exp Life Style/, exp Exercise/, Standard of Care/) and free-text terms encompassing a broad range of descriptors relevant to lifestyle modification and background care. These included combinations such as:

- ("life style" or lifestyle or weight or "weight loss") adj2 (change* or modification* or intervention* or management)
- (diet adj2 (change* or modification* or intervention* or management or restrict* or therap*))
- (physical adj2 (activity or exertion* or training))
- (calorie adj3 (control* or reduc* or restriction))
- ("standard management" or "standard of care" or "routine care")

The use of adjacency operators and truncation (e.g., change, modification, intervention) provided sufficient flexibility to retrieve relevant records without overextending the search to unrelated behavioural or weight-loss studies outside the NASH/MASH context. Broader truncation (e.g., modif*) was not applied, as this may have substantially increased the retrieval of irrelevant records without improving recall of NASH-relevant studies.

To confirm completeness, the final set of included studies was cross-checked against:

- Known pivotal and phase 2/3 trials of relevant interventions;
- Key systematic reviews and meta-analyses identified through hand-searching; and
- Reference lists of included studies.

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No additional eligible studies were identified through these supplementary validation steps, supporting the conclusion that no relevant evidence was missed as a result of the search structure or omission of the additional variants suggested.

C13. For the clinical searches in Appendix B, the search terms for some of the study types could have been more sensitive in numerous respects. It is unclear why the PubMed strategy has slightly more sensitive search terms for study types than the other databases. For example, it searches for clinical trial phases. The Embase strategy does not search for the Emtree term intervention study/ which has many results – instead it searches for intervention/ which has far fewer results. The same search term is also not searched for in any other search fields and there is a spelling error ‘non-random’ on Embase only. In the Medline strategy, intervention is searched for in the abstract field, but it’s not truncated to pick up interventional. As outlined, the terms for non-randomised studies and interventions studies lacked sensitivity. Please can the company clarify if any relevant evidence was missed as a result?

Company Response: We acknowledge the EAG’s observations regarding minor inconsistencies in the application of study design–related terms across databases and the typographical error (“non-random”) identified in the Embase search.

The search strategies were developed to capture all relevant interventional and comparative studies evaluating treatments for MASH or NASH. Each database was searched using both controlled vocabulary (e.g., randomized controlled trial/, clinical trial/, interventional study/ where applicable) and free-text terms to identify relevant records.

We acknowledge that the inclusion of certain terms (e.g., intervention study/ in Embase and truncation of intervention in MEDLINE) could have marginally increased sensitivity if applied consistently across all databases. However, given that relevant studies were comprehensively indexed under broader controlled vocabulary headings (e.g., clinical trial/, randomized controlled trial/), and that overlap between databases is extensive, these differences are unlikely to have materially affected retrieval.

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The typographical error (“non-radom”) affected only one search line in Embase and was redundant with correctly spelled terms (e.g., non-randomized, random, randomization), so it did not result in missed records.

To provide assurance on the adequacy of the search coverage, the retrieved records were cross-checked against known pivotal phase 2 and 3 clinical trials of key interventions (e.g., MAESTRO-NASH for resmetirom, ESSENCE for semaglutide). The identification of these expected studies confirmed that the searches were sufficiently sensitive to capture the principal body of interventional evidence. In addition, reference lists of included studies and relevant reviews were screened to identify any supplementary studies not retrieved through the database searches. No additional eligible studies were identified through these supplementary checks, supporting confidence that the identified evidence base was comprehensive for the purposes of this assessment.

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Single Technology Appraisal

Resmetirom for treating moderate to advanced liver fibrosis (without cirrhosis) caused by metabolic dysfunction-associated steatohepatitis [ID6529]

Patient Organisation Submission

Thank you for agreeing to give us your organisation's views on this technology and its possible use in the NHS.

You can provide a unique perspective on conditions and their treatment that is not typically available from other sources.

To help you give your views, please use this questionnaire with our guide for patient submissions.

You do not have to answer every question – they are prompts to guide you. The text boxes will expand as you type. [Please note that declarations of interests relevant to this topic are compulsory].

Information on completing this submission

- Please do not embed documents (such as a PDF) in a submission because this may lead to the information being mislaid or make the submission unreadable
- We are committed to meeting the requirements of copyright legislation. If you intend to include **journal articles** in your submission you must have copyright clearance for these articles. We can accept journal articles in NICE Docs.
- Your response should not be longer than 10 pages.

About you

1. Your name	
2. Name of organisation	British Liver Trust
3. Job title or position	
4a. Brief description of the organisation (including who funds it). How many members does it have?	The British Liver Trust is the UK's leading liver health charity, working to improve liver health for all and supporting all adults and children affected by liver disease or liver cancer. We are funded by voluntary donations, including community and event fundraising, individual donors, gifts in wills, corporate supporters and trust and foundation grants. We have recently merged with the Children's Liver Disease Foundation. We operate throughout the UK, reaching more than two million people each year. Our website has over 2.2 million unique visitors annually, our online forum has over 40,000 active patient members, our nurse-led Helpline handles c 500 enquiries a month, regular newsletter goes to circa 27,000 people with liver disease and liver cancer, we run around 350 support groups each year (a mix of virtual and face to face); and connect with around 45,000 people via social media.
4b. Has the organisation received any funding from the company bringing the treatment to NICE for evaluation or any of the comparator treatment companies in the last 12 months? [Relevant companies are listed in the appraisal stakeholder list.] If so, please state the name of the company,	The British Liver Trust has received the following grants in the last 12 months: Madrigal £93,100 to support our MASLD/MASH awareness work, MASLD/MASH patient information; our nurse led helpline and the funding for support groups Novo Nordisk £15,000 to support the charity's public Love Your Liver screening and scanning events to raise awareness of the risks of liver disease. All grants are arm's length and submitted through an independent portal. The company has no input into any content. The activities are not related to any product.

Patient organisation submission

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

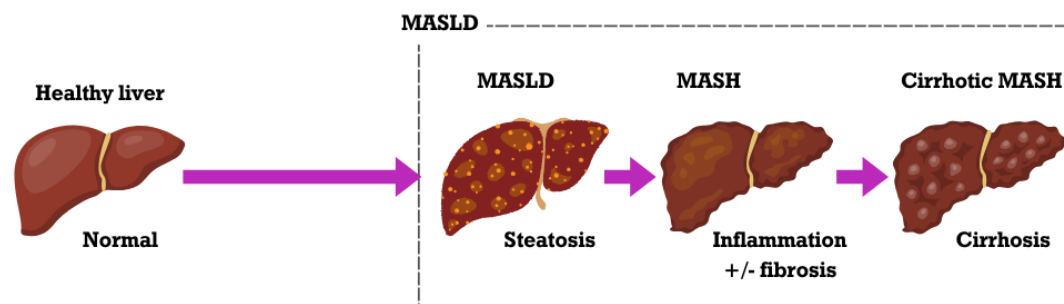
amount, and purpose of funding.	
4c. Do you have any direct or indirect links with, or funding from, the tobacco industry?	No
5. How did you gather information about the experiences of patients and carers to include in your submission?	The British Liver Trust has collated information for this submission via a variety of different sources and channels. These include: 1. Direct feedback and communication from patient and carers with MASLD and MASH via our nurse-led specialist helpline. The British Liver Trust nurse led helpline has a system to record and analyse helpline interactions. The Helpline Interaction Record system captures key details including: the reason for the enquiry, the stage the person is at in their healthcare journey (e.g., waiting for a GP appointment, under consultant care), the challenges they are experiencing (such as long waiting times or difficulties navigating NHS systems), and the guidance or resolution provided by our nurse team. By combining this information, we can build a clearer picture of the types of issues faced by callers and emailers—whether they are undiagnosed, newly diagnosed, or at end-of-life. This insight allows us to identify trends and patterns, giving us a deeper understanding of the challenges faced by people affected by all forms of liver disease. In addition, for the last six months we have been gathering specific issues/stories from patients with MASH who call the helpline. We have reviewed 930 enquires from patients or carers with MASH for this submission. 2. Feedback and comments via threads and a specific ask on our liver community forum (over 40,000 active members) and insight gained from MASH Facebook group. 3. Patient experience survey with 606 MASH patients and 93 family members of MASH patients. This includes over 500 qualitative statements. 4. Insight gained from patients attending British Liver Trust MASLD/MASH support groups. 5. Insight gained from a MASH focus group held in July 2025 6. Individual telephone interviews with patients – including patients who have been involved in clinical trials for Resmetirom 7. Literature search and review of current guidelines 8. Individual interviews with clinicians who have been involved in running the trials for Resmetirom

	9. Interview with MASLD patient group in USA where the medicine has been approved.

6. What is it like to live with the condition? What do carers experience when caring for someone with the condition?

Living with MASLD (Metabolic dysfunction-associated steatotic liver disease) or MASH (Metabolic dysfunction-associated steatohepatitis) can be physically and emotionally challenging—not just for the person diagnosed, but also for their carers.

MASLD and MASH are progressive liver conditions caused by fat buildup in the liver, often linked to obesity, type 2 diabetes, and metabolic syndrome. MASH is the more advanced form, involving inflammation and potential scarring (fibrosis). If left untreated this can progress to cirrhosis or decompensated cirrhosis.



MASH is the fastest rising cause of liver cancer death in the UK which itself is now the fastest rising cause of cancer death in the UK¹. Deaths from liver cancer in the UK have increased by 40% in the last decade. Sadly only 13% of patients with liver cancer survive for 5 years. MASH is also predicted to become the leading indication for liver transplantation in the next few years. People with MASH often have coexisting illnesses like type 2 diabetes, hypertension, and cardiovascular disease, and deaths are frequently attributed to those conditions. As a result, MASH-related mortality is underrecognized and reliable disease-specific death rates are lacking.

In our survey of patients with MASH (n=699), 72% of patients felt they had been diagnosed late, with 34% reporting that they were diagnosed at such a late stage, it was too late for any effective intervention. There are usually no symptoms in the early stages. Diagnosis usually comes as a huge shock, especially since symptoms can be silent or vague, and many patients report feeling extremely anxious and frightened when diagnosed.

	A female patient in her 40's when diagnosed said, "I took my children swimming as I did every week, I suddenly felt ill, I got out of the pool and felt faint. I rushed to the changing room and vomited a sink full of blood and was sent to hospital..... my diagnosis was MASH. For the next few years I had tests, I was mostly well but did end up in intensive care at one point. Then at a clinic visit my consultant informed me that the only option was a liver transplant..... my transplant has enabled me to live a normal life, and I will always be grateful to my donor and her family for giving me the gift of life. I feel if I had been diagnosed earlier, I would not have needed a transplant." Other quotes from patients included: "I was told to just lose weight for over a decade while my liver silently worsened — the shock of a late-stage diagnosis was devastating." "My care is about damage control rather than prevention. This disease needs more awareness"" " I felt angry and abandoned — the warning signs were in my records, but nobody acted." "Dad was failed by the system, he had 22 liver function tests over 11 years and they all came back abnormal, biut he was very blasé about MASLD because that's how medical professionals portrayed it to him. Liver disease is a a silent killer by the time he had symptoms it was end stage and he died. Watching him go in those final weeks was brutal – more needs to be done about this terrible disease." Once diagnosed, people with MASH commonly report persistent, disproportionate fatigue that is not relieved by rest and can be one of the most difficult symptoms of the condition. They describe feeling tired even after minimal activity and having reduced physical strength. This can severely reduce their ability to complete simple daily tasks, often means they have to leave their job or reduce their working hours and causes emotional distress such as frustration and anxiety about declining function. "I feel exhausted all the time — I used to love walking and now some days I can barely get to the local shop"

	"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." "Feeling tired all the time has made me cut back on everything I enjoyed; my social life has suffered, and I sometimes feel very isolated. This [support group] has been a lifeline." Patients may face judgment and stigma – often either due to misconceptions that liver disease is always alcohol-related or because they feel others believe that they have “brought it on themselves by overeating and gaining weight”. This can lead to feelings of shame or isolation and also act as a barrier to them seeking help. People with MASLD/MASH often don't “look sick,” which can make it harder for others to understand their struggles. Managing MASLD/MASH typically requires major changes—diet, exercise, weight management and these changes can feel overwhelming, and patients say they feel a sense of hopelessness. They are often scared or frightened of the disease progressing. When MASH progresses and patients have cirrhosis, fatigue and weakness dominate daily life. People describe their energy as a slowly shrinking currency: small tasks that used to be effortless — carrying shopping, climbing stairs, cooking a meal — now require planning and recovery. Appetite changes and nausea are common, and food can become an emotional burden as well as a physical necessity. Many patients struggle with muscle loss and weight changes that make movement harder and increase the risk of falls and infections. As the liver fails, complications arrive in ways that feel sudden and frightening. Fluid can build up in the belly (ascites), making clothes tight and breathing harder. Many patients who have ascites report having frequent trips to the hospital to have the fluid drained – in a separate survey carried out by the Trust, the average trip to the specialist centre to do this was 23 miles. “I used to manage the bus to the local hospital, but the specialist clinic is in Newcastle — it's a two-hour trip each way and I'm wiped out afterwards,” “My husband drives me; between petrol and parking it's a big weekly cost.” Variceal bleeding can be a terrifying event for those who experience it:

	"I woke up coughing blood and was in hospital within hours," Hepatic encephalopathy can cloud thinking, slow reaction times, and change mood — people report confusion, trouble finding words, and moments of disorientation that make them frightened to be alone. Some experience severe hallucination. Jaundice changes appearance and can feel like a visible marker of decline. The emotional burden is heavy and often overlooked. Anxiety over unpredictable flare-ups and hospital admissions sits alongside grief for the life a person had before illness. Depression is common, partly from biological changes and partly from the loss of identity and independence. "I feel like a different person — quieter, more careful, and often scared," Cognitive changes from liver-related brain effects can be humiliating and isolating; people worry they will be seen as unreliable or "not themselves." Life with advanced cirrhosis becomes organized around avoiding complications and preserving energy. Patients track fluid and salt intake, time their medicines, and learn to recognise early warning signs of infection or bleeding. There are frequent hospital visits and stays and blood tests, and procedures become routine. Nutrition is a constant concern: clinicians often recommend higher-protein food to prevent muscle loss, yet practical restrictions (salt limits, fluid limits, nausea) make this hard. Many adopt pacing strategies: breaking tasks into short bursts, prioritising essential activities, and asking for help for heavy chores. "I plan the week so I only go out on my best two days," Relationships change as roles shift; family members often become caregivers. Social invitations can feel stressful rather than joyful because of fatigue, dietary limits, or embarrassment about symptoms. Work may be reduced or stopped, affecting income and purpose. At the same time, supportive friends and steady medical teams can make a substantial difference; practical help with transport, shopping, and appointments alleviates daily pressure. "My daughter comes twice a week to help with laundry and it saves me," "My wife lost her job because she had to keep taking me to the hospital"

	Patients balance short-term symptom control with longer-term decisions. Some are evaluated for liver transplantation, which brings hope but also a new set of anxieties: tests, waiting lists, and the uncertainty of timing. For those not eligible, palliative care focuses on comfort, symptom control, and supporting dignity. Conversations about goals of care, advance wishes, and realistic expectations matter deeply but are often delayed. “I want to be lucid and present for my grandchild’s graduation, but I also want to be honest with my family about what might come next and don’t want to be a burden” Caring for someone with MASLD or MASH involves both practical and emotional responsibilities. Key challenges for carers include: • Understanding the disease: Since symptoms may not be visible, carers must learn to empathize with the patient’s internal experience. • Supporting lifestyle changes: Carers often help with meal planning, encouraging physical activity, and attending medical appointments. • Emotional toll: Witnessing a loved one struggle with a chronic condition can be draining. Carers may feel helpless, frustrated, or overwhelmed. Particularly when dealing with hepatic encephalopathy, their loved one can feel like a very different person and sometimes be aggressive and frightening. • Neglecting their own health: It’s common for carers to prioritize the patient’s needs and forget their own well-being. • Navigating stigma: Carers may also face judgment or misunderstanding from others who don’t grasp the nature of MASLD/MASH.

Current treatment of the condition in the NHS

7. What do patients or carers think of current treatments and care available on the NHS?	Patients are really shocked and despairing that there are currently no medicines available in the UK to specifically treat moderate to advanced fibrosis caused by MASLD. Patients are disbelieving and frustrated that doctors cannot do more for them. They feel hopeless. By the time there are symptoms, it is often too late to do much and end up either waiting for a transplant or palliative care. In recent years, there have been innovative advances in non-invasive tests that can diagnose people at an earlier stage. Treatment currently focuses slowing or reversing fibrosis through lifestyle changes. Patients often struggle and have limited access to dietary advice. When they do have dietary and exercise advice many find it difficult to make progress and halt the progression of the disease. Other patients do manage to successfully reverse the condition through exercise and diet. For example, one of our supporters (male, aged 66) shared this story: he had a routine test as part of his NHS HealthCheck. He had recently retired but previously been very active in the military. Since retiring had put on weight. The HealthCheck revealed elevated liver markers. He was referred for a FibroScan – which came back at 11.9 (indicative of cirrhosis). He then went for further investigations, and they found liver cancer. He had microwave ablation to remove the lesion and is now cancer free. The underlying cause of the liver cancer was MASH, after this shock diagnosis, he changed his lifestyle – changed his diet, became much more active and lost weight. His latest FibroScan showed it had dropped to 6.5 (within the normal range). If the patient also has type 2 diabetes their diabetes is managed, and they may also be given drugs to control cardiovascular risks. A very limited number of patients have had success with bariatric surgery. Patients with more advanced disease have treatments for the complications – hepatic encephalopathy, ascites, portal hypertension, varices and varices bleeding, thrombocytopenia, osteoporosis.

8. Is there an unmet need for patients with this condition?	Yes. There are currently no medicines available. Patients feel that the historical lack of available treatments means that GPs have sometimes ignored following up on their blood test results. They also feel angry that they don't get access to lifestyle support that patients with type 2 diabetes receive.

Advantages of the technology

9. What do patients or carers think are the advantages of the technology?	This medicine is for a limited specific group of patients with moderate disease. It is not for those with early-stage disease, and it is also not for those with cirrhosis or advanced disease. However, patients are extremely hopeful that for this group this medicine will stop disease progression and provide them with “additional time for the lifestyle factors to work”. One person who had been involved in the trial (we do not know whether they had the drug or a placebo) said: “Finally, a medicine that acts on the liver itself rather than only treating diabetes or cholesterol – this feels like a direct answer to a problem that until now had only lifestyle and risk-factor management. I have experienced some improvements in my test results” Patients see it as potentially disease-modifying rather than just symptom control. Carers often frame the benefit as more than numbers on a scan. “If it can slow scarring, it might buy time and better-quality days,” Taking a tablet is easier than extra clinics,” “Even small improvements in energy make visits less exhausting.” People are optimistic and when we asked about the side effects reported in trials (particularly nausea and diarrhoea) they said that they would be willing to put up with this if it would improve their liver disease.

Disadvantages of the technology

10. What do patients or carers think are the disadvantages of the technology?	One carer we spoke to stressed the need for clear advice on managing side effects so that benefits aren't undermined by new symptoms. Patients also want reassurance about interactions with other medicines they commonly take for diabetes, blood pressure or lipids.

Patient population

11. Are there any groups of patients who might benefit more or less from the technology than others? If so, please describe them and explain why.	Data from the Office for Health Improvement and Disparities highlights that premature mortality rates for fatty liver disease are now 6.4 times higher in the most deprived areas of England compared to the most affluent.

Equality

12. Are there any potential equality issues that should be taken into account when considering this condition and the technology?	

Other issues

13. Are there any other issues that you would like the committee to consider?	

Key messages

14. In up to 5 bullet points, please summarise the key messages of your submission.	• This devastating illness has no symptoms in early stages but if left to progress can cause serious complications (eg: ascites, hepatic encephalopathy, portal hypertension, varices and variceal bleeding) and lead to liver cancer or liver transplantation. • Patients are often relatively young and still of working age. • The disease seriously impacts quality of life and when it becomes advanced requires many hospital visits • There are currently no treatments available for treating moderate to advanced liver fibrosis other than lifestyle interventions • This medicine could offer real hope for a small subset of MASLD patients (those with moderate disease) enabling them to halt disease progression and giving them “additional time” for lifestyle interventions to work

Thank you for your time.

Please log in to your NICE Docs account to upload your completed submission.

Your privacy

Patient organisation submission

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

The information that you provide on this form will be used to contact you about the topic above.

Please select YES if you would like to receive information about other NICE topics - YES or NO

For more information about how we process your personal data please see our [privacy notice](#).

ⁱ Cancer Research UK (2021). Mortality trends over time for common cancers. Available at: <https://www.cancerresearchuk.org/health-professional/cancer-statistics/mortality/common-cancers-compared#heading=Three> (last accessed May 2023)
Daniel Huang et al, 'Global epidemiology of NAFLD-related HCC' (April 2021) NRGH 18(4)
<https://pubmed.ncbi.nlm.nih.gov/33349658/#:~:text=NAFLD%20is%20already%20the%20fastest,with%20the%20growing%20obesity%20epidemic> (last accessed May 2023)

Single Technology Appraisal

Resmetirom for treating moderate to advanced liver fibrosis (without cirrhosis) caused by metabolic dysfunction-associated steatohepatitis [ID6529]

Professional organisation submission

Thank you for agreeing to give us your organisation's views on this technology and its possible use in the NHS.

You can provide a unique perspective on the technology in the context of current clinical practice that is not typically available from the published literature.

To help you give your views, please use this questionnaire. You do not have to answer every question – they are prompts to guide you. The text boxes will expand as you type.

Information on completing this submission

- Please do not embed documents (such as a PDF) in a submission because this may lead to the information being mislaid or make the submission unreadable
- We are committed to meeting the requirements of copyright legislation. If you intend to include **journal articles** in your submission you must have copyright clearance for these articles. We can accept journal articles in NICE Docs.
- Your response should not be longer than 13 pages.

About you

1. Your name	
2. Name of organisation	The British Association for the Study of the Liver (BASL)
3. Job title or position	
4. Are you (please select Yes or No):	An employee or representative of a healthcare professional organisation that represents clinicians? Yes A specialist in the treatment of people with this condition? Yes A specialist in the clinical evidence base for this condition or technology? Yes Other (please specify):
5a. Brief description of the organisation (including who funds it).	The British Association for the Study of the Liver is the National Association for hepatology. BASL is dedicated to advancing knowledge and understanding of the biology and pathology of the liver for the optimal care of patients. BASL is composed of interested individuals from clinical medicine, clinical and basic research and allied professions. BASL is a not for profit Association whose income is derived from membership fees, donations and its various activities, such as the revenue of scientific meetings. Monies derived from such activities are used to support further educational events and the attendance thereto of its members
5b. Has the organisation received any funding from the manufacturer(s) of the technology and/or comparator products in the last 12 months? [Relevant manufacturers are listed in the appraisal matrix.] If so, please state the name of manufacturer, amount, and purpose of funding.	<u>BASL</u> Madrigal Pharmaceuticals (company) – BASL received £29,000 in sponsorship funding towards their annual conference and a MASLD special interest group symposium. Novo Nordisk Ltd (comparator) – BASL received £52,800 in sponsorship funding through a Partnership agreement (£48,000) towards their annual meeting and other educational events, with the remainder also towards other educational events.
5c. Do you have any direct or indirect links	NO

with, or funding from,
the tobacco industry?

The aim of treatment for this condition

6. What is the main aim of treatment? (For example, to stop progression, to improve mobility, to cure the condition, or prevent progression or disability.)	The main aim of this treatment is to reduce liver-related and all-cause mortality in metabolic dysfunction associated steatotic liver disease, specifically the group of patients with steatohepatitis (MASH) and significant to advanced liver fibrosis without cirrhosis. In practice, this is likely to represent regression of liver fibrosis and reduced progression to cirrhosis.
7. What do you consider a clinically significant treatment response? (For example, a reduction in tumour size by x cm, or a reduction in disease activity by a certain amount.)	A clinically significant treatment response would be: 1) ≥ 1 stage reduction in liver fibrosis (without worsening of liver fibrosis) 2) A verified and/or repeated $\geq 30\%$ reduction in liver stiffness (e.g. by FibroScan) 3) An equivalent reduction in other validated non-invasive markers of liver fibrosis, such as the ELF test
8. In your view, is there an unmet need for patients and healthcare professionals in this condition?	Yes. There are currently no licenced treatments for this condition which is the most common liver disorder and probably the second most common underlying cause of primary liver cancer and of liver transplantation after alcohol.

What is the expected place of the technology in current practice?

9. How is the condition currently treated in the NHS?	1) Lifestyle intervention (weight loss, alcohol reduction, smoking cessation) 2) Optimisation of cardio-metabolic risk factors (diabetes, hypertension, dyslipidaemia) with focus on treatments that encourage weight loss

Professional organisation submission

[Resmetirom for treating moderate to advanced liver fibrosis (without cirrhosis) caused by metabolic dysfunction-associated steatohepatitis]
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9a. Are any clinical guidelines used in the treatment of the condition, and if so, which?	Yes: 1) EASL-EASD-EASO Clinical Practice Guidelines for MASLD 2024 2) NAFLD Quality Standards (McPherson et al, Lancet Gastro Hep, 2022) 3) NICE guidance 2016 (out of date, under revision)
9b. Is the pathway of care well defined? Does it vary or are there differences of opinion between professionals across the NHS? (Please state if your experience is from outside England.)	Broadly, in the UK the pathway consists of: 1) Risk stratification in primary care (often 2-step with tests such as Fib4 + FibroScan or ELF) 2) Higher risk patients seen in secondary/tertiary care for management as per section 9 3) Monitoring of patients with advanced fibrosis for progression to cirrhosis The precise nature and make up of the community-based risk stratification varies across regions and hospitals depending on local resources and expertise. The provision of lifestyle interventions and weight loss services varies across regions. Weight loss services have insufficient capacity for demand.
9c. What impact would the technology have on the current pathway of care?	The technology would sit well in the current pathway of care and could be prescribed in secondary care after appropriate investigation and consideration of risks/benefits
10. Will the technology be used (or is it already used) in the same way as current care in NHS clinical practice?	The technology is not currently in use and could be used effectively if services are configured as per 9,9b
10a. How does healthcare resource use differ between the technology and current care?	Currently there is no liver-specific therapy for this condition, so resources are focused on diagnosis, risk stratification, optimisation of underlying causes and associated features and follow-up to detect progression to cirrhosis. Addition of this technology would add the prescribing and drug costs to the pathway but would not necessarily change the pathway overall.
10b. In what clinical setting should the technology be used? (For example, primary or secondary care, specialist clinics.)	Secondary care Gastroenterology (with Hepatology expertise), specialist hepatology clinics, sub-specialty MASLD clinics

10c. What investment is needed to introduce the technology? (For example, for facilities, equipment, or training.)	1) Widespread provision of specialist hepatology clinics 2) Universal access to community-based risk stratification 3) Widespread access to personalised lifestyle interventions including weight loss services, alcohol reduction and smoking cessation
11. Do you expect the technology to provide clinically meaningful benefits compared with current care?	Yes. If prescribed appropriately, it is likely that fewer people will progress to cirrhosis and suffer liver related mortality, but currently we do not have direct evidence that the drug will achieve this.
11a. Do you expect the technology to increase length of life more than current care?	Yes, but in a subset of patients
11b. Do you expect the technology to increase health-related quality of life more than current care?	Yes, but in a subset of patients
12. Are there any groups of people for whom the technology would be more or less effective (or appropriate) than the general population?	Patients with advanced liver fibrosis cause by MASLD/MASH without cirrhosis would likely benefit most, especially those whose liver disease is disproportionately severe compared with their cardiometabolic risk factors. Conversely, in someone with uncontrolled cardiometabolic risk factors (e.g poorly controlled type 2 diabetes or morbid obesity), optimal management of these risk factors will have greater effect in reducing all cause mortality and, in the case of weight loss, will improve the liver disease even without the resmetirom. Therefore optimal management of weight and cardiometabolic risk factors remains a priority in this group.

The use of the technology

13. Will the technology be easier or more difficult to use for patients or healthcare professionals than current care? Are there any practical implications for its use (for example, any concomitant treatments needed, additional clinical requirements, factors affecting patient acceptability or ease of use or additional tests or monitoring needed.)	To the patient there is little change as the treatment is a once daily tablet. For providers, it depends on whether treatment is prescribed in secondary care as bluetec, via shared care agreement or initiated in secondary care and continue in primary care. The BASL MASLD SIG reached consensus that patients in whom treatment is initiated should be reviewed for safety, tolerability and adherence at 3m then for signs of response/non-response at 12m then annually.
14. Will any rules (informal or formal) be used to start or stop treatment with the technology? Do these include any additional testing?	The BASL MASL SIG considered that either liver biopsy showing MASH with F2/F3 fibrosis or non-invasive tests such as FibroScan >10kPa (but without evidence cirrhosis) would be an indication to start treatment. It was felt that verified/repeated increase in liver stiffness $\geq 30\%$ or evidence of developing cirrhosis from baseline would indicated non-response and be used to stop treatment. Given the variability of liver stiffness measurement, smaller increases may not be clinically significant. This would be part of routine clinical management in many centres treating patients with MASLD.
15. Do you consider that the use of the technology will result in any substantial health-related	Probably not

benefits that are unlikely to be included in the quality-adjusted life year (QALY) calculation?	
16. Do you consider the technology to be innovative in its potential to make a significant and substantial impact on health-related benefits and how might it improve the way that current need is met?	Yes- this is the first FDA-approved therapy for the condition. It has potential to reduce liver-related morbidity and mortality in patients with MASLD, but the published evidence for benefit is currently only with surrogate markers of liver disease severity (liver fibrosis and steatohepatitis), so concrete evidence of benefit on hard outcomes is still awaited.
16a. Is the technology a 'step-change' in the management of the condition?	Yes
16b. Does the use of the technology address any particular unmet need of the patient population?	This would be the first drug to treat the liver disease <i>per se</i> as opposed to the upstream drivers (obesity and insulin resistance) or associated features (cardiometabolic risk factors).
17. How do any side effects or adverse effects of the technology affect the management of the condition and the patient's quality of life?	Side effect profile is good with nausea and diarrhoea most commonly reported. Diarrhoea episode(s) in c. 30% of treated vs 15% placebo, but overall side effects not significantly higher than placebo

Sources of evidence

18. Do the clinical trials on the technology reflect current UK clinical practice?	Patient population broadly similar in terms of age, sex, BMI and prevalence of diabetes. The main difference is that the clinical trials used liver biopsy to confirm eligibility and outcome, whereas the BASL MASL SIG consensus was that liver biopsy should not be required to determine eligibility in view of the risk to patients and the resource implications. The phase 3 trial was also 90% white with c.3% Asian (mainly SE Asian) and c. 2% Black, so may not fully represent UK ethnicity. Liver stiffness measurements were higher than expected in the phase 3 trial.
18a. If not, how could the results be extrapolated to the UK setting?	UK should use non-invasive testing to approximate to the biopsy-proven population.
18b. What, in your view, are the most important outcomes, and were they measured in the trials?	In my view the most important outcomes are: 1) All-cause mortality 2) Liver-related mortality 3) Hepatic decompensation events and or development of hepatocellular carcinoma (also known as major adverse liver outcomes (MALO)) These were not measured in the phase 3 study report (Harrison et al NEJM 2024), which used liver fibrosis and steatohepatitis as surrogate outcomes.
18c. If surrogate outcome measures were used, do they adequately predict	Liver fibrosis severity correlates with liver-related and all-cause mortality, and steatohepatitis is associated with more advanced liver fibrosis. These are both readily measurable making them attractive

long-term clinical outcomes?	surrogate markers for hard outcomes and as such they are approved by the FDA. What is currently less clear is whether resolution of steatohepatitis or reduction in liver fibrosis necessarily corresponds to a reduction in liver-related mortality.
18d. Are there any adverse effects that were not apparent in clinical trials but have come to light subsequently?	Not that I know of
19. Are you aware of any relevant evidence that might not be found by a systematic review of the trial evidence?	No
20. How do data on real-world experience compare with the trial data?	Similar side effect profile (Shuaibi et al Gastro Hep Advances 2025),

Equality

21a. Are there any potential equality issues that should be taken into account when considering this treatment?	The condition is closely associated with obesity and diabetes, hence negatively correlated with socio-economic status. The condition is also more prevalent and on average more severe in people of S Asian ethnicity.
21b. Consider whether these issues are different	This is known in current care pathways.

from issues with current
care and why.

Topic-specific questions

22. How are people with moderate to advanced liver fibrosis caused by metabolic dysfunction-associated steatohepatitis (MASH) who might be eligible for treatment with resmetirom identified in NHS practice?	Widely, but not universally: 1) 2-step community-based risk stratification (e.g. Fib4-FibroScan or Fib4-ELF) followed by 2) Further assessment in secondary care, including clinical assessment, blood tests, US scan and FibroScan and/or liver biopsy in selected cases)
23. How is the disease activity of MASH routinely assessed in the NHS? Which scales are used in clinical practice in the NHS to stage liver fibrosis?	Disease activity in MASH is not routinely assessed in the NHS and there are arguments that disease activity is not a meaningful endpoint but a surrogate for risk of fibrosis progression which is in itself a surrogate of risk of liver-related morbidity and mortality. Liver fibrosis is usually stage histologically F0-4 with 4 being cirrhosis (Brunt/Kleiner) and occasionally 0-6 (5-6 being cirrhosis) (Ishak). Sometimes the marketing for non-invasive tests claims to detect fibrosis stages (e.g F2 or F3). They do not. They can indicate that someone is more or less likely to have fibrosis of that stage. Non-invasive tests do, however, predict outcomes as well, if not better than, histological fibrosis stage (Mozes FE et al. Lancet Gastro Hep 2023) and provide a linear scale to allow thresholds to be established.

Key messages

Professional organisation submission

[Resmetirom for treating moderate to advanced liver fibrosis (without cirrhosis) caused by metabolic dysfunction-associated steatohepatitis]
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24. In up to 5 bullet points, please summarise the key messages of your submission.	• Resmetirom is the first treatment for MASLD to be licenced by the FDA based on phase 3 study data • Priority for treating MASLD remains weight loss and optimisation of cardiometabolic risk factors • Those with advanced liver fibrosis should be prioritised for liver-selective treatment • Liver biopsy should not be required to determine eligibility for treatment, but may be helpful in some cases • GLP-1 RAs would be an ideal first-line treatment for at-risk MASH/ MASL with significant to advanced liver fibrosis given the wealth of evidence for liver specific and cardiometabolic benefits and resmetirom would be well placed as second-line or for those with a liver phenotype

Thank you for your time.

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Single Technology Appraisal

Resmetirom for treating moderate to advanced liver fibrosis (without cirrhosis) caused by metabolic dysfunction-associated steatohepatitis [id6529]

Professional organisation submission

Thank you for agreeing to give us your organisation's views on this technology and its possible use in the NHS.

You can provide a unique perspective on the technology in the context of current clinical practice that is not typically available from the published literature.

To help you give your views, please use this questionnaire. You do not have to answer every question – they are prompts to guide you. The text boxes will expand as you type.

Information on completing this submission

- Please do not embed documents (such as a PDF) in a submission because this may lead to the information being mislaid or make the submission unreadable
- We are committed to meeting the requirements of copyright legislation. If you intend to include **journal articles** in your submission you must have copyright clearance for these articles. We can accept journal articles in NICE Docs.
- Your response should not be longer than 13 pages.

About you

1. Your name	
2. Name of organisation	British Hepatology Pharmacy Group (BHPG)
3. Job title or position	
4. Are you (please select Yes or No):	An employee or representative of a healthcare professional organisation that represents clinicians? Yes or No A specialist in the treatment of people with this condition? Yes or No A specialist in the clinical evidence base for this condition or technology? Yes or No Other (please specify):
5a. Brief description of the organisation (including who funds it).	We are the pharmacy affiliate Group for the British Association for the Study of the Liver. This is the National Association for specialists in liver disease (hepatology). BASL is funded through membership fees and organising and hosting an annual meeting and educational events.
5b. Has the organisation received any funding from the manufacturer(s) of the technology and/or comparator products in the last 12 months? [Relevant manufacturers are listed in the appraisal matrix.] If so, please state the name of manufacturer, amount, and purpose of funding.	No
5c. Do you have any direct or indirect links with, or funding from, the tobacco industry?	No

The aim of treatment for this condition

6. What is the main aim of treatment? (For example, to stop progression, to improve mobility, to cure the condition, or prevent progression or disability.)	Aimed at improving disease activity (liver inflammation) and preventing progression in non-cirrhotic non-alcoholic steatohepatitis (NASH) with moderate to advanced fibrosis (stages F2 to F3 fibrosis)
7. What do you consider a clinically significant treatment response? (For example, a reduction in tumour size by x cm, or a reduction in disease activity by a certain amount.)	NASH resolution with no worsening of fibrosis Fibrosis improvement by at least one stage with no worsening of the NAFLD activity score
8. In your view, is there an unmet need for patients and healthcare professionals in this condition?	Yes, there is a significant unmet need for both patients and healthcare professionals. Currently, no licensed pharmacological treatments are available in the UK. Off-label options such as pioglitazone or vitamin E are limited by safety concerns and inconsistent efficacy.

What is the expected place of the technology in current practice?

9. How is the condition currently treated in the NHS?	Intervention focuses on lifestyle modification such as physical activity and diet. Pioglitazone or vitamin E remain off-licensed options for selective patients in secondary or tertiary care centres, although their usage varies in clinical practice. Management is otherwise directed towards optimisation of comorbidities such as type 2 diabetes, dyslipidaemia, obesity, and hypertension, often in collaboration with multidisciplinary teams. Patients with advanced fibrosis or cirrhosis are monitored for complications, including hepatocellular carcinoma, and may be referred for liver transplantation if disease progression occurs.

9a. Are any clinical guidelines used in the treatment of the condition, and if so, which?	Yes, 1. NICE guideline on non-alcoholic fatty liver disease (NG49, 2016) 2. McPherson S et al. Quality standards for the management of non-alcoholic fatty liver disease (NAFLD): consensus recommendations from the British Association for the Study of the Liver and British Society of Gastroenterology NAFLD Special Interest Group. Lancet Gastroenterology and Hepatology 2022: https://doi.org/10.1016/S2468-1253(22)00061-9 3. British Society Gastroenterology: Abnormal Liver Function Blood Tests (LFTs) Guidelines https://www.bsg.org.uk/clinical-resource/guidelines-on-abnormal-liver-blood-tests
9b. Is the pathway of care well defined? Does it vary or are there differences of opinion between professionals across the NHS? (Please state if your experience is from outside England.)	The pathway of care for MASLD (and NASH) in the NHS is partially defined, with initial assessment in primary care and referral to specialists for suspected advanced disease. Variation exists between trusts in fibrosis assessment (referral thresholds), access to FibroScan, and structured lifestyle support.
9c. What impact would the technology have on the current pathway of care?	Resmetirom could transform the MASLD/NASH pathway by enabling earlier specialist referral, structured monitoring, and coordinated multidisciplinary care to improve patient outcomes.
10. Will the technology be used (or is it already used) in the same way as current care in NHS clinical practice?	No, resmetirom introduces a new approach in MASLD/NASH care.
10a. How does healthcare resource use differ between the technology and current care?	The technology may increase short-term resource use due to specialist initiation, monitoring, and multidisciplinary input, but could reduce long-term demand by preventing progression to advanced liver disease and related complications.
10b. In what clinical setting should the technology be used? (For example,	Secondary care, within specialist hepatology clinics supported by a multidisciplinary team including hepatology, endocrinology/diabetology, dietetics and pharmacy

primary or secondary care, specialist clinics.)	
10c. What investment is needed to introduce the technology? (For example, for facilities, equipment, or training.)	Investment in specialist hepatology clinic capacity, staff training for therapy initiation and monitoring, and systems for structured patient follow-up. Multidisciplinary team (MDT) support and existing laboratory and imaging equipment, including FibroScan, are generally already in place.
11. Do you expect the technology to provide clinically meaningful benefits compared with current care?	Yes, it provides benefits by directly reducing liver fat and fibrosis in NASH, slowing disease progression, and improving long-term patient outcomes.
11a. Do you expect the technology to increase length of life more than current care?	Long-term data are limited, but resmetirom is expected to reduce progression to cirrhosis and liver-related complications in NASH, which may increase life expectancy compared with current care.
11b. Do you expect the technology to increase health-related quality of life more than current care?	Long-term data are limited, but yes it is expected to improve health-related quality of life in NASH.
12. Are there any groups of people for whom the technology would be more or less effective (or appropriate) than the general population?	Resmetirom is likely to be most effective in patients with NASH and significant hepatic steatosis or fibrosis. Its efficacy may be reduced in individuals with minimal disease or decompensated cirrhosis, and outcomes could be influenced by poorly controlled comorbid conditions such as diabetes or cardiovascular disease.

The use of the technology

13. Will the technology be easier or more difficult to use for patients or healthcare professionals	It is an oral tablet with a generally mild side effect profile. Healthcare staff can be readily trained in its use and in the associated monitoring requirements.

Professional organisation submission

[Resmetirom for treating moderate to advanced liver fibrosis (without cirrhosis) caused by metabolic dysfunction-associated steatohepatitis]
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than current care? Are there any practical implications for its use (for example, any concomitant treatments needed, additional clinical requirements, factors affecting patient acceptability or ease of use or additional tests or monitoring needed.)	
14. Will any rules (informal or formal) be used to start or stop treatment with the technology? Do these include any additional testing?	The rules for use would include appropriate risk stratification, weight-based dosing, safety monitoring, and assessment of treatment response through regular liver function tests and non-invasive fibrosis or liver stiffness assessment.
15. Do you consider that the use of the technology will result in any substantial health-related benefits that are unlikely to be included in the quality-adjusted life year (QALY) calculation?	Yes, additional benefits may include reduced need for invasive procedures such as liver biopsy, improved patient engagement and adherence to lifestyle changes when treatment options exists and reduced future demand for liver transplantation.
16. Do you consider the technology to be innovative in its potential to make a significant and substantial impact on health-related benefits and how might it improve the	Yes, it is the first therapy to demonstrate clinically meaningful effects in achieving NASH resolution and improving liver fibrosis without worsening the NAFLD Activity Score (NAS). It goes beyond lifestyle and comorbidity management, with the potential to transform care pathways and reduce progression to advanced liver disease.

way that current need is met?	
16a. Is the technology a 'step-change' in the management of the condition?	Yes, resmetirom is the first disease-modifying therapy to demonstrate histological improvement in NASH.
16b. Does the use of the technology address any particular unmet need of the patient population?	Yes, resmetirom addresses an important unmet need in patients with NASH, particularly those at risk of progressive liver disease, including an increased likelihood of requiring liver transplantation or experiencing liver-related mortality.
17. How do any side effects or adverse effects of the technology affect the management of the condition and the patient's quality of life?	Resmetirom is generally well tolerated, with mild transient diarrhoea and mild nausea being the most common side effects. These are typically manageable and are not expected to significantly affect disease management or the patient's quality of life. Routine monitoring allows timely identification and management of any issues, supporting continued therapy and patient adherence.

Sources of evidence

18. Do the clinical trials on the technology reflect current UK clinical practice?	Yes, the pivotal Phase 3 MAESTRO-NASH trial broadly reflects UK clinical practice, including patients with biopsy-confirmed NASH and the use of non-invasive fibrosis assessments.
18a. If not, how could the results be extrapolated to the UK setting?	
18b. What, in your view, are the most important outcomes, and were they measured in the trials?	The key outcomes are NASH resolution, improvement in liver fibrosis, and safety. These were assessed in the trials using liver biopsy, non-invasive fibrosis measures, and adverse event monitoring.

18c. If surrogate outcome measures were used, do they adequately predict long-term clinical outcomes?	Yes, surrogate outcomes such as NASH resolution, NAS score, and non-invasive fibrosis assessments are generally accepted as predictors of long-term outcomes, including progression to cirrhosis and liver-related complications.
18d. Are there any adverse effects that were not apparent in clinical trials but have come to light subsequently?	To our knowledge, the side effect profile observed in clinical trials has remained consistent in real-world use.
19. Are you aware of any relevant evidence that might not be found by a systematic review of the trial evidence?	No, provided the systematic review includes real-world evidence, post-marketing studies, and health-economic analyses, all relevant evidence would be captured. If the review only includes clinical trials, additional real-world or modelling evidence may still be relevant.
20. How do data on real-world experience compare with the trial data?	Because it was only licensed by the FDA in March 2024 and received conditional approval in Europe in August 2025 (not yet in the UK), resmetirom is not widely used in routine practice, and robust real-world data are lacking. Its effectiveness and safety in broader populations and over longer periods remain to be confirmed.

Equality

21a. Are there any potential equality issues that should be taken into account when considering this treatment?	Potential equality issues include ensuring timely access for patients in rural or spoke centres, who might otherwise be disadvantaged in receiving specialist therapies such as resmetirom. Strong referral pathways and shared-care prescribing arrangements could help mitigate these disparities and promote equitable access.
21b. Consider whether these issues are different from issues with current care and why.	These equality issues are similar to those with current care, as patients in rural or spoke centres may already experience delayed access to specialist hepatology services. However, the introduction of a new therapy like resmetirom may exacerbate disparities if strong referral pathways and shared-care arrangements are not established.

Topic-specific questions

22. How are people with moderate to advanced liver fibrosis caused by metabolic dysfunction-associated steatohepatitis (MASH) who might be eligible for treatment with resmetirom identified in NHS practice?	Eligible patients are identified through a combination of clinical risk assessment, non-invasive fibrosis tests, and specialist hepatology review. Referral from primary or secondary care is based on elevated risk factors such as diabetes, obesity, or abnormal liver function tests. Liver biopsy may be used selectively to confirm diagnosis and fibrosis stage.
23. How is the disease activity of MASH routinely assessed in the NHS? Which scales are used in clinical practice in the NHS to stage liver fibrosis?	Liver function tests, imaging (ultrasound, elastography), and non-invasive fibrosis scores. Liver fibrosis is routinely staged with FibroScan (transient elastography) and serum-based scores such as FIB-4. Liver biopsy is reserved for cases where non-invasive assessments are inconclusive, or confirmation of advanced disease is required.

Key messages

24. In up to 5 bullet points, please summarise the key messages of your submission.	• Resmetirom is the first treatment to show meaningful improvements in NASH resolution and fibrosis without worsening disease activity. • It offers benefits beyond lifestyle and comorbidity management, potentially changing care pathways and slowing progression to advanced liver disease. • Patients are identified using risk factors, non-invasive fibrosis scores (e.g., FIB-4), and specialist assessment; ongoing monitoring includes liver function and fibrosis evaluation. • The drug is generally well tolerated, with mild, short-lived side effects such as diarrhoea and nausea; real-world data are consistent with trial findings. • Ensuring timely access for patients in rural or spoke centres is important, with referral pathways and shared-care arrangements helping to support equitable treatment access.

Thank you for your time.

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Single Technology Appraisal

Resmetirom for treating moderate to advanced liver fibrosis (without cirrhosis) caused by metabolic dysfunction-associated steatohepatitis [id6529]

Professional organisation submission

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You can provide a unique perspective on the technology in the context of current clinical practice that is not typically available from the published literature.

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- Your response should not be longer than 13 pages.

About you

1. Your name	██████████
2. Name of organisation	UK Clinical Pharmacy Association
3. Job title or position	██████████
4. Are you (please select Yes or No):	An employee or representative of a healthcare professional organisation that represents clinicians? ~~Yes~~ No A specialist in the treatment of people with this condition? ~~Yes~~ No A specialist in the clinical evidence base for this condition or technology? ~~Yes~~ No Other (please specify):
5a. Brief description of the organisation (including who funds it).	Professional body for clinical pharmacists practicing in the UK, funded by membership but also receives funding from pharma e.g. for event and educational support activities.
5b. Has the organisation received any funding from the manufacturer(s) of the technology and/or comparator products in the last 12 months? [Relevant manufacturers are listed in the appraisal matrix.] If so, please state the name of manufacturer, amount, and purpose of funding.	Annual corporate membership fee of £1000+VAT paid by Viatris, which Mylan is now part of.
5c. Do you have any direct or indirect links with, or funding from, the tobacco industry?	No.

The aim of treatment for this condition

6. What is the main aim of treatment? (For example, to stop progression, to improve mobility, to cure the condition, or prevent progression or disability.)	To prevent or reverse liver fibrosis, reducing the progression to liver cirrhosis and therefore the complications of decompensated cirrhosis and/or liver cancer and associated morbidity/mortality.
7. What do you consider a clinically significant treatment response? (For example, a reduction in tumour size by x cm, or a reduction in disease activity by a certain amount.)	MASH resolution (presence of any grade of steatosis, no ballooning, minimal [grade I] lobular inflammation) with no worsening of fibrosis Or Improvement of fibrosis by at least one stage without any worsening of MASH (no worsening of ballooning or lobular inflammation. 1-grade change in steatosis may be acceptable)
8. In your view, is there an unmet need for patients and healthcare professionals in this condition?	Yes, lack of licensed therapeutic options proven in randomised, double blind, controlled trials. Dietary and lifestyle intervention forms the mainstay of therapy as a result with little proven therapeutic option which such measures are unsuccessful.

What is the expected place of the technology in current practice?

9. How is the condition currently treated in the NHS?	Lifestyle intervention is the mainstay of treatment, advising targeting 5-10% loss of weight through calorie restriction and healthy balanced diet, alcohol avoidance, optimisation of diabetes if relevant. Pioglitazone and vitamin E are available but variable practice between clinicians and treatment centres due to weak evidence.
9a. Are any clinical guidelines used in the	Precedence is given to recent EASL guidelines on MASLD associated liver disease https://www.journal-of-hepatology.eu/article/S0168-8278(24)00329-5/fulltext .

Professional organisation submission

[Resmetirom for treating moderate to advanced liver fibrosis (without cirrhosis) caused by metabolic dysfunction-associated steatohepatitis]
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treatment of the condition, and if so, which?	Supported by past NICE guidelines https://www.nice.org.uk/guidance/ng49 and BSG quality standards https://www.thelancet.com/journals/langas/article/PIIS2468-1253(22)00061-9/abstract
9b. Is the pathway of care well defined? Does it vary or are there differences of opinion between professionals across the NHS? (Please state if your experience is from outside England.)	Not well defined due to large cohort of patients with MASLD, including many undiagnosed and lack of routine or standardised screening or assessment. This is at least in part due to a lack of pharmacological treatment options resulting in a sense of futility regarding screening programmes if there are few effective treatment options once diagnosed. Trusts and care boards have devised their own screening and referral pathways with variation nationally and regionally. Uptake of pioglitazone and vitamin E is variable due to limited evidence and licensing, and in some cases due to inconsistent supply chain/high cost of some vitamin E preparations.
9c. What impact would the technology have on the current pathway of care?	It would offer a viable funded pharmacological therapy for those who have failed lifestyle intervention (and diabetes optimisation, if relevant).
10. Will the technology be used (or is it already used) in the same way as current care in NHS clinical practice?	As a funded NICE approved treatment option with robust evidence base, NICE approval would likely displace any residual pioglitazone/vitamin E use, assuming recommended as a first line therapy.
10a. How does healthcare resource use differ between the technology and current care?	Current pharmacological treatment with pioglitazone and vitamin E is non-reimbursable with a weak evidence base, therefore little uptake. Approval of resmetirom would likely change the landscape of MASH care and require redefining treatment pathways to offer more proactive and responsive care, including monitoring and follow-up, and so with an impact on provider and imaging capacity.
10b. In what clinical setting should the technology be used? (For example, primary or secondary care, specialist clinics.)	Expectation of secondary care initially, with potential to move into primary care in future once protocols and pathways are well developed (this may be with or without the necessity for secondary care guidance depending on the experience of the prior phase).
10c. What investment is needed to introduce the technology? (For example, for facilities, equipment, or training.)	Investment in hepatology outpatient services including multidisciplinary clinicians (medical, nursing and pharmacy) capacity and training, as well as increasing capacity for transient elastography, imaging and histology services.

11. Do you expect the technology to provide clinically meaningful benefits compared with current care?	Yes, based on results of MAESTRO-NASH demonstrating superiority to placebo with regards to NASH resolution and improvement in liver fibrosis. Would reduce disease burden and therefore reduce proportion of patients progressing to decompensated liver disease, transplant and liver cancer (and therefore improving capacity of downstream services).
11a. Do you expect the technology to increase length of life more than current care?	Yes, but no data to support this yet.
11b. Do you expect the technology to increase health-related quality of life more than current care?	Yes, but no data to support this yet. The psychological benefit to patients, through availability of therapeutic interventions, should not be overlooked.
12. Are there any groups of people for whom the technology would be more or less effective (or appropriate) than the general population?	Patients with additional risk factors such as obesity and diabetes, as well as those populations higher rates of progression of liver disease and poorer outcomes, such those of South Asian ethnicity. They may be expected to obtain greater benefit as within higher risk categories, but no evidence to support this assumption yet. It may in fact be the case that those with the highest risk are still likely to suffer progression of liver disease despite resmetirom due to overwhelming pathology. In which case those with lesser risk factors, such as those who are borderline for decompensated liver disease, may benefit most. No safety or efficacy data has been established for paediatric patients. Avoid in patients with decompensated cirrhosis. No data for use in severe renal impairment (eGFR <30ml/minute). No available data for use in pregnancy to evaluate for drug-related risk of major birth defects, miscarriage or other adverse maternal or foetal outcomes. However risks to the mother and foetus related to underlying maternal MASH with liver fibrosis include risk of gestational diabetes, hypertensive complications, preterm birth and postpartum haemorrhage. No data for use in breastfeeding.

The use of the technology

13. Will the technology be easier or more difficult to use for patients or healthcare professionals than current care? Are there any practical implications for its use (for example, any concomitant treatments needed, additional clinical requirements, factors affecting patient acceptability or ease of use or additional tests or monitoring needed.)	More difficult as adds an additional therapeutic option and so requires redevelopment of pathways, which will inevitably be more complex. Practical complications relate mostly to capacity and access to care providers and imaging/histology. Depending on the cost, the additional complexity of homecare for medication provision may also be required, with homecare services in most secondary care facilities already overwhelmed.
14. Will any rules (informal or formal) be used to start or stop treatment with the technology? Do these include any additional testing?	Initial trial of non-pharmacological lifestyle interventions prior to considering resmetirom, with the parameters of this to be determined. Otherwise too early to say, as depends on UK product licence.
15. Do you consider that the use of the technology will result in any substantial health-related benefits that are unlikely to be included in the quality-adjusted life year (QALY) calculation?	Effect on improving capacity on services to more advanced liver disease, compensated and decompensated cirrhosis, liver cancer and liver transplant, as stated above.

16. Do you consider the technology to be innovative in its potential to make a significant and substantial impact on health-related benefits and how might it improve the way that current need is met?	Yes, new mode of action and well evidenced pharmacological intervention meeting a significant unmet need for those who fail non-pharmacological interventions.
16a. Is the technology a 'step-change' in the management of the condition?	Yes, for reasons stated above.
16b. Does the use of the technology address any particular unmet need of the patient population?	Yes, by opening up new therapeutic options for those who fail non-pharmacological interventions.
17. How do any side effects or adverse effects of the technology affect the management of the condition and the patient's quality of life?	No apparent significant safety signal from MAESTRO-NASH compared, though a potential increased risk of adverse effects and drug discontinuations with the higher 100mg dose. Gastrointestinal adverse effects most prevalent which may pose a transient impact on quality of life if not tolerated, until discontinuation.

Sources of evidence

18. Do the clinical trials on the technology reflect current UK clinical practice?	Yes, particularly via use of non invasive assessment rather than universal histology, which is the direction of UK hepatology practice. However there was a lack of assessment against pioglitazone and

	vitamin E so will be less applicable (or pose uncertainty) to centres and practitioners utilising these options.
18a. If not, how could the results be extrapolated to the UK setting?	N/A
18b. What, in your view, are the most important outcomes, and were they measured in the trials?	Disease progression/resolution – reported. Long term all cause mortality, liver cancer, liver transplant, liver decompensation events – not reported.
18c. If surrogate outcome measures were used, do they adequately predict long-term clinical outcomes?	Yes, standard surrogate outcomes for MASH trials utilised.
18d. Are there any adverse effects that were not apparent in clinical trials but have come to light subsequently?	None known.
19. Are you aware of any relevant evidence that might not be found by a systematic review of the trial evidence?	Comparison to pioglitazone and vitamin E as not directly compared. >52 week outcomes for all cause mortality, liver cancer, liver transplant, liver decompensation events. Not aware of any unpublished data for comparisons.

20. How do data on real-world experience compare with the trial data?	Not yet in widespread use in UK, no experience of use within a trial). Unaware of any discrepancy based on real world use in the USA.

Equality

21a. Are there any potential equality issues that should be taken into account when considering this treatment?	Identifying those groups and ethnicities who would be most likely to benefit and ensuring access to care for underserved populations who have a higher risk of poor outcomes from MASH. The commissioning route of this medicine needs to be taken into consideration. If this medicine is only available via ODN hubs this can reduce access to therapy if a patient needs to travel over a wide geographic area. This disproportionately affects those with advanced age or disability, as well as those of lower socioeconomic status, which is therefore more likely to disadvantage ethnic minorities and would likely result in worse outcomes for those with protected characteristics compared to the wider population with MASH.
21b. Consider whether these issues are different from issues with current care and why.	Issues with identifying those most at risk in underserved populations already exist in general MASLD/MASH care provision.

Topic-specific questions

22. How are people with moderate to advanced liver fibrosis caused by metabolic dysfunction-associated steatohepatitis (MASH) who might be eligible for treatment with resmetirom identified in NHS practice?	Often through investigation of incidental abnormal LFTs, or following acute severe liver injury related to MASH.
23. How is the disease activity of MASH routinely assessed in the NHS? Which scales are used in clinical practice in the NHS to stage liver fibrosis?	Combination of blood results, non-invasive tests such as Fib-4/ELF and transient elastography, liver ultrasound and biopsy staged using Metavir or Ishak.

Key messages

24. In up to 5 bullet points, please summarise the key messages of your submission.	• New pharmacological therapy/mode of action • Meets an unmet therapeutic need • Likely significant impact on existing hepatology service capacity due to large patient cohort • Requires redesign/re-development of existing patient pathways • Further longer term, real world outcome data required on mortality and liver morbidity

Thank you for your time.

Please log in to your NICE Docs account to upload your completed submission.

Professional organisation submission

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Single Technology Appraisal

Resmetirom for treating moderate to advanced liver fibrosis (without cirrhosis) caused by metabolic dysfunction-associated steatohepatitis [ID6529]

NHS organisation submission

Thank you for agreeing to give us your views on the technology and the way it should be used in the NHS.

The Department of Health and Social Care and the Welsh Government provide a unique perspective on the technology, which is not typically available from the published literature. NICE believes it is important to involve NHS organisations that are responsible for commissioning and delivering care in the NHS in the process of making decisions about how technologies should be used in the NHS.

To help you give your views, we have provided a template. The questions are there as prompts to guide you. You do not have to answer every question. Short, focused answers, giving a Department of Health and Social Care and Welsh Government perspective on the issues you think the committee needs to consider, are what we need.

About you

Your name	
Name of your organisation	NHS England
Please indicate your position in the organisation	NHS England Medicines Value & Access; plus, input from NHS England IRLSS, Specialised Commissioning and Prevention & Long-Term Conditions teams.
Do you have any links with, or funding from, the tobacco industry? Please declare any direct or indirect links to, and receipt of funding from the tobacco industry	Not Applicable

What is the expected place of the technology in current practice?

How is the condition currently treated in the NHS? Is there significant geographical variation in current practice? Are there differences in opinion between professionals as to what current practice should be? What are the current alternatives (if any) to the technology, and what are their respective	How is the condition currently treated in the NHS? • Currently there is no licensed medical treatment that has been shown to improve clinical outcomes in patients with MASLD and liver fibrosis. The current management focusses on advice and support for lifestyle changes (based on the evidence that weight loss could potentially prevent disease progression or even improve fibrosis) and treatment of the metabolic comorbidities. • Lifestyle intervention with calorie restriction and physical activity (for MASLD) – weight reduction achieved by calorific restriction, either with or without increased physical activity, can lead to some improvement in MASLD biomarkers, including liver enzymes, steatosis, MASH, and fibrosis. • Bariatric surgery (for MASH) – effectively promotes weight loss and its maintenance; the effects on body weight largely exceed the 10% weight loss target associated with clearance of liver fat, resolution of MASH and reversal of fibrosis. However, there is only a small eligible population that could benefit.

advantages and disadvantages?	• NICE NG49 outlines the lifestyle changes and off-label pharmacological treatments that can manage MASLD and advanced liver fibrosis. • Pioglitazone or vitamin E can be considered for adults with advanced liver fibrosis (i.e. MASH $\geq$F3), whether they have diabetes or not (in secondary or tertiary care settings only), and vitamin E can be considered for children with advanced liver fibrosis (i.e. MASH $\geq$F3) in tertiary care settings only, and in young people in secondary or tertiary care settings. Whilst these options are available, they are not widely used in practice (estimated less than 5% of eligible population is receiving these interventions). Concerns about weight gain, fluid retention and cardiovascular risk have limited the use of pioglitazone and similar cautions have been raised regarding cardiovascular risk and Vitamin E. Is there significant geographical variation in current practice? Throughout the pathway we found significant variance in both the sequencing of tests and the availability of tests for patients. Detailed observations: • Mobile or community-based Fibroscan screening services are not common. Service may also perform other tests i.e. liver enzymes, ELF etc. and generate Fibrosis (FIB)-4 Score (FIB-4) for patients. • iLFT (Intelligent Liver Function Testing) is not widely available in England. • Regional differences in the standard tests required before referral to secondary care. • ELF Testing is relatively expensive and not commissioned in all regions. • In some areas, Fibroscan may not be available in any setting. • Ultrasound is prioritised over Fibroscan in some areas; albeit these two tests provide different information and should not be directly compared • Ultrasound is only available in CDCs or community hospitals in some regions. • ARFI is not widely available in England but may be offered for patients with unclear Fibroscan result. This may occur in patients with BMIs over 30. The test result threshold values vary between local pathways, both in terms of what thresholds are tested (i.e. what is included in a standard LFT panel) as well as what the results are deemed to mean (i.e. what the LFT results say about a patient's condition).

Detailed observations:

- Markers included in standard LFT vary which has implications, as if AST is not included then the FIB-4 cannot be calculated. This can lead to patients having to attend their GP for a 2nd blood test.
- Threshold value varies across different guidance/pathways.
- If Fibroscan result not clear, patient may be offered ELF test or ARFI if available for fibrosis staging.

The local service models for diagnosing MASLD were also seen to be different based on location. In some areas proactive case finding was present or in others hot clinics were available. However, this was not consistent across the national picture.

Detailed observations:

- Case finding not present in all regions. At risk is often deemed to be patients with Type 2 Diabetes and/or obesity with 1 or more features of a metabolic syndrome but can include other factors.
- Regional differences in whether FIB-4 or NAFLD fibrosis score is used. FIB4 generally preferred, even within regions currently using NAFLD fibrosis score.
- One-stop clinic in some regions. Patients have diagnostics, consultation and lifestyle advice if required in single appointment.
- Lifestyle advice may be provided during appointments and referrals made for lifestyle interventions.
- Hot clinics are available in some areas for urgent referrals from primary care.
- Availability of lifestyle support in secondary care varies significantly.

Are there differences in opinion between professionals as to what current practice should be?

As to be expected when various local pathways are present, there was also significant variance in the approach taken by clinicians within many elements of the pathway.

Detailed observations:

- Some use automated system to get FIB-4 which helps to identify patients for follow up.

- Clinicians have different thresholds for referring into secondary care.
- According to some hepatologists, patients referred with possible MASLD are often identified to be drinking over the recommendations when further assessments undertaken by Hepatology.
- Clinicians in secondary care may repeat diagnostics that have already taken place in primary care/community.
- Variation across regions around preference for monitoring patients with moderate fibrosis in primary or secondary care.
- Some clinicians routinely recommend biopsy for formal diagnosis of MASH. Some clinicians reserve biopsies for when diagnostic uncertainty from non-invasive tests.
- Some clinicians may diagnose MASH without biopsy.

Another feature highlighted in the pathway was the differing levels of clinical understanding of MASLD/MASH as a condition. This also meant that emphasis on MASLD as a serious but treatable condition varied between clinicians, and as a result was often communicated differently to patients based on the clinician they were seeing.

Detailed observations:

- Clinicians have different thresholds for conducting further tests following abnormal LFT.
- Clinicians may refer directly to secondary care without further investigation if LFT raises significant concerns.
- Variation in when clinicians will diagnose MASLD and code this in patient record. This can and does regularly occur prior to FIB-4 score.
- Clinicians may communicate diagnosis with varying emphasis on the significance of the condition

To what extent and in which population(s) is the technology being used in your local health economy? Is there variation in how it is being used in your local health economy? Is it always used within its licensed indications? If not, under what circumstances does this occur? What is the impact of the current use of the technology on resources? What is the outcome of any evaluations or audits of the use of the technology? What is your opinion on the appropriate use of the technology?	No response.

Potential impact on the NHS if NICE recommends the technology

What impact would the guidance have on the delivery of care for patients with this condition?	New technologies in this disease area would provide support for patients unable to benefit from lifestyle changes alone, which remain the cornerstone of MASLD management. This technology has also demonstrated improved liver and metabolic outcomes such as: • Reduction in hepatic steatosis • Improvement in liver enzyme levels • Better glycaemic and lipid control

NHS submission

[Resmetirom for treating moderate to advanced liver fibrosis (without cirrhosis) caused by metabolic dysfunction-associated steatohepatitis]
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	Potential reversal of fibrosis in people with significant or advanced fibrosis but no cirrhosis Given the anticipated significant eligible population sizes and resultant capacity challenges for delivery, there is expected impact on both diagnostic and primary care resources. Currently, based on scoping information only, implementation to the full population within a 90-day timeframe is unlikely to be feasible and a funding variation will likely be required.
In what setting should/could the technology be used – for example, primary or secondary care, specialist clinics? Would there be any requirements for additional resources (for example, staff, support services, facilities or equipment)?	The technology is seen to have greatest benefit and impact for those patients with significant or advanced (F2, F3) fibrosis. It can be also argued that younger patients are in greater need due to their life expectancy and the prospect of progressing to cirrhosis. The cost and clinical effectiveness in patients at F0-F2 is less clear, and there are more significant challenges in identifying these patients who are more likely to be asymptomatic. Disease progression is a key consideration but at this time there is not sufficient or compelling evidence on this. Pooled data from paired biopsy studies suggest patients will progress from one disease stage to the next after an average of approximately seven years. A study highlights that a significant placebo response in MASH trials is influenced by biopsy-related variability and natural disease fluctuations, which can complicate the assessment of treatment outcomes (Rowe et al., 2022). There is currently no effective mechanism to identify patients in the absence of a structured screening process. A standalone screening approach is unlikely to be practical or feasible in this context. Therefore, consideration must be given to how screening can be effectively integrated into existing primary care pathways. However, integrating this process into primary care presents a significant capacity challenge, given current workload and system constraints. Overall, the consensus from clinicians interviewed leaned towards initial specialist involvement with a potential shift to primary care for ongoing management. In this model, initially secondary care hepatology or

	gastroenterology consultants would prescribe the medication, secondary care liver nurses would oversee any drug titration, and manage the patient until they are stabilised (c. 6 months) under consultant supervision. A considerable proportion of interviewed primary care staff stated that they would not feel comfortable initiating a patient on a liver fibrosis reduction drug due to their new and unknown nature. They also flagged that some primary care clinicians have a more limited awareness of MASLD and MASH as a condition, so they would not feel confident in placing prescribing responsibility on GPs who may already require additional support in this area.
Can you estimate the likely budget impact? If this is not possible, please comment on what factors should be considered (for example, costs, and epidemiological and clinical assumptions).	Resmetiron is expected to be indicated in conjunction with diet and exercise for the treatment of adults with noncirrhotic metabolic dysfunction-associated steatohepatitis (MASH) with moderate to advanced liver fibrosis (fibrosis stages F2 to F3). NHS England BIT submission will focus on this full potential eligible population. In addition, NHS England will set out costs associated with the diagnosis (where appropriate), initiation and management of patients on treatment. This will include a cost for a consultant led first appointment plus required diagnostic testing. After initiation of therapy, all patients should be monitored for progression, and liver- or gall-bladder related AEs, with laboratory and clinical assessment. The frequency and costs will be worked up in conjunction with the NICE RIA team. As detailed cost model has been generated, and NHS England welcome an opportunity to share this with the NICE technical team. Given the significant costs estimated with delivering these treatments to all eligible patients, there may be a requirement for subgroup modelling if the company limit submission to targeting those populations with the most to benefit from treatment. Due to the diagnostic investigation requirements, the patient monitoring and activity costs, the BIT is expected to breach in all 3 years if NICE recommended treatment of the full indicated population. Based on scoping information only, implementation to the full eligible population within a 90-day timeframe is unlikely to be feasible and a funding variation will likely be required.
Would implementing this technology have resource implications for other services (for example, the	<u>Successful delivery of proposed new MASLD/MASH treatment pathways relies on non-invasive testing to accurately indicate fibrosis staging such as FIB-4 (which requires a liver panel that includes both ALT and AST)</u>

trade-off between using funds to buy more diabetes nurses versus more insulin pumps, or the loss of funds to other programmes)?	<u>and either ELF or Fibroscan (or even both of them in some cases) will be required, with limited capacity and regional variation in access to FibroScan and ELF tests.</u> ICBs have advised that access to FibroScans varies significantly, and more rapid expansion is needed to meet demand. In an engagement exercise with ICBs they indicated that the Community Diagnostic Centre (CDC) would be the preferred model for roll out but currently only 25 of 170 CDCs offer FibroScan. A recent Pathway Development Fund award attracted applications seeking to extend and expand FibroScan capacity for a further 11 CDCs (approvals process underway). There is significant variation across regions for FibroScan activity planned by CDCs during 2025/26, ranging from only 1% of total CDC FibroScan activity within the Midlands region to 27% of all planned CDC activity planned within the South West region. Availability and uptake of ELF testing is particularly limited with less than 32% of the national population having access currently and significant variation in access across regions, ranging from 14% - 59%. It is anticipated to meet the diagnostic demand that there would need to be significant investment in FibroScan and ELF testing capacity across the country. <u>Additionally, there are currently no recommendations for case finding approaches for at risk patients in primary care. NG49 considered this but did not find in favour, given the current changes in MASLD / MASH care this may need to be revisited.</u> With disease being typically asymptomatic at earlier stages, there are no standardised detection triggers for liver disease in primary care, nor are there consistent diagnostic pathways. Identification is typically through incidental findings to other investigations (e.g. abnormal LFTs or ultrasound being conducted for another reason) or identification of risk factors prompting further investigation. However, there is substantial potential to reduce duplication and costs in primary care through the development of standardised pathways across England.
Would there be any need for education and training of NHS staff?	Specialist care clinicians emphasise the lack of education for primary care clinicians in diagnosing MASLD and liver fibrosis. This concern is supported by anecdotal evidence from primary care. All clinicians who participated in an NHSE survey identified education and training programs as the most desired improvement for diagnosing MASLD. This education gap contributes to delayed diagnoses, missed opportunities for intervention, and negative health outcomes. Moreover, an NHSE primary care clinician survey results indicate that the majority of respondents did

	not know the ranges for diagnostic tests including FIB-4, Nonalcoholic fatty liver disease Fibrosis Score (NFS), ELF, FibroScan, and FibroTest. The EASL guidelines strongly advocate for raising awareness of MASLD among healthcare professionals.

Equality

Please let us know if you think that this appraisal: Could exclude from full consideration any people protected by the equality legislation who fall within the patient population for which [the treatment(s)] is/are/will be licenced Could lead to recommendations that have a different impact on people protected by the equality legislation than on the wider population, e.g. by making it more difficult in practice for a specific group to access the technology Could lead to recommendations that have any adverse impact on people with a particular disability or disabilities.	There are known differences in MASH prevalence between ethnic groups (Office for Health Improvement & Disparities, 2024). It is not year clear how patients could be clinically prioritised if demand for the technology is greater than the NHS capacity to deliver treatment. However, consideration is likely to be focused on disease state and setting of care. A pragmatic approach could be to prioritise patients who are already diagnosed in secondary care, whilst capacity for non-invasive testing is increased. It should also be noted that existing local variation in primary care practice and diagnostic capacity is likely to impact the number of patients identified and could lead to potential geographical inequity in access to treatment.
Please tell us what evidence should be obtained to enable the committee to identify and consider such impacts.	

NICE is committed to promoting equality of opportunity, eliminating unlawful discrimination and fostering good relations between people with particular protected characteristics and others.

Other issues

Please include here any other issues you would like the appraisal committee to consider when appraising this technology	To note: NHS England, In the context of a rapidly growing pipeline of potential treatments and a focus on earlier planning and preparation to ensure system readiness, a project was undertaken to create a current diagnosis pathway for MASLD, due to the need for a stronger national insight on the current landscape for this condition and associated services. This current pathway will act as a crucial element for any future pathway mapping exercises to understand key challenges and areas for meaningful improvement. The output of this project was a full report, the content of this report is used within this submission. Clinical input into the report: • Dr Helen Williams National Speciality Advisor for Cardiovascular Prevention • Dr Rani Khatib National Speciality Advisor for Cardiovascular Disease • Dr Kiren Collinson Deputy Medical Director for Primary Care • Dr Richard Aspinall National Speciality Advisor and Chair of the Hepatobiliary & Pancreas Clinical Reference Group • Helen Ashcroft Head of Programmes, Transformation, Liver & Recovery • Suzette Fernandes Community Diagnostic Centres Senior Programme Manager, System Improvement • Divine Azange Pathology Transformation Implementation Lead, System Improvement • Mhukti Perumal Liver Early Diagnosis, Senior Programme Manager, NHS Cancer Programme

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[Resmetirom for treating moderate to advanced liver fibrosis (without cirrhosis) caused by metabolic dysfunction-associated steatohepatitis]
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EXTERNAL ASSESSMENT GROUP REPORT

Resmetirom for treating moderate to advanced liver fibrosis (without cirrhosis) caused by metabolic dysfunction-associated steatohepatitis [ID6529]

Produced by

York Technology Assessment Group, University of York, Heslington, York, YO10 5DD

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Declared competing interests of the authors

None.

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Richard Parker, Leeds Teaching Hospitals NHS Trust.

Rider on responsibility for report

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Contributions of authors

VGC performed the critical review of cost-effectiveness evidence, validated the company's economic model, conducted EAG additional analyses, and contributed to drafting Sections 1, 5 of the report. EU drafted section 3 and contributed to sections 1 and 2 of the report. DC and NJD performed the critical review of the cost-effectiveness evidence and contributed to drafting Sections 1, 4, and 5 of the report. CUC drafted section 2 of the report and reviewed other sections of the report. CR performed the critical review of the cost-effectiveness evidence, provided expert advice and reviewed sections of the report. RH oversaw the review of the cost-effectiveness evidence, conducted EAG additional analyses, contributed to drafting Sections 1, 4, and 5 of the report, commented on drafts of the report and takes joint responsibility for the report as a whole. LT provided expert clinical advice to the EAG. MS oversaw the review of clinical evidence, supported the validation of the company's economic model, commented on drafts of the report and takes joint responsibility for the report as a whole.

Note on the text

All commercial-in-confidence (CON) data have been redacted.

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List of abbreviations

AASLD	American Association for the Study of Liver Diseases
AE	Adverse event
ALD	Advanced liver disease
ALT	Alanine aminotransferase
AST	Aspartate aminotransferase
BASL	British Association for the Study of the Liver
BMI	Body mass index
CAP	Controlled Attenuation Parameter
CC	Compensated cirrhosis
CEA	Cost-effectiveness analysis
CI	Confidence interval
CLDQ	Chronic Liver Disease Questionnaire
CPRD	Clinical Practice Research Datalink
CRN	Clinical Research Network
CS	company submission
CSR	Clinical Study Report
CV	Cardiovascular
CVD	Cardiovascular disease
DCC	Decompensated cirrhosis
EAG	Evidence Assessment Group
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
EC	European Commission
ELF	Enhanced Liver Fibrosis
EMA	European Medicines Agency
EQ-5D	Euroqol-5 Dimensions
EU	European Union
F1	Fibrosis stage 1
F2	Fibrosis stage 2
F3	Fibrosis stage 3
F4	Fibrosis stage 4
FDA	Food and Drug Administration
FT4	Free thyroxine
GLP-1 RA	Glucagon-like peptide-1 receptor agonist
HbA1c	Glycated haemoglobin
HCC	Hepatocellular carcinoma
HCRU	Healthcare resource use
HDL-C	High-density lipoprotein-cholesterol
HES	Hospital Episode Statistics
HR	Hazard ratio
HRG	Healthcare Research Group
HRQoL	Health-related quality of life
HTA	Health Technology Assessment
HUI	Health Utilities Index
ICER	Incremental cost-effectiveness ratio
ITT	Intention-To-Treat

Kg	Kilogram
kPa	kilopascal
LB	Liver biopsy
LDL-C	Low-density lipoprotein-cholesterol
LDQoL	Liver Disease Quality of Life
LSM	Liver stiffness measurement
LT	Liver transplant
MASH	Metabolic dysfunction-associated steatohepatitis
MASL	Metabolic dysfunction-associated steatosis liver
MASLD	Metabolic dysfunction-associated Steatotic liver disease
mITT	Modified Intention-To-Treat
MRE	Magnetic resonance elastography
MRI	Magnetic resonance imaging
MRI-PDFF	MRI-based proton density fat fraction
MSM	microsimulation models
N/A	Not applicable
NAFLD	Non-alcoholic fatty liver disease
NAS	NAFLD Activity Score
NASH	Non-alcoholic steatohepatitis
NG	NICE Guideline
NHS	National Health Service
NICE	National Institute for Health and Care Excellence
NIT	Non-invasive test
NR	Not reported
OCA	Obeticholic acid
OR	Odds ratio
PAS	Patient Access Scheme
PfC	Point for clarification
PLB	Placebo
PLT	Post–liver transplantation
PRISMA	Preferred Reporting Items for Systematic reviews and Meta-Analyses
PSS	Personal Social Services
PSSRU	Personal Social Services Research Unit
QALY	Quality-adjusted life year
QoL	Quality of life
RCT	Randomised controlled trial
RR	Risk ratio
SAE	Serious adverse event
SAP	Statistical analysis plan
SD	Standard deviation
SE	Standard error
SLR	Systematic literature review
SmPC	Summary of product characteristics
SoC	Standard of care
STA	Single Technology Appraisal
T2D	Type 2 diabetes
T2DM	Type 2 diabetes mellitus
TC	Total Cholesterol

TEAE	Treatment-emergent adverse event
THR- α	Thyroid hormone receptor-alpha
THR- β	Thyroid hormone receptor-beta
TRAE	Treatment-related adverse event
TSD	Technical Support Document
U.S.	United States
UK	United Kingdom
UKPDS	United Kingdom Prospective Diabetes Study
VCTE	Vibration-Controlled Transient Elastography

1 EXECUTIVE SUMMARY

This summary provides a brief overview of the key issues identified by the external assessment group (EAG) as being potentially important for decision making. It also includes the EAG's preferred assumptions and the resulting incremental cost-effectiveness ratios (ICERs).

Section 1.1 provides an overview of the key issues. Section 1.2 provides an overview of key model outcomes and the modelling assumptions that have the greatest effect on the ICER. Section 1.3 explains the key issues in more detail. Secondary issues and modelling errors identified by the EAG are explored in sections 1.4 and 1.5. Background information on the condition, technology and evidence, and non-key issues are presented in later sections of the EAG report.

All issues identified represent the EAG's view, not the opinion of NICE.

1.1 Overview of the EAG's key issues

Table 1 Summary of key issues

ID[6529]	Summary of issue	Impact on results	Report sections
1	<u>Trial population does not match the population in scope.</u> The MAESTRO-NASH trial required three metabolic risk factors and assessed fibrosis via liver biopsy, whereas the scoped population has no such restrictions and liver biopsy is not routinely used in NHS practice.	Unknown	2.3.1; 3.2.2.1; 3.2.2.2;4.2.3
2	<u>Reliance on Surrogate Endpoints:</u> The short duration of the MAESTRO-NASH trial means there is no direct evidence that resmetirom treatment reduces liver-related morbidity or mortality.	Unknown	2.3.4; 3.3.3;4.2.2
3	<u>Modelled population:</u> Treatment effects in the model are based on a retrospectively defined subset of patients from the ITT population who have a paired liver biopsy. This assumes missing liver biopsy data are missing completely at random.	Unknown	3.3.1; 3.3.2;4.2.3
4	<u>Validation of the company model and programming complexity:</u> The EAG has not been able to successfully validate the company model and has identified several potential errors via black box testing. Additionally, the EAG has substantive concerns regarding how the model has been programmed, as it does not follow coding best practices.	Unknown	5.2.1

ID[6529]	Summary of issue	Impact on results	Report sections
5	<u>Response to treatment not captured by the current model structure:</u> Published and unpublished guidance suggests that patients treated with resmetirom will be periodically assessed for response using non-invasive tests. The company's model, however, makes no provision for response-based assessments.	Unknown	4.2.2
6	<u>Stopping rules and discontinuation of resmetirom treatment:</u> It is unclear if the modelled stopping rules (which relate to fibrosis changes) could be implemented in practice without the use of repeat biopsies.	Unknown	2.3.1;4.2.4
7	<u>Repeated application of transition probabilities and short-term trial follow-up:</u> The company's economic analysis applies the same one-year transition probabilities across the entire time horizon, which results in an increasing proportion of patients being projected to achieve MASH resolution.	Unknown	4.2.2;4.2.5.1
8	<u>Misinterpretation of Singh et al (2015):</u> The company uses data from Singh et al. (2015) to estimate the number of fibrosis stage changes patients experience per annum. This misinterprets the reported data, as Singh et al. (2015) do not provide information on annual changes.	Unknown	4.2.5.1
9	<u>Natural history of MASH and face validity of model progression rates:</u> The company's model predicts that standard of care patients will spend a substantial proportion of time in the ALD health states, particularly F4 CC. This appears inconsistent with clinical experience and rates of progression estimated in the published literature.	Unknown	2.1;4.2.5.1
10	<u>Limited justification for selected input parameters, poor referencing, and and lack of clarity regards how some input values are generated:</u> Many of the inputs used in the model are selected without clear reference as to why they have been selected or how they were identified. The company's assumptions also make extensive use of secondary citations, and it is unclear how some inputs were derived based on the data reported in the cited literature.	Unknown	4.2.5.2;4.2.5.3;4.2.5.4
11	<u>Appropriateness of modelled utility values and MASH resolution increment:</u> The EAG does not consider the company's source of utility values to be consistent with NICE guidance and believes there is weak evidence supporting the utility increment applied for MASH resolution.	Unknown	3.3.3.2;4.2.6

ID[6529]	Summary of issue	Impact on results	Report sections
12	Health state costs and the interpretation of the Davidson study: The health state costs applied in the model, particularly those for F4 compensated cirrhosis, do not accurately reflect the values reported by Davidson (the company's source of health state costs).	Unknown	4.2.7.4

1.2 Overview of key model outcomes

NICE technology appraisals compare how much a new technology improves length (overall survival) and quality of life in a quality-adjusted life year (QALY). An ICER is the ratio of the extra cost for every QALY gained.

Overall, the technology is modelled to affect QALYs by:

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

Overall, the technology is modelled to affect costs by:

- Increasing drug acquisition costs
- Reducing care costs associated with advanced fibrosis

The EAG considers that the following modelling assumptions are likely to that have the greatest effect on the ICER but is currently unable to verify this due to validation issues with the company's model.

These assumptions concern:

- The population used to generate modelled transition probabilities
- Stopping rules applied
- The rate of progression in the standard of care arm
- HRQoL used in the model particular those applied in the F4 compensated cirrhosis health state
- Management costs applied in the F4 compensated cirrhosis health state

1.3 EAG's key issues

Issue 1 The trial population does not match the population in scope.

Report section	2.3.1; 3.2.2.1; 3.2.2.2;4.2.3
Description of issue and why the EAG has identified it as important	Clinical advice to the EAG indicates the MAESTRO-NASH population is a selective population with ≥ 3 cardiometabolic risk factors, and with eligibility decided by liver biopsy. As a result, there is no evidence of the efficacy of resmetirom for a substantial proportion of UK patients with MASH and one or two cardiometabolic risk factors. Clinical advisers rule out using liver biopsies to identify patients eligible for resmetirom in practice. Different criteria have been proposed for the identification and selection of patients eligible for resmetirom, based on which [REDACTED] of the trial population would be eligible.
What alternative approach has the EAG suggested?	The EAG has no suggestions
What is the expected effect on the cost-effectiveness estimates?	Increased uncertainty
Could any additional evidence or analyses be provided to resolve this key issue?	Further information on the patient population eligible for resmetirom and how this compares to the MAESTRO-NASH trial would be informative. Clinical opinion on the most appropriate criteria would also help to interpret the relevance of the trial population.

Issue 2 Reliance on Surrogate Endpoints

Report section	2.3.4; 3.3.3:4.2.2
Description of issue and why the EAG has identified it as important	The company's model assumes cost-effectiveness arises from reduced comorbid events, avoidance of advanced liver complications (DCC and HCC), and improved survival. These outcomes are not directly observed in the MAESTRO-NASH trial, instead intermediate endpoints like NASH resolution and fibrosis improvement at 52 weeks are used as proxies for outcomes with substantial impacts on quality of life. The company was not able to report long-term outcomes listed in the NICE scope. Clinical advice to the EAG indicated that progression of fibrosis is typically slow and death due to liver disease is uncommon. It is unclear how effects of resmetirom demonstrated in the relatively short period of follow-up in MAESTRO-NASH translate to future impacts on long-term outcomes and quality of life. The modelled benefits of resmetirom therefore rely on surrogate relationships between fibrosis stage, liver-related events and mortality. However, the fibrosis stage has not been formally validated as an acceptable surrogate endpoint. In particular, there is no interventional evidence demonstrating that treatments which improve fibrosis stage also lead to corresponding improvements in clinical outcomes such as liver-related events or mortality.
What alternative approach has the EAG suggested?	Given the trial evidence available, there are no alternatives.
What is the expected effect on the cost-effectiveness estimates?	Increased uncertainty in modelled benefits.

Could any additional evidence or analyses be provided to resolve this key issue?	Further evidence on the validity of fibrosis as a surrogate may be helpful, although it is unlikely that additional evidence exists beyond what has already been presented. The forthcoming 54-month follow-up may provide further data to support the modelled reductions in liver-related complications and mortality; however, this is not likely to be available until [REDACTED] at the earliest.

Issue 3 Differences between the ITT population and paired liver biopsy population

Report section	3.3.1; 3.3.2;4.2.3
Description of issue and why the EAG has identified it as important	The evidence used in the economic model relies on the PLB-W52 F2/F3 sample (N=739), which includes patients with a baseline biopsy and a readable week 52 biopsy. This selective sample may be biased by discontinuation, for example, due to adverse events relating to resmetirom. Discontinuation rates were substantially higher in the resmetirom 100 mg arm ([REDACTED]) and the 80 mg arm ([REDACTED]) than in the placebo arm ([REDACTED]). Also, the PLB-W52 F2/F3 sample was restricted to data for primary outcomes where two clinicians agreed on the assessment of liver biopsy images, which led to effect estimates for the primary outcomes biased in favour of resmetirom.
What alternative approach has the EAG suggested?	The EAG suggest applying relative treatment effects from the mITT-LB-W52 population for the mASH resolution outcome to better reflect the primary analysis of MAESTRO-NASH trial
What is the expected effect on the cost-effectiveness estimates?	Likely to increase the ICER
Could any additional evidence or analyses be provided to resolve this key issue?	Further information or analysis beyond the suggested scenario is unlikely to be helpful, as this is an inherent limitation of the trial evidence.

Issue 4 Validation of the company model and programming complexity

Report section	5.2.1
Description of issue and why the EAG has identified it as important	The company's R-based economic model is presented as extensively quality-checked, but the documentation lacks detail on what internal validation and cross-checking actually entailed. When the EAG conducted independent black-box tests, it identified several inconsistencies that suggest errors in the R code. For example, changing utility values resulted in changes in the number of life-years. Similarly, setting all treatment effects to standard-of-care values continued to produce non-zero incremental QALYs and LYs. This indicates structural coding errors. The EAG also has broader concerns about the way in which the model has been coded, which does not adhere to best practice. Inputs are read in multiple locations, variables are duplicated, and the ordering of code obscures the logic of calculations. This disorganisation increases the risk of implementation errors and makes it difficult to verify that the model uses the intended parameter values. Given these concerns, the EAG considers the model's internal validity uncertain and believes further verification is required before results can be relied upon.

What alternative approach has the EAG suggested?	The company must carry out a thorough validation of the economic model and should consider revising the code to increase transparency and ease of use. Specific suggestions as to how this can be achieved are outlined in the main report.
What is the expected effect on the cost-effectiveness estimates?	Unclear. Due to the complexity of the model, the EAG has been unable to establish the source of these issues.
Could any additional evidence or analyses be provided to resolve this key issue?	To address this issue, the company should provide a fully revised and transparently documented version of the R model, accompanied by a structured verification report detailing all internal quality-control checks, cross-validation procedures, and their outcomes. The TECH-VER checklist should be completed, with the results of all tests clearly presented to facilitate independent verification. Additionally, the R code should be reorganised to ensure that all model inputs are read from a single, clearly defined location, improving transparency, usability, and confidence in the accuracy of the model's calculations.

Issue 5: Response to treatment not captured by the current model structure

Report section	4.2.2
Description of issue and why the EAG has identified it as important	The introduction of resmetirom would be a major shift in MASH/MASLD management, but the lack of established treatment pathways creates substantial uncertainty about its real-world use. The company's model assumes continuous treatment while patients remain in F2–F3, regardless of other response criteria. . However, expert guidance (e.g., Nouredin et al., 2024) proposes response assessment at 12 months using non-invasive tests (NIT)s, with treatment stopped if NIT results worsen, continued if NIT results improved and considered for continuation if NIT results show no change.. Although the company acknowledged that response assessment is likely to be implemented in UK practice, its model includes no response-based stopping rule. The company argues MAESTRO-NASH does not support such modelling, but the EAG considers this a major limitation. Further evidence is required to substantiate the modelled treatment paradigm, which EAG considers has not been adequately justified. The omission of a response-based stopping rule represents a significant uncertainty that potentially undermines the suitability of the model for decision-making.
What alternative approach has the EAG suggested?	The EAG suggest that the model structure be adapted to more appropriately consider assessments based on response as measured by NITs
What is the expected effect on the cost-effectiveness estimates?	Unknown
Could any additional evidence or analyses be provided to resolve this key issue?	Further evidence on how resmetirom is likely to be used in practice and decision criteria that could be applied to inform treatment discontinuation decisions. Appropriate revisions to the company's economic analysis to explore NIT-based assessments most likely to reflect usage decisions in the NHS .

Issue 6: Stopping rules and discontinuation of resmetirom treatment

Report section	2.3.1; 4.2.4
Description of issue and why the EAG has identified it as important	The EAG has major concerns about the model's stopping rules, which require discontinuation of resmetirom when fibrosis regresses or when patients progress to advanced liver disease, including compensated cirrhosis. The EAG considers these rules biologically and clinically questionable. Fibrosis regression without MASH resolution may not justify stopping therapy, and the EAG's clinical advisers were not aligned on whether progression to F4 CC reflects treatment failure or insufficient treatment. The Summary of Product Characteristics (SmPC) offers no discontinuation guidance, and the company's assumption that patients must stop treatment when moving outside the F2–F3 is not explicitly stipulated in the marketing authorisation, and requires further validation by clinical experts. Practical implementation is also problematic. Fibrosis staging in the MAESTRO-NASH trial relied on liver biopsy, which is unsuitable for routine care. NITs are expected to be used for fibrosis staging in the NHS, although MASH resolution is not definitively assessable by NIT. Consequently, the suitability of NITs for guiding treatment decisions remains uncertain.
What alternative approach has the EAG suggested?	The EAG suggests that alternative stopping rules are explored with specific reference to NIT that could be undertaken in practice.
What is the expected effect on the cost-effectiveness estimates?	Unclear
Could any additional evidence or analyses be provided to resolve this key issue?	Further clinical opinion is needed on how resmetirom is likely to be used in practice, including appropriate criteria for assessing treatment response and changes in fibrosis stage based on NITs.

Issue 7: Repeated application of transition probabilities and short-term trial follow-up

Report section	4.2.5.1
Description of issue and why the EAG has identified it as important	The EAG is concerned that the model applies the same transition probabilities for MASH resolution throughout the entire time horizon, implying that patients remain equally likely to resolve MASH after 1 year or 30 years of treatment. The EAG considers this biologically implausible for both resmetirom and standard of care (SoC), as clinical advice indicates diminishing returns and an eventual plateau in treatment effect. The 12-month MAESTRO-NASH follow-up provides only limited insight into longer-term resolution, and there is no evidence that continued treatment yields additional improvements beyond year 1. Evidence from long-term follow-up of patients on the SoC indicates that weight loss (the primary driver of histological improvement under usual management) tends to plateau after the first year. This would rule out any repeated application of SoC transitions. Further, long-term observation evidence on the effectiveness of SoC suggests weight-loss benefits plateau within 1 year. These uncertainties affect both treatment-effect plausibility and model structure, including whether a stopping rule is appropriate.

What alternative approach has the EAG suggested?	Given the lack of evidence, the EAG considers it more appropriate to set the probability of MASH resolution to zero after the first year of treatment with either remeteriom or SoC. If further treatment with resmetirom is modelled to provide limited or no additional benefit, reopsne based stopping rules should also be considered, see issue .
What is the expected effect on the cost-effectiveness estimates?	Unclear, but likely results in the ICER being underestimated.
Could any additional evidence or analyses be provided to resolve this key issue?	Long-term evidence on the effectiveness of resmetirom. Further information on the biological rationale for the modelled assumptions.

Issue 8: Misinterpretation of Singh et al (2015)

Report section	4.2.5.1
Description of issue and why the EAG has identified it as important	Singh et al. (2015) conducted a systematic review and meta-analysis summarising fibrosis stage transitions observed in the included studies. These studies followed patients for variable durations, with a minimum follow-up of one year. The EAG is concerned that the company has misinterpreted these data by using them to estimate the number of fibrosis stages an individual patient may transition through within a single annual model cycle. When asked for justification, the company cited the review's quality and argued that multi-stage progression was biologically plausible and supported by clinical opinion. However, the EAG notes that the review reported a mean time of 7.1 years to progress by one stage, making rapid multi-stage progression within a year implausible. Clinical advisors similarly agreed that such fast progression would be very uncommon.
What alternative approach has the EAG suggested?	The EAG considers it more appropriate to adopt a conservative approach in which patients are limited to progressing (or regressing) by a maximum of one fibrosis stage per model cycle.
What is the expected effect on the cost-effectiveness estimates?	Moderate increase in the ICER
Could any additional evidence or analyses be provided to resolve this key issue?	Evidence of multistate progressions should ideally be generated from the MAESTRO-NASH trial. If this data cannot be provided, a more appropriate data source should be selected.

Issue 9: Natural history of MASH and face validity of model progression rates

Report section	2.1; 4.2.5.1
Description of issue and why the EAG has identified it as important	In the base case, the company models natural history by repeating the one-year transitions from MAESTRO-NASH and rejects external evidence such as Le et al. (2023), which indicates that fibrosis progression slows as disease advances. The company argues that Le et al.'s findings are clinically implausible, citing evidence that advanced fibrosis is associated with worse outcomes and referring to the concept of " <i>fast progressors</i> ". However, these arguments do not demonstrate that progression accelerates with advancing fibrosis, and there is no consensus on a fast-progressor phenotype or evidence that most resmetirom-eligible patients fall into this group. The EAG notes that Le et al. (2023) is consistent with earlier studies (e.g., Singh et al., 2015) showing slower progression at higher fibrosis stages.

What alternative approach has the EAG suggested?	The EAG recommends that scenarios be explored using natural history data from Le et al. to model standard-of-care outcomes, or alternatively that the model be calibrated to generate fibrosis progression rates that more closely reflect this external evidence. However, the EAG notes that calibrating the model may be challenging given the current simulation design.
What is the expected effect on the cost-effectiveness estimates?	Likely to increase the ICER.
Could any additional evidence or analyses be provided to resolve this key issue?	Further evidence on the rate of progression to advanced liver disease in patients with F2 and F3 fibrosis would help validate both the modelled transition rates and the data available from natural history studies such as Le et al. (2023).

Issue 10: Limited justification for selected input parameters, poor referencing, and lack of clarity regards how some input values are generated

Report section	4.2.5.2;4.2.5.3;4.2.5.4
Description of issue and why the EAG has identified it as important	The EAG is concerned that many of the inputs used in the economic model lack a clear justification, and it is unclear how the company selected these values. This issue is particularly relevant for several transition probabilities used to model the risk of liver-related events and mortality. Without a transparent rationale, there is a risk that values may have been chosen selectively to produce favourable results rather than derived through a systematic and reproducible evidence-identification process. The EAG is also concerned about the company's extensive use of secondary citations, which makes it difficult to determine the provenance of individual parameters. In several instances, it is unclear how specific values were derived from the cited sources. For example, the EAG could not establish how the transition probabilities for liver transplantation were estimated.
What alternative approach has the EAG suggested?	Not applicable
What is the expected effect on the cost-effectiveness estimates?	Unknown
Could any additional evidence or analyses be provided to resolve this key issue?	The company should provide a clear rationale and detailed description of the methods used to select all input parameters in the model. Where appropriate, it should also outline any calculations or assumptions applied when transforming reported data into the values used in the model.

Issue 11: Appropriateness of modelled utility values and MASH resolution increment

Report section	3.3.3.2;4.2.6
Description of issue and why the EAG has identified it as important	The EAG questioned the company's use of NG49 utility values, which were not derived from a MASH/MASLD population. The provenance of NG49 values is also not fully clear, and they may not be EQ-5D-based. Several values lack face validity: early fibrosis stage utilities (NAFL to F2) are implausibly high, often matching or exceeding general population values, despite many patients having a range of comorbidities and a large proportion with obesity. The steep decline in HRQoL from F3 to F4 compensated cirrhosis (CC) in NG49 is also inconsistent with clinical expert advice, which suggests the largest decline occurs between F4 and decompensated cirrhosis. The EAG is also unclear whether the MASH resolution increment applied in the model is appropriate, as it lacks clear empirical support. Regression analysis of HRQoL data shows that the statistical significance of MASH in the presented regression models available.
What alternative approach has the EAG suggested?	The EAG prefers a base-case approach combining MAESTRO-NASH trial based utilities for F0–F3, and data Papatheodoridi et al. (a UK HRQoL study of MASLD patients) for F4 CC.
What is the expected effect on the cost-effectiveness estimates?	Increases the ICER.
Could any additional evidence or analyses be provided to resolve this key issue?	Further analysis of the MAESTRO-NASH trial data, with full reporting of the present regression analysis, may help resolve uncertainty regarding the appropriateness of applying a MASH resolution increment. The EAG is otherwise satisfied that its proposed scenarios utilise the best available evidence.

Issue 12: Health state costs and the interpretation of the Davidson study

Report section	4.2.7.4
Description of issue and why the EAG has identified it as important	Davidson et al. (2025) report annualised healthcare resource use (HCRU) and costs for a retrospective cohort of 2,696 adults with MASH in England, with a mean follow-up of four years. The company's model, however, uses substantially higher costs than those published, drawing on unpublished data that inflate costs for non-progression (F0–F3) and progression to cirrhosis (F4/CC, DCC, HCC). The model also inconsistently assigns higher costs to CC than DCC and lower costs to HCC than DCC, contrary to published evidence and expert opinion, which suggest DCC is typically costlier than CC but less costly than HCC. The EAG notes that reliance on unpublished data limits transparency and the ability to justify the inputs, and the differences from the published Davidson et al. data are unexplained. Comparisons with alternative sources (Morgan et al. [2021]) suggest that the costs reported by Davidson et al. are broadly consistent with other estimates from the UK.
What alternative approach has the EAG suggested?	The EAG recommends scenario analyses using only published Davidson et al. values, applying non-progression costs to F0–F3 and progression costs to CC and DCC states without year-specific distinctions.
What is the expected effect on the cost-effectiveness estimates?	Increases the ICER

Could any additional evidence or analyses be provided to resolve this key issue?	Further information on the unpublished data the company used to generate its preferred values would help the EAG understand the company's rationale.

1.4 Secondary issues identified by the EAG

Issue 13 Differences in dosing of resmetirom between trial and clinical practice

Report section	2.3.2;4.2.4
Description of issue and why the EAG has identified it as important	MAESTRO-NASH participants were randomised to 80 or 100 mg resmetirom once daily, or placebo. It is anticipated that in practice, patients weighing < 100 kg will receive 80 mg resmetirom once daily, and patients weighing ≥ 100 kg will receive 100 mg resmetirom. Receiving 100 mg rather than 80 mg resmetirom daily appears to be associated with higher discontinuation due to adverse events, and higher efficacy for patients weighing ≥ 100 kg. MAESTRO-NASH result may therefore underestimate the efficacy of resmetirom and the chance of discontinuation for patients weighing ≥ 100 kg.
What alternative approach has the EAG suggested?	The EAG considers pooling data from the 80 mg and 100 mg trial arms the most appropriate approach, as it preserves randomisation, pragmatically addresses weight-based dosing limitations, and avoids the complexity of modelling weight-specific transition probabilities.
What is the expected effect on the cost-effectiveness estimates?	Unknown
Could any additional evidence or analyses be provided to resolve this issue?	The EAG does not consider there to be any other solution or data sources that could be used to resolve this issue at this time.

Issue 14 Current and anticipated use of GLP-1 antagonists in the UK

Report section	2.3.3; 3.2.2.1;4.2.4
Description of issue and why the EAG has identified it as important	The company excluded semaglutide, standalone pioglitazone, vitamin E, and their combination as comparators, arguing that pioglitazone and vitamin E are rarely used in UK clinical practice and form part of standard care. Clinical advice and trial data support this, and the EAG is broadly satisfied with their exclusion. While the EAG accepts the exclusion of semaglutide, as it is not currently approved for treating MASH, semaglutide is recommended for weight management in adults with overweight or obesity and for some patients with T2DM. This could lead to overlap with the modelled population. Evidence supports its effectiveness in MASH, and clinicians would be reluctant to prescribe resmetirom alongside successful GLP-1 therapy. A parallel NICE appraisal of semaglutide for MASH is also underway, which may mean that semaglutide will become a relevant comparator at the time of decision-making.
What alternative approach has the EAG suggested?	Not applicable
What is the expected effect on the cost-effectiveness estimates?	Unknown

Could any additional evidence or analyses be provided to resolve this issue?	Further information on the current use of GLP-1 agonists in this population would be helpful. An analysis comparing resmetirom with semaglutide would also be appropriate if semaglutide becomes a relevant comparator.

Issue 15 Deviations for HTA Lab recommendations

Report section	4.1.3.1
Description of issue and why the EAG has identified it as important	The company submission made limited reference to the NICE HTA Innovation Lab report on MASLD treatments, despite its relevance in the NICE scope. The HTA Lab outlined key modelling challenges and recommended specifications to support consistent and robust evaluation of emerging therapies. While the company's <i>de novo</i> microsimulation model reflects some of these principles, it departs from the recommendations in several important areas, including modelling of disease natural history, reporting of hepatic outcomes, population stratification, consideration of infrastructure and diagnostic costs, scenario analysis, and model flexibility. The EAG considers these omissions particularly concerning, given the company's role as a HTA Lab stakeholder and believes they increase uncertainty and undermine consistency in decision-making.
What alternative approach has the EAG suggested?	The EAG suggests that the company should have aligned its economic model with the NICE HTA Innovation Lab recommendations wherever possible and more thoroughly justified any deviations.
What is the expected effect on the cost-effectiveness estimates?	Unknown
Could any additional evidence or analyses be provided to resolve this issue?	Where the company base case deviates from The HTA Lab recommendations, the robustness of model results should be explored in scenario analysis, e.g. reversal from DCC. The company should also provide key scenarios suggested in the HTA Lab report, e.g. assumptions regarding progression rates on SoC and duration of treatment effects.

Issue 16 Extrahepatic treatment effects

Report section	4.2.5.3
Description of issue and why the EAG has identified it as important	The EAG has concerns about the assumptions underlying the durability of treatment effects in the company's model. For lipids, the model assumes the 12-month effects on LDL-C and HDL-C persist indefinitely, which is unrealistic given limited long-term data, the lack of statistically significant HDL-C changes, and inconsistent application of triglyceride effects. For weight, the model applies a continuous, cycle-by-cycle treatment effect, resulting in ongoing weight loss in both arms and faster decline with resmetirom. The EAG considers this implausible, as long-term weight management is rarely sustained, and the MAESTRO-NASH trial showed no significant difference between arms. In both cases, the EAG prefers returning lipid and weight values to baseline after the first year, applying only natural history thereafter. Regarding fibrosis, the model assumes advanced fibrosis increases CVD risk, based on the US HTA Agency (US ICER) assumptions. The EAG considers fibrosis a marker of cumulative cardiometabolic risk rather than a causal driver, and modelling it as directly influencing CVD events is unsupported by evidence.
What alternative approach has the EAG suggested?	In both the case of lipid and weight-related effects, the EAG prefers returning values to baseline after the first year, applying only natural history thereafter. The EAG considers it inappropriate to elevate the risk of CVD events in advanced fibrosis states without clear evidence of a mechanistic link.
What is the expected effect on the cost-effectiveness estimates?	A small increase in the ICER is likely.
Could any additional evidence or analyses be provided to resolve this issue?	Further information supporting the biological rationale for these modelled effects is necessary. In particular, it would be helpful for the company to provide a more comprehensive overview of the literature describing the relationships between fibrosis stage and cardiovascular events or mortality.

1.5 Company's modelling errors identified by the EAG

The EAG conducted black-box and validation tests, which indicated possible implementation errors and undermined confidence in its internal validity. These tests included the following:

- Adjusting utility and disutility inputs caused LYs to change when they should have remained constant, suggesting that utilities are improperly influencing LY calculations and that disutilities may disproportionately drive incremental QALYs.
- Removing disease-specific mortality should have resulted in zero incremental LYs, but LYs remained >0, while QALYs changed very little, indicating structural problems in mortality implementation.
- When the treatment effect and cost for resmetirom were set to zero, the model still generated incremental QALYs, suggesting that treatment effects are not correctly applied.

The EAG also reviewed the model's coding framework and identified several structural and transparency problems that hinder reproducibility and testing:

- Model inputs are loaded across multiple sections of the code rather than in a single, logical location, contrary to the user manual. This leads to confusion and risks incorrect parameter updates.
- Probabilities and utility values are sometimes read from multiple files or stored in multiple objects, which is poor practice and can introduce divergence between intended and actual inputs.
- Random seeds must be changed in multiple locations, increasing the risk of inconsistent results.
- Cycle-specific discounting and within-cycle correction code is not placed where users would logically expect to update parameters.
- Numerous unused or intermediate objects remain in the environment, reducing clarity and increasing error risk.

Due to the model's complexity and lack of coding transparency, the EAG has been unable to identify the source of these issues. The model requires further verification and testing, as the failures raise concerns about its face validity and internal consistency.

1.6 Summary of EAG's preferred assumptions and resulting ICER

Due to the issue summarised in Section 1.5, the EAG is unable to present any scenario analysis at this time.

2 BACKGROUND

This report critiques the clinical and cost-effectiveness evidence submitted by Madrigal to the National Institute for Health and Care Excellence (NICE) in support of resmetirom (80mg and 100 mg) as a therapy for adults with non-cirrhotic, moderate to advanced liver fibrosis (consistent with stage 2 or 3) caused by metabolic dysfunction-associated steatohepatitis (MASH).

Resmetirom is an active treatment that works directly in the liver by stimulating thyroid hormone receptor – beta (THR- β) to improve critical hepatic process and reduce fibrosis^{1, 2}. Resmetirom is administered orally. It was approved as a first line treatment for liver fibrosis caused by non-cirrhotic MASH on March 14, 2024, by the Food Administration Agency (FDA) in United State of America (US)³. In August 2025, the European Commission (EC) granted resmetirom conditional marketing authorisation in conjunction with diet and exercise for the treatment of adults with non-cirrhotic MASH with moderate to advanced liver fibrosis (fibrosis stages F2 to F3)⁴. Presently, resmetirom does not have a marketing authorisation (MA) in the UK for treating non-cirrhotic MASH with moderated to advanced liver fibrosis.

2.1 Critique of the company's description of underlying health problem

The EAG considers the company's description of the underlying health condition (CS Doc B, Section 1.3.1) to be appropriate and relevant to the decision problem.

The EAG's clinical advisers agree with the CS that the time of progression of Metabolic Dysfunction – Associated Steatotic Liver Disease (MASLD) from one stage to another is highly heterogeneous and can depend on various factors such as genetics, lifestyle, comorbidities and other individual patient risk factors. Not every patient diagnosed with MASH will progress to decompensated cirrhosis (DCC), and fibrosis progression from one stage to another is generally slow and can take between five and ten years for the earlier stages F1, F2, and F3. However, there could be some patients whose fibrosis stage progresses rapidly (rapid progressors) and clinical advice to the EAG indicates this depends on comorbidities and the stage of disease at diagnosis. However, there is no validated tool to differentiate rapid progressors in the MASH population.

The company describes the burden of disease, and associated health-related quality of life (HRQoL) to relate to the severity of fibrosis (CS p. 33). The EAG's clinical advisers considered impacts on quality of life to be milder in the earlier stages of disease and considered any detrimental impact to be largely the result of the anxiety surrounding a diagnosis of liver disease and symptoms relating to comorbidities. The largest drop in quality of life, according to both clinical experts, is observed when patients move from compensated cirrhosis (CC) to decompensated cirrhosis (DCC).

2.2 Critique of the company's overview of current service provision

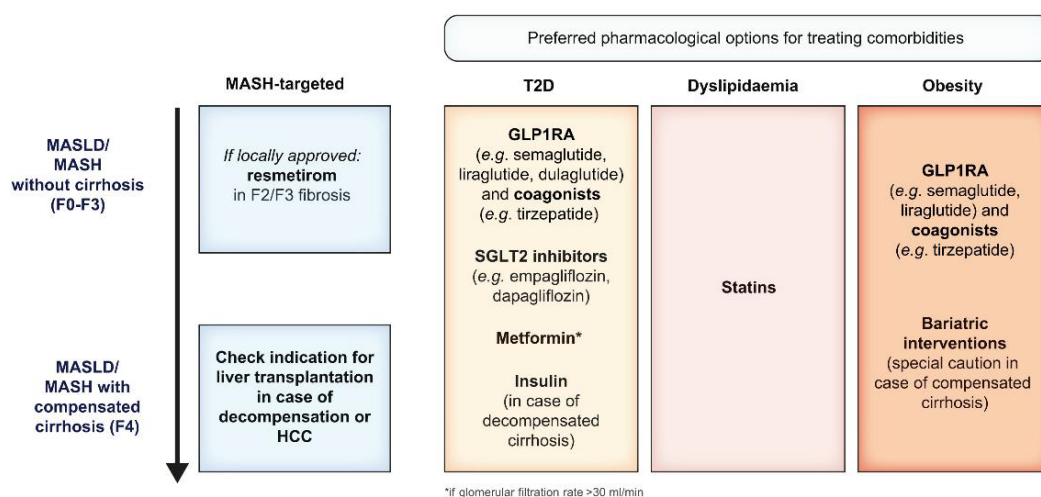
The EAG considers the CS description of the diagnostic pathway of MASH (CS, Section 1.3.1.8, pp 37 - 39) and treatment pathway (CS, Section 1.3.1.9, pp 40) to be broadly appropriate.

There is no licenced therapy on NHS England for the treatment of MASH. Upon diagnosis, patients are generally offered lifestyle modification intervention such as dietary changes, weight loss and exercise. Clinical advice to the EAG noted that lifestyle interventions can be effective if patients lose weight significantly; however, it may be less effective for MASH patients with lower body mass index (BMI), which constitute about 19.2% of MASLD population⁵ and is more common in the South-Asian population.

Although pioglitazone and vitamin E have been recommended as part of the standard of care (SoC) within the NHS for patients with MASH, clinical advice to the EAG suggests that they are rarely used, and they are used as add-ons to diet and exercise. Use of pioglitazone may also vary between treatment centres. The EAG notes that semaglutide and other GLP-1 RA therapies are not currently approved for the treatment of MASH but are used for management of obesity and Type II diabetes and may have a beneficial effect on the symptoms of MASH.^{6, 7}

The proposed position of resmetirom in the NHS clinical pathway, for adults with non-cirrhotic MASH with moderate to advanced liver fibrosis (fibrosis stages F2 – F3), if approved by NICE is presented in Figure 1. The company further proposes that resmetirom would be used in conjunction with diet and exercise, and other SoC therapies (such as pioglitazone and / or vitamin E) used within the NHS.

Figure 1: Proposed positioning of resmetirom in the NHS clinical pathway



Abbreviations: ALK, anaplastic lymphoma kinase; NSCLC, non-small-cell lung cancer.

Source: CS, Document B, Figure 5

According to Figure 1, the proposed positioning of resmetirom does not replace other therapies administered to patients with comorbidities like T2DM, dyslipidaemia and obesity. The EAG clinical advisers noted that they would not prescribe resmetirom to patients already on GLP-1 RA for weight loss or diabetes treatment. Hence, if NICE grant authorisation for resmetirom to be used in NHS, then patients living with obesity and those with T2DM already receiving semaglutide or similar therapies might not be considered for resmetirom. For patients without obesity ineligible for GLP-1 RAs, clinical advice to the EAG agreed that resmetirom could be an option to help slow down fibrosis progression and improve liver health.

2.3 Critique of company's definition of decision problem

CS Document B, Table 1 presents a description of the NICE final scope, the decision problem addressed within the CS and the rationale for any difference between the two. This information, along with the EAG comments is presented in Table 2.

2.3.1 Population

The population addressed in the company decision problem matches the NICE scope. However, there are discrepancies between the NICE scope and the clinical evidence presented from the MAESTRO-NASH trial (See Section 3.2.2). The trial includes some patients with fibrosis stage F1B (15% of the trial population). The trial recruited only patients with three or more cardiometabolic risk factors (e.g. obesity, type II diabetes), and most participants had a confirmed diagnosis of MASH from a liver biopsy test.

The EAG's clinical advisers noted that MASH patients staged at F1B often progress to F2-F3. Despite some clinical differences between fibrosis stages and lower rates of comorbidities for patients with F1B, the EAG's clinical advisers do not expect a different clinical response for F1B MASH patients compared to F2 or F3 MASH patients. The EAG agrees that the inclusion of these patients does not undermine the clinical effectiveness of resmetirom. The economic model does not include patients with fibrosis stage F1B (Section 4.2.3).

Nearly all patients in the MAESTRO-NASH trial had a baseline liver biopsy (98.4%) (CS Table 9, p. 57). The EAG's clinical advisers noted that liver biopsy is not required nor desirable as a diagnostic test for MASH in the UK. Non-invasive tests like imaging and blood tests, which put less strain on the patients and NHS resources, and are safer, are frequently used in the diagnosis of MASH. Currently, it is unclear which set of diagnostic criteria would be used to determine eligibility for resmetirom (see Section 3.2.2.2).

Given the restriction of the MAESTRO-NASH trial population to patients with three or more cardiometabolic risk factors, trial participants are likely to have a higher risk of progression and

cardiovascular outcomes than the wider patient population with MASH in the UK. Although the company indicated that NHS patients with one or more cardiometabolic risk factors would be eligible for resmetirom (clarification response QA2), there is no evidence of efficacy in this broader population.

2.3.2 Intervention

The EAG considers the intervention, resmetirom, to be in line with the NICE final scope. Although the NICE scope did not specify the dosing for resmetirom, the company's recommended dose for resmetirom is 80mg for MASH patients whose body weight is less than 100kg, and 100mg for MASH patients whose body weight is more than 100kg (CS, Doc B, Table 2). The proposed dosing is inconsistent with random allocation of resmetirom 80 mg and 100 mg in the MAESTRO-NASH trial (Section 3.2).

2.3.3 Comparator

The CS did not consider semaglutide or standalone pioglitazone, vitamin E or a combination of pioglitazone and vitamin E as comparators. The combination of pioglitazone and vitamin E was approved in the NICE guideline (NG49)⁸ as a treatment option for patients with MASH but during the NICE scoping consultation for resmetirom, pioglitazone and vitamin E were considered as part of the SoC to which resmetirom would be added (CS, Doc B pp 40). The EAG's clinical advisers noted that pioglitazone and vitamin E are not routinely used for MASH in UK. The EAG therefore accepts that it is appropriate to exclude pioglitazone and vitamin E as comparators in the decision problem.

The EAG also accepts that semaglutide could not reasonably be included as a direct comparator in this assessment. This is because semaglutide is not approved for the treatment of MASH in the UK as at the time of the company's submission to NICE. The appraisal of semaglutide for treatment of MASH [ID6458] is planned to start in November 2025⁹. However, semaglutide and other GLP-1 RAs are commonly used by patients living with obesity or diabetes. There is evidence that these therapies (especially semaglutide) might also be effective in the management of MASH¹⁰. The EAG agrees with the company that resmetirom might have broader benefits for managing metabolic conditions than just its impact on liver function.

2.3.4 Outcomes

The outcomes reported in the CS decision problem (Table 2) included outcomes specified in the NICE final scope, and some additional outcomes not listed in the NICE scope. The EAG's clinical advisers thought that the additional outcomes reported in the submission, (such as NAS, change in lipid profile and MRI) were appropriate outcomes relating to MASH. Several outcomes, including cirrhosis, liver transplant, HCC, metabolic and cardiovascular outcome, and overall survival were included in the CS decision problem, but no results were reported. Data on these outcomes was requested by the EAG via

the point of clarification (PfC) questions (A6, A7). The company responded that long-term clinical outcomes like progression to cirrhosis, hepatic compensation, liver transplant and mortality are still being assessed and that the regulator would not allow for these data to be shared until pre-specified timepoints are reached. The company also noted that metabolic and cardiovascular outcome data were collected (A7, PfC), but this data was not presented by study arm because of concerns that reporting rare events would risk unblinding participants.

2.3.5 Subgroup analyses

Subgroup analyses of the dual primary outcomes were reported by liver fibrosis stages, and people with T2DM alongside some baseline characteristics like by age, sex, body mass index (BMI), and body weight (Appendix C, CS). However, the economic modelling does not estimate the cost-effectiveness in subpopulation by fibrosis stages.

Table 2 Summary of decision problem

	Final scope issued by NICE	Decision problem addressed in the company submission	Rationale if different from the final NICE scope	EAG comment
Population	Adults with non-cirrhotic, moderate to advanced liver fibrosis (consistent with stage 2 or 3) caused by MASH.	Adults with non-cirrhotic MASH with moderate to advanced liver fibrosis (fibrosis stages F2-F3).	N/A – In line with final NICE scope.	The population addressed in the company decision problem matches the NICE scope. However, the population recruited in the MAESTRO-NASH trial does not match the NICE scope. The trial includes some patients with fibrosis stage F1B and patients with three or more cardiometabolic risk factors and required a confirmed diagnosis of MASH from a liver biopsy test.
Intervention	Resmetirom in addition to established clinical management.	Resmetirom in addition to established clinical management.	N/A – In line with final NICE scope.	Resmetirom use is in line with NICE's final scope.
Comparator(s)	Established clinical management without resmetirom, which may include: • lifestyle modification interventions (such as advice on healthy diet, weight loss when required, and regular exercise); • unlicensed use of pioglitazone and vitamin E. Semaglutide (subject to a NICE evaluation).	Established clinical management without resmetirom, including: • lifestyle modification interventions (such as advice on healthy diet, weight loss when required, and regular exercise) – use of pioglitazone and vitamin E may be permitted in conjunction.	As per NICE's methods and process guide (19), appropriate comparators should be technologies that are recommended by NICE and available for routine use in the National Health Service (NHS). At the time of this submission, semaglutide is not currently licensed in the UK or recommended for MASH. Including it as a comparator falls outside of NICE's established procedural framework, which states "technologies that do not have regulatory approval for the population defined in the scope if they are considered to be established clinical practice for	The CS did not consider the comparators semaglutide, pioglitazone or vitamin E. Semaglutide is not yet a licenced treatment for MASH adult patients within the UK; pioglitazone and / or vitamin E are rarely used in NHS practice and are considered as add-ons to standard care or resmetirom. The EAG agrees that excluding these comparators is reasonable. However, we note that for the subset of patients with metabolic risk factors such as obesity and or type 2 diabetes, semaglutide should ideally be considered as a comparator, as those patients may be eligible to receive semaglutide.

	Final scope issued by NICE	Decision problem addressed in the company submission	Rationale if different from the final NICE scope	EAG comment
			the population in the NHS". Semaglutide, pioglitazone, and vitamin E are not therapies established in clinical practice for the treatment of patients with MASH fibrosis stages F2-F3. Please see text for rationale around active comparators.	
Outcomes	The outcome measures to be considered include: • resolution of MASH • change in fibrosis stage • progression to cirrhosis • occurrence of hepatic decompensation events, including development of ascites, hepatic encephalopathy, variceal bleeding • liver transplantation (LT) • hepatocellular carcinoma (HCC) • overall survival • adverse effects of treatment health-related quality-of-life (HRQoL).	The outcome measures considered include: • MASH resolution • improvement (reduction) and progression (worsening) in fibrosis stage • improvement in NAFLD Activity Score (NAS) • change in lipid profile • change in magnetic resonance imaging (MRI)-based proton density fat fraction (PDFF) • change in liver function tests • change in MASH inflammation and fibrosis biomarkers	Outcome measures included in this submission are based on those outcomes that have been included in the pivotal clinical trial of resmetirom for the indication of interest (MAESTRO-NASH [NCT03900429]) (17), or have been included in the economic modelling. These endpoints have been recommended by the FDA (20) and by the European Medicines Agency (EMA) (21). They were also endorsed during the HTA Lab report for this topic (22). Individual clinical events associated with DCC (ascites, hepatic encephalopathy, variceal bleeding) were not individually modelled owing to a lack of reliable event probabilities; instead these events were modelled in aggregate based on average costs and disutility obtained from prior health	The outcomes reported in the CS did not cover all the outcomes required in NICE's final scope. Most of the long-term outcomes (progression to cirrhosis mortality etc.) are not reported. The CS reported additional outcomes which are appropriate to MASH improvement or progression. However, some of the outcomes like NAS, are less applicable to NHS practice because not all MASH patients get confirmed diagnosis via liver biopsy test.

	Final scope issued by NICE	Decision problem addressed in the company submission	Rationale if different from the final NICE scope	EAG comment
		• change in metabolic, liver, and cardiovascular assessments • non-invasive imaging outcomes • progression to cirrhosis and decompensated cirrhosis (DCC) with associated DCC events • LT • HCC • overall survival • adverse effects of treatment • HRQoL.	economic evaluations in this therapy area. Non-invasive imaging outcomes (e.g., MRI -PDFF) are included in the clinical write-up because they were captured in the pivotal trial, however they are not expected to be reflected in the diagnostic or therapeutic pathway for MASH in the NHS and are therefore not included in the economic evaluation.	
Economic analysis	The reference case stipulates that the cost-effectiveness of treatments should be expressed in terms of incremental cost per quality-adjusted life year (QALY). The reference case stipulates that the time horizon for estimating clinical and cost-effectiveness should be sufficiently long to reflect any differences in costs or outcomes between the technologies being compared.	The economic analysis adheres to the NICE reference case.	N/A – In line with final NICE scope.	See Table 11.

	Final scope issued by NICE	Decision problem addressed in the company submission	Rationale if different from the final NICE scope	EAG comment
	Costs will be considered from an NHS and Personal Social Services (PSS) perspective. The availability of any commercial arrangements for the intervention, comparator and subsequent treatment technologies will be taken into account.			
Subgroups	If the evidence allows, the following will be considered: - subgroups by liver fibrosis stage. - people with type 2 diabetes mellitus (T2DM).	The following subgroups are considered: people with T2DM.	Subgroup analyses are provided for the pivotal trial results by fibrosis stage and T2DM, however the economic model does not estimate cost-effectiveness in subpopulations by fibrosis stage. This is because the study remains protocol-blinded through month 54 (17), and to preserve the integrity of the confirmatory clinical outcomes analyses, detailed arm-level data on fibrosis stage progression cannot be disclosed.	Subgroup analyses were restricted to primary outcomes and are not available for longer-term outcomes of key clinical relevance. Cost-effectiveness of resmetirom was evaluated in T2DM population but not in liver fibrosis stage.
Abbreviations: N/A not applicable; DCC, decompensated cirrhosis; EMA, European Medicines Agency; F2-F4, fibrosis stages 2-4; FDA, Food and Drug Administration; HCC, hepatocellular carcinoma; HRQoL, health-related quality of life; HTA, Health Technology Assessment; LT, liver transplantation; MASH, metabolic dysfunction-associated steatohepatitis; MRI, magnetic resonance imaging; N/A, not applicable; NAS, NAFLD Activity Score; NHS, National Health Service; NICE, National Institute for Health and Care Excellence; PDFF, proton density fat fraction; PSS, Personal Social Services; QALY, quality-adjusted life year; T2DM, type 2 diabetes mellitus. Source: NICE [ID6529], CS, Document B, Table 1.				

3 CLINICAL EFFECTIVENESS

This section presents a summary and critique of the clinical-effectiveness evidence included in the company's submission. Section 3.1 focuses on the company's review of clinical and safety evidence. Sections 3.2 and 3.3 provide a critique of the included studies and clinical effectiveness analyses.

3.1 *Critique of the methods of review*

The systematic literature review (SLR) is described on page 46 of the CS, and more detail is provided in Appendix B. The EAG had some concerns with the searches but, due to staff absence, the EAG cannot currently provide a critique of the search strategies.

Selection criteria of the review were mostly appropriately defined to allow the inclusion of studies matching the NICE final scope. Studies of semaglutide were eligible for inclusion despite not being considered a relevant comparator for this appraisal. The EAG considers the exclusion of secondary and post-hoc analyses of relevant studies undesirable, as such reports may contain data on outcomes in scope. Nine full-text reports were excluded because they were not written in English.

The review included seven reports of three studies of resmetirom.

- MGL-3196-05 (NCT02912260) was conducted in the US to evaluate the safety and efficacy of resmetirom versus placebo. Between December 2017 and May 2018, 125 patients with biopsy-confirmed NASH and fibrosis stage 1 to 3 were enrolled.¹¹
- MAESTRO-NAFLD-1 (NCT04197479) was a placebo-controlled trial of resmetirom in the US, with 972 patients with presumed NASH randomised between December 2019 and December 2021.¹²
- MAESTRO-NASH (NCT03900429) is a multi-national RCT of resmetirom versus placebo in patients with biopsy-confirmed NASH and predominantly fibrosis stage 2 to 3. From March 2019 to July 2021, 1,050 patients were randomised.¹³

The CS only reports results of the MAESTRO-NASH trial, and this is the only clinical evidence used in the economic model. MGL-3196-05 was omitted from the list of relevant clinical evidence presented in section 2.2 of the submission (p. 47), because of the smaller sample size and variable drug dosage (CS p. 46, clarification response QA17). Also, a larger proportion of patients had stage 1 fibrosis (F1). MAESTRO-NAFLD-1 was not included in the clinical evidence or economic model because participants had presumed NASH, which was not confirmed by biopsy (CS pp. 46-47). The EAG believes data from both trials could have been presented by the company. The MAESTRO-NAFLD-1 population may be more representative of practice, as it did not rely on liver biopsies, although it did include patients with mild fibrosis (Stage 1). In the

clarification response (QA18), the company supplied interim Clinical Study Reports (CSRs) of the additional trials but declined to provide tabulations of results for outcomes listed in the scope. The EAG has provided key results in section 3.3.5.

3.2 Critique of the methods of the trials of the technology of interest

We provide an overview of the methodology of the trials relevant to this appraisal in Table 3. Section 3.2.2 describes the design of the MAESTRO-NASH trial in more detail, in the context of current NHS practice.

Table 3 Clinical effectiveness studies of technology of interest

	MGL-3196-05¹¹	MAESTRO-NAFLD-1¹²	MAESTRO-NASH¹³
Role in this evaluation	Not used	Not used	Evidence of clinical effectiveness presented in submission. Informs economic model.
Study type	Placebo-controlled phase II RCT	Placebo-controlled phase III RCT	Placebo-controlled phase III RCT
Period of recruitment	December 2017 – May 2018	December 2019 – December 2021	March 2019 – July 2021
Patient group	Adults with biopsy-confirmed NASH, fibrosis stage 1-3, and hepatic fat fraction $\geq 10\%$.	Adults with NAFLD and presumed NASH.	Adults with biopsy-confirmed NASH and fibrosis stage 1B, 2, or 3.
Subgroups	Resmetirom exposure, $<5\%$ weight loss.	Resmetirom exposure, weight loss and gain, statins, GLP-1 RA, T2DM status, sex.	Fibrosis stage, baseline NAS, age, sex, baseline T2DM status.
Exclusion criteria	Alcohol consumption > 20 g/day for women, >30 g/day for men. HbA1c level $> 9.5\%$. GLP-1 RA use with doses not stable in last 6 months. Weight change $>5\%$ in 6 months or $> 10\%$ in 12 months.	Significant alcohol consumption. HbA1c level $> 9.0\%$. Weight change of $>5\%$ in 3 months. GLP-1 RA use with doses not stable in last 6 months.	Alcohol consumption > 20 g/day for women, >30 g/day for men. HbA1c level $> 9.0\%$. Weight change of $>5\%$ in 3 months. GLP-1 RA use with doses not stable in last 6 months.
Intervention	80 mg resmetirom (60, 80, or 100 after 4 weeks), oral tablet, once daily	80 and 100 mg resmetirom blinded, 100 mg resmetirom open-label; oral tablet, once daily	80 mg and 100 mg resmetirom; oral tablet, once daily
Comparator	Placebo; oral tablet, once daily	Placebo; oral tablet, once daily	Placebo; oral tablet, once daily
Primary outcome(s)	Liver fat reduction.	TEAEs	NASH resolution without worsening of fibrosis; fibrosis improvement without worsening of NAS.
Duration	36 weeks	52 weeks	54 months; dual primary outcomes assessed at week 52.
Location	25 US sites	80 US sites	245 sites globally

Abbreviations: GLP-1 RA, glucagon-like peptide-1 receptor antagonist; NAFLD, non-alcoholic fatty liver disease; NAS NAFLD, activity score; NASH, non-alcoholic fatty liver disease; RCT, randomised controlled trial; T2DM, type 2 diabetes mellitus; TEAE, treatment-emergent adverse event.

3.2.1 Critical appraisal of MAESTRO-NASH

The company critically appraised all included studies using appropriate tools; the Risk of Bias 2.0 tool for RCTs and ROBINS-I for one non-randomised study (Appendix B, section 1.3). A comparison between the company's and EAGs assessment of the MAESTRO-NASH trial is shown in Table 4 (CS pp. 63-64).

Table 4 Comparison of critical appraisal MAESTRO-NASH

Risk of bias item	Company's judgement	EAG's judgement	EAG justification
Randomisation process	Low	Low	Central assignment using interactive voice and web response system.
Deviation from intended interventions	Low	Low	Double-blind trial design. In 114 cases, concomitant treatment not allowed according to the protocol was used. Treatment compliance of allocated doses was high and comparable across study arms.
Missing outcome data	Low	Some concerns	Withdrawal due to adverse events was most common in the resmetirom 100 mg study arm (6.8% vs 1.9% resmetirom 80 mg and 2.2% placebo). Loss to follow-up was most common in the resmetirom 80 mg arm (4.0% vs 2.2% resmetirom 100 mg and 1.9% placebo). Primary endpoint results are presented for the mITT-LB-W52 population, which excludes data from those without a week 52 liver biopsy, [REDACTED] [REDACTED] Safety data reported for all patients who received ≥ 1 dose of study medication.
Outcome measurement	Low	Low	Measurement of primary outcomes was complicated by the subjective nature of interpreting digitised images of biopsies. Additional analyses testing robustness of results undertaken and reported.
Selection of reported result	Low	Low	Pre-specified analyses plan followed.
Overall risk of bias	Low	Some concerns	Trial is generally at low risk of bias. However, there is some evidence of outcome data missing not-at-random.

Abbreviations: EAG; Evidence Assessment Group.

There was some deviation from intended interventions in the trial, for example in 114 cases where concomitant treatment was used which was not allowed according to the protocol. The EAG did not have access to the CSR appendices listing concomitant prohibited treatment by study arm.

In a response to clarification questions (QA2), the company described lifestyle advice provided to all three study arms as part of 'treatment as usual', consisting of advice on diet, nutrition, exercise, and physical activity. Compliance was recorded as part of the study but not reported in the main body of the CSR that the EAG was given access to. Given the blinded trial design, the EAG considers the risk of bias due to differences in the delivery of lifestyle advice across arms to be low. However, the EAG could not investigate whether compliance with lifestyle advice interacted with treatment effects.

Some outcome data, most importantly for the primary outcomes relying on liver biopsies, was missing. Missing week 52 biopsies were more likely in the resmetirom study arms than in the placebo arm, which may be related to withdrawal due to adverse events (Table 4). The EAG is concerned that imputation of results for the primary outcomes under the ‘missing at random’ assumption led to biased results (see sections 3.3.1,3.3.2).

3.2.2 Critique of MAESTRO-NASH trial design

The EAG considers the study design of MAESTRO-NASH appropriate to evaluate the efficacy and safety of resmetirom versus placebo. However, discrepancies between aspects of the trial design and anticipated eligible NHS patients and NHS practices cause uncertainty around the applicability of evidence from MAESTRO-NASH in clinical practice.

3.2.2.1 Selection criteria

The final scope, in line with the anticipated indication for the NHS, concerns adults with non-cirrhotic MASH with moderate to advanced (stage F2-F3) liver fibrosis (Section 2.3). Eligibility criteria for MAESTRO-NASH stipulate participants have three or more metabolic risk factors (obesity, pre-diabetes or type 2 diabetes mellitus, dyslipidemia, and hypertension) (CS Table 8, pp. 51-52). In the Clinical Practice Research Datalink (CPRD) cohort described by the company in Section 3.2 of the CS (pp. 100-102), 16.6% of patients with a MASH-coded primary or secondary care record had at least three metabolic risk factors.¹⁴ Two clinical experts advised the EAG that the proportion of T2DM was higher than in hepatology departments in the UK. One clinical adviser stressed that the trial sample is a highly select group of patients with a more severe (cardio)metabolic risk profile, which is not representative of NHS patients. As described in Section 2.3.1, the company anticipates resmetirom to be prescribed to MASH patients with one or more cardiometabolic risk factors. In response to a request for clarification (QA1), the company stated that they assume resmetirom to be equally effective in patients with three or more, or fewer cardiometabolic risk factors. In the absence of evidence to support this claim, the EAG considers the extent to which resmetirom is effective in patients with one or two cardiometabolic risk factors to be uncertain.

Participation in MAESTRO-NASH allowed concomitant use of GLP-1 RAs only if doses had been stable for at least six months prior to the baseline biopsy. In the mITT-W52 trial population, 14.2% of participants used GLP-1 RAs during the trial (CS Table 10, p. 58). The company considered this representative of current UK practice, citing data from a 2023-2024 diabetes audit (clarification response QA4). One of the EAG’s clinical advisers explained that patients are increasingly taking GLP-1 RAs, either prescribed for obesity or diabetes, or privately funded. Since recruitment for MAESTRO-NASH finished in July 2021, semaglutide has been recommended in the UK for adults with obesity, or overweight in some cases (TA875, published March 2023), and for a subset of

patients with T2DM.¹⁵ Two clinical advisers to the EAG indicated they would not, or would be hesitant to, prescribe resmetirom concomitantly to patients successfully losing weight with a GLP-1 RA. This is at odds with the position of the company, which is that eligible patients should be able to receive resmetirom regardless of whether they are indicated for a GLP-1 RA to treat underlying comorbidities (clarification response QA4).

The company explained that clinical experts expected MAESTRO-NASH participants to be broadly similar to the UK MASH population which may receive resmetirom in practice. The company declined to make results from these meetings available to the EAG (PfC response, QC5).

3.2.2.2 Identification of patients with MASH F2-F3

All trial participants either had a liver biopsy at baseline, or in the two years prior to randomisation. Both clinical advisers to the EAG believed liver biopsy as a requirement for resmetirom would be undesirable. This is due to the risk of complications associated with liver biopsy, the invasiveness and hence burden on the patient, and the practicalities of organising a liver biopsy pathway with involvement of a specialist radiologist. One of the clinical advisers expressed concern that a biopsy as a prerequisite for treatment would limit use of resmetirom to teaching hospitals and larger treatment centres, potentially promoting inequality in access to treatment. The company explained in the clarification response (QA1) that they do not expect a biopsy to be required before administering resmetirom in practice, instead relying on NITs. However, there is no set of agreed and tested criteria currently used in the NHS to identify patients with MASH and stage 2 or 3 fibrosis. Table 5 summarises potential criteria as used in the MAESTRO-NASH trial, as proposed by an expert panel, as suggested in a recent, unpublished consensus meeting, and as stated in updated AASLD guidance (clarification response QA15).

Table 5 Suggested criteria for the identification of patients with F2/F3 fibrosis.

Source	Criteria	Proportion of MAESTRO-NASH trial participants eligible to receive resmetirom*
MAESTRO-NASH trial ¹³	- Historic liver biopsy demonstrating fibrosis F1B, 2, or 3 with NASH, OR - AST >17 (women) or AST > 20 (men) AND FibroScan/ VCTE kPa ≥ 8.5 CAP ≥ 280.	94.9% (excluding N=49 patients with fibrosis stage F1B)
2024 EASL-EASD-EASO strategy for non-invasive evaluation of advanced fibrosis risk (CS Figure 4, p. 38) ¹⁶	- FIB-4 > 1.3 AND - VCTE ≥ 8.0 kPa, OR alternative test.	Unclear
Noureddin 2024 expert panel ¹⁷	- ELF 9.2-9.7 AND a second NIT, OR - ELF 9.8-11.3, OR - MRE 3.3-4.9 kPa, OR - VCTE 10-19.9 kPa	██████

BASL MASLD SIG consensus meeting (unpublished, reported in clarification response QA15)	• VCTE ≥ 10 kPa, AND • no clinical evidence of cirrhosis	████
Updated AASLD guidance ¹⁸	• VCTE 8-15 kPa, OR • Other non-invasive assessment consistent with F2/F3, AND • no evidence of cirrhosis	████

Abbreviations: AST, aspartate aminotransferase; kPa, kilopascal; NIT, non-invasive test; VCTE, Vibration-Controlled Transient Elastography.

* As calculated by the company (clarification response QA15).

As illustrated in Table 5, the company estimates that the proportion of trial participants eligible to receive resmetirom in UK clinical practice may vary between █████ and █████, depending on the guidance followed.

3.2.2.3 Resmetirom dosing

The dosing of resmetirom applied in the MAESTRO-NASH trial does not match the description of posology in the Summary of Product Characteristics (SmPC).

Trial participants were assigned 100 mg of resmetirom daily, 80 mg of resmetirom daily, or placebo. Doses of resmetirom were reduced by 20 mg at week 12 if free thyroxine (FT4) had decreased by 30% or more from baseline, with another dose reduction at week 24 for those in the resmetirom 100 mg study arm with continued decrease of FT4 of 30% or more from baseline (CS Section 2.3.1.5, p. 53). Dose reductions based on FT4 were rare (N=12) (MAESTRO-NASH CSR p. 138). The SmPC states dosing is based on patient body weight; 80 mg orally once daily for patients weighing < 100 kg and 100 mg orally once daily for patients weighing ≥ 100 mg. See Section 3.3.4.1 for a post-hoc analysis of improvement in fibrosis by patient weight and resmetirom dosing.

3.2.2.4 Outcomes and follow-up

The dual primary efficacy endpoints were resolution of NASH, without worsening of fibrosis, and improvement in fibrosis without worsening of the NAFLD Activity Score (NAS). Assessments for both outcomes were based on a liver biopsy taken 52 weeks after starting treatment and will be assessed again 54 months after treatment (████████████████████, clarification response QC7). Clinical advisers explained to the EAG that they perceive improvement in fibrosis to be the more informative downstream outcome measure, as changes in NAS can be expected to lead to changes in fibrosis stage over time. The outcome of change in NAS has limited relevance for practice, as it relies on the assessment of liver biopsies, which are not routinely performed in the NHS. The clinical advisers were not certain that 52 weeks is sufficiently long to measure all change in fibrosis resulting from resmetirom treatment.

Change in fibrosis is measured as a proxy for outcomes which substantially impact on quality of life, such as decompensated cirrhosis, T2DM, cardiovascular disease, and mortality related to liver disease and comorbidities. The EAG considers the uncertain link between fibrosis and these long-term outcomes an important limitation of the trial. Clinical advice to the EAG suggested progression from fibrosis is slow, varies widely, and estimates are unlikely to represent NHS practice as they tend to come from literature based on a highly selected samples from secondary or tertiary care, or from clinical trials. Both of the EAG's clinical advisers were unsure how to differentiate 'rapid progressors' (CS p. 29) from other patients, and one of the advisers did not recognise the phenomenon of the 'rapid progressor' in clinical practice. Both clinical advisers pointed out that most patients will never progress to cirrhosis. Their information is confirmed by a US cohort study of patients with MASLD reporting on mortality in patients with and without cirrhosis.¹⁹ For patients with MASLD at risk of MASH (FIB-4 score > 2.67), the ten-year cumulative incidence of death from liver disease was 2.6%. For patients with MASH and cirrhosis, the ten-year cumulative incidence of death from liver disease was 9.2%.

The EAG asked the company whether metabolic and cardiovascular outcome data were collected (PfC QA7). The company listed events for various outcomes, but declined to provide these data by study arm, citing low event rates and blinding obligations. Cardiovascular events were [REDACTED] in the overall sample ([REDACTED] myocardial infarction, [REDACTED] myocardial ischemia, [REDACTED] transient ischaemic attack, [REDACTED] cerebrovascular accident).

In conclusion, interpreting MAESTRO-NASH evidence requires extrapolation of patient benefits from data measured over a relatively short timeframe, using proxy measures which lack a strong and clearly defined relationship with longer-term outcomes.

3.3 Critique of the results of the trials of the technology of interest

To inform the critique of the results of MAESTRO-NASH, the EAG asked for the full CSR, including appendices containing outcome tables (PfC QC4). The company was unable to supply this information.

3.3.1 MAESTRO-NASH samples

The Intention-to-Treat (ITT) population included 1050 randomised patients (CS p. 55). Baseline characteristics are presented for a subset of 966 participants from the ITT population with fibrosis stage F1B, F2, or F3 who received at least one dose of medication (safety population), and results for outcomes not relying on liver biopsy are presented for this subset (mITT-W52). A subset of 955 participants selected from the mITT-W52 set with available baseline liver biopsies was used to report on the dual primary endpoints (LB-W52). Of note, not all participants in the LB-W52 population had

a week 52 liver biopsy (Table 6). To derive key transition estimates in the economic model, a subset of 739 patients with both a baseline and a week 52 liver biopsy which was interpretable by a central reader was selected from the mITT- LB-W52 sample (PLB-W52).

The limited number of baseline characteristics available for comparison of the mITT-W52 and the paired biopsy PLB-W52 samples suggests there were mostly only small differences between the two samples in terms of baseline characteristics, [REDACTED]

[REDACTED] which may represent an important difference (Table 6). There were substantial numbers of patients with no biopsies at 52 weeks. Furthermore, week 52 biopsies [REDACTED]

[REDACTED] In the resmetirom 100 mg arm, [REDACTED] of patients had discontinued by week 52, compared to [REDACTED] in the resmetirom 80 mg arm and [REDACTED] in the placebo arm (CSR Table 7, p. 66). This was partly but not completely driven by a higher rate of adverse events in the resmetirom 100 mg arm, for example diarrhoea (Section 3.3.3.1). This could have biased results of the primary outcomes presented in the clinical section of the CS, which were imputed under the missing at random (MAR) assumption, in favour of resmetirom.

Consequently, substantial missing data could lead to bias in the results of the smaller paired biopsy sample (PLB-W52).

Table 6 Comparison of MAESTRO-NASH study samples

	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	951	NR	782	739
Patients with week 52 liver biopsy**	[REDACTED]	NR	782	739
Baseline characteristics				
Age, mean (years)	56.6	NR	NR	[REDACTED]
Female (%)	56.1	NR	NR	[REDACTED]
Type 2 diabetes mellitus (%)	67.0	NR	NR	[REDACTED]
Hypertension (%)	78.1	NR	NR	[REDACTED]
Fibrosis stage (%)		NR	NR	[REDACTED]
F1B	5.1			[REDACTED]
F2	33.0			[REDACTED]

F3	60.4			

Abbreviations: NR = not reported.

* Source = Appendix Harrison 2024, Table S4.

** Source = CSR Table 7, p. 66.

3.3.2 Primary outcomes

Main results for the primary outcomes NASH resolution (no worsening of fibrosis) and fibrosis improvement (no worsening of NAS) are reported in Table 13 of the CS (p. 65). Participants in the 80 mg and 100 mg resmetirom study arms were more likely to experience resolution of NASH than participants in the placebo group. Similarly, participants in the 80 mg and 100 mg resmetirom study arms were more likely to experience improvement in fibrosis than participants in the placebo group. No comparisons were made between the 80 mg and 100 mg resmetirom study arms, though numerically the 100 mg resmetirom arm had higher proportions of NASH resolution and fibrosis improvement.

Both primary outcomes rely on the pathologists' interpretation of digitised images of biopsies. This led to some discrepancies, with pathologist A more likely to report NASH resolution and fibrosis improvement than pathologist B (CS Table 15 and Table 16, pp. 67-68). The EAG's clinical advisers judged these disagreements to be consistent with the nature of the outcome measurement, and the company took steps to explore and mitigate risk of bias.

For the primary analyses of the dual primary outcomes, a score was assigned depending on agreement level between pathologists: 1 if both pathologists agreed response criteria were met, 0.5 if a single pathologist thought response criteria were met, and 0 if neither pathologist thought response criteria were met (PfC QA11c).

Consensus reads (██████ for NASH resolution, ██████ for fibrosis improvement) were conducted by two central pathologists if they had previously disagreed on the response category (PfC QA10a). The consensus exercise produced results similar to the primary results described above (CS Table 13, p. 65).

Sensitivity analyses using multiple imputation (CS Table 14, pp. 66-67) and generalised estimating equation models (CS Table 15 and Table 16, pp. 67-68) did not change conclusions. Additionally, "tipping point" analyses (CS Table 17, pp. 68-69) found that it would require around 18.8% of patients on placebo to have NASH resolution or fibrosis improvement (compared to the observed rates of 9.7% for NASH resolution and 14.2% for fibrosis improvement) before resmetirom ceased to be statistically significantly superior to placebo. The EAG agrees that this is implausible.

Because various sensitivity analyses were performed in the submission, and because the population reported in the clinical sections (LB-W52) differs from the paired biopsy population used in the economic analyses (See Section 4.2.3), the EAG includes a summary of various analyses of the two primary outcomes in Table 7 and

Table 8. This includes results presented in the CS and additional analyses by the EAG (where marked). The EAG has also calculated relative risks in addition to the risk differences supplied in the CS, to aid comparison.

Considering NASH resolution, there was some modest variation in effect estimates depending on the choice of analysis. However, excluding patients where there were disagreements in the biopsy interpretation produced results clearly more favourable to both 80mg and 100mg resmetirom than either the primary or consensus analysis. Consequently, more favourable relative risk estimates for resmetirom 80 mg and resmetirom 100 mg versus placebo were observed when restricting analysis to the PLB-W52 population (N=782) and in the PLB-W52 F2, F3 population (N=739) than in the LB-W52 population (N=955) (Table 7). The EAG is therefore concerned that use only of the paired biopsy population (PLB-W52) in the economic model may overestimate the benefits of resmetirom. The same pattern of effects, with greater benefits in the paired biopsy population, was also observed, but to a lesser extent, for the outcome of fibrosis improvement (Table 8). The EAG notes that resmetirom is statistically superior to placebo in all analyses.

Table 7 Summary of analyses NASH resolution (no worsening of fibrosis)

Population	Analysis method	Comparison	Risk difference	Relative risk
LB-W52	Primary analysis*	Resmetirom 80mg vs placebo	16.4 (11.0, 21.8)	2.66
		Resmetirom 100mg vs placebo	20.7 (15.3, 26.2)	3.07
	Consensus analysis	Resmetirom 80mg vs placebo	16.8 (11.3, 22.4)	3.02
		Resmetirom 100mg vs placebo	20.7 (15.0, 26.3)	3.39
	Multiple imputation	Resmetirom 80mg vs placebo	17.7 (11.3, 24.1)	2.29
		Resmetirom 100mg vs placebo	23.2 (16.8, 29.6)	2.67
	Excluding disagreements**	Resmetirom 80mg vs placebo	16.3	3.64
		Resmetirom 100mg vs placebo	18.3	3.98
PLB-W52	Primary analysis*	Resmetirom 80mg vs placebo	■	■
		Resmetirom 100mg vs placebo	■	■
	Excluding disagreements**	Resmetirom 80mg vs placebo	■	■
		Resmetirom 100mg vs placebo	■	■
PLB-W52 F2, F3	Primary analysis*	Resmetirom 80mg vs placebo	■	■
		Resmetirom 100mg vs placebo	■	■
	Consensus analysis	Resmetirom 80mg vs placebo	■	■

	Multiple imputation	Resmetirom 100mg vs placebo	██████████	████
		Resmetirom 80mg vs placebo	██████████	████
		Resmetirom 100mg vs placebo	██████████	████
	Excluding disagreements**	Resmetirom 80mg vs placebo	████	████
		Resmetirom 100mg vs placebo	████	████

* Disagreements counted as 0.5.

** Calculated by the EAG.

Table 8 Summary of analyses fibrosis improvement (no worsening of NAS)

Population	Analysis method	Comparison	Risk difference	Relative risk
LB-W52	Primary analysis*	Resmetirom 80mg vs placebo	10.2 (4.8, 15.7)	1.68
		Resmetirom 100mg vs placebo	11.8 (6.4, 17.2)	1.81
	Consensus analysis	Resmetirom 80mg vs placebo	12.2 (6.3, 18.2)	1.96
		Resmetirom 100mg vs placebo	13.4 (7.4, 19.3)	2.03
	Multiple imputation	Resmetirom 80mg vs placebo	11.4 (5.1, 17.8)	1.64
		Resmetirom 100mg vs placebo	14.1 (7.9, 20.4)	1.79
	Excluding disagreements**	Resmetirom 80mg vs placebo	9.62	1.98
		Resmetirom 100mg vs placebo	9.99	2.01
PLB-W52	Primary analysis*	Resmetirom 80mg vs placebo	████	████
		Resmetirom 100mg vs placebo	████	████
	Excluding disagreements**	Resmetirom 80mg vs placebo	████	████
		Resmetirom 100mg vs placebo	████	████
PLB-W52 F2, F3	Primary analysis*	Resmetirom 80mg vs placebo	██████████	████
		Resmetirom 100mg vs placebo	██████████	████
	Consensus analysis	Resmetirom 80mg vs placebo	██████████	████
		Resmetirom 100mg vs placebo	██████████	████
	Multiple imputation	Resmetirom 80mg vs placebo	██████████	████
		Resmetirom 100mg vs placebo	██████████	████
	Excluding disagreements**	Resmetirom 80mg vs placebo	████	████
		Resmetirom 100mg vs placebo	████	████

* Disagreements counted as 0.5.

** Calculated by the EAG.

3.3.3 Secondary outcomes

Other outcomes specified in the final scope issued by NICE include progression to cirrhosis, occurrence of hepatic decompensation events, liver transplantation, HCC, overall survival, adverse effects, and HRQoL (Section 2.3.4). Of these, the company shared results on adverse effects (AEs) of

treatment and HRQoL. Multiple additional outcomes were also reported in section 2.6.2 and 2.6.3 of the company submission.

3.3.3.1 Adverse events

The company reported data on adverse events in the safety population (N=966) in section 2.11 (pp. 83-86) of the CS.

Discontinuation due to AEs was more common in the 100 mg resmetirom study arm (6.8%) than in the 80 mg resmetirom arm (1.9%) and the placebo arm (2.2%) (CS p. 84). The proportions of people experiencing a severe AE ($\geq$ grade 3) was not significantly different between the 100 mg resmetirom arm (14.6%), the 80 mg resmetirom arm (13.4%), and the placebo arm (16.2). Four fatal AEs occurred during the trial (N=2 resmetirom 100 mg, N=1 resmetirom 80 mg, N=1 placebo).

The EAG's clinical advisers judged the type of adverse events experienced by patients in the resmetirom study arms to be expected and acceptable. Patients in the resmetirom study arms were more likely to experience nausea (80 mg arm 22.0%, 100 mg arm 18.9%) than patients in the placebo arm (12.5%) (CS Table 22, p. 85). Other AEs reported in $<10\%$ of the total sample but more prevalent in the resmetirom study arms include vomiting, abdominal pain, constipation, dizziness, gastroesophageal reflux (resmetirom 80 mg), and decreased appetite (resmetirom 100 mg) (CS Table 23, p. 85).

3.3.3.2 HRQoL

A brief summary of changes in HRQoL is reported for the mITT population (N=966) on pages 81 and 82 of the CS. Two measures were used to assess HRQoL; the Chronic Liver Disease Questionnaire-NAFLD (CLDQ-NAFLD) and the Liver Disease Quality of Life (LDQoL) instrument.

The company concludes in the CS (p. 82) that "In summary, resmetirom treatment was associated with statistically significant and clinically meaningful HRQoL improvements [...]". Greater HRQoL improvements were observed among responders in the resmetirom study arms compared to non-responders. However, this conclusion is at odds with the reporting on HRQoL in the CSR, which states that "No meaningful changes were observed between baseline and week 52 across all drug treatment groups, including placebo, and across all patient subgroups." (CSR Section 11.4.4.5, p. 122).

Both EAG's clinical advisers indicated that any impact of MASH on quality of life would be relatively minor for patients with fibrosis stage F1, F2, or F3, and mostly related to the anxiety of the diagnosis rather than specific symptoms. It therefore seems unlikely that improvement in NAS or moving down fibrosis stages F1B, F2, and F3 as a result of treatment with resmetirom would lead to significant improvements in HRQoL for this population.

3.3.4 Subgroup analyses

Subgroup analyses for key variables are referred to in section 2.8 (p. 82) of the CS, and were presented as an appendix (CS appendix C). The CSR reports results for the primary outcomes in the mITT (N=966) population. Results were consistently better in the resmetirom study arms compared to the placebo arm across subgroups for NASH improvement. In terms of fibrosis response, resmetirom study arms outperformed the placebo arm for all subgroups, with two exceptions. The difference in fibrosis response between the 80 mg resmetirom and placebo study arms in patients without type 2 diabetes was not statistically significant. Likewise, the difference in fibrosis response between the 100 mg resmetirom and placebo arms for patients aged 65 and over was not statistically significant. The company was unable to provide outcome data by baseline fibrosis stage per study arm, citing concerns of unblinding risk (PfC QA9).

Additional subgroup analyses were conducted for variables relating to response and concomitant medication. These did not show meaningful differences in NASH resolution. For patients who received GLP-1 RAs and resmetirom concomitantly, the point estimate of fibrosis reduction was lowest in the resmetirom 100 mg study arm, and there was no statistically significant difference in fibrosis reduction between placebo and 100 mg resmetirom (CSR Figure 8, p. 94).

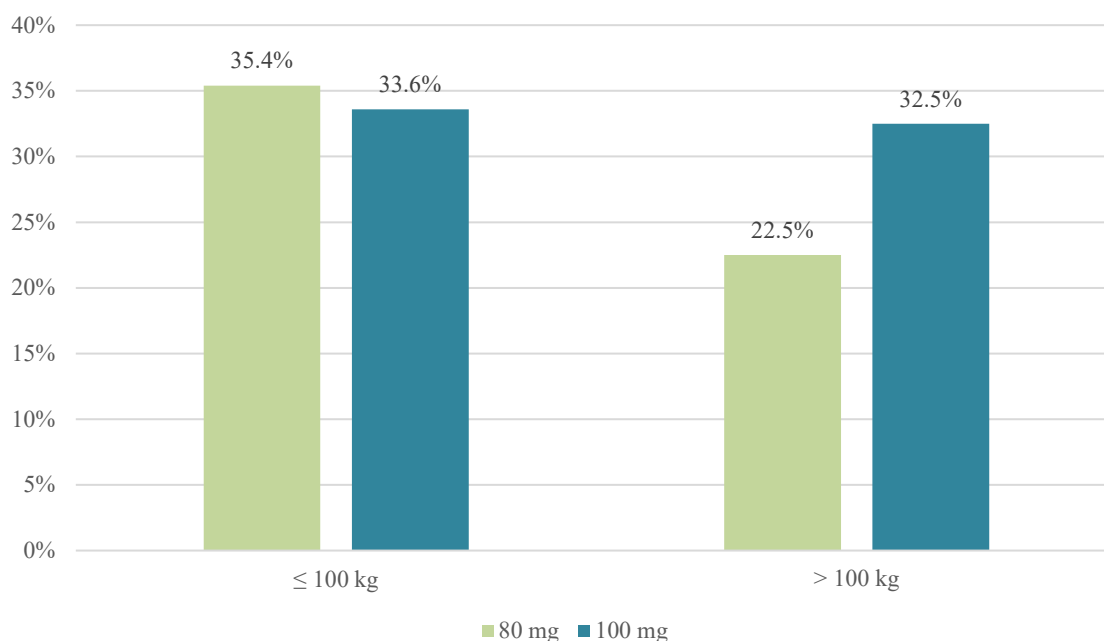
For patients with weight loss $\geq 5\%$, there was no statistically significant difference in fibrosis reduction between resmetirom 80 mg and placebo, nor between resmetirom 100 mg and placebo. Confidence intervals were large and sample sizes for these subgroups were not reported (CSR Figure 8, p. 94). Only relative differences, rather than proportions of fibrosis change per subgroup, were reported.

Subgroup results, though likely underpowered, suggest that weight loss and the use of GLP-1 RAs may interact with the effects of resmetirom on fibrosis. This adds uncertainty to the potential implementation of resmetirom in clinical practice alongside GLP-1 RAs, which are increasingly used for obesity and diabetes and may be licensed for MASH in the future.

3.3.4.1 *Improvement in fibrosis by patient weight*

A published post-hoc analysis of the MAESTRO-NASH data showed that patients over 100 kg were less likely to have improvement in fibrosis without worsening of NAS if they were allocated 80 mg compared to 100 mg tablets.²⁰ These data suggest the effect of resmetirom on improvement in fibrosis may have been greater among patients weighing over 100 kg with 100 mg compared to 80 mg dosing. The trial may therefore underestimate the effectiveness of resmetirom in patients over 100 kg.

Figure 2 Improvement in fibrosis by patient weight and resmetirom dosing



3.3.5 Evidence from two additional trials of resmetirom

Though the SLR identified three included studies relevant to the scope of this submission (Table 3), the company only reported results of MAESTRO-NASH. Results of the two other trials are summarised below. Given the similarities in study design between the three trials, the EAG believes that the company could have used evidence on NASH resolution from the MGL-3196-05 trial, and adverse events data from both trials, in this submission.

3.3.5.1 MGL-3196-05

This US phase 2 trial compared resmetirom (N=84) and placebo (N=41), with primary endpoint ‘change in MRI-PDFF’ measured at week 12.²¹ Participants in the resmetirom arm received 80 mg daily for the first four weeks, and between 60 and 100 mg thereafter. Change in hepatic fat, measured with MRI-PDFF, was greater in the resmetirom study arm (-32.9%) compared to the placebo arm (-10.4%). This difference was sustained at week 36 (resmetirom -37.3%, placebo -8.5%). Various measures relating to NASH resolution, based on a liver biopsy at week 36, showed greater improvement for patients receiving resmetirom compared to placebo. This was particularly true for patients received a higher dose of resmetirom. However, the proportion of patients who had NASH resolution and no worsening of fibrosis was similar between resmetirom and placebo.

In the first twelve weeks, diarrhoea was more common in the resmetirom arm (N=33%) than the placebo arm (7%). Nausea (baseline to 12 weeks) was more frequent in the resmetirom arm (14%) than in the placebo arm (5%).

Based on findings from this trial, the authors concluded that the preferred dosing for resmetirom is between 80 and 100 mg, rather than 60 mg.

3.3.5.2 MAESTRO-NAFLD-1

The primary outcome of the trial was treatment-emergent AEs (TEAEs).¹² As in MAESTRO-NASH, patient withdrawal due to AEs was more common in the resmetirom arms (N=9 80 mg resmetirom, N=10 100 mg resmetirom) than in the placebo arm (N=4). TEAEs were most common in the resmetirom 100 mg arm, but for TEAEs grade 3 and higher there was no clear difference between study arms. Patients in the resmetirom study arms were more likely to experience diarrhoea and nausea, with the highest proportion of AEs in the resmetirom 100 mg arm. These findings are in line with results from MAESTRO-NASH (Section 3.3.3.1).

Secondary outcomes included change in hepatic fat fraction measured by MRI-PDFF, and FibroScan controlled attenuation parameter (CAP) and vibration-controlled transient elastography (VCTE). At week 52, the least squared mean (LSM) difference in reduction of fat fraction was [REDACTED] for resmetirom 100 mg compared to placebo, and [REDACTED] for resmetirom 80 mg compared to placebo (CSR MAESTRO-NAFLD-1). This [REDACTED] results from MAESTRO-NASH (CS Table 19, p. 74).

Results at week 52 for FibroScan CAP were [REDACTED] for resmetirom 100 mg versus placebo [REDACTED] and resmetirom 80 mg versus placebo [REDACTED] results from MAESTRO-NASH. There [REDACTED] in FibroScan VCTE for patients with baseline VCTE ≥ 7.2 kPa for resmetirom 100 mg versus placebo [REDACTED] for resmetirom 80 mg versus placebo ([REDACTED]). In MAESTRO-NASH, differences in VCTE change were small, and mostly not statistically significant, between study arms (CS Table 4, Appendix J).

3.4 Critique of studies identified and included in the indirect treatment comparison or multiple treatment comparison

Not applicable.

3.5 Critique of the indirect comparison or multiple treatment comparison

Not applicable.

3.6 Additional work on clinical effectiveness done by the EAG

See Section 3.3.2 for additional calculations of the results of the primary outcomes.

See Section 3.3.5 for the EAG's summary of two relevant studies of resmetirom not included as part of the cost-effectiveness evidence submitted by the company.

3.7 Conclusions of the clinical-effectiveness section

The SLR appeared well-conducted and detailed information on review methodology was reported. Due to staff absence, the EAG could not critique the search strategies. Out of three relevant studies of resmetirom identified in the SLR, the company included evidence from one study, the MAESTRO-NASH RCT, in the clinical effectiveness section of the submission.

The EAG's main concern pertaining to the critical appraisal of MAESTRO-NASH is that the results of the biopsy-dependent primary outcomes may be biased by the discontinuation of participants, which was more common in the resmetirom study arms than in the placebo arm. Data for the primary outcomes were imputed under the missing at random assumption, which the EAG believes to be unjustified. This is of particular concern because the economic analysis is based on the smaller subpopulation with biopsies at 52 weeks.

Resmetirom, if approved, would be the first pharmacological treatment for MASH in the UK. The applicability of MAESTRO-NASH trial results to UK clinical practice is uncertain. The study sample was limited by including only patients with three or more cardiometabolic risk factors. The use of GLP-1 inhibitors was relatively low compared to current practice and was only allowed if doses were stable, whilst clinical advisers informed the EAG they would be unlikely to use resmetirom and GLP-1 inhibitors concomitantly in patients with MASH. Additional differences between the trial and anticipated NHS practice include the identification of patients suitable to receive resmetirom, as liver biopsies would not be used commonly in practice, and resmetirom dosing which was allocated randomly in the trial and is anticipated to be based on patient weight in practice.

The results of the MAESTRO-NASH trial show a benefit of resmetirom compared to placebo in terms of NASH resolution, fibrosis improvement, and secondary outcomes. Long-term outcomes included in the NICE scope, such as progression to cirrhosis, occurrence of hepatic decompensation events, and mortality would typically occur many years after fibrosis progression. These outcomes were not reported due to the relatively short trial follow-up period of 52 weeks.

The EAG considers it likely that the sample used in the economic model (PLB-W52 F2, F3) results in an overestimation of the treatment effect. This may be due to disproportionate rates of discontinuation in the resmetirom study arms compared to the placebo arm, and the exclusion of data of primary outcomes for which two clinicians rated images of biopsies differently.

In summary, the MAESTRO-NASH trial shows short-term benefits of resmetirom compared to placebo for trial participants who were included in the week 52 efficacy analyses. The applicability of results to UK clinical practice and the long-term effects of resmetirom remain uncertain.

4 COST-EFFECTIVENESS

This section presents a summary and critique of the cost-effectiveness evidence included in the company's submission. Section 4.1 focuses on the company's review of the cost-effectiveness evidence and section 4.2 covers the company's economic evaluation.

4.1 *Critique of the review of cost-effectiveness evidence*

The company conducted two systematic literature review (SLRs) related to cost-effectiveness. The first SLR aimed to identify i) published economic evaluations and ii) data on costs and healthcare resource use (HCRU) associated with treatments for MASH/NASH and liver fibrosis or MASLD/NAFLD. The second SLR aimed to identify relevant health-related quality of life (HRQoL) studies for these patients. Detailed descriptions of the methods and results of the SLRs are reported in Appendix E, F and G of the CS.

4.1.1 Search strategy

Appendix E of the CS included the searches to identify both economic evaluations of treatments for MASH/NASH and liver fibrosis or MASLD/NAFLD and Cost and HCRU studies relating to this population. Appendix F of the CS included the searches to identify for HRQoL. For both SLRs, population was the same and searches were undertaken between March and July 2025. Due to staff absence, the EAG could not provide a critique of the search strategies.

Inclusion/exclusion criteria

The PICOS criteria used by the company to determine eligibility are presented in Appendix E, Table 1 of the CS for the review of cost effectiveness studies (also applied to the cost and HCRU review), and in Appendix F, Table 1 of the CS for HRQoL review.

For the economic SLR, studies including adults (≥ 18 years) diagnosed with MASH/NASH and liver fibrosis or MASLD/NAFLD and presumed/suspected MASH, who received any interventions, pharmaceutical or non-pharmaceutical, that were not focused on diagnosis or screening. In the HRQoL SLR, interventional study designs were excluded, meaning that only studies with no intervention were eligible.

Screening was conducted at both the title/abstract and full-text stages by two independent reviewers, with any disagreements resolved by a third reviewer. The reported methods do not describe how data extraction was performed.

The EAG considers the selection criteria applied in the cost-effectiveness and HCRU reviews to be broadly appropriate. However, it has concerns that the eligibility criteria for the HRQoL review are

overly restrictive. Specifically, limiting the review to patients with MASH or suspected/presumed MASH may have excluded relevant studies. While the EAG acknowledges the distinction between MASH and MASLD, these populations often overlap, and published studies do not always clearly differentiate between them. As discussed further in Section 4.2.6, the EAG has identified at least one study providing potentially relevant HRQoL data that was not included in the company's review.

4.1.2 Identified studies

A total of 58 included studies were identified and included in the economic review, of which 21 were classified as economic evaluations and incorporated into the cost-effectiveness review. A summary of these 21 studies is reported in the CS (Table 25, p.95-100). The remaining 37 studies were classified as costing or HCRU studies (presented in Appendix G of the CS).

None of the studies included in the cost-effectiveness review was conducted from a UK NHS perspective. Instead, the majority were performed considering a U.S. payer settings. Treatments evaluated included resmetirom, obeticholic acid (OCA), vitamin E, pioglitazone, bariatric surgery, and hypothetical curative or disease-modifying therapies. According to the company, these studies varied in terms of population (fibrosis stage, cirrhotic vs. non-cirrhotic), perspective, and model structure. Most adopted a Markov cohort simulation over a patients' lifetime, with health states reflecting fibrosis stage and liver related events, including DCC, HCC and liver transplantation (LT). Key model drivers included treatment efficacy in slowing fibrosis progression or achieving NASH resolution, health state utility values, and costs associated with advanced liver disease (Appendix E, Table 2, p11-20).

The company highlighted that the US value-based pricing study by Le *et al.* (2025)²² offers some relevant insights, but its conclusion should be interpreted with caution, as it is not directly applicable to UK decision-making. Both the US ICER study (Tice *et al.* 2023)²³ and Gal *et al.* (2023)²⁴ incorporated aspects of patient-level microsimulation models (MSMs) to estimate costs and benefits. The company indicated that several studies included in the economic SLR findings informed the design and parameterisation of *de novo* model presented in the CS.

From the 37 studies identified as Cost and HCRU studies, seven publications had England/UK-specific patients.^{14, 25-30} The company highlighted Davidson *et al.* 2025¹⁴, which analysed electronic health records (CPRD-Hospital Episode Statistics (HES) data) in England detailing rates of hospitalisation, outpatient hepatology visits, and monitoring procedures. These utilisation estimates were the basis for nine health states [fibrosis stages (F0-F3) and advanced liver outcomes (CC, DCC, HCC)] costs used in the economic model. The company selected this company-sponsored publication for the base-case analysis because it provides more granular, disease-specific estimates for MASH

populations than can be obtained from Healthcare Resource Groups (HRG)-level tariffs. See Section 4.2.7 for more details.

For the HRQoL review, 169 full text screening studies were reviewed, yielding 27 included studies. None of the findings from the HRQoL SLR was used to inform the company's economic model base-case or scenario analyses. See Section 4.2.6 for more details.

4.1.3 Interpretation of the review

Although the studies identified in the company's cost-effectiveness review do not adopt an NHS perspective and are therefore of limited relevance to UK decision making, they nonetheless provide a useful reference point for comparing structural assumptions, data sources, and parameter uncertainties, and offer context for the magnitude of QALY gains expected with resmetirom.

At PfcS, the EAG requested (B2) that the company undertake a comparative review of the cost-effectiveness studies evaluating resmetirom, focusing on several key features. Namely, model structure, natural history, and modelled treatment effect, utility values used and stopping rules applied. Table 9 presents pertinent details of the studies the company's response. The CS also provides additional information on key model drivers identified from these studies was provided (Appendix E, Table 2), which is discussed in the following narrative.

Table 9 Previous resmetirom studies identified in the CEA review

Study	Summary of model	Natural history & treatment effects	Utility values	Stopping/ discontinuation rules	Key results (context)	Critique/Comments	Comparison with company <i>de novo</i> model
Le et al. 2025 ²²	Agent-based microsimulation with 14 fibrosis/clinical states (F0–F4 ± MASH, DC, HCC, LT, death); lifetime horizon	Natural history from meta-analysis of paired biopsies; treatment effects from MAESTRO-NASH (RRs for fibrosis improvement / MASH resolution). No cardiometabolic module.	Early stages mapped from SF-36 → HUI; advanced stages from hepatitis C sources; age/sex adjustments	Stop at F4/DC/HCC; restart if F4 → F3; 21.3 % annual discontinuation; no treatment disutility.	+0.26 QALYs; +\$36 k; ICER ≈ \$140 k/QALY. Resmet: 10.74 SoC: 10.48 Diff: 0.26	Heterogeneous natural-history inputs and no CV effects; results sensitive to utilities. For more detailed, please see our explanations in section 3.3.2 CS	CS model uses MAESTRO-NASH patient-level transitions with separate resolution and fibrosis effects, and an explicit CV risk module → more biologically realistic captures total QALY gain.
Kim et al. 2024 ³¹	Cohort state-transition Markov model for adults (F2–F3) over 50 years; 1-year cycles; US private-payer perspective.	Non-cirrhotic transition probabilities from MAESTRO-NASH placebo arm + literature; resmetirom effects on progression, regression and NASH resolution from MAESTRO-NASH. Excluded lipid benefits.	Non-cirrhotic utilities from MAESTRO-NASH; advanced states from published sources	Discontinuation and AE rates from MAESTRO-NASH; permanent stop at cirrhosis.	11.91 vs 10.02 QALYs; +\$213,948; ICER \$113,391/QALY; cost-effective at ≤\$110 k/QALY. Resmet: 11.91 SoC: 10.02 Diff: 1.89	Well-calibrated US CEA using phase III data; excluded CV effects and assumed US costs only.	CS model builds on this foundation but adds dual-endpoint microsimulation, UK NHS costs, empiric relapse logic, and label-aligned on/off rules , capturing the dynamic interaction of fibrosis improvement and MASH resolution more precisely.
Tice et al. 2023 ²³	Cohort Markov model (no / prior CV event sub-models); fibrosis ladder F0–F4 → DC, HCC, LT, death; annual cycles; lifetime horizon.	Natural history from NAFLD/NASH meta-analyses; treatment effects from top-line MAESTRO-NASH applied uniformly across stages; includes CV event module (Framingham).	Disease-stage utilities from GAIN EQ-5D-5L; AE disutilities applied.	Stop at F4; base case AE + all-cause discontinuation ≈ 16 %/yr	Resmetirom cost-saving or ≤ \$30 k/QALY at placeholder prices. Resmet: 10.66 SoC: 10.05 Diff: 0.61	Mature framework with CV module; relied on early efficacy and placeholder price.	Company model refines with full phase III patient-level data and UK resource costs, ensuring relevance for NICE while retaining CV effects.

Javanbakht et al. 2023 ³²	Cohort Markov with parallel CV sub-model (no / prior CV event); lifetime horizon.	Transition rates from phase II trial mapped to fibrosis states; long-term extrapolation to 30 yrs.	Early NAFLD/NASH utilities; advanced stages from hepatitis C studies; sensitivity noted.	Fixed treatment duration (95 % adherence); discontinuation not parameterised.	\$53,929 /QALY (2021 USD); price threshold ≈ \$50–94/day. Resmet: 12.71 SoC: 11.48 Diff: 1.23	First formal CEA; transparent thresholds; limited by phase II data .	<i>De novo</i> model uses phase III biopsy-based transitions, UK utility sources, and explicit relapse / re-initiation rules.
Company <i>de novo</i> model (2025)	Patient-level microsimulation calibrated to MAESTRO-NASH paired-biopsy transitions; lifetime horizon.	Dual-endpoint (MASH resolution and ≥ 1-stage fibrosis improvement) structure; includes CV and T2DM event risk modifiers.	Contemporary HRQoL data for MASLD/MASH and advanced states; mutually exclusive utility gains for resolution vs fibrosis improvement.	Permanent stop at F4/DCC/HCC; temporary stop if < F2 with re-start at F2–F3; dose-specific discontinuation from MAESTRO-NASH.	Incremental QALY gain > literature; ICER well below NICE thresholds. Resmet: 11.05 SoC: 9.54 Diff: 1.52	Strengths: trial-anchored, UK inputs, explicit relapse logic; Limitations: long-term effect extrapolated beyond 52 wks.	Integrates regulatory-accepted endpoints, label-consistent eligibility, and NHS costs—addressing key gaps in prior models.
Source: Adapted from Table 10, PfC							

Abbreviations: AE, adverse event; CEA, cost-effectiveness analysis; CS, company submission; CV, cardiovascular; DCC, decompensated cirrhosis; EQ-5D, Euroqol-5 Dimensions; F0-F4, fibrosis stages F0-F4; HCC, hepatocellular carcinoma; HRQoL, health-related quality of life; HUI, Health Utilities Index; ICER, incremental cost-effectiveness ratio; LT, liver transplantation; MASH, metabolic dysfunction-associated steatohepatitis; MASLD, metabolic dysfunction–associated steatotic liver disease; NAFLD, non-alcoholic fatty liver disease; NASH, non-alcoholic steatohepatitis; QALY, quality-adjusted life year; Resmet, Resmetirom; RR, risk ratio; SF-36, Short Form-36.

Modelled health states across evaluations captured fibrosis stage and liver-related events. Some models also included a cardiovascular module to account for extrahepatic outcomes, although this was not consistent. The limited impact of cardiovascular events on both QALY gains and the ICER in the company's *de novo* analysis indicates that differences in cardiovascular modelling are unlikely to explain the observed variation in results. Heterogeneity is also evident in the modelling of disease progression. The company's *de novo* analysis, where possible, applied trial-based transition probabilities, whereas Le et al. 2025 model²² used data from Le et al, 2023³³ which meta-analysed available natural history evidence. The other independent study²³ also adopted this latter approach using data from Singh et al. 2015³⁴, while company-sponsored models^{31 32} relied on trial-based data, which may partly account for differences in predicted QALY gains. Differences in utility sources are also apparent. Some models used published values, often substituting hepatitis C-related utilities for advanced NASH health states, while others incorporated trial-based estimates, including values from the MAESTRO-NASH trial. The company's *de novo* analysis, however, did not use trial-derived utilities, instead drawing on published sources (See Section 4.2.6).

Stopping rules were generally consistent across studies, with all but one model using trial-reported event rates to capture all-cause treatment discontinuation and assuming that patients discontinued therapy upon progression to F4 cirrhosis. The exception, Javanbakht et al. (2023), assumed a fixed treatment duration³². The company's *de novo* model represents a notable departure from this approach, as it also assumes treatment discontinuation upon regression to F1 or F0 fibrosis. Several authors highlighted that model outcomes were particularly sensitive to the assumed discontinuation rates. For example, Le et al. noted that increasing the discontinuation rate reduced drug costs, lowered estimated treatment effectiveness, and increased medical costs, yet the ICER declined²². This seemingly counterintuitive result was explained by the rapid improvement in fibrosis with resmetirom and the slow progression of MASLD; over a lifetime horizon, extended treatment provides only a modest incremental health benefit relative to shorter durations, which does not offset the high lifetime drug costs.

Economic evaluations of resmetirom in the published literature also show considerable variation in predicted QALY gains. The EAG notes that independent (^{22, 23}) models report lower QALY gains (0.26 to 0.61) than company-sponsored models (^{31, 32}) analyses (1.23 to 1.89). Reported ICERs also varied substantially, from dominant to between \$53,929 to \$140,134 per QALY. The US ICER study²³ assumed a placeholder price of \$19,000 per year (\$52.05 per dose) as the company did not provide the list price, which is substantially lower than the [REDACTED] per dose used in this NICE company submission. Although these estimates are not directly comparable with the company's *de novo* analysis because of the US payer perspective, they remain considerably higher than the £21,422 per QALY estimated in the company's base-case analysis.

Validation is essential for ensuring confidence in model results, yet approaches and reporting vary across studies. Some models, such as those by Tice et al. (2023) ²³ and Gal et al. (2023) ²⁴, combined internal verification, sensitivity analyses, stakeholder input, and external checks, with Gal et al. providing detailed documentation of corrections in a formal report. Other models, such as Le et al. (2025) ²², demonstrated alignment with observed clinical data, while Javanbakht et al. (2023) ³² performed both internal and external validation but offered limited methodological detail. These examples illustrate the range of validation strategies in health economic modelling and highlight the importance of transparency and thorough reporting to support confidence in model findings.

4.1.3.1 HTA Lab report

A notable omission in the company submission was reference to the NICE HTA Innovation Laboratory (HTA Lab) report on the evaluation of MASLD treatments, which was highlighted in the economic analysis section of the NICE scope.³⁵ The HTA Lab report aimed to support upcoming appraisal of therapies and aimed to:

- Identify potential challenges in evaluating MASLD treatments.
- Co-develop specifications for an economic model concept to assess the cost-effectiveness of these treatments.

Table 10 summarises the HTA Lab’s recommended economic model specifications alongside the assumptions used in the company’s submission. While the company’s *de novo* model aligns with several elements of the HTA Lab recommendations, it diverges in a number of important respects. The EAG is aware that the HTA Lab is not intended to represent prescriptive recommendations, but considers these deviations disappointing, particularly given that the company participated as a stakeholder in developing the HTA Lab report. The EAG believes that the company should have better justified deviations from the HTA Lab recommendations and that the failure to adopt the NICE HTA Lab recommendations undermines the broader aim of promoting consistency in decision making. The implications of these deviations are discussed further in the relevant sections of the EAG critique.

Table 10 Comparison of NICE HTA Lab recommendations and company model

Specifications	NICE HTA Innovation Lab	Company Submission
Type of economic model	A state transition modelling approach, either as a cohort or individual patient-level simulation for treatments for MASH, would meet these requirements and address the decision problem	The <i>de novo</i> patient-level MSM was developed in R. The MSM framework reflects the complexity of MASH, a progressive metabolic condition with heterogeneous trajectories and frequent comorbidities.
Capturing the natural history of the condition	Assumptions around the natural history of the condition should be	CS states: Although the SoC arm of MAESTRO-NASH cannot provide a

	tested to quantify the underlying uncertainty in scenario analysis	definitive natural history for the condition, it represents the most relevant empirical foundation currently available for modelling regression, stability, and progression of fibrosis in this population.
Outcomes	Hepatic outcomes: fibrosis, cirrhosis, liver cancer and liver transplant should be captured in health states. Non-hepatic outcomes for treatments that have an impact on underlying metabolic mechanisms.	Hepatic outcomes are captured as health states but not reported <i>per se</i> in the CEM. (e.g. predicted number of LTs) Non-hepatic outcomes incorporation of cardiometabolic predictors of T2DM and cardiovascular events
Transition between health states	If there is potential for reversal of decompensated cirrhosis even in a minority of the population, then the model should allow movement from decompensated cirrhosis to less severe health states	No movement back from decompensated cirrhosis to less severe health states.
Stratification of model population & subgroup analysis	Stratification based on BMI should split the model into 3 sub-populations: patients with obesity, overweight and healthy weight. Subgroup analyses for people with hypertension should be carried out	Stratification based on BMI was not conducted. Subgroup analyses for people with hypertension was not carried out.
Infrastructure costs	The need for widespread introduction to identify people with MASH who are eligible for treatment will require capturing in evaluations of MASH treatment.	CS states: resmetirom is expected to integrate into existing NHS hepatology services without significant additional resource requirements. Resource burden in the context of NHS expanding & screening for eligibility (p.93). EAG: Missing is the diagnostic costs associated with discontinuation of resmetirom because of regression and progression (assumed to align with current practice)
Surrogate endpoints	Follow guidance in the NICE DSU ³⁶ report for validation of surrogate endpoints	No reference to this specific DSU document made.
Scenario analysis	The following assumptions should be varied in sensitivity analysis and presented alongside any other appropriate scenario analysis: 1. Assumptions around long term treatment effectiveness: a. Variation over time (for example, waning of effect over time). b. Duration of treatment effect. 2. Assumptions around naturally occurring differences in rates of progression within the MASH population to account for heterogeneity.	None of these scenario analyses were reported except a scenario where a patient receives 2 years of resmetirom.

	3. Exploring the impact of different predictive risk equations for surrogate endpoints. 4. Testing the impact of using health state utility values from different sources	
Flexibility	Models should have built-in mechanisms (for example, switches) to allow the generation of cost-effectiveness results based on a subset of outcomes, particularly when both hepatic and non-hepatic outcomes are included.	Such ‘switches’ are not easily implementable in the R code.

Abbreviations: CS, Company submission; CEM, Company executable model; EAG, External assessment group; LT, Lung transplantation; MASH, metabolic dysfunction-associated steatohepatitis; MSM, Micro simulation model; NICE DSU, Decision support unit; T2DM, type 2 Diabetes Mellitus.

4.2 Critique of the submitted economic evaluation

4.2.1 NICE reference case checklist

Table 11 summarises the EAG’s assessment of whether the company’s economic evaluation meets the NICE reference case and other methodological recommendations.

Table 11 NICE reference case checklist

Element of health technology assessment	Reference case	EAG comment on company’s submission
Perspective on outcomes	All health effects, whether for patients or, when relevant, carers	QALY benefits for treated individuals were considered.
Perspective on costs	NHS and Personal Social Services	NHS and PSS costs were considered.
Type of economic evaluation	Cost–utility analysis with fully incremental analysis	Cost-utility analysis. Fully incremental analysis is not relevant as only one comparator.
Time horizon	Long enough to reflect all important differences in costs or outcomes between the technologies being compared	The economic model evaluates patients over 72 years, commensurate with a lifetime horizon.
Synthesis of evidence on health effects	Based on a systematic review	The company undertook a systematic review to identify relevant data sources. Model treatment effects are sourced primarily from the MAESTRO-NASH trial. Evidence on the magnitude of fibrosis stage changes was, however, informed by external data (Singh et al.) This was not identified via a systematic review.
Measuring and valuing health effects	Health effects should be expressed in QALYs. The EQ-5D is the preferred measure of health-related quality of life in adults.	EQ-5D values were derived from a cohort of patients with obesity, including those with both obesity and hepatitis B. A scenario analysis was conducted using SF-36v2 data collected in the MAESTRO-NASH trial, mapped to SF-6D utility values.

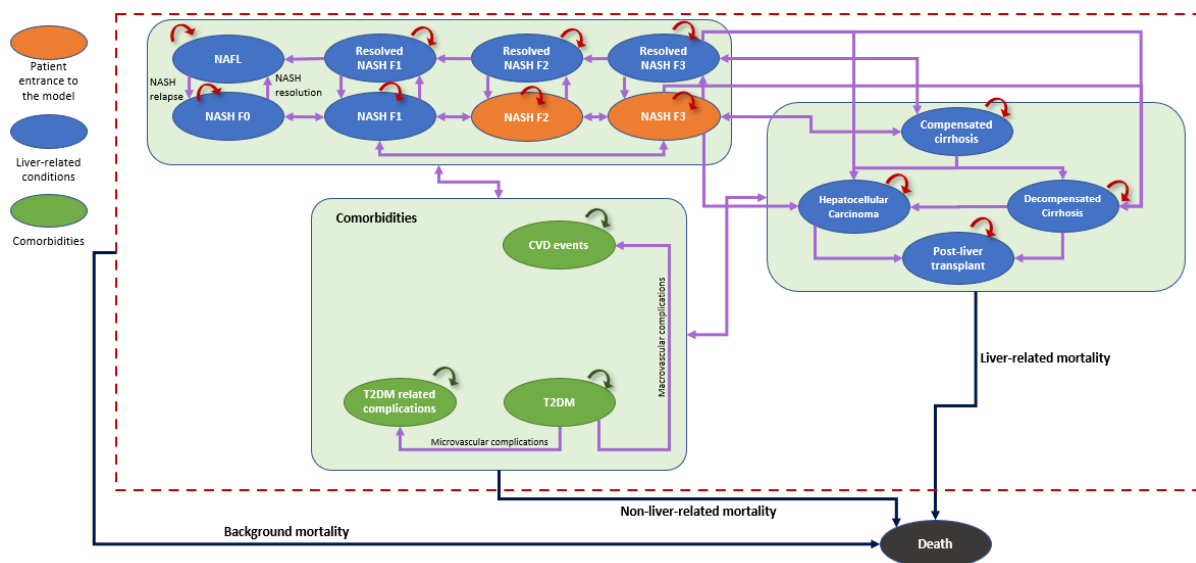
Element of health technology assessment	Reference case	EAG comment on company's submission
Source of data for measurement of health-related quality of life	Reported directly by patients, carers or both	Yes, but the values were derived from patients with obesity, or with both obesity and hepatitis B.
Source of preference data for valuation of changes in health-related quality of life	Representative sample of the UK population	Yes
Equity considerations	An additional QALY has the same weight regardless of the other characteristics of the people having the health benefit, except in specific circumstances	Yes
Evidence on resource use and costs	Costs should relate to NHS and PSS resources and should be valued using the prices relevant to the NHS and PSS	Costs based on UK sources, including NHS reference costs. Resource use and costs applied to health states were based on the CPRD and clinical advice.
Discounting	The same annual rate for both costs and health effects (currently 3.5%)	Costs and benefits were discounted at 3.5% per annum.

4.2.2 Model structure

The company developed a *de novo* individual patient simulation model in *R* to estimate the lifetime cost-effectiveness of resmetirom for treating adults with non-cirrhotic MASH. The model compared resmetirom with standard of care, which includes lifestyle modifications such as a healthy diet, weight loss, and regular exercise.

Figure 3 illustrates a schematic of the model structure. Health states within the economic model were mainly defined by MASH resolution status and fibrosis stage, comprising eight states that indicated whether MASH was present (yes or no) and the fibrosis stage (F0 to F3). Patients could also progress to advanced liver disease (fibrosis stage F4), which includes four additional states: CC, DCC, HCC, and LT. At any point during the model's time horizon, patients could experience comorbid events such as T2DM and cardiovascular disease (CVD), which were determined based on individual patient characteristics (including age, sex, BMI, and history of previous CVD events) and liver fibrosis stage. In addition to the 'alive' health states, an absorbing death health state was modelled.

Figure 3 Model structure



Abbreviations: CVD: cardiovascular disease; F0-F3: fibrosis stages 0-3; NAFL: non-alcoholic fatty liver; NASH: non-alcoholic steatohepatitis; T2DM: type 2 diabetes mellitus.

Patients enter the model in the NASH F2 or NASH F3 fibrosis health states. During each annual cycle, individuals may remain in their current state, transition to a different fibrosis stage, or resolve MASH, in which case they transition to the corresponding non-MASH state in the top row of the model schematic. From either F3 state, patients may also progress to one of the four advanced liver disease (ALD) states.

Health benefits in the model are primarily accrued through avoidance of progression to the ALD state, which is associated with increased mortality (the main driver of incremental QALY gains) and reduced HRQoL. Additional health benefits are accrued through the resolution of MASH (improved quality of life), avoidance of progression to F3 disease (reduced quality of life), and prevention of comorbidities (reduced quality of life and increased mortality). Costs in the model are primarily accrued through time on resmetirom treatment and avoidance of progression to the ALD state, which is associated with substantially higher health state costs. A smaller contribution to incremental costs is accrued through the avoidance of comorbidities, which comprise only a small proportion of both total and incremental costs.

The model uses data from the MAESTRO-NASH trial to inform transition probabilities between fibrosis stages and to determine MASH status, with arm specific values applied to estimate both sets of transitions. Transitions to other health states, including movement between ALD health states, and mortality from all states, are informed by external data. Transitions between ALD health states and mortality risk are assumed to be independent of treatment received. Consequently, modelled improvements in survival and avoidance of liver complications (DCC and HCC) were inferred

indirectly, through a greater proportion of patients achieving MASH resolution and relative improvements in fibrosis stage, rather than being directly observed in trial evidence.

The probability of comorbid events is modelled using relevant risk equations, with benefits generated through changes in risk factors such as BMI, LDL-C, HDL-C, and triglycerides. As with liver-related outcomes, reductions in these events are inferred from improvements in intermediate outcomes rather than being directly observed in trial evidence.

4.2.2.1 Points for critique

The company's model structure and approach are broadly consistent with previous cost-effectiveness analyses identified in the cost-effectiveness review. The adoption of an individual patient simulation approach, in which outcomes are evaluated by simulating each patient in the target population separately, aligns with several recent evaluations and provides greater flexibility by enabling simultaneous modelling of liver and non-liver related outcomes. The EAG recognises the advantages of this approach in the context of MASLD, where treatments may have multisystemic effects, but notes that it substantially increases model complexity. Given the limited evidence supporting extrahepatic effects and their relatively small contribution to overall costs and QALYs, it is unclear whether this additional complexity is justified. Nonetheless, this approach is consistent with several recent analyses, and the EAG is satisfied that the model structure appropriately captures the key aspects of MASH and MASLD.

The company's model also differs from most previous analyses in that it distinguishes between MASH and non-MASH patients. The EAG considers this an advantage, as MASH is the primary driver of fibrosis progression and regression. This distinction allows for a more nuanced and accurate representation of transitions between fibrosis stages.

Reliance on surrogate relationships

The key drivers of cost-effectiveness in the company's model are reduced comorbid events, avoidance of liver complications (DCC and HCC), and improved survival. However, none of these benefits are directly observed in the MAESTRO-NASH trial. Instead, the model infers these outcomes indirectly, through intermediate changes in fibrosis stage, MASH resolution, and risk factors such as BMI, LDL-C, HDL-C, and triglycerides.

This approach reflects the limitations of the MAESTRO-NASH trial data available, which currently do not capture long-term outcomes such as liver-related complications, comorbidity incidence, or mortality. Rather, within the current data cut (limited to 12 months follow-up) the trial focuses on intermediate endpoints. To bridge this gap, the company constructed a chain of assumptions that links treatment effects on intermediate outcomes to final outcomes. The EAG emphasises that these links in

the causal chain are not informed by direct trial evidence but are instead derived from multiple external data sources. Owing to the complexity of the model, a large number of individual parameters contribute to the determination of final outcomes. As discussed in subsequent sections, the rationale for many of the parameter selections and inclusion criteria is not clearly justified in the company's submission. The incorporation of a large number of parameters from disparate sources introduces a substantial degree of compounded uncertainty, which is not fully captured in the company's sensitivity analyses.

Moreover, the company submission provides only limited justification for the model surrogate relationships. The EAG considers this a significant omission. The NICE methods manual (Section 5.4.14) is explicit that when final outcomes cannot be modelled directly, evidence supporting the relationship between intermediate and final outcomes must be provided, together with an explanation of how these relationships are quantified for use in the model. In this case, the company has not provided empirical evidence to establish the validity or strength of the surrogate links underpinning its model³⁷.

At the clarification stage, the EAG requested that the company provide an overview of the evidence supporting the validity of the proposed surrogate relationships, specifically the link between fibrosis stage and both liver-related outcomes and mortality. In response, the company cited several published studies, including systematic reviews, that demonstrate an association between fibrosis stage and risk of liver-related events and all-cause mortality.^{7, 38-40} The EAG agrees that there is substantial evidence of a correlation between fibrosis severity and relevant clinical outcomes. However, as acknowledged by the company (and noted in several of the cited sources), fibrosis stage has not been formally validated as an acceptable surrogate endpoint. In particular, there is no direct evidence from pharmacotherapy trials demonstrating that treatments which improve fibrosis stage also lead to corresponding improvements in clinical outcomes such as liver-related events or mortality.

In the absence of direct evidence or validated surrogate relationships, the modelled reductions in comorbid events, avoidance of advanced liver disease, and improvements in survival remain highly uncertain. These assumptions represent a major source of uncertainty in the company's cost-effectiveness results, as they underpin much of the incremental QALY gain and projected cost savings. Further data cuts from the MAESTRO-NASH trial, including the forthcoming 54-month follow-up (expected [REDACTED]), may provide additional evidence to support the modelled reductions in liver-related complications and mortality. These data will also be important in assessing the validity of the surrogate relationships used in the model.

Response to treatment not modelled

The introduction of resmetirom into NHS practice would represent a step change in the management

of MASH and MASLD in the UK, as no pharmacological treatments are currently available for this population. While this indicates that resmetirom could address an important unmet clinical need, it also introduces considerable uncertainty regarding its use in clinical practice, given the absence of any established treatment pathways or precedents for therapy in this setting.

The company's economic model assumes that patients will continue resmetirom treatment while they remain in the F2 and F3 health states, and that ongoing treatment provides benefit regardless of whether MASH resolution is achieved or fibrosis progression occurs. Within the model, discontinuation occurs only when patients move out of the F2 or F3 health states, either through regression or progression of disease.

Expert opinion reported in Nouredin et al. (2024),¹⁷ however, proposes that treatment response should be assessed after 12 months, using a composite assessment of NITs. Specifically, a $\geq 30\%$ reduction in MRI-PDFF, improvement in alanine aminotransferase (ALT), and liver stiffness trends. Treatment discontinuation is recommended when ≥ 2 NITs worsen.

At clarification, the company indicated that it considered the currently unpublished BASL MASLD SIG guidance more relevant to NHS clinical practice. However, the company accepted the general principle that the assessment of response is likely to be part of routine UK clinical practice. Despite this, the company's economic model does not include any mechanism for response-based treatment discontinuation. The company stated that evidence from MAESTRO-NASH could not sufficiently inform alternative stopping rules beyond those linked to fibrosis progression, noting that the trial was designed and powered for histological endpoints rather than NIT-based endpoints.

The EAG considers this a major limitation of both the company's economic analysis and the current clinical evidence base. There is a substantial disconnect between the structure of the company's model and the treatment paradigm likely to be adopted in NHS practice, as outlined by multiple expert panels. This issue is particularly important in the context of the modelled treatment effects. The company assumes that continued resmetirom treatment leads to compounding benefits, such that the probability of achieving MASH resolution in subsequent years is independent of previous treatment. These assumptions lack any evidentiary foundation and are inconsistent with both the response-based treatment approaches described in Nouredin et al. (2024)¹⁷ and the unpublished BASL MASLD SIG guidance, which indicate that treatment in non-responders should be discontinued.

Further evidence is required to substantiate the modelled treatment paradigm, which EAG considers has not been adequately justified. The omission of a response-based stopping rule represents a significant uncertainty that potentially undermines the suitability of the model for decision-making.

4.2.3 Population

The population considered in the company's base-case analysis comprised individuals with non-cirrhotic MASH and moderate to advanced fibrosis (fibrosis stages F2 and F3). This population aligns with both the marketing authorisation for resmetirom and the NICE scope.

The modelled population for the purposes of deriving the modelled treatment effect was based on a subgroup of the MAESTRO-NASH trial, the Paired Liver Biopsy Population at Week 52 (PLB-W52) (n = 782). This was further restricted to F2 and F3 patients only, excluding patients with F1B fibrosis (n = 43) and resulted in a final modelled sample of 739 patients. The PLB-W52 population, therefore, differs from the Liver Biopsy Modified Intention-to-Treat Population (mITT-LB-W52) (n = 955) reported in Section 3 of the EAG report and Section B2 of the company's submission.

The PLB-W52 population represents a subset of the mITT-LB-W52 population, excluding patients without a usable follow-up biopsy sample or without follow-up biopsy data, as well as cases where assessors disagreed on response outcomes. According to the company's submission, restricting the modelled population to PLB-W52 was necessary because estimation of transition probabilities for MASH resolution and changes in fibrosis stage required complete paired biopsy data at the individual patient level. These data limitations did not affect the estimation of treatment effects reported in Section B2 of the company submission, which were derived from aggregate-level analyses.

The model incorporated a wide range of population characteristics, including age, sex, fibrosis stage, metabolic risk factors. Modelling this large set of characteristics was necessary because they informed the risk equations for cardiovascular (CVD) events and the incidence of T2DM. Age and sex were also used to determine background mortality, and age-related adjustments were applied to utility values.

Population characteristics were sampled from the full safety population (n = 966) by drawing a sample of 10,000 individual patients from the MAESTRO-NASH trial's individual patient data (IPD). Consequently, the modelled cohort reflects the actual patients enrolled in the pivotal trial (confirmed at PfC).

To illustrate that the PLB-W52 subset of MAESTRO-NASH patients is comparable to England and Wales MASH population the CS compared baseline characteristics with patients (n = 2,696) from a larger company-funded study using the CPRD-HES database [(n=2,696). Table 26, CS]. This is the same study that is used to estimate costs for health states (See Section 4.2.7).

The two populations were broadly similar demographically, with comparable mean age (56.2 vs 56.0 years) and sex distribution (56.4% vs 54.5% female). However, a higher proportion of South Asian patients was observed in CPRD (9.5%) compared with MAESTRO-NASH (2.7%). Obesity

prevalence was similar between cohorts (46.7% vs 44.7%), but notable differences were evident in comorbidities. Hypertension was present in 78.6% of the MAESTRO-NASH population compared with 47.3% in CPRD, and T2DM was more prevalent in the MAESTRO-NASH population (66.9% vs 40.9%).

4.2.3.1 Points for critique

Generalisability of MAESTRO-NASH trial

As discussed in Sections 2.3.1; 3.2.2.1 and 3.2.2.2, the EAG identified several concerns regarding the generalisability of MAESTRO-NASH and its applicability to NHS practice. First, the trial's requirement for biopsy-confirmed disease is unlikely to reflect NHS practice, as liver biopsy is invasive, resource-intensive, and typically restricted to specialist centres, potentially exacerbating inequalities in access. Although the company proposes that non-invasive tests (NITs) would be used in clinical practice, there are currently no validated NHS criteria for identifying eligible patients. Furthermore, as shown in Section 3.2.2.2, it is uncertain whether all MAESTRO-NASH participants would meet eligibility criteria for resmetirom in practice. Criteria proposed by an expert panel, a soon-to-be-published consensus guideline from BASL, an unpublished consensus meeting, and updated AASLD guidance suggest that between [REDACTED] and [REDACTED] of the trial population would be eligible, indicating a mismatch between the trial and NHS populations.

Second, MAESTRO-NASH enrolled an enriched population with a higher cardiometabolic disease burden than typically seen in UK clinical practice. Eligibility required participants to have at least three metabolic risk factors (obesity, pre-diabetes or T2DM mellitus, dyslipidaemia, and hypertension), reflected in higher rates of hypertension and T2DM compared with the CPRD population. Given these differences, it is uncertain whether the relative treatment effects observed in MAESTRO-NASH can be reliably extrapolated to the broader NHS population. Moreover, as discussed in Section 4.2.5, it is unclear whether outcomes in this enriched population reflect the natural history of patients currently managed with standard care, particularly as the modelled progression to advanced liver disease appears faster than that suggested by available natural history studies.

Paired liver biopsy subgroup

The EAG has concerns regarding the company's modelled population, particularly the restriction to patients with complete and readable biopsy data for estimating treatment effects. The CS states that the focus on the PLB-W52 dataset was necessary because the mITT-LB-W52 dataset includes all biopsy data, regardless of acceptability. The company emphasised issues arising from samples without consensus between histological assessors (coded as 0.5 in the aggregate analysis of MASH resolution) and argued that the PLB-W52 dataset avoids complications introduced by the scoring

system used in the aggregate analysis, which does not allow the derivation of transition probabilities in patients without complete individual-level data.

At the clarification stage, the EAG requested further details on the reasons for exclusion from the mITT-LB-W52 dataset. The company's response indicates that disagreements between assessors were not the primary reason for exclusion from the PLB-W52 dataset. Instead, most exclusions were due to missing or unusable samples. Based on the clarification response, it remains unclear whether any samples were excluded solely due to a lack of consensus between assessors. Contrary to the explanation provided in the CS, the company further stated that the PLB-W52 population is considered a fairer and more representative sample than the mITT-LB-W52 population, as samples without liver biopsy data were coded as 0 (non-responders) in the primary analysis. Consequently, the primary analysis of the mITT-LB-W52 population is less favourable to resmetirom than the company's analysis of the PLB-W52 dataset (Section 3.3.2).

While the EAG recognises that there may be a pragmatic rationale for using the PLB-W52 dataset, it does not concur with the company's reasoning. The EAG considers the primary planned analysis of the mITT-LB-W52 population to be the most representative of the effectiveness of resmetirom and is concerned that the PLB-W52 population is likely subject to attrition bias. The company's analytical approach implicitly assumes that the missing data are missing completely at random. However, this assumption is highly implausible, as sample availability is explicitly related to trial discontinuations, which are often due to adverse events or lack of treatment response (Section 3.2.1). Consequently, the PLB-W52 population is unlikely to be representative of the full trial cohort, and transition probabilities derived from this subset are likely to be biased. Further there are also some differences between in the characteristics of patients in the PLB-W52 compared with the mITT-LB-W52. For example, the proportion of patients in F3 health state is higher in the PLB-W52 cohort than in the mITT-LB-W52 population (66.4% vs 60.4%).

At the clarification stage, the EAG also requested that the company conduct an additional analysis applying the relative treatment effects for MASH resolution from the mITT-LB-W52 population to the baseline risks observed in the PLB-W52 dataset. The company partially complied but extended the analysis by applying relative treatment effects for both MASH resolution and fibrosis stage to the PLB-W52 baseline risks. Although the EAG acknowledges the company's efforts to align modelled treatment effects with those observed in the mITT-LB-W52 population, it does not consider this extended analysis useful.

The EAG's request to focus solely on the relative treatment effect for MASH resolution (rather than fibrosis stage) was based on the fact that estimating a relative treatment effect for fibrosis

improvement is not feasible without relying on strong assumptions. Specifically, the company's scenario analysis assumes that:

1. The probability of NASH resolution without fibrosis worsening in CS Table 13 directly corresponds to the probability of NASH resolution used in the model for the PLB-W52 placebo arm.
2. The probability of fibrosis improvement is identical for patients with and without MASH resolution, due to the absence of subgroup-specific data.
3. Among patients without fibrosis improvement, the proportions with fibrosis no change or fibrosis worsening are distributed proportionally based on the PLB-W52 placebo arm.

None of these assumptions is likely to hold. In particular, the second assumption is highly likely to lead to substantial overestimation of the relative treatment effect because fibrosis improvement is mechanistically linked to MASH resolution. Assuming the probability of fibrosis improvement is the same in patients with and without MASH resolution conflates the effect of treatment on MASH resolution with any independent effect on fibrosis, effectively double-counting the impact of treatment on MASH resolution.

In summary, the EAG does not consider the company's use of the PLB-W52 population to derive modelled transition probabilities fully justified, nor does it consider the scenario analysis presented at clarification to adequately address the issue. While it may not be possible to fully resolve this problem, the EAG considers the most reasonable approach to be using the mITT-LB-W52 population to inform the probability of MASH resolution, while retaining the transition probabilities for fibrosis changes derived from the PLB-W52 population. These fibrosis probabilities are much less vulnerable to selection bias because they are conditional probabilities and cannot be generated from the mITT-LB-W52 population without resorting to strong assumptions that would likely introduce additional bias.

Model implementation

The company's approach to generating the modelled population is based on resampling the IPD from the MAESTRO-NASH trial with replacement. In this approach, the model operates on the same set of 966 trial participants, with each individual trial participant potentially being sampled multiple times to make up the 10,000 simulated patients.

This approach has several limitations. First, sampling the same set of patients does not fully capture the heterogeneity of a real-world population, as the combinations of patient characteristics are limited to those observed in the trial. Second, sampling with replacement introduces the possibility of over- or

under-sampling individual patients; some may not be sampled at all, while others may be sampled multiple times. Analysis implemented by the EAG suggests that this can materially affect results, as when with model is run with a different random selection of patients (by selecting an alternative seed number) the ICER varies by approximately up to £1,600 per QALY. Third, this approach limits the ability to explore alternative population characteristics. For example, the MAESTRO-NASH population includes a higher proportion of patients with T2DM than is observed in the CPRD cohort, but the resampling method does not allow the proportion of T2DM to be changed.

A more appropriate approach would have been to draw individual population characteristics from parameter distributions that reflect the target population, while preserving observed correlations between baseline characteristics. Alternatively, a fully synthetic population could have been constructed based on individual characteristics of the MAESTRO-NASH trial population, see Section 5.2.1.3 for further discussion of this point.

4.2.4 Interventions and comparators

In line with the MAESTRO-NASH trial, and as per the anticipated (UK) marketing authorisation, the modelled intervention is resmetirom in combination with diet and exercise. Dosing for the intervention was modelled in line with the relevant SmPC. This indicates a weight-based posology where patients <100 kg are recommended a dose of 80 mg once daily and patients ≥ 100 kg are recommended a dose of 100 mg once daily. Patients receiving concomitant CYP2C8 are modelled to receive a lower dose of 60 mg per day in patients <100 kg and 80mg per day in patients ≥ 100 kg.

Due to a flat pricing model, the daily dose does not alter drug acquisition costs. Dose, however, does impact on modelled treatment effects. Treatment effects (including transition probabilities and impacts on cardiometabolic predictors, e.g. BMI, LDL-C) for patients receiving 100mg of resmetirom were sourced from the 100mg arm of the MAESTRO-NASH trial, while treatment effects in patients receiving either 60 mg or 80 mg of resmetirom were modelled using data from the 80 mg arm.

The SmPC for resmetirom does not include any specific stopping rule, though it notes that resmetirom should not be used in patients with moderate to severe hepatic impairment. Nonetheless, two stopping rules are applied in the economic model. Firstly, patients who improve their fibrosis stage to F0 or F1 (regardless of MASH resolution) are assumed to stop treatment. Patients stopping treatment in this way may, however, recommence treatment on progression to F2 or F3 fibrosis. Secondly, patients entering any of the ALD health states (F4 CC, F4 DCC, HCC or LT) are assumed to stop treatment. Patients may also stop treatment at any time base on discontinuation rates observed in the MAETRO-NASH trial.

The NICE scope identifies established clinical management without resmetirom and semaglutide (which is subject to ongoing NICE evaluation) as potential comparators. Established clinical management is outlined to include: i) lifestyle modification interventions (such as advice on healthy diet, weight loss when required, and regular exercise) and ii) (unlicensed) pioglitazone and vitamin E. The company modelled only established clinical management, including both lifestyle modification interventions and concomitant use of pioglitazone and vitamin E, but did not present analyses on semaglutide as a comparator. The company justified this omission on the grounds that semaglutide is not currently licensed in the UK or recommended by NICE and therefore does not represent established clinical practice in the NHS.

4.2.4.1 Points for critique

Modelled comparators

As noted above, the company submission did not include semaglutide or standalone pioglitazone, vitamin E, or the combination of pioglitazone and vitamin E as comparators. The company argued that pioglitazone and vitamin E are rarely used in clinical practice and do not constitute distinct treatment options but instead form part of standard care. Clinical advice to the EAG supports this view, indicating that neither pioglitazone nor vitamin E is routinely used for MASH in the UK. This is also consistent with the MAESTRO-NASH trial, in which only a very small proportion of participants received these treatments. The EAG is therefore broadly satisfied with their exclusion.

However, the EAG has concerns regarding the exclusion of semaglutide. Although semaglutide is not currently approved specifically for MASH, it is recommended in TA875 for weight management in adults who have overweight or obesity, and in NG28 for some patients with T2DM ⁴¹. As a result, there is likely to be some overlap between the modelled population and patients who are already receiving semaglutide. This is relevant because evidence supports the effectiveness of semaglutide in managing MASH, and clinical advisers indicated that they would be reluctant to prescribe resmetirom alongside semaglutide or other GLP-1 receptor agonists in patients who are successfully losing weight with these agents. In addition, a parallel NICE appraisal of semaglutide for MASH is underway, meaning that semaglutide may become a relevant comparator at the time of decision-making.

Dosing and generalisability of trial data

As highlighted in Section 2.3.2, the dosing of resmetirom in the MAESTRO-NASH trial does not align with the SmPC. In the trial, participants were randomised to receive 80 mg or 100 mg resmetirom once daily, or placebo, whereas the SmPC specifies weight-based dosing: patients weighing less than 100 kg are expected to receive 80 mg daily, and those weighing 100 kg or more are expected to receive 100 mg. Consequently, the clinical efficacy observed in MAESTRO-NASH may not fully reflect how resmetirom will be used in practice. It is unclear whether this mismatch introduces systematic bias, as some participants received a lower dose than they would in clinical

practice, while others received a higher dose. In the mITT-LBW52 population, █% of participants weighed less than 100 kg, meaning that █ patients received a higher dose than they would in practice, although it is uncertain whether this had any material impact on clinical outcomes.

The EAG does not consider the company's approach, which involves deriving transition probabilities for patients weighing 100 kg or more from the 100 mg arm and for those weighing less than 100 kg from the 80 mg arm, to be particularly informative, because it does not resolve the fundamental mismatch between trial dosing and the SmPC. An alternative would be to use subgroup data, restricting the analysis to participants weighing less than 100 kg in the 80 mg arm and those weighing 100 kg or more in the 100 mg arm. However, because weight was not a stratification factor, this would break randomisation and would substantially reduce the sample size available for estimating transitions.

The EAG therefore considers it most appropriate to pool data from the 80 mg and 100 mg trial arms to inform transition probabilities for all patients. Although imperfect, this approach preserves randomisation, acknowledges that trial data do not fully reflect weight-based dosing in the SmPC, and provides a pragmatic solution that avoids the unnecessary complexity of modelling weight-specific transition probabilities.

Stopping rules and discontinuation

The EAG has substantive concerns regarding the stopping rules applied in the economic model, which require patients to discontinue treatment either on regression to a lower fibrosis stage (F0 or F1) or upon progression to ALD, including F4 CC. These concerns relate both to the biological rationale for these stopping rules and to their feasibility in clinical practice.

With respect to regression, the EAG accepts that continued treatment with resmetirom may offer limited benefit for patients whose fibrosis has meaningfully improved. However, it is less clear that treatment should stop when fibrosis improves in the absence of MASH resolution, as this suggests that the underlying driver of fibrosis has not been addressed. Similarly, the EAG is uncertain whether patients would discontinue treatment upon progression to F4 CC. While this could indicate treatment failure, clinical advice to the EAG did not provide a clear consensus. Advisers noted that progression to F4 CC might instead reflect insufficient treatment rather than a reason to stop therapy.

The EAG also notes that the SmPC provides no explicit guidance on when treatment should be discontinued, other than stating that resmetirom should not be used in patients with moderate to severe hepatic impairment. This excludes patients with DCC but not those with CC. Likewise, the MAESTRO-NASH trial did not impose stopping rules based on regression or progression. The company justifies its approach by stating that the marketing authorisation limits treatment initiation to

patients with F2 or F3 fibrosis, implying that patients should discontinue treatment if they move outside this population. The EAG considers this a misinterpretation: the SmPC defines who should initiate treatment, not when treatment should be stopped. This interpretation aligns with US economic evaluations of resmetirom, which generally do not assume discontinuation upon regression of disease. Although these models typically assume stopping at progression to F4 CC, some include scenario analyses in which patients remain on treatment, reflecting the underlying clinical uncertainty.

From a practical standpoint, the EAG is unclear how regression or progression could be reliably assessed in routine clinical practice. In the MAESTRO-NASH trial, MASH resolution and fibrosis stage were determined by liver biopsy. Clinical advice to the EAG indicated that biopsy would not be suitable for routine monitoring because it is invasive, requires specialised staff, and carries safety risks including bleeding, infection, pain, perforation, and, in rare cases, death (Section 2.3.1).

NITs, such as FibroScan (transient elastography), magnetic resonance elastography (MRE), and serum biomarkers (FIB-4, ELF score), could provide a safer alternative. However, NITs have limitations: they are less accurate at distinguishing intermediate fibrosis stages (for example, F1 versus F2), cannot provide detailed information on MASH resolution, and results may vary depending on patient factors such as BMI or inflammation. Consequently, the suitability of NITs for guiding treatment decisions remains uncertain. The company has not specified how fibrosis would be assessed in practice, including which tests would be used or the criteria that would indicate treatment discontinuation.

The EAG proposed a plausible scenario, based on clinical advice, in which patients regressing to F0/F1 would undergo repeated NITs over six months, remaining on treatment throughout. The company declined to implement this scenario during clarification. The EAG acknowledges that this analysis does not fully resolve the underlying issues, as it does not define specific criteria for when treatment should be stopped.

4.2.5 Treatment effectiveness and extrapolation

Hepatic-related treatment effects in the model are represented through a set of transition probabilities that govern movement between health states. These probabilities are divided into two groups: those applied to patients without ALD, which include individuals with and without MASH up to and including fibrosis stage F3, and those applied to patients with ALD, which encompass the F4 CC, F4 DDC, HCC, and liver transplant health states.

4.2.5.1 Hepatic-related treatment effects: patients without advanced liver disease

For patients without ALD, transition probabilities are primarily informed by evidence from the MAESTRO-NASH trial, supplemented where necessary with external data. These probabilities are

treatment-specific, with separate values applied for patients receiving resmetirom and those receiving SoC. Resmetirom-specific transition probabilities are applied only while patients remain on treatment. Patients discontinuing resmetirom (for any reason) revert to SoC transition probabilities.

To model transitions between non-ALD health states, the company derived transition probabilities from the MAESTRO-NASH trial, which estimated the probability of MASH resolution and, conditional on MASH resolution status, the probability that a patient improves, remains stable, or progresses in fibrosis stage. Transition probabilities used for the base-case population are summarised in Table 12, with corresponding values for the T2DM subpopulation presented in Table 29 of the company submission.

Table 12 (Year 1) joint transition probabilities (mean (95% CI)); (MAESTRO-NASH, paired-biopsy population; base case)

	MASH resolution	MASH Resolution: YES		MASH Resolution: NO	
		Fibrosis improvement	Fibrosis worsening	Fibrosis improvement	Fibrosis worsening
Placebo					
Resmetirom 100 mg					
Resmetirom 80 mg					

Abbreviations: MASH, metabolic dysfunction-associated steatohepatitis. Source: CS Table 28 pg. 111.

A key feature of the model is that the same transition probabilities are applied throughout the model time horizon, conditional on patients remaining on their assigned treatment. Furthermore, MASH resolution is a central driver of the model's dynamics: patients achieving MASH resolution are, on average, expected to improve in fibrosis stage, whereas those without resolution tend to progress to more severe fibrosis stages over time. Consequently, the proportion of patients achieving MASH resolution is the principal determinant of both modelled health benefits and costs.

An additional important feature of the transition probabilities presented in Table 12 is that they do not directly describe transitions between health states. Rather, they capture only the likelihood of MASH resolution and/or the probability of regression or progression in fibrosis stage. The final set of health state transition probabilities applied in the model allows for changes of more than one fibrosis stage within a single model cycle.

To derive these final transition probabilities, the company combined the trial-informed probabilities presented in Table 12 with a second set of probabilities (Table 13) that specify the likelihood of moving one, two, or three fibrosis stages within a given cycle. This second set of transition probabilities was not informed by MAESTRO-NASH data, as the company stated that such detailed

information was not available from the trial. Instead, these probabilities were informed by evidence from a systematic review conducted by Singh et al. (2015)³⁴.

Table 13 Probability distribution of fibrosis stages (F0–F4) allocated to ‘worsening’ and ‘improvement’ outcomes in MAESTRO-NASH, Singh et al. 2015

Health states	Mean	Low value - High value	Distribution
F0 to F1 (worsening)	0.64	0.51 - 0.76	Dirichlet
F0 to F2 (worsening)	0.18	0.15 - 0.22	Dirichlet
F0 to F3 (worsening)	0.09	0.07 - 0.11	Dirichlet
F0 to F4 (worsening)	0.09	0.07 - 0.11	Dirichlet
F1 to F2 (worsening)	0.6	0.48 - 0.72	Dirichlet
F1 to F3 (worsening)	0.33	0.27 - 0.40	Dirichlet
F1 to F4 (worsening)	0.07	0.05 - 0.08	Dirichlet
F2 to F0 (improvement)	0.23	0.08 - 0.38	Beta
F2 to F1 (improvement)	0.77	0.62 - 0.92	Beta
F2 to F3 (worsening)	0.5	0.40 - 0.60	Beta
F2 to F4 (worsening)	0.5	0.40 - 0.60	Beta
F3 to F0 (improvement)	0	0.00 - 0.00	Dirichlet
F3 to F1 (improvement)	0.5	0.40 - 0.60	Dirichlet
F3 to F2 (improvement)	0.5	0.40 - 0.60	Dirichlet
F4 to F0 (improvement)	0	0.00 - 0.00	Dirichlet
F4 to F1 (improvement)	0	0.00 - 0.00	Dirichlet
F4 to F2 (improvement)	0	0.00 - 0.00	Dirichlet
F4 to F3 (improvement)	0	0.00 - 0.00	Dirichlet

Abbreviations: F0-F4, fibrosis stages 0-4. F4 is equal to compensated cirrhosis (CC) in the economic model. Source: CS Table 30, pg.112.

Points for critique

Repeated application of transition probabilities and short-term trial follow-up

The EAG has significant concerns regarding the repeated use of the same set of transition probabilities throughout the entire model time horizon. This assumption suggests that patients continuing treatment with resmetirom and SoC will lead to an increasing proportion of the modelled population achieving MASH resolution; MASH resolution is fundamental to changes in fibrosis within the model and this assumption implies that the likelihood of achieving MASH resolution is entirely independent of the duration of treatment, meaning your chance of resolution remains the same whether you have never been treated before or have been on the same treatment for 30 years.

The EAG considers this entirely implausible for both the resmetirom and SoC arms. There is no evidence or biological rationale to suggest ongoing treatment will produce continued benefits as modelled. Clinical advice received by the EAG confirmed that while it is plausible some additional patients might achieve MASH resolution in year 2 and beyond, they expect diminishing returns from ongoing treatment, ultimately reaching a plateau.

During clarification, the EAG asked the company to comment on whether the 12-month follow-up period in the MAESTRO-NASH trial is sufficient to assess MASH resolution. The company responded that the follow-up period was guided by pharmacodynamic data showing reductions in liver fat after 16 weeks of resmetirom treatment, with these effects maintained through week 52. These findings suggest that resmetirom produces early and sustained effects on hepatic fat content, which could plausibly result in MASH resolution within a 52-week timeframe. However, the mechanistic link between early reductions in liver fat and histological resolution of MASH remains uncertain,^{42, 43} and it is unclear whether longer treatment might lead to additional cases of MASH resolution. Since inflammation and hepatocellular ballooning may resolve more slowly than steatosis, the 12-month follow-up offers a reasonable, but not definitive, window to observe treatment-related resolution.

Unfortunately, the limited follow-up duration in the MAESTRO-NASH trial means it is not possible to estimate the proportion of patients who might achieve MASH resolution beyond the first year. Evidence from long-term follow-up of patients on standard care indicates that weight loss (the primary driver of histological improvement under usual management) tends to plateau after the first year and often partially rebounds towards baseline levels.⁴⁴ This would rule out any repeated application of SoC transitions but says nothing about how longer-term treatment with resmetirom may impact patient outcomes.

These limitations in the evidence are not only important in terms of evaluating the plausibility of the modelled treatment benefits but also central to the choice of model structure (see Section 4.2.2). If further treatment with resmetirom provides limited or no additional benefit, this potentially implies the need for a response-based stopping rule. At the clarification stage, the EAG requested that the company provide an additional scenario in which treatment benefits (in terms of MASH resolution) were set to zero after the first year. The company, however, declined to provide this analysis, which is disappointing and substantially constrained the EAG's ability to explore plausible scenarios regarding continued treatment benefit. Due to the complexity of the model, the EAG was unable to implement this analysis independently.

Misrepresentation of Singh et al.

Singh et al. (2015)³⁴ conducted a systematic review and a meta-analysis of paired-biopsy studies. As part of their analysis, they summarised transitions between fibrosis stages observed in the included studies. These studies followed patients for variable durations, though inclusion required a minimum follow-up of one year. This is not consistent with the way the data were used in the company's model where they informed the number of fibrosis stages a patient can transition through in those who had already been categorised as improving or worsening fibrosis .

At clarification, the EAG requested justification for this approach. The company emphasised that Singh et al. (2015)³⁴ was a well-conducted, PRISMA-based systematic review (a point the EAG does not dispute) and argued that progression by more than one fibrosis stage within a year was biologically plausible and supported by clinical expert opinion. However, the EAG considers that this response does not adequately address the discrepancy between the intended use of the data in the model and the nature of the data reported by Singh et al.

Furthermore, as noted in the EAG's clarification questions, Singh et al. (2015)³⁴ reported a mean time to progress by one fibrosis stage of 7.1 years. Even acknowledging that this population had earlier-stage disease, it appears implausible that patients would typically progress through more than one fibrosis stage in a single annual cycle (see discussion below regards the company's claim that progression accelerates as patients' fibrosis stage advances). The EAG's clinical advisors similarly indicated that such rapid progression would be very uncommon and indeed emphasised that most patients would not progress at all.

While the company's argument that multi-stage transitions are *theoretically possible* is noted, the Singh et al. (2015)³⁴ data do not provide empirical support for this assumption and are not informative for parameterising such transitions. The EAG therefore considers it more appropriate to adopt a conservative approach in which patients are limited to progressing (or regressing) by a maximum of one fibrosis stage per model cycle.

Natural history of MASH and face validity of model progression rates

In the base-case analysis, natural history is modelled by repeating the 1-year transitions observed in the MAESTRO-NASH trial. In their submission, the company explicitly rejects using external data, citing Le et al. (2023),³³ which pooled data from placebo arms of RCTs and real-world observational studies to estimate fibrosis progression. The company's rationale for rejecting Le et al. is that the results are clinically implausible, as they suggest that progression slows with advancing fibrosis (see Table 31 of the CS).

The company appears to rely on two arguments to support this position. First, they cite Luthra et al. (2025),⁴⁵ which concludes that advanced fibrosis is associated with liver-related complications and mortality. This, however, does not imply that fibrosis progression accelerates; it simply indicates that patients with advanced fibrosis experience worse outcomes. Second, they repeatedly refer to the concept of "fast progressors." The evidence supporting a clinical phenotype of fast progressors is, however, still emerging, and clinical advice received by the EAG confirms that there is no universal consensus on a definitive phenotype. Moreover, even if such a phenotype exists, the company does not demonstrate that all (or even the majority) of patients eligible for resmetirom fall into this category.

The EAG also notes that the findings of Le et al. (2023)³³ are consistent with earlier work by Singh et al. (2014), which similarly shows that the annual fibrosis progression rate decreases with increasing baseline fibrosis stage. On this basis, the EAG rejects the company's assertion that fibrosis progression accelerates as the disease advances.

In the context of the model, it is not possible to directly estimate the mean time to progress by one stage. However, the Markov trace shows that patients receiving SoC spend a substantial proportion of time in the ALD health states, particularly F4 CC. This appears inconsistent with the findings of Le et al. (2023)³³ and Singh et al. (2014), which indicate that progression to ALD typically occurs only after a prolonged period. Furthermore, given the competing risk of death (whether from background mortality or extra-hepatic causes), many patients would not be expected to reach the ALD states at all. This pattern is not reflected in the model's predictions and represents a significant concern regarding the face validity of the model's projections. The EAG also highlights that the approach taken by the company will explicitly prevent any new treatments from making a consistent comparison to resmetirom, as they are based on confidential trial data. This is at odds with the aims and conclusions of the NICE HTA Innovation Lab report,³⁵ which emphasised the importance of consistency in decision-making.

4.2.5.2 Hepatic related treatment effects: patients with advance liver disease

Table 14 summarises the transition probabilities applied in the model, which dictate the annual probabilities of DCC, HCC and liver transplantation. The model also makes the simplifying assumption that MASH status in F3 does not influence transition to either DCC or HCC.

The sources used to inform these transition probabilities include Vilar-Gomez et al. (2018)⁴⁶, a prospective multinational study of 459 patients with advanced fibrosis (F3 and F4) conducted in Spain, Australia, Hong Kong, and Cuba; Ascha et al. (2010)⁴⁷, a single-centre US study of 195 MASH patients with hepatic DCC. The company submission does not provide details on how these specific sources were identified or selected, nor does it indicate whether other relevant evidence was considered.

Table 14 Annual transition probabilities to advanced liver complications

Health state transition	Mean annual probability	Low value; High value	Source
F3 & MASH to DCC	0.004	0.003 – 0.005	Vilar-Gomez et al. 2018 ⁴⁶
F3 & MASH resolved to DCC	0.004	0.003 – 0.005	Assumed equivalent to patients with MASH
F3 & MASH to HCC	0.003	0.002 – 0.004	Vilar-Gomez et al. 2018 ⁴⁶
F3 & MASH resolved to HCC	0.003	0.002 – 0.004	Assumed equivalent to patients with MASH
F4 & MASH to DCC	0.019	0.015 – 0.023	Vilar-Gomez et al. 2018 ⁴⁶

Health state transition	Mean annual probability	Low value; High value	Source
F4 & MASH resolved to DCC	0.019	0.015 – 0.023	Assumed equivalent to patients with MASH
F4 & MASH to HCC	0.014	0.011 – 0.017	Vilar-Gomez et al.2018 ⁴⁶
F4 & MASH resolved to HCC	0.014	0.011 – 0.017	Assumed equivalent to patients with MASH
DCC to HCC	0.026	0.021 – 0.031	Ascha et al. 2010 ⁴⁷
DCC to liver transplant 1st year	0.43	0.344 – 0.561	Vilar-Gomez et al.2018 ⁴⁶
DCC to liver transplant 2nd year	0.008	0.344 – 0.561	Vilar-Gomez et al. 2018 ⁴⁶ – Calibrated
DCC to liver transplant 3rd year	0.008	0.344 – 0.561	Vilar-Gomez et al. 2018 ⁴⁶ – Calibrated
DCC to liver transplant 4th year	0.008	0.344 – 0.561	Vilar-Gomez et al. 2018 ⁴⁶ – Calibrated
DCC to liver transplant +5th year	0.008	0.344 – 0.561	Vilar-Gomez et al. 2018 ⁴⁶ – Calibrated
HCC to liver transplant 1st year	0.557	0.446 – 0.688	Vilar-Gomez et al. 2018 ⁴⁶
HCC to liver transplant 2nd year	0.017	0.446 – 0.688	Vilar-Gomez et al. 2018 ⁴⁶ – Calibrated
HCC to liver transplant 3rd year	0.017	0.446 – 0.688	Vilar-Gomez et al. 2018 ⁴⁶ – Calibrated
HCC to liver transplant 4th year	0.017	0.446 – 0.688	Vilar-Gomez et al. 2018 ⁴⁶ – Calibrated
HCC to liver transplant +5th year	0.017	0.446 – 0.688	Vilar-Gomez et al. 2018 ⁴⁶ – Calibrated

Abbreviations: DCC, decompensated cirrhosis; F3-F4, fibrosis stages 3-4; HCC, hepatocellular carcinoma; MASH, metabolic dysfunction-associated steatohepatitis. F4 is compensated cirrhosis (CC) in the model. Source: CS Table 32, g. 120.

Points for critique

Data sources and calculations

As noted above, the EAG is unclear about the process used to identify or select the studies informing these parameters. While both sources appear broadly reasonable, the EAG cannot exclude the possibility that better alternatives exist. The absence of a clear rationale for study selection raises concerns about potential cherry-picking. Furthermore, neither study includes UK patients, which may limit the generalisability of the findings to a UK setting, and event rates were small for some outcomes. For example, among patients with F3 fibrosis, only two HCC events were reported.

In addition to these concerns, the EAG cannot determine how the input values were derived from the data reported in Vilar-Gomez et al. (2018)⁴⁶. Specifically, for the transition probabilities governing progression to either DCC or HCC, the company's reported values do not correspond to any of those presented in Table 3 of Vilar-Gomez et al. (2018)⁴⁶. For instance, Vilar-Gomez et al. (2018)⁴⁶ report an incidence rate of 0.006 for hepatic decompensation in patients with bridging fibrosis (F3), whereas

the model applies a value of 0.004. The EAG is unable to ascertain how the company's values were generated from the source data.

Similarly, the EAG cannot identify how the transition probabilities for liver transplantation (LT) were estimated. In response to clarification, the company stated that these values were based on cumulative incidence rates of LT using an approach outlined in the US ICER report. However, the values applied in the company's model do not match those reported in US ICER report. Specifically, the US ICER report applies different transition values for years two to four, whereas the company's model applies the year-five transition rate from year two onwards. More importantly, the EAG cannot determine how these values were derived from Vilar-Gomez et al. (2018)⁴⁶, as they appear inconsistent with the data presented in that study.

First, Vilar-Gomez et al. (2018)⁴⁶ do not report cumulative incidence data for LT in either DCC or HCC patients. Second, the values cited in the US ICER report²³ appear implausible in light of the data presented. Vilar-Gomez et al. (2018)⁴⁶ report that 26 of 88 (32%) patients with DCC underwent liver transplantation, making it implausible that 43% had a transplant within the first year. Likewise, only 6 of 41 (15%) HCC patients underwent transplantation, making it impossible that 55.7% received a transplant within one year.

Given these inconsistencies, the EAG does not consider the values used by the company to be justifiable and requests that the company provide further clarification on how their input values were derived.

4.2.5.3 Extra-hepatic related treatment effects

In addition to hepatic-related treatment effects, the model also considers extrahepatic outcomes. Specifically, the model considers cardiovascular events: MI and stroke, as well as the onset of T2D. These events impact quality of life through utility decrements, costs and mortality.

Incidence of CVD events is determined using the QRISK 3 risk equation, which predicts the onset of an individual's risk of developing cardiovascular disease over a specified period based on factors such as age, sex, blood pressure, cholesterol levels, smoking status, and diabetes. Recurrent CVD events are modelled using the Framingham risk equation and, in patients with T2D the UKPDS-OM2 risk equation is used instead of QRISK 3. Onset of T2D is similarly modelled using the equation is used instead. Similarly, the incidence of T2D is modelled using the QDiabetes-2018 risk equation.

The individual risk of an event was calculated for each patient in each model cycle using the relevant risk equation, based on that patient's individual characteristics. Baseline characteristics were derived from participants in the MAESTRO-NASH trial and were assumed to remain constant over the model time horizon, except for age, BMI, LDL-C, HDL-C, and triglycerides, which were modelled to vary

over time. For BMI, LDL-C, HDL-C, and triglycerides, a treatment effect was also applied to capture the impact of resmetirom on these parameters. Table 15, informed by the company's clarification response, summarises how each characteristic was modelled over time.

Table 15. Annual updating of metabolic risk factors in the microsimulation

Risk factor	Function (in code)	Mechanism / formula	Data source or calibration	Units used	Persistence assumption	Notes / relevant parameters
Body Mass Index (BMI)	n_BMI_update(male, age, dosage, bmi)	Applies absolute population Δ BMI from NHS Digital trends (l_BMI_change) + arm-specific % effect from MAESTRO-NASH (l_BMI_effect); capped at n_BMI_max .	NHS Digital (UK population trends); MAESTRO-NASH trial	kg/m ²	Treatment % effect applied annually while on therapy; background age–sex trend continues each year.	Used to update Weight, obesity flags, and cancer risks.
Weight	Derived ($BMI \times Height^2$)	Deterministic update after BMI	Derived from BMI	Kg	Same as BMI	Height fixed at baseline.
LDL-C	n_LDL_C_update(ldl, age, dosage)	Year 1: trial-based % change ($n\_LDL\_C\_effect$) from MAESTRO-NASH. Year 2+: adds drift +0.1 mg/dL/year ($n\_LDL\_C\_incr$).	MAESTRO-NASH; Domanski et al. 2020 (34)	mg/dL (converted to mmol/L for UKPDS: $\times 0.0259$)	Year 1 % effect persistent for 1 cycle; after Year 1, natural upward drift.	$n\_cycles\_risk\_factor\_effect=1$; drift from Year 2 onward.
HDL-C	n_HDL_C_update(hdl, age, dosage)	Year 1: trial-based % change ($n\_HDL\_C\_effect$) from MAESTRO-NASH. Year 2+: -0.1 mg/dL/year ($n\_HDL\_C\_decr$).	MAESTRO-NASH; Domanski et al. 2020 (34)	mg/dL (converted to mmol/L $\times 0.0259$)	Year 1 % effect persistent for 1 cycle; thereafter gradual decline.	Matches Year-1 TE persistence; then background drift.
Triglycerides	n_trigl_update(trigl, age, dosage)	Year 1: trial-based % change (n_trigl_effect) from MAESTRO-NASH. Year 2+: reverts to baseline.	MAESTRO-NASH	mg/dL	Trial % effect for Year 1 only; returns to baseline from Year 2 onward.	Conservative assumption in the absence of other data; no persistence beyond first year. If sustained benefit occurred, this assumption would underestimate long-term cardiovascular benefit

Risk factor	Function (in code)	Mechanism / formula	Data source or calibration	Units used	Persistence assumption	Notes / relevant parameters
Total cholesterol (TC)	Recalculated: LDL + HDL + (TG / 5)	Friedewald formula recomputed annually.	Derived	mg/dL	Updated each year with current LDL, HDL, TG	Used in TC/HDL ratio and QRISK3 equation.
TC/HDL ratio	Recalculated: TC / HDL	Derived from updated TC and HDL	Derived	Unitless	Updated annually	Used in QRISK3 and Framingham risk equations.

Abbreviations: BMI, body mass index; HDL, high-density lipoprotein; KG, kilogram; LDL, low-density lipoprotein; mg, milligram; TC, total cholesterol. Source: Clarification response Table 17, pg. 60.

Linking the hepatic and extra hepatic outcomes, fibrosis stage was also modelled to impact the risk of both CVD events, with increasing risks modelled in patients with more severe fibrosis, CC and DCC. This was modelled by applying a relative risk to the baseline risks predicted by the QRISK 3 (or in T2D patients UKPDS-OM2) risk equations. The relative risks applied are reported in Table 35 of the CS and are based on values used in the US ICER assessment of resmetirom.

Points for critique

Durability of modelled treatment effects: lipids

The EAG is broadly satisfied with the choice of risk equations but notes that these were developed to estimate 10-year rather than annual risks. However, the EAG disagrees with how treatment effects on lipid parameters have been implemented. In the company's model, the 12-month treatment effects on LDL-C and HDL-C observed in MAESTRO-NASH are assumed to persist over the entire model time horizon. The EAG considers this assumption unrealistic.

First, many patients are unlikely to remain on long-term resmetirom therapy, meaning any treatment-related changes in LDL-C or HDL-C are unlikely to be sustained. While it is possible that lipid changes might relate to persistent improvements in MASH or fibrosis severity, these relationships are complex and not well established.

Second, the reported difference between treatment arms for HDL-C in MAESTRO-NASH was not statistically significant, so there is no robust evidence that resmetirom meaningfully affects HDL-C - let alone that such an effect would persist indefinitely.

Third, the company's approach lacks internal consistency: it assumes a one-cycle treatment effect for triglycerides, but a permanent effect for LDL-C and HDL-C. Given the limited evidence on the long-term trajectory of lipid parameters, the EAG considers it more appropriate to assume that lipid values revert to baseline from the second annual cycle onward, with only natural history effects applied thereafter.

Durability of modelled treatment effects: weight

The EAG does not agree with the company's approach to modelling a weight-related treatment effect. Unlike the treatment effect applied to lipids, where a one-off, permanent change is assumed for LDL-C and HDL, the model applies the treatment effect on weight in every cycle. This implementation has two key implications. First, it results in all patients experiencing a continuous decline in weight (and BMI) throughout the entire time horizon in both the resmetirom and SoC arms. Second, the decline is modelled to be more rapid in the resmetirom arm, reflecting the numerically greater weight loss observed in the MAESTRO-NASH trial.

The EAG considers both effects to lack clinical validity and to be unjustifiable given the available evidence. With respect to the continuous weight loss assumption, it is implausible to repeatedly apply the treatment effect observed at one year across all subsequent cycles. At clarification, the company attempted to justify this assumption by arguing that patients would receive clinical weight management as part of standard care and would therefore continue to lose weight. However, long-term follow-up studies in patients with MASH or MASLD indicate that clinically supervised weight management is rarely successful, and most patients fail to sustain meaningful reductions in weight.⁴⁴ The modelled continuous weight loss is therefore inconsistent with established natural history in MASH/MASLD patients.

Moreover, the assumption that patients receiving resmetirom would experience a faster decline in weight is equally unrealistic. As discussed in relation to the permanent treatment effects applied to lipids, there is no long-term evidence to support the notion that treatment with resmetirom results in sustained weight loss, nor is there a mechanistic rationale to suggest that such an effect would continue after discontinuation of treatment. Furthermore, the MAESTRO-NASH trial did not demonstrate a statistically significant difference in weight loss between treatment arms. It is therefore not clear whether any treatment effect should be applied.

Consistent with its position on lipid effects, the EAG therefore prefers to assume that weight returns to baseline from the second annual cycle onward, with only natural history effects applied thereafter.

Impact of fibrosis on risk of CVD

As noted above, the company applied a set of relative risks to increase the likelihood of CVD events among patients with more advanced fibrosis stages. The values used are based on those applied in the US ICER model of resmetirom. However, these effects are not supported by empirical evidence and instead represent assumed values, likely informed by clinical opinion.

While the EAG acknowledges that observational studies have reported an association between increasing fibrosis stage and higher rates of cardiovascular events and cardiovascular mortality,^{48, 49}

these associations are also driven by shared cardiometabolic risk factors such as obesity, diabetes, and hypertension. Moreover, there is no direct evidence from clinical trials (including the MAESTRO-NASH trial) demonstrating that regression of fibrosis leads to a reduction in future CVD events.

Accordingly, the EAG considers fibrosis stage to be a marker of cumulative cardiometabolic risk rather than a proven independent causal determinant of CVD outcomes. The EAG therefore does not consider it appropriate to model fibrosis stage as directly influencing CVD event rates in the absence of robust causal evidence.

4.2.5.4 Mortality

The model incorporates background mortality, liver related specific mortality, and excess mortality from CVD. Background mortality (based on age and sex) is informed by ONS life tables and is applied to all modelled patients regardless of health state.

Excess liver-related mortality is modelled for patients with ALD (CC, DCC, HCC, liver transplant) with rates derived from published literature sources. Table 16 summarises the values applied in the company base case analysis. Liver-related mortality probabilities are applied in addition to background mortality. The total risk of death in a given cycle is therefore the sum of background mortality and liver-related mortality.

The sources used to inform these transition probabilities include Pearson et al. (2016), a cost-effectiveness analysis by the US ICER group evaluating obeticholic acid for MASLD⁵⁰; Thuluvath et al. (2019)⁵¹, a retrospective analysis of 7,935 patients with HCC awaiting liver transplantation in the US; and Lidgren et al. (2007), a cost-effectiveness analysis evaluating treatments for hepatitis C in a Swedish setting⁵². The company's submission does not describe how these specific sources were identified or selected, nor does it indicate whether other potentially relevant evidence was considered.

Table 16 Liver related mortality probabilities

Health state transition	Mean annual probability	Low value; High value	Source
F4 to death	0.021	0.0168 – 0.0252	Pearson et al. 2016 ⁵⁰ Ascha et al. 2010 ⁴⁷
DCC to death	0.130	0.1040 – 0.1560	Pearson et al. 2016 ⁵⁰ - Ascha et al. 2010 ⁴⁷
HCC to death year 1	0.144	0.1152 – 0.1728	Thuluvath et al. 2019 ⁵¹
HCC to death year 2	0.044	0.0352 – 0.0528	Thuluvath et al. 2019 ⁵¹
HCC to death year 3	0.012	0.096 – 0.144	Thuluvath et al. 2019 ⁵¹
HCC to death year 4	0.009	0.072 – 0.108	Thuluvath et al. 2019 ⁵¹
HCC to death year 5+	0.008	0.064 – 0.096	Thuluvath et al. 2019 ⁵¹
LT to death	0.098	0.0784 – 0.118	Lidgren et al. 2007 ⁵²

PLT to death	0.057	0.0456 – 0.0684	Lidgren et al.2007 ⁵²

Abbreviations: DCC, decompensated cirrhosis; F4, fibrosis stage 4; HCC, hepatocellular carcinoma; LT, liver transplantation (first year); PLT, post-liver transplantation (subsequent years). F4 is compensated cirrhosis in the model (CC). Source CS Table 36, pg. 127.

Excess mortality from non-liver comorbidities was modelled using event-specific mortality rates applied upon the occurrence of a CVD event. Mortality risk varied depending on whether the event was a first or subsequent occurrence, with recurrent CVD events associated with higher mortality risk. The applied mortality risks were informed by published literature. Although these values were not reported in the company submission, they were identifiable within the company's executable model. Myocardial infarction (MI)-related mortality was informed by Smolina *et al.* (2012)⁵³, who reported case fatality rates for acute MI based on English registry data. Stroke-related mortality was informed by Lee *et al.* (2011)⁵⁴, who described the incidence of stroke and associated mortality using data from the UK General Practice Research Database. The onset of T2DM also contributed to increased mortality risk over time, which was modelled using the UKPDS risk engine.

Points for critique

Data Sources

The EAG is concerned by the absence of a clear rationale for the selection of model input values and the lack of transparency regarding how the underlying evidence was identified. For example, Pearson et al. report several data points that could plausibly inform parameters related to mortality and transitions between health states; however, these have been disregarded in favour of alternative values without justification. Referencing of data sources is also inadequate. Neither Pearson et al. nor Lidgren et al. represents the primary source for the parameters used in the model, and the reliance on secondary citations of this kind is particularly problematic. Such practice substantially hinders the EAG's ability to verify the provenance and appropriateness of the inputs. In a large and complex model with numerous parameters, such as this one, the EAG is not resourced to retrieve and assess all original sources. Consequently, the EAG cannot provide assurance regarding the suitability of these values beyond confirming that they exhibit basic face validity and have been used in other recent economic evaluations.

4.2.5.5 Adverse events

The economic model did not include AE. The company justified this approach, stating that TRAE reported in the MAESTRO-NASH were unlikely to result in sustained QoL decrements or meaningful healthcare costs.

Points for critique

While the EAG considers the exclusion of AEs) to be inconsistent with standard practice, the omission is acceptable in this case. The incidence of serious AEs in the MAESTRO-NASH trial was

relatively low in both the resmetirom and standard of care arms, with no meaningful differences between treatments. It is therefore unlikely that including AEs would materially affect the ICER. The EAG does, however, note the relatively high rate of trial discontinuations and the increased frequency of some less serious AEs, including diarrhoea and nausea (see Section 3.3.3.1), may indicate tolerability concerns. Nevertheless, discontinuities are incorporated into the model, and their implications are therefore reflected in the company's analysis.

4.2.6 Health related quality of life

The company stated that trial-derived utilities were not appropriate for use in the base-case analysis due to inconsistencies in the derived values, which did not follow a clinically plausible pattern. Consequently, the company chose to use values identified from published sources. A description of the systematic searches for relevant HRQoL data is provided in Appendix F, along with details of the identified studies, including those with UK participants and their limitations.

Briefly, 169 full-text screening studies were reviewed, yielding 27 included studies. Among these, eight studies were identified that included patients from the UK and reported HRQoL outcomes. According to the company, disease staging was frequently based on non-invasive tests (NITs) or physician assessment rather than biopsy (as in the MAESTRO-NASH trial population), and none of the studies met the methodological requirements (of NICE reference case) for informing utilities in the economic model. The main limitations were: (i) multinational cohorts rather than UK-specific samples, (ii) reliance on the EQ-5D-5L rather than the preferred EQ-5D-3L, and (iii) the use of condition-specific (in some cases) rather than preference-based measures. None of the findings from the HRQoL SLR was used to inform the company's economic model base-case or scenario analyses.

The company considered the most relevant reference for the UK context to be NICE guideline NG49 (2016)⁵⁵, which provides health-state utilities for fibrosis stages, CC and DCC, HCC, and PLT (Table 17). However, as noted in the company's clarification response, the NG49 values were not derived from a MASH/MASLD population. According to the guideline, these values were based on previous analyses reported in PH53 and proportionally adjusted HRQoL values for people with obesity, and utility values from a hepatitis B subgroup.

The PH53 report is no longer available and has been superseded by NG246, which does not provide further details on the original analysis, data sources, or the value set used in PH53. Therefore, the source of the utility values adopted in the company's base case is unclear. Contrary to the company's clarification response, it is also uncertain whether these values are based on EQ-5D-3L.

Table 17 Summary of utility values for CEA – Base-case analysis

State	Utility value: mean (standard error)	95% CI	Reference
F0 without MASH (NAFL)	0.870	0.705 – 1.000	NG49 – 611 ⁵⁵
F0 + MASH	0.840	0.680 – 1.000	
F1 without MASH	0.870	0.705 – 1.000	
F1 + MASH	0.840	0.680 – 1.000	
F2 without MASH	0.870	0.705 – 1.000	
F2 + MASH	0.840	0.680 – 1.000	
F3 without MASH	0.750	0.705 – 1.000	
F3 + MASH	0.720	0.680 – 1.000	
F4 (Cirrhosis)	0.600	0.483 – 0.717	
DCC	0.540	0.435 – 0.645	
HCC	0.540	0.435 – 0.645	
PLT First year	0.800	0.646 – 0.954	
PLT subsequent years	0.850	0.688 – 1.000	
Source CS: Table 37 corrected to reflect typo error for F3 without MASH and F3 + MASH; Correct in CEM.			

Abbreviations: CEM, Company executable model; CI, confidence interval; DCC, decompensated cirrhosis; F0-F4, fibrosis stages 0–4; HCC, hepatocellular carcinoma; MASH, metabolic dysfunction-associated steatohepatitis; NAFL, non-alcoholic fatty liver; NG, NICE guideline; PLT, post-liver transplantation.

In the CS, the company stated that the base-case analysis did not incorporate age adjustment, reasoning that the model already included several decrements for age-related events such as CVD and T2DM, and that adding age adjustment could risk double-counting. The company also expressed concerns that age adjustment might systematically undervalue improvements in life expectancy. However, following clarification, the company acknowledged that age adjustment had inadvertently been included in the base-case analysis and confirmed that they were satisfied it was appropriate and consistent with the NICE reference case.

Points for critique

Appropriateness of NG49

The EAG has substantive concerns regarding the company's use of NG49 (NICE, 2016) as the primary source of utility values. Although NG49 was developed to inform the cost-effectiveness analysis of diagnostic strategies for MASLD and advanced fibrosis, the EAG considers the utility estimates to have significant limitations that reduce their suitability for this appraisal. The provenance of the NG49 values is unclear: NG49 reports that the estimates were derived from analyses in PH53, together with proportionally adjusted HRQoL values for people with obesity and supplementary data from a hepatitis B subgroup. However, PH53 is no longer publicly available and has been superseded by NG246, meaning that the underlying data sources, assumptions, and methods cannot be verified.

The EAG also considers the NG49 utility values to lack face validity for some health states. For early fibrosis stages (NAFL to F2), the values are similar to, or higher than, UK general population norms, which is inconsistent with the considerable comorbidity burden typically observed in MASLD populations. In MAESTRO-NASH, for example, around 45% of participants had obesity and at least three metabolic risk factors. The company acknowledged at PfC that HRQoL in MASLD populations is generally lower than in the general population. In addition, NG49 reports marked decrements in HRQoL between F2 and F3 (0.84 to 0.72) and between F3 and compensated F4 cirrhosis (0.72 to 0.60), which the EAG considers clinically implausible.

Clinical advisors to the EAG indicated that HRQoL is generally stable across compensated fibrosis stages and that substantial deterioration is typically observed only when patients progress to decompensated cirrhosis (DCC), when complications such as ascites, variceal bleeding, or hepatic encephalopathy emerge. There is no clear biological or clinical rationale for the large decline in HRQoL between F3 and F4 compensated cirrhosis implied by NG49.

The NG49 values are also inconsistent with other UK evidence. Papatheodoridi et al. (2023), a UK study of 513 patients with MASLD using EQ-5D-5L, reported that MASLD patients have lower HRQoL than matched healthy controls (0.77 vs 0.84; $P < 0.001$), but found minimal, non-significant differences between patients with and without advanced fibrosis (F0 vs F3: 0.777 vs 0.786; $P = .570$). The decline between F3 and F4 in this study was modest (0.79 vs 0.73; $P < 0.032$), which is more consistent with clinical advice received by the EAG expectations. Although excluded from the company's SLR because it included a broader MASLD population and used EQ-5D-5L, the EAG considers this evidence informative given the limited availability of MASH-specific utility data.

Given these limitations, the EAG does not consider NG49 to be an appropriate source of HRQoL values for the F0 to F4 health states.

Appropriateness of trial data

The EAG considers the MAESTRO-NASH trial to be a relevant and important source of HRQoL data. While the EAG acknowledges that the fibrosis-stage utility values derived directly from the trial do not appear logically consistent, it does not consider this sufficient ground to disregard the trial data altogether. The MAESTRO-NASH HRQoL data are broadly representative of the modelled population and reasonably aligned with expected NHS population characteristics, subject to the usual considerations regarding generalisability. Given the scarcity of robust alternative sources identified in the HRQoL review, the EAG considers the trial data to be the most appropriate available source of HRQoL evidence for this population.

To better utilise the MAESTRO-NASH data, the EAG requested at PfC that the company re-analyse the HRQoL data, excluding fibrosis stage from the regression model, in order to generate utility estimates independent of assumed fibrosis progression. In response, the company submitted GLM regression results based on both beta and Gaussian distributions. However, the link function used for the beta model was unclear. The company stated that an identity link was applied, but this appears inconsistent with the coefficients reported, and consequently, the beta results cannot be reliably interpreted.

By contrast, the results from the Gaussian model are interpretable. Using baseline characteristics for the mITT-LBW52 population, the predicted mean EQ-5D utility is approximately [REDACTED] for patients without MASH resolution and [REDACTED] for patients with MASH resolution. These values are lower than those reported in NG49 and align more closely with those reported in Papatheodoridi et al. (2023), providing estimates that the EAG considers more clinically plausible for the modelled population.

The EAG's preferred approach is therefore to use either the MAESTRO-NASH data or the values reported in Papatheodoridi et al. (2023) for health states F0–F3. For the compensated F4 health state, the EAG prefers to use the value from Papatheodoridi et al. (2023), as this better reflects clinical expectations and is more representative of the modelled population. For advanced liver disease health states (DCC, HCC, and LT), the company's values appear reasonable. Although the EAG identified plausible alternative sources in the literature, these are unlikely to materially affect the cost-effectiveness results.

The EAG considers it important that predicted values are generated from the company's regression models for both the beta and Gaussian specifications using the characteristics of the analysed population. The EAG also emphasises that, where possible, baseline utility values, treatment effects, and population-level estimates should be derived from a consistent population to ensure internal coherence within the model.

MASH decrement

The company applies a MASH-specific utility decrement; however, the EAG considers it unclear whether such an adjustment is appropriate. MASH resolution reflects disease activity rather than liver function, and there is no clear biological rationale for it to have a direct effect on HRQoL. Evidence from MAESTRO-NASH is mixed and not consistently statistically significant across the regression models submitted at PfCs. In the GLM EQ-5D analysis using a Gaussian distribution with an identity link, the estimated utility decrement associated with MASH resolution [REDACTED] is similar in magnitude to the value used in the company's model ([REDACTED]), but it is not statistically significant. Given the available trial data and the absence of conclusive supporting evidence in the literature, the EAG is uncertain that a MASH-specific decrement should be applied. Should such a decrement be included,

the EAG considers that it should be derived directly from an appropriate regression analysis of the trial HRQoL data using a consistent modelling approach, rather than being informed by external sources.

4.2.7 Resources and costs

The CS (Section B.3.5) details the resource use and associated costs applied in the model. This comprised costs relating to drug acquisition, monitoring and follow-up, and medical costs for complications, which included management of advanced liver disease, cardiovascular events and T2DM complications.

HCRU data from unpublished and published sources were used to derive cost values for the model. These values were inflated to current prices using the Hospital & Community Health Services pay-and-prices index (as reported in Unit Costs of Health and Social Care (PSSRU))⁵⁶ or, where the index was unavailable, the HM Treasury GDP deflator.⁵⁷

4.2.7.1 Health resource literature review

The company conducted a SLR of costs and HCRU studies together with the review of economic evaluations; full details are provided in Appendix G of the CS.

The SLR identified 37 studies, of which seven reported UK- or England-specific costs and HCRU data, summarised in Table 2 of Appendix G. Of these, the company considered Davidson et al. 2025¹⁴ the most relevant evidence to inform annual healthcare costs for fibrosis and advanced liver outcomes, including CC, DCC, HCC, and LT. A UK cost of illness study by Morgan et al., 2021²⁷ was considered a complementary source of evidence, providing annual health system costs for these same health states.

Other studies, specifically Younossi et al., 2016³⁰ and Schattenberg et al. 2021²⁹, both estimated the disease burden and economic impact of NASH and reported medical cost estimates across NASH stages. However, these studies were based on non-UK specific sources but were deemed valuable for validating the costs applied in the model.

Of the remaining 3 UK studies, O'Hara et al., 2020²⁸ and Balp et al., 2019²⁵ reported costs based on patient-reported outcomes surveys, while Carruthers et al., 2017²⁶ looked at trends in the burden of diagnosed NASH over time but did not report any cost data.

4.2.7.2 Drug acquisition costs

The intervention arm is defined as the combination of pharmacological treatment with resmetirom and lifestyle management, while the SoC arm involves only lifestyle management. However, the costs associated with lifestyle management are assumed to be identical for both arms and are therefore

excluded from the incremental cost comparison. This approach was taken to ensure that only the additional cost attributable to the drug is captured in the treatment arm.

Acquisition costs for resmetirom are based on an indicative UK list price of [REDACTED] per treatment day, applied equally to 80 mg and 100 mg orally administered tablets and requiring no administration cost. The drug costs are accrued to patients only while on active treatment, with costs reduced pro rata by time off therapy where there are temporary interruptions, and costs stopped altogether where there is permanent discontinuation of resmetirom. Drug wastage is not modelled. This was justified by the company on the basis that resmetirom is an oral formulation, has a long shelf-life, and that treatment costs are calculated per treatment day. No drug acquisition costs were modelled in the SoC arm.

Points for critique

Drug wastage is excluded from the model on the basis that the unit-dose form of resmetirom tablets aligns with the duration of active treatment. This assumption is likely reasonable while patients remain on treatment. However, it may lead to underestimation of drug costs in cases of temporary or permanent discontinuation.

In the company's model, drug costs are adjusted pro rata for temporary interruptions and cease entirely following permanent discontinuation. Although this reflects administered treatment time, it does not account for partial pack wastage when patients discontinue early, particularly where medication has already been dispensed but remains unused. In routine practice, unused oral medication is generally not reused, implying that some degree of wastage is likely for permanent discontinuation. Wastage may be minimal in temporary interruptions if patients continue to use the same supply on resumption, although this depends on the duration of the interruption. In such cases, the model may underestimate drug costs because treatment costs restart in full when therapy resumes.

Given these considerations, the EAG considers it appropriate to include drug wastage, incorporating a proportion of unused medication, while recognising that temporary treatment pauses may not always incur wastage, in order to better reflect prescribing and dispensing practice.

4.2.7.3 Monitoring and follow-up

Monitoring and follow-up costs were modelled as equal in both the resmetirom and SoC arms. These costs comprised non-invasive staging with TE (Fibroscan) and an ELF test at baseline, with annual ELF monitoring thereafter. The unit costs were £55.42 for Fibroscan and £54.14 for the ELF test.

Commissioning for resmetirom is expected to be in secondary care, with dispensing mostly through outpatient pharmacy or via home delivery. It is assumed that the drug will not require additional clinic visits beyond those already delivered in current practice. Therefore, the referral resource use,

frequency and type of secondary care visits are modelled as identical in both the resmetirom and SoC arms.

Points for critique

The source for the monitoring and follow-up costs was initially reported inconsistently between the original CS and Appendix K, Table 7, which provides a list of model input parameters. At PfC, the company confirmed that the unit test costs were sourced from Srivastava et al., 2019, a cost-comparison analysis of non-invasive liver fibrosis tests in community pathways for NAFLD and subsequently inflated to current prices. While the CS was updated to reflect this change, an incorrect reference to NG49⁵⁵, which reports an ELF test cost of £111.06 (2013/14 prices) compared to the modelled cost of £42 (2014/15 prices), remains in the updated CS.

The EAG is satisfied with the monitoring and follow-up costs applied in the model.

4.2.7.4 Health state unit costs and resource use

The model includes costs, categorised by fibrosis health state and advanced liver outcomes, which were derived from a company-sponsored study by Davidson et al., 2025¹⁴ that estimated HCRU associated with MASH. Costs associated with liver transplantation (LT) and subsequent follow-up were derived from the NG49 guideline⁵⁵ and were annualised to reflect the model cycle length. These costs are presented in Table 40 of the updated CS.

Medical costs for MI and stroke were derived from Brennan et al., 2014, a systematic review of costs related to MI or stroke in patients with T2DM.⁵⁸ These costs are detailed in Table 41 of the updated CS. Costs for renal complications were based on renal transplantation costs, excluding dialysis, in alignment with the NICE NG203 guideline⁵⁹ for CKD as reported in NG28.¹⁵ The therapy modality distributions used for these costs were estimated using UK Renal Registry data, as reported in NG28.¹⁵ Costs for retinopathy were based on the expected inpatient costs for blindness in one eye. These costs were derived from Alva et al., 2015⁶⁰, a study estimating the costs associated with T2DM-related complications for UK patients, as reported in NG28. This study specifically estimated inpatient care costs for a representative example of a male, aged 60 years. The first- and subsequent-year cost estimates for renal complications and retinopathy were each converted to, and modelled as, weighted annualised costs, as reported in Table 42 of the updated CS.

Points for critique

Health state costs

Davidson et al. (2025) report annualised HCRU and cost estimates for a retrospective cohort of adults in England with a MASH-coded diagnosis (defined as MASH, end-stage liver disease, or a major adverse cardiovascular event).¹⁴ The study used CPRD linked to HES and death registrations over

2011–2020, including 2,696 patients with a mean follow-up of four years. HCRU and costs were reported for all-cause and MASH-related admissions, with subgroup analyses for patients with T2DM, overweight/obesity, cardiovascular disease, or progression to cirrhosis.

The costs applied in the company's model (updated CS, Table 40) for non-progression (F0–F3) and progression to cirrhosis (F4/CC) are substantially higher than the figures reported in Davidson et al. The study reports mean annualised MASH-related costs per patient of £248 for non-progressed patients and £2,044 for patients progressing to cirrhosis. In contrast, the model uses values derived from the supplementary material of Davidson et al., adjusted for comorbidity and continuous follow-up time, of £1,472 for non-progressed patients and £8,874 for patients progressing to CC. However, these supplementary values represent costs over the study follow-up period (mean 4 years), rather than annual costs, meaning the costs for progressed patients include periods prior to progression.

The company's model also assigns higher annual costs to the CC state than to DCC, and lower costs to HCC compared to DCC. This contrasts with the published Davidson et al. study, which reports higher incremental adjusted costs for progression from MASH to DCC than to CC. Over the study follow-up, using non-progressed patients as a reference, MASH-related adjusted costs were £12,037 for progression to DCC and £8,874 for progression to CC.¹⁴ Evidence from other sources also indicates that DCC is generally associated with higher costs than CC but lower costs than HCC (Younossi et al., 2016³⁰; Morgan et al., 2021²⁷; Schattenberg et al., 2021²⁹; CS Appendix G, Table 2), consistent with the published literature and cost comparisons presented in Table 18.

The EAG queried these discrepancies at PfC (question B22). In response, the company stated that modelled costs for DCC and HCC were obtained from unpublished data from Davidson et al. (2025), provided via internal communication, to better reflect real-world resource use. Reliance on unpublished data limits the EAG's ability to assess the appropriateness and transparency of these inputs. It remains unclear why the unpublished estimates differ from those reported in the published study. The EAG considers it important that the company fully justifies the use of the unpublished data and clearly explains the discrepancies between the unpublished and published figures from the same source.

In its SLR, the company identified the Morgan et al., 2021 study²⁷, which estimated the disease burden and economic impact of diagnosed NASH in the UK adult population in 2018, as a valuable source for alignment of unit costs and NHS-based evaluations. This study estimates costs for diagnosed NASH in the UK based on published data and expert elicitation. It reports per person health system costs by disease stages: F0–F4, DCC, HCC and LT. These costs are NASH-specific only, excluding comorbidities. While Morgan et al. (2021) provide relevant UK-specific cost data, the EAG considers this a less reliable source as the prevalence estimates used in the analysis rely on an

assumption of proportionate diagnosis, and an age distribution from a US modelling study. The published values in Davidson et al., are comparable to those reported in Morgan et al. than the unpublished values used in the company's model, as demonstrated in Table 18. Note that the health state values for Morgan et al., 2021 were incorrectly summarised in Table 2 of Appendix G of the CS but the correct values were included the 'cost_inputs.xlsx' file for the company model. The correct values are reflected in Table 18 below.

Table 18 Comparison of health state costs (after inflation)

Health states	Modelled values from Davidson et al., 2025 ¹⁴	Annualised costs published in Davidson et al., 2025 ¹⁴	Morgan et al., 2021 ²⁷
F0-F1	£1,676	£282	£225
F2	£1,676	£282	£473
F3	£1,676	£282	£588
F4/CC	£10,103	£2,327*	£985
DCC, year 1	██████ (unpublished)	NR	£6,984
DCC, year 2+	██████ (unpublished)	NR	£6,984
HCC, year 1	██████ (unpublished)	NR	£8,522
HCC, year 2+	██████ (unpublished)	NR	£8,522

Abbreviations: CC, compensated cirrhosis; DCC, decompensated cirrhosis; F0-F4, fibrosis stages 0–4; HCC, hepatocellular carcinoma; NR, not reported * Annualised costs are reported for progression to overall cirrhosis.

The EAG considers it important to present cost-effectiveness results in a scenario analysis that uses only the published values from Davidson et al., 2025 because clear justification for using the unpublished data has not been presented. The published study by Davidson et al., reports annualised costs for non-progressed and progressed patients, where the latter is largely comprised of CC and DCC patients however there is no granularity in costs reported for the advanced liver disease states. Therefore, it would seem reasonable to apply the reported non-progression costs to the F0-F3 states from Davidson et al., and to use costs reported in Morgan et al., 2021 to inform F4/CC, DCC year 1 and year 2+ and HCC year 1 and 2+.

Costs associated with liver transplantation

The EAG questions the validity and transparency of the LT and LT year 1 and 2+ health state costs. These values were sourced from NG49 and based on HBV/HCV cohorts, which appear to originate from Wright et al. (2006), a UK HTA and economic evaluation for hepatitis C with a 2002/03 price year.⁶¹ The LT values reported in NG49 (£29,575; 2016) differ from those in Wright et al. (£27,330; 2002/03) by just over £2,000. While this discrepancy could reflect adjustments for inflation, the EAG considers this unlikely, as an appropriate inflation adjustment would be larger. It therefore remains unclear how these costs were derived.

The EAG is also concerned that the company has misinterpreted the reported LT costs. The LT transplant costs reported in Wright et al. refer to a transplant stay cost, whereas NG49 reports this as a 6-month value in the company model this value is doubled to derive an annual cost applied in the first year following LT. The EAG questions whether this is appropriate, as a transplant stay is a one-off procedural event, and doubling the 6-month cost appears to be an arbitrary adjustment to match the model's one-year cycle length.

Similarly, the company applied the same doubled 6-monthly post-transplant cost from NG49 to both LT year 1 and 2+, which does not reflect clinical practice. Resource use is highest in the first 12 months post-transplant due to intensive monitoring and follow-up, with both NG49 and Wright et al. reporting lower follow-up costs (less than 50%) in subsequent years. A comparison of costs applied in the company model and unadjusted costs reported in NG49 and Wright et al., (2006) is presented in Table 19 below.

Table 19 Comparison of liver transplantation costs

Company model*	NG49 (2013/14 prices) ⁵⁵	Wright et al., 2006 (2002/3 prices) ⁶¹
£76,762 (LT, procedure)	£29,574.51 (LT, Year 1)	£27,330 (Transplant stay)
£10,896 (LT, year 1 follow-up)	£9185.77 (LT, Year 2)	£9,458 (Year 1 follow up)
£10,896 (LT year 2+ follow-up)	£4198.03 (Post LT)	£1,385 (Year 2 follow up)
NA	NA	£3,727 (waiting list)
NA	NA	£8,413 (Assessment phase)

Abbreviations: LT, liver transplant; NA, not applicable. *These costs are based on NG49 and doubled to reflect annual costs.

Costs associated with complications

Costs for CVD events were derived from Brennan et al., 2014⁵⁸, which in turn relies exclusively on data from the UKPDS Study No. 65 by Clarke et al., 2003⁶². This study has since been updated by Alva et al., 2015 (UKPDS 84)⁶⁰, providing more recent cost estimates associated with diabetes-related complications. While the use of UKPDS 65 is acceptable, the EAG considers it more appropriate to use the updated values from UKPDS 84, which more accurately reflect the current healthcare structures.

The EAG is satisfied with the costs associated T2DM complications applied in the model.

4.2.7.5 Adverse event costs

The company did not include costs associated with the management of adverse events, reasoning that TRAEs were for the most part mild to moderate and transient, with no meaningful incremental HCRU.

Points for critique

The EAG is satisfied with the company's approach not to model costs related to TRAEs owing to the limited impact on the ICER.

5 COST-EFFECTIVENESS RESULTS

Section 5.1 summarises the company's base case cost-effectiveness results, and section 5.2 presents the EAG's additional work on model validation and face validity check.

5.1 Company's cost effectiveness results

The EAG identified significant validation issues with the model. While we present the results, the EAG makes no guarantee of their accuracy.

5.1.1 Company's base case

The cost-effectiveness results presented in the CS are based on the list price of [REDACTED] per tablet for resmetirom. The company's base-case results are not adjusted by any severity modifier. The company states that *"Although this condition is progressive, associated with impaired HRQoL, and has an increased risk of advanced liver outcomes, patients retain a substantial life expectancy, and the absolute and proportional QALY shortfalls relative to the general population are not sufficient to qualify for a severity weight"*; therefore, the company did not apply severity modifier in the economic analysis.

Table 20 and Table 21 show the company's base case deterministic and probabilistic results, respectively.

Table 20 Company's deterministic base-case cost-effectiveness results (reproduced from Table 44 of the CS)

	Total costs (£)	Total LYGs	Total QALYs	Incremental costs (£)	Incremental LYGs	Incremental QALYs	ICER (£/QALY)
SoC	[REDACTED]	[REDACTED]	[REDACTED]	NA	NA	NA	NA
Resmetirom	[REDACTED]	[REDACTED]	[REDACTED]	[REDACTED]	[REDACTED]	[REDACTED]	21,422

Abbreviations: ICER, incremental cost effectiveness ratio; LYG, life years gained; QALYs, quality-adjusted life years; SoC, standard of care.

Table 21 Company's probabilistic base-case cost-effectiveness results (reproduced from Table 46 of the CS)

	Total costs (£)	Total LYGs	Total QALYs	Incremental costs (£)	Incremental LYGs	Incremental QALYs	ICER (£/QALY)
SoC	[REDACTED]	[REDACTED]	[REDACTED]	NA	NA	NA	NA
Resmetirom	[REDACTED]	[REDACTED]	[REDACTED]	[REDACTED]	[REDACTED]	[REDACTED]	19,495

Abbreviations: ICER, incremental cost effectiveness ratio; LYG, life years gained; QALYs, quality-adjusted life years; SoC, standard of care.

5.2 EAG's additional analyses

5.2.1 Model validation and face validity check

The model was built in R, and the CS states that the model underwent extensive quality control checks, with the model structure and key assumptions validated by a UK advisory board comprising hepatology specialists and a health economic expert (see Section 3.14, CS). However, the company does not detail what the internal checks and cross-validation entailed. The company provided, on EAG's request, a user manual and description of the coding logic. It also implemented some additional functionality requested at the clarification stage to allow additional analyses.

5.2.1.1 Validation tests

The company states that extreme-value testing was performed (section 3.14, CS) to assess the model's behaviour and outcomes, and that two independent modellers reviewed the code to confirm internal consistency and the accuracy of calculations. As part of the EAG assessment of the economic analysis, the EAG checked the internal validity of the model and considered the face validity of the model's predictions. This included a series of model's black box and validation tests to evaluate the robustness of the company's economic model. The model has failed several of these tests, suggesting one or more errors in the calculation. Details of all the tests undertaken by the EAG are reported in Appendix 1. Several tests failed by the company model are discussed below.

In scenario 1, the EAG tested the model across different utility and disutility values. When all utility values were set to 1, disutilities values to 0, and age-adjustment of utility values was removed, the life years (Table 22) were different from the base case (Table 20).

Table 22: Scenario 1a: Model results when setting all utilities to 1, disutilities to 0 and removing age-adjustment

Strategy	Cost	QALYs	Inc Cost	Inc QALYs	ICER	Status	LYs	ILYs
SoC	████	████	████	████	████	████	████	████
Resmetirom	████	████	████	████	████	████	████	████

Abbreviations: ICER, incremental cost-effectiveness ratio; LYG, life years gained; QALYs, quality-adjusted life years; SoC, standard of care.

Likewise, the LYs were different from the results above while running the model by setting all utility values to 1 and including age adjustment (Table 23).

Table 23: Scenario 1b: Model results when setting all utilities to 1, disutilities to 0

Strategy	Cost	QALYs	Inc Cost	Inc QALYs	ICER	Status	LYs	ILYs
SoC	████	████	████	████	████	████	████	████
Resmetirom	████	████	████	████	████	████	████	████

Abbreviations: ICER, incremental cost-effectiveness ratio; LYG, life years gained; QALYs, quality-adjusted life years; SoC, standard of care.

Across the utility and disutility tests described above, life-years should remain unchanged. However, the results indicate that utility inputs are intrinsically affecting the LY calculations, when in both scenarios the LYs should match the base case. Moreover, the findings in Table 23 suggest that the applied disutilities have a substantial impact on incremental QALYs. While this may stem from specific aspects of the model's parameterisation, it may also point to an additional face-validity concern.

In Scenario 2, cause-specific mortality (both liver-related and non-liver-related) was set to zero to assess the influence of disease-specific mortality on QALYs and LYs. Under this scenario, incremental LYs should be zero, because both arms should face an identical background mortality risk. However, the observed incremental LYs (Table 24) were greater than zero, indicating potential issues with the LY calculations. The EAG is also concerned that this scenario has minimal impact on incremental QALYs, whereas one would expect LY differences rather than quality-of-life improvements to be the primary driver of incremental QALYs.

Table 24: Scenario 2: model results while setting cause-specific mortality to zero

Strategy	Cost	QALYs	Inc Cost	Inc QALYs	ICER	Status	LYs	ILYs
SoC	████	████	████	████	████	████	████	████
Resmetirom	████	████	████	████	████	████	████	████

Abbreviations: ICER, incremental cost effectiveness ratio; LYG, life years gained; QALYs, quality-adjusted life years; SoC, standard of care.

In scenario 3, the treatment effects for resmetirom were set equal to the SoC arm, i.e., the transition probabilities (NASH outcomes) and impact on cardiometabolic risk factor values for Resmet80 and Resmet100 were set to those of SoC, and the cost of Resmetirom was set to Zero. The results are reported in Table 25 still shows a residual difference in incremental QALYs when this should be zero.

Table 25: Scenario 3: model results while setting treatment effect to zero

Strategy	Cost	QALYs	Inc Cost	Inc QALYs	ICER	Status	LYs	ILYs
SoC	■	■	■	■	■	■	■	■
Resmetirom	■	■	■	■	■	■	■	■

Abbreviations: ICER, incremental cost-effectiveness ratio; LYG, life years gained; QALYs, quality-adjusted life years; SoC, standard of care.

The above tests are a subset of the tests from the TECH-VER checklist ⁶³, which aims to help identify model implementation errors and their root causes while improving the transparency and efficacy of the verification efforts. Given that the model failed several of these tests, the EAG is concerned about the model's face validity and transparency. Furthermore, given the model complexity, it was not possible to identify the root cause of these errors. The model requires further verification and testing, as it impedes assessment of its internal validity. This should include more detailed black box tests. The EAG considers model verification using the TECH-VER checklist as an essential first step towards increasing the model's face validity.

5.2.1.2 Decision model implementation

The EAG appreciates the company's efforts to make the model user-friendly via a Shiny interface and using the coding framework as suggested by Alarid-Escudero (2019).⁶⁴ However, these considerations suggest that further efforts should have been made to improve model transparency by arranging the code chunks and model inputs in a more logical order.

For example, when the general-purpose R functions are loaded, the script not only imports the functions used later in the model but also loads model inputs such as probabilities. This is problematic because the user manual states that model inputs are read in Section 03.1. The current structure creates unnecessary confusion and increases the risk of errors when testing the model (e.g., when using alternative probability values). Section 03.1 of the main Rmd file is explicitly designated for reading input parameters, so users would reasonably expect to modify inputs in that section rather than in Section 02 (load functions).

Greater consideration should therefore be given to the organisation and sequencing of input loading. A clearer separation between function definitions and input parameter assignment would help users follow the logic of the code, improve transparency, and increase confidence in the model's implementation. At present, inputs are not read in a sequential or centralised manner, and users must modify parameter values in multiple locations when testing alternative scenarios to ensure the model uses the intended values. For example, the seed value must be updated in more than one place if a

different seed is required. The EAG would strongly encourage the company to consider the following modifications to the R model to improve transparency and model usability:

- Centralise the random seed: Consolidate all `set.seed()` calls by defining a single seed variable and referencing it throughout the script.
- Relocate discounting and within-cycle correction code: Moving the cycle specific discount weights and within-cycle correction code from Section 3.5 to Section 6 would allow users to adjust discount rates and weights immediately before running the simulation.
- Consolidate NASH resolution probabilities: NASH resolution probabilities are currently read from two different files. Although the values match, the model uses the probabilities from the `df_NASH_outcome_by_age` dataframe (created within `get_subpopulation_data()`), while the values from `input_parameters.xls` are also loaded into the global environment. Good coding practice would avoid creating and storing multiple objects for the same parameter.
- Streamline HSUV handling: Once utility values are stored in the `hsuv_values` list, all unused utility values, depending on the chosen source, should be removed from the environment to avoid ambiguity and reduce clutter.
- Remove unused objects: Many intermediate objects created during data processing are retained even though they are not used later in the analysis. Clearing these objects from the environment would improve code hygiene and reduce potential sources of confusion.

5.2.1.3 Approach used to simulate baseline population characteristics

The individual patient characteristics used in the company's model are sampled directly from the MAESTRO-NASH individual patient-level dataset (company response to PfC question B5a). To generate *n* individuals for the simulation, the model draws observations from the IPD using uniform sampling with replacement (Section 4.2.3). This approach raises concerns about overrepresentation, inflated variability, and restricted diversity, since individuals can be sampled repeatedly. In the current implementation, some individuals were sampled as few as three times and others as many as twenty-three times. While this method can be acceptable when drawing from a very large dataset, that is not the case here.

The EAG strongly recommends revisiting the method used to simulate baseline characteristics. A preferable approach would be to generate a synthetic population informed by the observed trial data. Standard R packages such as `synthpop`⁶⁵ and `simstudy`⁶⁶, allow users to define variable distributions and specify relationships between covariates and outcomes. Constructing a fully synthetic population would also enable testing the generalisability of trial results. Under the current sampling procedure, it is not possible to introduce meaningful variability, such as altering the population's mean age.

5.2.1.4 Model code optimisation and improving efficiency

Given the complexity associated with MSM and specifically involving a complex disease, it is understandable that the model run time is longer than a standard Markov model. However, EAG is concerned about the PSA runtime, even though not all the model inputs are parameterised. To improve code efficiency and decrease runtime, the EAG suggests two approaches:

1. Use R packages that have been specifically developed to implement microsimulation for health-economic analysis, such as Simmer and Microsimulation. These have been used previously to implement MSM and are tested, reliable and optimised for performance.
2. Optimise specific parts of code where time and memory are spent. There are bottlenecks in the code, specifically as.data.frame.matrix. EAG suggests profiling and benchmarking codes to measure the performance of specific pieces of code, then optimising code where time and memory are spent, and improving the efficiency of the workflow. This could, for example, be using data.table instead of data.frame.

5.2.1.5 Transcription errors

The EAG notes that there was unreasonable number of transcription and reporting errors in the CS and PfC response. These repeated errors make it difficult for the EAG to understand the company's intentions and at times have limited the EAG's ability to evaluate the data provided. These errors include differences between the values reported in the CS/PfC response and those used in the model; mislabelled figures; or incomplete reporting. Table 26 summarises the errors identified by the EAG.

Table 26 Summary of transcription and reporting errors

Issue	Type	Description														
1	Transcribed from source incorrectly	At PfCs, the company provided details of their mapping methodology included significant interactions terms that have been wrongly transcribed from the source paper (Rowen et al. 2009). The EAG considers these as the significant interactions: <table><tr><td>PF x VIT</td><td>-0.132*</td></tr><tr><td>PF x RE</td><td>0.047*</td></tr><tr><td>RP x SF</td><td>0.067*</td></tr><tr><td>BP x GH</td><td>-0.217*</td></tr><tr><td>BP x MH</td><td>0.131*</td></tr><tr><td>GH x SF</td><td>-0.157*</td></tr><tr><td>VIT x SF</td><td>0.143</td></tr></table> And not what was provided in the PfC response: Significant interaction terms included PF × BP (−0.031), PF × SF (−0.023), PF × MH (+0.014), RP × SF (+0.049), BP × MH (−0.113), GH × MH (−0.066), and VT × MH (+0.148).	PF x VIT	-0.132*	PF x RE	0.047*	RP x SF	0.067*	BP x GH	-0.217*	BP x MH	0.131*	GH x SF	-0.157*	VIT x SF	0.143
PF x VIT	-0.132*															
PF x RE	0.047*															
RP x SF	0.067*															
BP x GH	-0.217*															
BP x MH	0.131*															
GH x SF	-0.157*															
VIT x SF	0.143															

2	Transcribed incorrectly from model	Table 38 in the original and updated CS had the numbers (n=) for F1, F2 and F3 without MASH and +MASH the wrong way round. Similarly, the utility mean values and 95% CI are transcribed incorrectly from the model. <table><tr><td>F1 without MASH (n=)</td><td></td><td></td><td>MAESTRO-NASH</td></tr><tr><td>F1 + MASH (n=)</td><td></td><td></td><td>MAESTRO-NASH</td></tr><tr><td>F2 without MASH (n=)</td><td></td><td></td><td>MAESTRO-NASH</td></tr><tr><td>F2 + MASH (n=)</td><td></td><td></td><td>MAESTRO-NASH</td></tr><tr><td>F3 without MASH (n=)</td><td></td><td></td><td>MAESTRO-NASH</td></tr><tr><td>F3 + MASH (n=)</td><td></td><td></td><td>MAESTRO-NASH</td></tr></table> The EAG believes it should be: <table><tr><th>State</th><th>Utility value: mean</th><th>95% CI</th></tr><tr><td>F1 without MASH (n=)</td><td></td><td></td></tr><tr><td>F1 + MASH (n=)</td><td></td><td></td></tr><tr><td>F2 without MASH (n=)</td><td></td><td></td></tr><tr><td>F2 + MASH (n=)</td><td></td><td></td></tr><tr><td>F3 without MASH (n=)</td><td></td><td></td></tr><tr><td>F3 + MASH (n=)</td><td></td><td></td></tr></table> Source: Based on PfC - Table 38, CS The EAG acknowledges that the values in the model are correct.	F1 without MASH (n=)			MAESTRO-NASH	F1 + MASH (n=)			MAESTRO-NASH	F2 without MASH (n=)			MAESTRO-NASH	F2 + MASH (n=)			MAESTRO-NASH	F3 without MASH (n=)			MAESTRO-NASH	F3 + MASH (n=)			MAESTRO-NASH	State	Utility value: mean	95% CI	F1 without MASH (n=)			F1 + MASH (n=)			F2 without MASH (n=)			F2 + MASH (n=)			F3 without MASH (n=)			F3 + MASH (n=)		
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F2 + MASH (n=)																																															
F3 without MASH (n=)																																															
F3 + MASH (n=)																																															
3	Missing values	In Tables 37 and 38 in the updated CS, the standard errors are missing. It's not clear to the EAG what these values are and how they are implemented in the model from the source NG49 which refers to utility decrements.																																													
4	Transcribed from source incorrectly	In the PfC response to Q. B16d, the EAG believes that the GLM regression results for EQ-5D utility at 52 weeks (miTT population) for Table 30 is likely transcribed incorrectly from source. Also, Table 28 and Table 30 have the same title.																																													
5	Input error in model	The EAG believes that there is an input value error in the model. In Table 6 (Year 1) Joint transition probabilities (mean (95%CI); (MAESTRO-NASH, paired-biopsy population; base-case) [Updated Table 28 in CS] The value for Resmetirom 100mg: MASH Resolution: NO, Fibrosis worsening is																																													

		In the model, the value is [REDACTED] The EAG believes that this is an error as the sum of the probabilities is 1.107 <table><tr><td>[REDACTED]</td><td>Probability</td><td>Year</td><td>[REDACTED]</td></tr><tr><td>[REDACTED]</td><td>Probability</td><td>Year</td><td>[REDACTED]</td></tr><tr><td>[REDACTED]</td><td>Probability</td><td>Year</td><td>[REDACTED]</td></tr></table>	[REDACTED]	Probability	Year	[REDACTED]	[REDACTED]	Probability	Year	[REDACTED]	[REDACTED]	Probability	Year	[REDACTED]
[REDACTED]	Probability	Year	[REDACTED]											
[REDACTED]	Probability	Year	[REDACTED]											
[REDACTED]	Probability	Year	[REDACTED]											
6	Input error in model	Villar-Gomex et al. (2018) report an incidence rate of 0.006 for hepatic decompensation in patients with bridging fibrosis (F3), whereas the model applies a value of 0.004. The EAG is unable to ascertain how the company’s values were generated from the source data.												
7	Clarification point	The EAG believe that the proportion of participants in MAESTRO-NASH population that are starting in F3 (baseline, week 0 of trial) is different in the mITT population (n=966) and the PLB-W52 population (n=739). Is that correct? The EAG considers the baseline characteristics relative to those in W0 (start of the trial) and not based on those at W52 retrospectively linked back to their baseline characteristics. Can the company please comment/clarify this issue? The EAG based this inference by looking at F3 fibrosis (%) in Table 9 (mITT) and Table 26 (PLB-W52) taken into account F1 patients in the mITT baseline population.												
8	Discrepancy with published data on health state costs	The modelled health state costs (Table 40) for fibrosis and progression to cirrhosis reflect adjusted costs over a 4-year period rather than annualised costs from Davidson et al., 2025. Furthermore, the costs applied in the DCC and HCC health states are from unpublished data from the same source, therefore it is not clear to the EAG whether these are also adjusted costs or how they were derived. The model also assigns higher costs in the CC state compared to DCC, contrary to what is reported in the published source Davidson et al., 2025. The study reports greater adjusted costs for progression from MASH to DCC (£12,037) compared to CC (£8,874).												
9	Error in transcription	Appendix G, Table 2 details health state costs from the company’s SLR. The annual health system costs by health state from Morgan et al., 2021 are incorrectly reported, however, the correct values are detailed in the company model ‘cost_inputs.xlsx’ file.												
10	Referencing error	The company model’s an ELF unit test cost of £42 (2014/15 prices) from Srivastava et al., 2019. However, in Appendix K, Table 7, the company references also references NG49 for this value. NG49 reports an ELF test cost of £111.06 (2013/14 prices).												

Abbreviations: CC, compensated cirrhosis; CI, confidence interval, CS, company submission; DCC, decompensated cirrhosis; EAG, External Assessment Group; ELF, Enhanced Liver Fibrosis; F0-F4, fibrosis stages 0-4. mITT, Modified Intention-to-Treat; NG, NICE guidelines; PfC, point for clarification.

5.2.1.6 EAG expectation

To assess the robustness of the results and build confidence in the model, the EAG expects the following updates:

1. Validate the model using the TECHnical VERification (TECH-VER) checklist and provide the corresponding validation results.
2. Reconsider the approach used to simulate baseline population characteristics. At a minimum, allow users to vary key characteristics such as (a) age and (b) the proportion of the F2 and F3 population.
3. Add an indicator variable to `df_X` to capture treatment restarts. Currently, `df_X` only includes a variable for permanent treatment discontinuation.
4. Reading external data and user documentation
 - a. The EAG welcomes the section-by-section user guide. However, the guide instructs users to update values in `input_parameters.xlsx` wherever possible, even though some values in this file are not used by the model (for example, `df_NASH_outcome_by_age`).
 - b. Ensure that each model input is read from a single source. It is acceptable to organise inputs across multiple CSV files, but they should not be duplicated.
 - c. Provide clear instructions on how to change probabilities, costs, and utilities within the model.
5. Minimising duplication and optimising code efficiency
 - a. It is good practice not to leave original lists in the environment after unpacking them. Similarly, unused objects, often intermediate objects created during processing, should be removed. This avoids maintaining multiple versions of the same data, keeps the workspace tidy, reduces confusion, and prevents accidental name collisions.
 - b. Some components of the `MicroSim()` function require substantial time and memory. The EAG recommends profiling and benchmarking the code to identify bottlenecks, then optimising the relevant sections. For example, using `data.table` instead of `data.frame` may improve performance.
6. Some probabilities in the model, such as non-liver-related mortality, vary over time, whereas treatment-specific transition probabilities are fixed. The model should incorporate functionality to allow these treatment-specific transition probabilities to vary over time, which is essential for testing assumptions and supporting model validation.

5.2.2 EAG's exploratory analyses using company's base case

The EAG agreed with the NICE team not to provide additional analyses at this time due to the outlined issues with the company model.

5.3 Decision modifiers

In the original CS, a severity modifier was not sought and therefore not applied in the economic analysis. At PfC, the EAG asked that the company include the calculation of the disease severity modifier in line with the NICE methods manual (B. 24).

This analysis was undertaken using the QALY Shortfall Calculator in R developed by the University of York (<https://shiny.york.ac.uk/shortfall/>). Inputs were said to be aligned with the modelled population in the base case, reflecting a mean age of 56.2 years and lifetime QALYs under SoC and resmetirom treatment.

The EAG notes that the company is using the baseline characteristics of the paired-biopsy population (PLB-W52 where n=739) where mean age is [REDACTED] years. The EAG notes that the % female in this patient population is [REDACTED]% (Table 26, CS) and not [REDACTED] as per company submission.

The EAG is unable to produce an EAG base-case for the QALY shortfall as explained in Section 5.2. The EAG believe the modelled population is in fact the mITT-W52 population (where n=966) and that the QALY shortfall calculation should be based on these patients. The mean age of the placebo group is 57.1 years and 55.5% are female (Table 9, CS). Table 27 is a summary of the QALY shortfall analysis.

Table 27 Summary of QALY shortfall analysis

	Expected total QALYs for the general population	Total QALYs that people living with a condition would be expected to have with current treatment	Absolute QALY shortfall	Proportional QALY Shortfall
Company base case				
Resmetirom	14.04	[REDACTED]		
SoC	14.04	[REDACTED]	[REDACTED]	[REDACTED]
Company base case (corrected)				
Resmetirom	13.73	[REDACTED]		
SoC	13.73	[REDACTED]	[REDACTED]	[REDACTED]
EAG base case				
Resmetirom	13.73	[REDACTED]		
SoC	13.73	[REDACTED]	NR	NR

Abbreviations: EAG, External Assessment Group; QALY, Quality Adjusted Life Years; SoC; Standard of Care; NR, Not Reported.

5.3.1 QALY weighting for severity

The EAG preferred assumptions for general population QALY shortfall estimates are detailed in Table 28. These are based on the mITT-W52 population.

Table 28 Summary of company's or EAG's preferred assumptions for general population QALY shortfall estimates

Factor	Value or source (reference to appropriate table or figure in submission)	Reference to section in submission or rationale
Sex distribution	44.5 % Male: 55.5% Female	CS Table 9; Demographic and baseline characteristics (mITT-W52 population, n=966; placebo arm
Starting age	57.1	CS Table 9; Demographic and baseline characteristics (mITT-W52 population, n=966; placebo arm
Expected years of life	13.73	Reference case: MVH value set + HSE 2014 ALDVMM model (Hernandez Alava et al. 2022) ⁶⁷
Quality of life by age	Y	As per company base case analysis
Discount rate	3.5%	NICE reference case ⁶⁸

Abbreviations: ALDVMM, Adjusted limited dependent variable mixture model; CS, Company submission; EAG, External Assessment Group; mITT, modified Intention-to-Treat; MVH, Measurement and valuation group; NICE, National Institute for Health and Care Excellence.

Table 29 Summary of company's base-case QALY shortfall analyses and preferred QALY weighting

	Expected total QALYs for the general population	Expected total QALYs for people living with a condition on current treatment	Absolute QALY shortfall	Proportional QALY shortfall	Preferred QALY weight
Company's base case	13.73	████	████	████	None

Abbreviations: QALY, Quality Adjusted Life Years.

5.3.2 Uncaptured benefits

In the original CS, the company presented (in Section 3.13; CS, pp. 155–156) a set of bullet-pointed benefits of resmetirom that it considered not to be captured in the QALY calculation. These included: (1) avoidance of compensated cirrhosis (CC) and other ALD health states, (2) improvements in energy and daily functioning leading to enhanced (work) productivity, (3) favourable effects on lipids and blood pressure (based on MAESTRO-NASH), and (4) meaningful improvements in domains such as fatigue, emotional wellbeing, disease-related worry, and stigma (also based on MAESTRO-NASH).

The EAG has several concerns regarding these purported uncaptured benefits. First, avoidance of CC is explicitly incorporated in the company's economic model and constitutes the primary driver of QALY gains; it therefore cannot be considered an uncaptured benefit. Second, improvements in

energy levels and daily functioning should be reflected in quality-of-life instruments. The EQ-5D includes a domain on usual activities, and any such effects should therefore be captured in the model. Moreover, evidence suggesting that resmetirom produces direct improvements in HRQoL is limited. Third, potential improvements in cardiometabolic risk factors, including lipid levels, are also incorporated in the model and contribute to QALY gains through reductions in CVD events and T2DM. Notably, differences in lipid changes between resmetirom and standard care were not consistently statistically significant.

The EAG does not rule out the possibility that resmetirom affects outcomes such as fatigue, emotional wellbeing, disease-related worry, or stigma, which may not be fully reflected in generic quality-of-life measures. However, the majority of patients treated with resmetirom did not achieve a minimally important clinically difference in any of these domains. Any uncaptured benefits are therefore likely to be modest.

5.3.3 Health inequalities

The company notes that MASH disproportionately affects individuals with multiple comorbidities, including obesity and T2DM, and that mortality related to fatty liver disease is highest among populations experiencing greater socioeconomic deprivation. These points highlight the substantial health inequalities associated with MASH and the broader public health consequences of the condition.

The EAG agrees that obesity and its associated comorbidities represent major priorities for the NHS. The EAG also concurs that patients with MASH are disproportionately drawn from the most deprived communities, reflecting well-established links between socioeconomic status, metabolic disease burden, and progression to advanced liver disease.

5.4 Confidential comparator and subsequent treatment prices

No confidential comparator discounts are relevant to this appraisal.

5.5 Conclusions of the cost-effectiveness section

The EAG considers that while the company's economic model addresses the decision problem and is structured in a way that is broadly consistent with modelling MASH progression, the model as implemented raises substantial concerns regarding its internal validity, transparency, and robustness. A series of black-box and validation tests conducted by the EAG identified several implausible results and internal inconsistencies, suggesting potential errors in how key components of the model are coded and parameterised. Furthermore, there are several substantial areas of uncertainty that materially undermine the reliability of the modelled cost-effectiveness of resmetirom. These concerns

span the assumptions underpinning the model structure and assumptions made regarding how resmetirom will be used as practice, as well as key uncertainties regarding the generalisability of the clinical evidence to the NHS, the populations used to estimate treatment effects, and the evidence informing health-related quality of life. Collectively, these issues meaningfully weaken confidence in the economic model and the conclusions drawn from it.

The first area of uncertainty concerns the clinical evidence and its generalisability to the NHS setting. The pivotal MAESTRO-NASH trial enrolled patients on the basis of biopsy-confirmed disease, which does not reflect routine diagnostic practice within the NHS. Biopsy is rarely used outside specialist centres, particularly given the absence of established criteria for determining who should undergo invasive testing. The lack of consensus agreement on NIT thresholds for identifying resmetirom-eligible patients further limits the applicability of the trial evidence. The EAG notes that a potentially large proportion of MAESTRO-NASH participants would not meet the proposed NIT-based definitions for eligibility, depending on the criteria applied. These discrepancies, combined with a more pronounced metabolic risk burden among trial participants, introduce considerable uncertainty into the extrapolation of trial findings to UK clinical practice.

A second related area of uncertainty is the population upon which the modelled treatment effects are based on the PLB-W52. This is motivated by the need to have complete histological assessments to generate transition probabilities, which cannot be achieved with the mITT-LB-W52 population due to missing samples. This approach is, however, likely to overestimate modelled treatment effects as it assumes that the missing data are missing completely at random. However, this assumption is highly implausible, as sample availability is explicitly related to trial discontinuations, which are often due to adverse events or lack of treatment response. Consequently, the PLB-W52 population is unlikely to be representative of the full trial cohort, and transition probabilities derived from this subset are likely to be biased.

A third important uncertainty is the company's reliance on unvalidated surrogate relationships to project long-term outcomes. The model assumes that short-term improvements in fibrosis stage and MASH resolution directly translate into substantial reductions in liver-related morbidity, mortality, and associated healthcare use over the lifetime horizon. However, fibrosis stage is not an accepted surrogate endpoint for hard clinical outcomes in MASH, and the strength of association between trial-observed histological changes and subsequent clinical events remains highly uncertain. Given that these surrogate relationships drive much of the modelled benefit of resmetirom, particularly the projected QALY gains, the EAG considers this a major structural limitation that substantially increases uncertainty in model outcomes.

A fourth significant area of uncertainty relates to the structural assumptions underpinning the company's economic model, particularly the absence of any NIT based response assessment to guide ongoing treatment. The EAG's clinical experts and published expert opinion suggest that real-world management would involve periodic response-based assessment using NITs. The company's model and submission, however, do not make clear how such response-based assessment would be implemented in practice, focusing only on histological outcomes, which the EAG considers a major limitation of both the company's economic analysis and current clinical evidence base. It is particularly important in the context of the modelled treatment effects, which assume continued resmetirom treatment leads to compounding benefits, such that the probability of achieving MASH resolution in subsequent years is independent of previous treatment. The EAG considers this approach to lack any evidentiary foundation and to be inconsistent with a response-based treatment approach, which necessarily suggests diminishing returns from continued treatment.

A fifth uncertainty related to the above is the treatment stopping rules implemented in the model. The company assumes stopping upon regression to F0/F1, regardless of MASH resolution, or upon progression to F4 or advanced liver disease. These rules are not supported by the SmPC, current clinical guidelines, or expert advice. Moreover, it is not fully clear how assessment of histological outcomes would be assessed in practice as the trial relied on repeated liver biopsies, which are not feasible in routine NHS care. Moreover, the model implies that patients will restart treatment if the patient progresses to back to F2/F3 fibrosis. However, this would require a continuation of monitoring, which is unlikely to take place in the current NHS pathway as patients with F0/F1 fibrosis are currently treated and monitored in primary care.

A sixth key uncertainty concerns the HRQoL data used in the model. The EAG has substantive concerns regarding the company's reliance on NG49 (NICE, 2016) as the primary source of utility values. The provenance of the NG49 values is unclear, and the values do not pertain to patients with MASH or MASLD. Several utilities also lack face validity, with some matching or exceeding those of the general population, and the sharp decline in HRQoL between F3 and F4 CC is inconsistent with clinical advice and published evidence. The EAG considers that utility values generated from the mITT population of MAESTRO-NASH trial represent a superior alternative that much better matches the modelled population and aligns more closely with clinical expectations than NG49 values. Published values from Papatheodoridi et al. (2023)⁶⁹ also represents a viable alternative.

In addition to the above, the EAG has substantive concerns regarding how the company has interpreted several published sources of evidence used to populate key assumptions and parameter values in the model. These concerns include: key assumptions related to the modelled treatment effect and the number of fibrosis stages that patients progress through in a single model cycle; the transition

probabilities applied within the ALD health states; and key assumptions regarding management costs in F4 CC, which substantially exceed the values reported in the cited literature.

Taken together, these issues introduce substantial structural and evidential uncertainty into the company's economic model. Although the EAG was unable to explore these uncertainties using alternative assumptions due to practical challenges in validating the company's model and implementing scenario analyses, it expects these issues to have a considerable impact on model outcomes. The EAG considers that the company's cost-effectiveness estimates should therefore be interpreted with caution, and that additional evidence and further model refinement will be required to support a robust assessment of the clinical and economic value of resmetirom.

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7 APPENDICES

Appendix 1: Resmetirom Black box testing

To evaluate the robustness of the company's economic model, the EAG has conducted a series of black-box pressure tests. The model has failed several of these tests, suggesting one or more errors in the calculations. The tests implemented by the EAG are outlined below.

1. Utilities

Base case

Strategy	Cost	QALYs	Inc Cost	Inc QALYs	ICER	Status	LYs	ILYs
Standard of Care	████	████	████	████	████	████	████	████
Resmetirom	████	████	████	████	████	████	████	████

Scenario 1a. Set all utilities to 1 (NAFL, Fs, DCC, HCC, Liver transplant, post-liver transplant) and disutilities to 0; age adjustment = 0

Strategy	Cost	QALYs	Inc Cost	Inc QALYs	ICER	Status	LYs	ILYs
Standard of Care	████	████	████	████	████	████	████	████
Resmetirom	████	████	████	████	████	████	████	████

Fail:

- Costs remain the same (pass)
- QALYs are equal to LYs (pass)
- LYs should be the same as base case (fail)

This suggests an interaction between the applied utility values and estimated LYs

Scenario 1b. Set all utilities to 1 (NAFL, Fs, DCC, HCC, Liver transplant, post-liver transplant) and disutilities to 0; age adjustment =1

Strategy	Cost	QALYs	Inc Cost	Inc QALYs	ICER	Status	LYs	ILYs
Standard of Care	████	████	████	████	████	████	████	████
Resmetirom	████	████	████	████	████	████	████	████

Fail:

- Costs remain the same (pass)
- QALYs are not equal but similar to LYs (pass)
- LY should be the same as scenario 1a (pass)
- LYs should be the same as base case (fail)

This suggests that the issue does not relate to age adjustment

Scenario 1c. Set all utilities to 1 (NAFL, Fs, DCC, HCC, Liver transplant, post-liver transplant) ; age adjustment =1

Strategy	Cost	QALYs	Inc Cost	Inc QALYs	ICER	Status	LYs	ILYs
Standard of Care	████	████	████	████	████	████	████	████
Resmetirom	████	████	████	████	████	████	████	████

- Costs remain the same (pass)
- QALYs are not equal but similar to LYs (pass)
- LY should be the same as scenario 1a (fail)
- LYs should be the same as base case (fail)

This suggests that the issue may relate to the disutilities applied. The results also suggest that the applied disutilities contribute significantly to incremental QALYs. This may be due to how the model is parameterised, but it also potentially represents an additional face validity issue.

Scenario 1d. Utilities (and disutilities) = 0 ; age-adjustment = 0

Strategy	Cost	QALYs		Inc Cost	Inc QALYs	ICER	Status	LYs	ILYs
Standard of Care	████	████	████	████	████	████	████	████	████
Resmetirom	████	████	████	████	████	████	████	████	████

Fail:

- Costs remain the same (pass)
- QALYS should be zero (pass)
- LYs should be the same as base case (fail)

This suggests that utility values are intrinsically linked to the LY calculations.

2. Cost

Base case

Strategy	Cost	QALYs	Inc Cost	Inc QALYs	ICER	Status	LYs	ILYs
Standard of Care	████	████	████	████	████	████	████	████
Resmetirom	████	████	████	████	████	████	████	████

Scenario 2a. Set all costs to 0

Strategy	Cost	QALYs	Inc Cost	Inc QALYs	ICER	Status	LYs	ILYs
Resmetirom	████	████	████	████	████	████	████	████
Standard of Care	████	████	████	████	████	████	████	████

Pass:

- Total costs are equal to zero (pass)
- No impact on total QALYs or LYs (pass)

3. Discount rate

Base case

Strategy	Cost	QALYs	Inc Cost	Inc QALYs	ICER	Status	LYs	ILYs
Standard of Care	████	████	████	████	████	████	████	████
Resmetirom	████	████	████	████	████	████	████	████

Scenario 3a. Set discount rates = 0

Strategy	Cost	QALYs	Inc Cost	Inc QALYs	ICER	Status	LYs	ILYs
Standard of Care	████	████	████	████	████	████	████	████
Resmetirom	████	████	████	████	████	████	████	████

Pass:

- Total costs, QALYs and LYs increase (pass)
- Incremental costs, QALYs and LYs increase (pass)

4. Time horizon

Base case = 72

Strategy	Cost	QALYs	Inc Cost	Inc QALYs	ICER	Status	LYs	ILYs
Standard of Care	████	████	████	████	████	████	████	████
Resmetirom	████	████	████	████	████	████	████	████

Scenario 4a. Time horizon = 10

Strategy	Cost	QALYs	Inc Cost	Inc QALYs	ICER	Status	LYs	ILYs
Standard of Care	████	████	████	████	████	████	████	████
Resmetirom	████	████	████	████	████	████	████	████

Scenario 4b. Time horizon = 50

Strategy	Cost	QALYs	Inc Cost	Inc QALYs	ICER	Status	LYs	ILYs
Standard of Care	████	████	████	████	████	████	████	████
Resmetirom	████	████	████	████	████	████	████	████

Scenario 4c. Time horizon = 100

Strategy	Cost	QALYs	Inc Cost	Inc QALYs	ICER	Status	LYs	ILYs
Standard of Care	████	████	████	████	████	████	████	████
Resmetirom	████	████	████	████	████	████	████	████

Pass:

- Total costs, QALYs and LYs increase as the time horizon increases (pass)
- Small difference between Scenario 4b and base case in line with the expectation that most patients will have died after 50 years. (pass)
- Scenario 4c equals base case as all patients have died. (pass)

5. Mortality

Base case

Strategy	Cost	QALYs	Inc Cost	Inc QALYs	ICER	Status	LYs	ILYs
Standard of Care	████	████	████	████	████	████	████	████
Resmetirom	████	████	████	████	████	████	████	████

Scenario 5a. Background mortality = 0

Strategy	Cost	QALYs	Inc Cost	Inc QALYs	ICER	Status	LYs	ILYs
Standard of Care	████	████	████	████	████	████	████	████
Resmetirom	████	████	████	████	████	████	████	████

Pass:

Total QALYs and total LYs increase. (Pass)

5b. Background mortality = yes, cause-specific mortality = 0

Strategy	Cost	QALYs	Inc Cost	Inc QALYs	ICER	Status	LYs	ILYs
Standard of Care	████	████	████	████	████	████	████	████
Resmetirom	████	████	████	████	████	████	████	████

Fail:

- Incremental LYs should be zero (fail)

This is likely due to issues with calculating LYs. The EAG, however, is also concerned that this scenario does not significantly impact incremental QALYs, as the expectation was that LYG would be the main driver of QALY differences rather than improvements in quality of life.

5c. 1a+5b (Utilities =1, disutilities = 0, age-adjustment=0, cause-specific mort = 0)

Strategy	Cost	QALYs	Inc Cost	Inc QALYs	ICER	Status	LYs	ILYs
Standard of Care	████	████	████	████	████	████	████	████
Resmetirom	████	████	████	████	████	████	████	████

Fail:

- Total QALYs and LYs are equal (pass)
- Incremental QALYs and LYs should be zero (fail)

This suggests issues with state occupancy, as no incremental QALYs or life years should be possible.

Scenario 5d: 5a+5c

Strategy	Cost	QALYs	Inc Cost	Inc QALYs	ICER	Status	LYs	ILYs
Resmetirom	████	████	████	████	████	████	████	████
Standard of Care	████	████	████	████	████	████	████	████

Pass:

- Total QALYs and LYs are equal (pass)
- Incremental QALYs and LYs should be zero (pass)

This suggests the issues in 5c relate to the application of background mortality

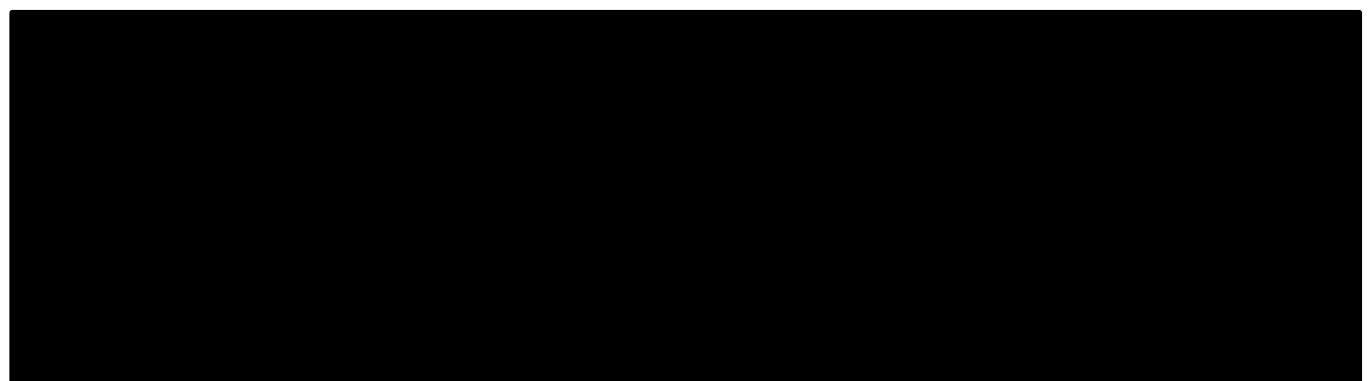
6. Treatment effect

Base case

Strategy	Cost	QALYs	Inc Cost	Inc QALYs	ICER	Status	LYs	ILYs
Standard of Care	████	████	████	████	████	████	████	████
Resmetirom	████	████	████	████	████	████	████	████

Scenario 6a. NASH resolution transition probabilities set to 0

Strategy	Cost	QALYs	Inc Cost	Inc QALYs	ICER	Status	LYs	ILYs
Standard of Care	████	████	████	████	████	████	████	████
Resmetirom	████	████	████	████	████	████	████	████

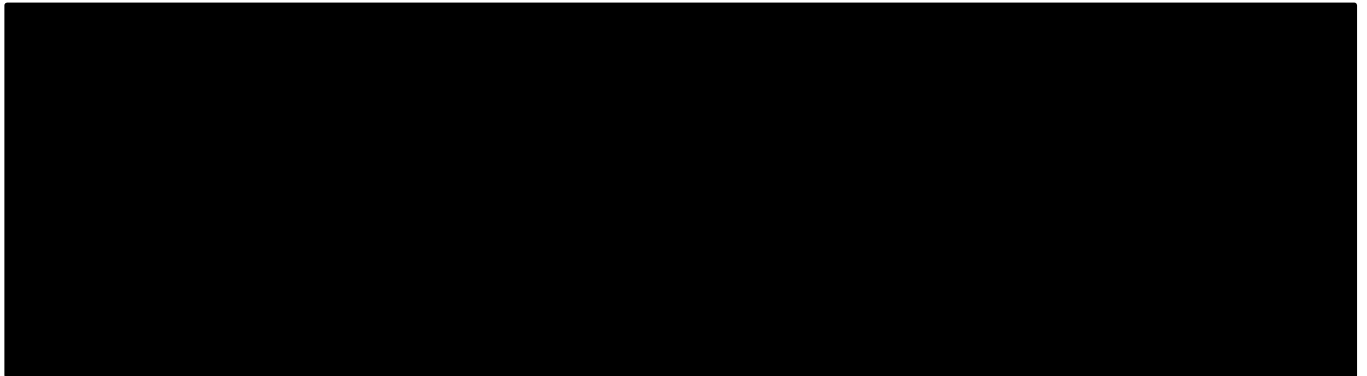


Pass:

- Markov trace – no QALYs and costs accrued on F1R, F2R and F3R (pass)

Scenario 6b. NASH transition probabilities resolution set to 0 and all transition probabilities (stable_no_NASH) = 1

Strategy	Cost	QALYs	Inc Cost	Inc QALYs	ICER	Status	LYs	ILYs
Standard of Care	████	████	████	████	████	████	████	████
Resmetirom	████	████	████	████	████	████	████	████



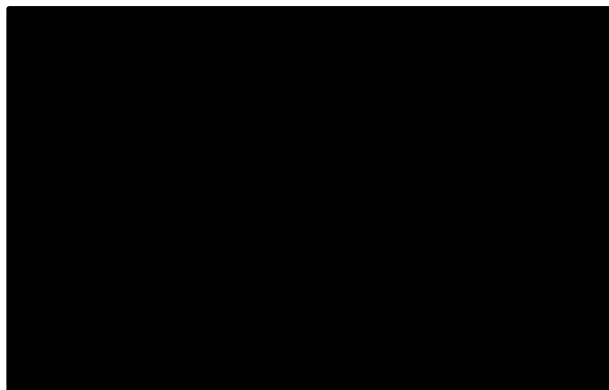
Fail:

- Patients should be able to move from NASH_F3 to DCC and HCC. (Fail)

This suggests the F3 to DCC and F3 to HCC transition probabilities are not being used, or the transition isn't possible.

6b. 6a + set TP for advance liver disease set to 0 (HCC, DCC)

Strategy	Cost	QALYs	Inc Cost	Inc QALYs	ICER	Status	LYs	ILYs
Standard of Care	████	████	████	████	████	████	████	████
Resmetirom	████	████	████	████	████	████	████	████



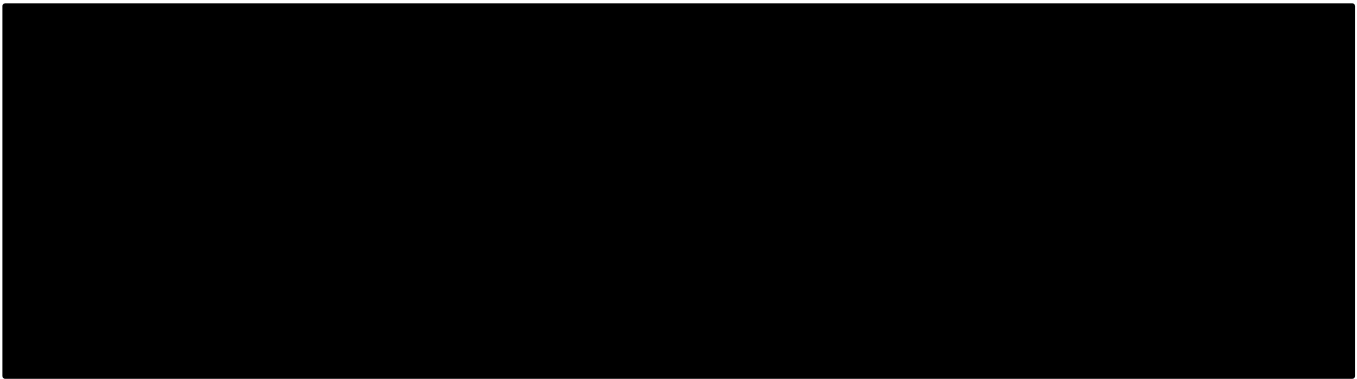
- Large reduction in incremental QALYs and LYs (pass)

While the other tests are technically in line with expectations, the fall in incremental QALYs to near zero implies that nearly all incremental QALY differences are due to hepatic effects.

6c. Stop people having CVD and T2DM events (QRISK, Framingham, UKDPDS set to zero)

n_switch_micro =0, n_switch_macro = 0, n_switch_CVD_non_diab=0

Strategy	Cost	QALYs	Inc Cost	Inc QALYs	ICER	Status	LYs	ILYs
Standard of Care	████	████	████	████	████	████	████	████
Resmetirom	████	████	████	████	████	████	████	████

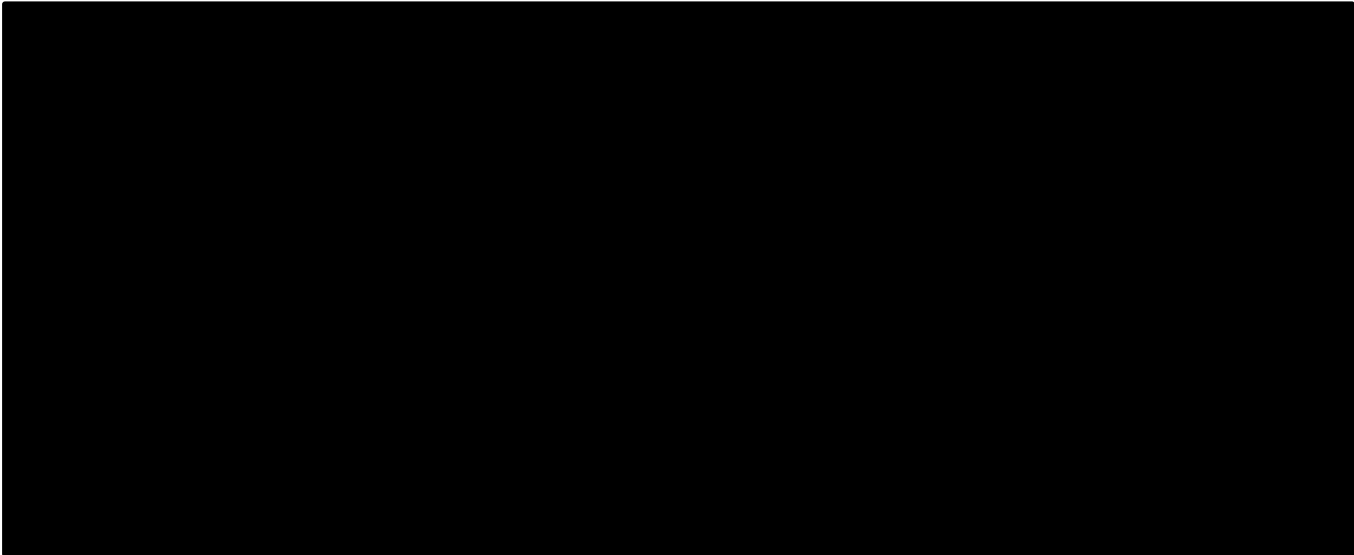


Pass:

- Confirms contribution of extrahepatic effects is small (pass)

Scenario 6d. 6b + 6c

Strategy	Cost	QALYs	Inc Cost	Inc QALYs	ICER	Status	LYs	ILYs
Standard of Care	████	████	████	████	████	████	████	████
Resmetirom	████	████	████	████	████	████	████	████



Fail:

- Time spent in F2/F3 health states is not identical. (fail)
- We would expect zero incremental QALYs and LYs as all treatment effects set to zero. (fail)

This is likely due to the distribution of patients across F2 and F3 health states being different.

Single Technology Appraisal

Resmetirom for treating moderate to advanced liver fibrosis (without cirrhosis) caused by metabolic dysfunction-associated steatotic liver disease [ID6529]

EAG report – factual accuracy check and confidential information check

“Data owners may be asked to check that confidential information is correctly marked in documents created by others in the evaluation before release.” (Section 5.4.9, [NICE health technology evaluations: the manual](#)).

You are asked to check the EAG report to ensure there are no factual inaccuracies or errors in the marking of confidential information contained within it. The document should act as a method of detailing any inaccuracies found and how they should be corrected.

If you do identify any factual inaccuracies or errors in the marking of confidential information, you must inform NICE by the end of **8 December 2025** using the below comments table.

All factual errors will be highlighted in a report and presented to the appraisal committee and will subsequently be published on the NICE website with the committee papers.

Please underline all confidential information, and information that is submitted as **confidential** should be highlighted in turquoise and all information submitted as **depersonalised data** in pink.

Issue 1 The trial population does not match the population in scope [EAG issue 1]

Description of problem	Description of proposed amendment	Justification for amendment	EAG response
Section 3.2.2.1, Page 39 Incorrect simplification of company response as 'assume'	Amend text: "In response to a request for clarification (QA1), the company stated that they assume resmetirom to be equally effective in patients with three or more, or fewer cardiometabolic risk factors." To "In response to a request for clarification (QA1), the company referenced the medicine's mode of action as well as published MASH guidelines from AASLD, BSG and BASL, which all specify NIT cutoffs for pharmacotherapy that are independent of CMRFs. The company concluded based on this evidence that the number of CMRFs is unlikely to affect the efficacy of resmetirom versus placebo."	The current wording inaccurately summarises the company response to QA1 as "they assume" without recounting evidence provided to support this.	We do not consider this to be factually inaccurate.

Section 4.2.3.1; Page 68 Incomplete of NIT threshold sources Inaccurate representation of alignment between MAESTRO-NASH and NIT thresholds	Amend: “Criteria proposed by an expert panel, an unpublished consensus meeting, and updated AASLD guidance suggest that between [REDACTED] and [REDACTED] of the trial population would be eligible, indicating a potentially substantial mismatch between the trial and NHS populations.” To: “Criteria proposed by an expert panel, an unpublished consensus statement from BASL, and updated AASLD guidance suggest that between [REDACTED] and [REDACTED] of the trial population would be eligible, depending on the threshold used for NIT measurements of liver stiffness.”	The EAG’s wording omits that it was BASL that authored the “unpublished consensus meeting” but correctly attributes AASLD guidance. This is unbalanced and should be clarified. The words ‘potentially substantial mismatch’ are vague and incorrectly infer potentially complex and problematic misalignment of patient characteristics between MAESTRO-NASH and anticipated NHS population, when in fact there is a simple explanation: different guidelines recommend varying strict thresholds for NIT fibrosis markers (especially VCTE), which caused patients with lower NIT fibrosis marker scores from MAESTRO-NASH to be excluded.	We have edited this section to note that it was BASL-authored guidance. The phrase ‘potentially substantial mismatch’ has been edited to ‘mismatch’ for clarity.
Section 5.5: Page 110 Incorrect characterisation of NIT thresholds as unvalidated	Amend: “The lack of validated NIT thresholds for identifying resmetirom-eligible patients	NIT thresholds for MASH (especially those based on VCTE) are documented and published in peer-reviewed	Not a factual inaccuracy. The point being made is that there are no agreed NIT criteria, and that the trial and modelled

Inaccurate wording around proportions	further limits the applicability of the trial evidence.” To: “How NIT thresholds are selected to identify resmetirom-eligible patients significantly impacts the applicability of MAESTRO-NASH. Many NIT thresholds would omit patients studied in MAESTRO-NASH.” And Amend: “The EAG notes that a large proportion of MAESTRO-NASH participants would not meet the proposed NIT-based definitions for eligibility, suggesting that the trial population may represent a narrower or more severe subset of the NHS population or one with faster progression.” To: “The EAG notes that different proportions of MAESTRO-NASH participants may not meet NIT-based definitions, depending on the thresholds set for VCTE liver stiffness measurements.”	literature and well-supported by the clinical community. EAG should amend the words ‘large proportion’ since the proportion of MAESTRO-NASH patients excluded by application of NIT thresholds depends on the guideline/threshold used. The eligibility discrepancy between MAESTRO-NASH and guideline NIT thresholds is not because MAESTRO-NASH represents a “narrower, more severe subset” but rather the opposite: NIT thresholds limit treatment to patients with more severe fibrosis markers than those recruited to the trial.	populations are not fully aligned with the population that would be eligible under NIT-based criteria. For clarity we have edited as follows: “The lack of validated NIT thresholds” has been changed to “The lack of consensus agreement on NIT thresholds” “The EAG notes...” has been changed to “The EAG notes that a potentially large proportion of MAESTRO-NASH participants may not meet NIT-based definitions, depending on the criteria applied.”

Section 5.5: Page 110 Ambiguous wording Misuse of “regression”	Amend: “Moreover, they rely on repeated liver biopsies, which are not feasible in routine NHS care. Moreover, the model implies that patients will restart treatment if the patient regresses to back to F2/F3 fibrosis.” To: “Moreover, their implementation in NHS practice would require repeat assessment by NIT and generates uncertainty since the manufacturer’s model is based on biopsy scores. Moreover, the model implies that patients will restart treatment if the patient progresses back to F2/F3 fibrosis.”	The report’s assertion regarding repeat biopsy is contradicted by other EAG statements in this report and in the CS and responses to clarification questions, which acknowledge repeat NITs will need to be used. Minor corrections of ‘regression’ – in liver disease this word always means reversal of fibrosis whereas ‘progression’ signifies worsening.	This has been edited as follows: “These rules are not supported by the SmPC, current clinical guidelines, or expert advice. Moreover, it is not fully clear how assessment of histological outcomes would be assessed in practice as the trial relied on repeated liver biopsies, which are not feasible in routine NHS care. Moreover, the model implies that patients will restart treatment if the patient progresses to back to F2/F3 fibrosis.

Issue 2 Reliance on Surrogate Endpoints [ERG Issue 2]

Description of problem	Description of proposed amendment	Justification for amendment	
Section 4.2.2; Page 65 Incorrect date	Change “Further data cuts from the MAESTRO-NASH trial, including the forthcoming 54-week follow-up (expected [REDACTED])...”	Change “week” to “month”	Edited as suggested

	To: “Further data cuts from the MAESTRO-NASH trial, including the forthcoming 54-month follow-up (expected [REDACTED])...		
Section 4.2.2; Page 65 Incorrect statement of no evidence for relationship of liver fibrosis improvement and long-term outcomes	Amend: “In particular, there is no interventional evidence demonstrating that treatments which improve fibrosis stage also lead to corresponding improvements in clinical outcomes such as liver-related events or mortality.” To: “There is as yet no direct evidence from pharmacotherapy trials showing that a medicine’s reduction in fibrosis stage can also be associated with long-term liver-related outcomes or mortality.”	Bariatric surgery to treat obesity is a comparable intervention with proven benefit in improving fibrosis and reducing long-term mortality and liver outcomes. Although not a pharmacotherapy and only indirectly relevant, we would amend the wording to qualify that the evidence available is highly limited for pharmacotherapies.	Edited as suggested.

Issue 3 Differences between the ITT population and paired liver biopsy population [EAG Issue 3]

Description of problem	Description of proposed amendment	Justification for amendment	EAG response
Section 3.3.1; Page 43 Section 3.3.2; Page 44 Unidirectional representation of	The EAG report omits additional analyses and information provided in the company’s clarification responses (PfC QA5, QA12,	The report makes a misleading blanket statement implying a unidirectional bias in PLB-W52 favouring resmetirom.	Not a factual inaccuracy. The EAG’s concerns regarding direction of bias are set out in EAG report Tables 7 and 8.

statistical uncertainty about paired-biopsy population (PLB-W52)	QA13, QB4 and Appendix A-A), particularly regarding the missing-data sensitivity analyses and the empirical comparisons between the ITT and PLB-W52 populations. As there is no evidence of bias in any one direction, the report should be amended to replace the term “overestimate” with statistically appropriate wording such as: “Treatment-effect estimates differ modestly across analytic populations (LB-W52 vs. PLB-W52), reflecting differences in sample definition and handling of missing data.”	In PfC we provided extensive analysis showing that there was no evidence of a systematic bias, therefore the EAG language should be revised to offer a balanced assessment of uncertainty rather than implying a direction.	

**Issue 4 Validation of the company model and programming complexity [EAG Issue 4] - N.B. BLACK BOX ISSUES
ADDRESSED IN APPENDIX**

Description of problem	Description of proposed amendment	Justification for amendment	EAG response
Section 5.2.2.1; Page 99 <i>The EAG reports that when utility values were set to 1, disutilities to 0, and age-adjustment removed (Scenario 1a), the model produced LYs that differed from those in the base case. Similarly, when utility values were set to 1 while retaining age adjustment (Scenario 1b), the LYs again differed from both the base case and Scenario 1a. The EAG considers that, under these conditions, LYs should remain unchanged, as utility parameters should not influence survival outcomes. These findings led the EAG to conclude that the utility inputs were inadvertently affecting LY calculations, which they interpreted as a potential implementation error and a concern regarding the model's face validity</i>	The interpretation of the EAG is inaccurate and it is based on a typo in the model. We kindly propose that the EAG report be amended to reflect that the observed changes in life-years under Scenario 1a and 1b stemmed from a typographical error in the LY calculation code, rather than from utilities or disutilities affecting survival. This issue has already been identified and corrected in the model. Specifically, in line 2278 of 03_R/01_model_inputs_PC EM_functions.R, the term "QALYs" was used in place	We sincerely appreciate the EAG's careful review and the identification of this issue. We fully agree that utility parameters should not influence LY calculations, and we apologise for the typographical error that led to this unintended behaviour. Correcting the code resolves the discrepancies observed in Tables 22 and 23, and the model now behaves consistently with theoretical expectations—producing unchanged LYs when utilities and disutilities are modified. Updating the report to reflect that the issue arose from an isolated coding error, now corrected, will help avoid misinterpretation that the model's structure or survival logic is intrinsically linked to utility inputs. It also ensures that the face validity concerns raised by	Not a factual inaccuracy. While we acknowledge this was an honest mistake and that it likely does not impact the ICER, this is factually accurate. We also appreciate that the company has made efforts to provide a correction, but we are not able to retrospectively change the report to reflect new information.

	of “LYs,” and has now been corrected to: m_LY[, t + 1] <- effs_result\$LYs Following this correction, we re-ran the scenarios reported by the EAG and confirmed that LYs remain constant as expected when utility and disutility inputs are varied. We propose that this Clarification be incorporated into the report to ensure accurate interpretation of the validation test results.	the EAG in this section are fully addressed and resolved. Please see Appendix 1: Company responses to EAG black box testing	
Section 5.2.2.1; Page 100 <i>The EAG reports that when cause-specific mortality was set to zero, the model produced non-zero incremental LYs and showed minimal change in incremental QALYs. Because both arms should face identical background mortality under this scenario, the EAG expected incremental LYs to be zero and interpreted the observed results as a potential issue with the</i>	We propose that the EAG report be updated to clarify that, in an individual-level microsimulation model, Scenario 2 would not be expected to produce exactly zero incremental LYs. Small non-zero differences can arise purely from random sampling variation, even when both arms face identical background	The non-zero incremental LYs observed in Scenario 2 do not indicate an error in the LY calculations but instead reflect normal stochastic variation inherent to microsimulation. Acknowledging this in the report helps ensure an accurate interpretation of model behaviour and prevents the misunderstanding that these	Not a factual inaccuracy. The EAG recognises that differences between arms can be the consequence of stochastic error. The EAG, however, does not believe this is the case here due to the use of a common seed.

<i>LY calculations or the model's face validity.</i>	mortality risks. This differs from deterministic cohort models, where incremental LYs would be expected to equal zero which is not relevant to this model.	results signal a structural problem in the model.	
Section 5.2.2.1; Page 100 <i>The EAG reports that when treatment effects, transition probabilities, and cardiometabolic impacts for resmetirom were set equal to those of SoC—and the drug cost set to zero—the model continued to produce a small incremental QALY difference between arms. Because both arms were intended to be identical under this scenario, the EAG expected incremental QALYs to be exactly zero and interpreted the observed non-zero results as a potential issue with the model's validity.</i>	We propose that the EAG report be amended to clarify that, in an individual-level microsimulation model, Scenario 3 would not be expected to produce exactly zero incremental QALYs even when treatment effects, transition probabilities, and costs are set equal across arms. Small residual differences can occur purely due to stochastic variation in simulated outcomes, rather than any underlying issue with the model's structure or calculations.	As with Scenario 2, non-zero differences between arms in a microsimulation arise naturally from random sampling, even when all model inputs are identical. These minor residual QALY differences therefore do not indicate an error in the model but reflect normal variability inherent to person-level simulation.	See previous response
Section 5.2.2.1; Page 101 <i>The EAG states that several of the model verification tests drawn from the TECH-VER checklist were not</i>	We propose that the EAG report be amended to acknowledge that several TECH-VER tests referenced	This clarification is needed because the TECH-VER checklist includes tests whose expectations rely on deterministic	The EAG emphasises the importance of the company demonstrating the robustness of the economic

<i>passed and interprets these findings as indications of potential implementation errors, reduced face validity, and limited transparency. The EAG further notes that, due to the model's complexity, the root causes of these issues could not be identified and concludes that additional verification—including more extensive black box testing—is required. The EAG views application of the TECH-VER checklist as an essential step in establishing confidence in the mode</i>	were designed for deterministic cohort models and may not directly apply to individual-level microsimulation models. As a result, small non-zero differences or stochastic variation observed in extreme-scenario tests should not be interpreted as evidence of model implementation errors or lack of face validity.	behaviour, whereas microsimulation models produce stochastic outputs even when inputs are identical between arms. Therefore, some of the reported “failures” reflect normal simulation variability rather than structural or coding errors. Updating the wording in the report would help avoid misinterpretation of these results, ensure that the model is assessed using methods appropriate to microsimulation, and maintain an accurate and balanced representation of model validity. We would like to note that the developers of the TECH-VER checklist explicitly acknowledge that several verification tests are model-dependent and may not be applicable to all model types.	model to ensure both the EAG and, ultimately, the committee have confidence in the results. The TECH-VER checklist, a widely recognised validation tool, is suitable for use with microsimulations. The EAG advises the company to either modify the economic model to eliminate any sources of stochastic error or provide a detailed explanation of the discrepancies, specifically identifying where these differences arise in the model code.
Section 5.2.1.6; Page 106 <i>The EAG states that the company should reconsider the approach used to simulate baseline population characteristics and recommends that the model allow</i>	EAG report should acknowledge that such changes cannot be simply implemented in microsimulation but rather require defining and	In the model framework, characteristics such as age, fibrosis stage, and risk-factor profiles interact to determine individual transition probabilities, costs, and outcomes. As a result,	Not a factual inaccuracy. The EAG is fully aware that joint modelling implies an interdependence between individual characteristics. This does not change the

<i>users to vary key inputs such as age and the proportion of F2 vs F3 patients. The EAG implies that these characteristics can be adjusted directly as in a cohort-based Markov model.</i>	simulating new patient subgroups with internally consistent joint distributions of characteristics.	adjusting a single summary parameter (e.g., average age or the F2/F3 split) is not sufficient, because it does not automatically generate the joint distribution of covariates that drive disease progression. The EAG's current wording fails to reflect this complexity and we feel it would be fair if it did.	substance of the EAG's critique.

Issue 5 Response to treatment not captured by the current model structure [EAG Issue 5]

Description of problem	Description of proposed amendment	Justification for amendment	EAG response
Section 1.3; Page 18 Mischaracterisation of “response-based treatment rules” and incorrect representation of modelled discontinuation rates	Change wording from “The company’s model assumes continuous treatment while patients remain in F2–F3, regardless of response, and allows discontinuation only when patients leave these fibrosis states.” to “The company’s model uses fibrosis response-based treatment rules only, regardless of MASH resolution status to inform discontinuation related to fibrosis stage. It assumes patients continuously receive resmetirom whilst in fibrosis stages F2 or F3, discontinuing permanently if fibrosis worsens to F4 (compensated cirrhosis), or temporarily suspending resmetirom if fibrosis improves to F1 or better. Furthermore, dose-specific annual resmetirom discontinuation rates (2.8% for 80mg, 7.7% for 100mg) derived	The current EAG wording can be interpreted to mean that changes in fibrosis stage - used to determine treatment start/stop decisions in our model - do not constitute a relevant response variable. In addition, as explained in CS Section 3.3.2.2 and explored through a scenario analysis, the model includes all cause discontinuation from resmetirom or placebo as informed by the MAESTRO-NASH trial in addition to discontinuation based on transitioning to fibrosis stages outside F2 and F3.	Not a factual inaccuracy. Response may also be defined with respect to non-histological outcomes. For clarity, we have edited as follows: “...regardless of other response criteria, and allows discontinuation only...” While the company is correct, the model also applies an annual discontinuation rate. This information is not necessary to understand the issue highlighted in the executive summary.

	from all-cause discontinuation in MAESTRO-NASH were applied throughout the time horizon, regardless of fibrosis stage.”		
Section 1.3; Page 13 Mischaracterisation of “response-based assessments”	Amend: “Appropriate revisions to the company’s economic analysis to include response-based assessments.” To: “Appropriate revisions to the company’s economic analysis to explore NIT-based assessments most likely to reflect usage decisions in the NHS throughout scenario analyses.”	The current wording incorrectly states that a) that our base case model does not capture “response to therapy”, and b) that we have omitted other, specific “response” criteria anticipated, but not yet established, in NHS practice. This misrepresents the MAESTRO-NASH clinical trial data as well as currently (e.g. Nouredin et al 2024) and soon-to-be published NIT thresholds (BASL MASLD SIG), for initiation and discontinuation with resmetirom. In our model, treatment response is assessed at 12 monthly intervals. Fibrosis responders either improve or remain stable in their baseline group of fibrosis stages F2 or F3. Worsening to F4 (CC) leads to permanent discontinuation and can be considered non-response. Improvement to F1 or better, also	Edited as suggested

		the result of fibrosis response, leads to an assumed suspension of therapy unless F2 or F3 fibrosis develops again. These approaches for discontinuation of therapy in stages outside of F2 and F3 are in line with the Nouredin et al. 2024 publication's recommendations not to treat cirrhotic (F4) or early stage (F0, F1) patients with resmetirom and also align with its response-based rules for discontinuation. Please see below.	
Section 1.3; Page 13 and Section 4.2.2; Page 65 Incorrect representation of guidance from Nouredin et al. 2024 regarding NITs thresholds informing discontinuation of resmetirom	Page 13: Amend: "However, expert guidance (e.g., Nouredin et al., 2024) proposes response assessment at 12 months using non-invasive tests (NIT)s, with treatment stopped if no response is observed or if tests worsen." To: "By comparison, expert guidance (Nouredin et al., 2024) proposes response assessment at 12 months using non-invasive tests (NIT)s, with resmetirom	The EAG's summary of Nouredin et al 2024 is factually incorrect. Both Figure 2 and the text in Nouredin et al specify that resmetirom discontinuation is recommended if: • No response is observed in MRI-PDFF (if MRI-PDFF was obtained at baseline); or • There is a >30% increase in liver stiffness (measured by	Edit as suggested

	treatment stopped if NIT results worsen, continued if NIT results improved and considered for continuation if NIT results show no change. Page 65: Amend: “Treatment discontinuation is recommended when no response is observed by 12 months or when ≥ 2 NITs worsen.” To correctly reflect guidance in Nouredin et al 2024 both in terms of discontinuation and treatment continuation.	MRE or VCTE) or >2 NITs worsen; or • Drug not tolerated. Proton Density Fat Fraction, obtained via MRI (MRI-PDFF) is not a fibrosis marker but a marker of effect on steatosis and hardly ever assessed in NHS liver clinics. Nouredin et al. recommend this variable can be used if it was collected at baseline and 12-month follow-up. Nouredin et al’s recommendations around treatment continuation relate primarily to liver stiffness measurements that indicate fibrosis: either magnetic resonance elastography (MRE) or vibration controlled transient elastography (VCTE) at levels reported in the publication. The EAG report should correctly summarise that Nouredin’s recommendations to discontinue resmetirom are not conditional on	

		a minimum improvement level being missed (excepting MRI-PDFF, if available) but rather, as per our economic model, on a worsening of liver stiffness/fibrosis NITs (pragmatically, this means progression from F2 or F3 to F4 since smaller changes within F2/3 are neither distinguishable nor clinically meaningful if assessed by VCTE or MRE).	
Section 4.2.2; Page 65 Paragraph 3, Mischaracterisation of company response to Noureddin	Correct: “At clarification, the company was dismissive of these criteria, citing unpublished BASL MASLD SIG guidance as more relevant to NHS clinical practice.” To: “At clarification, the company indicated that it considered the currently unpublished BASL MASLD SIG guidance to be most relevant to NHS clinical practice, as it is authored by UK clinicians and based on the NITs most likely to be used in clinics in England and Wales.”	The characterization of our attitude to Noureddin et al as “dismissive” is factually incorrect. The EAG has not substantiated it with quotations from our response. We believe a misunderstanding has arisen from the EAG’s write-up of the Noureddin paper stopping rules (see previous row). For further clarity, consider the AASLD guideline rationale which aligns closely with Noureddin: <i>“An important consideration is that stabilization of fibrosis may portend important long-term benefits; for persons with advanced fibrosis, apparent lack of fibrosis</i>	Edited to “At clarification, the company indicated that it considered the currently unpublished BASL MASLD SIG guidance more relevant to NHS clinical practice.”

		<i>improvement should not mandate discontinuation of resmetirom therapy.”</i>	
Section 4.2.2; Page 65 Paragraph 3, Mischaracterisation of company rationale for using MAESTRO-NASH data	Amend: “The company stated that evidence from MAESTRO-NASH was not sufficient to inform a response-based stopping rule, noting that the trial was designed and powered for histological endpoints rather than NIT-based endpoints.” To “The company stated that MAESTRO-NASH evidence could not sufficiently inform alternative stopping rules beyond those linked to fibrosis progression. This leaves unquantified uncertainty about cost-effectiveness if its modelled stopping rules are translated to NITs used in NHS practice.”	The EAG wording risks conflating issues regarding response-based modelling with the issue of NIT-versus biopsy-defined fibrosis assessments. We have hopefully clarified that the stabilisation or reversal of fibrosis constitutes the key goal of MASH treatment; its attainment warrants treatment continuation in published guidelines including Nouredin et al. Nouredin also stipulates MRI-PDFF score thresholds, but these are primarily presented as a safeguard against accidental discontinuation of resmetirom: “Based on MAESTRO-NASH, histologic improvements may occur without corresponding changes in VCTE or liver enzymes, emphasizing the importance of considering MRI-PDFF or liver biopsy before labeling patients as unresponsive to treatment.”	Edited as suggested

Section 4.2.2; Page 65 Paragraph 5	To remain accurate and consistent, the EAG should review this paragraph in the light of our previous comments about response-based stopping rules and how they are defined in terms of fibrosis/liver stiffness.	In our model treatment discontinuation due to non-response occurs when a patient progresses to F4 – this is consistent with liver stiffness worsening detectable on NITs (F2 and F3 are not distinguished by NITs). Noureddin et al 2024 explicitly state: “the drug should not be used in patients diagnosed with or suspected to have cirrhosis until full efficacy and safety data in patients with cirrhosis are published”, and “Patients with early stage MASLD (no or early fibrosis [eg, stage 0 or 1]) should not be considered for resmetirom treatment because they are at very low risk for adverse liver-related outcomes.” Patients who improve or maintain stable fibrosis markers (within F2 F3) are considered responders and kept on treatment. Percentage MRI-PDFF reduction in liver fat as a response criterion is clinically valid but rarely collected	While the EAG appreciates the point being made, this is not a factual inaccuracy.

		in the NHS and is an optional criterion to consider in Nouredin, and absent from the BASL MASLD SIG consensus statement for this reason.	
Section 5.5; Page 111	Amend: “A fourth significant area of uncertainty relates to the structural assumptions underpinning the company’s economic model, particularly the absence of any clinically plausible response assessment to guide ongoing treatment. The EAG’s clinical experts and published expert opinion suggests that real-world management would involve periodic response-based assessment using NITs. The company’s model, however, includes no such response-based assessment, focusing only on histological outcomes, which the EAG considers a major limitation of both the company’s economic analysis and current clinical evidence base.”	Please see our other points regarding response-based assessment and clarification of the Nouredin guideline. The paragraph at left needs re-writing avoid factual inaccuracy about what ‘clinical response’ means in MASH and how it leads to treatment decisions. All guidelines include NIT-derived liver stiffness measurements (e.g. VCTE) which indicate fibrosis stabilization or improvement as the most clinically relevant and plausible response characteristics. Non-response is defined as a worsening in these NIT-derived liver stiffness measurements. In our model, this is reflected in the discontinuation rule upon progression to F4.	While the EAG has some sympathy for the outlined position, neither the company model nor the submission more broadly makes it clear how histological outcomes correlate with NIT-derived outcomes, such as liver stiffness. The EAG has, however, softened the language in this paragraph and shifted the focus to lack of clarity regarding how NITs would be used.

	To reflect points outlined in this FAC related to response-based assessment.		

Issue 6 Stopping rules and discontinuation of resmetirom treatment [EAG Issue 6]

Description of problem	Description of proposed amendment	Justification for amendment	EAG response
Section 1.3; page 19 Claim that manufacturer has misinterpreted marketing authorisation for resmetirom.	Amend: “the company’s assumption that patients must stop treatment when moving outside the F2–F3 initiation population appears to misinterpret the marketing authorisation.” To: “the company’s assumption that patients must stop treatment when attaining fibrosis stages other than F2 and F3 is not explicitly stipulated in the marketing authorisation, and requires further validation by clinical experts. The uncertainty around assumed stopping rules and its impact on ICERs should also be explored in	It is factually incorrect to state that our model misinterprets the marketing authorisation. EAG provides no valid grounds, semantic, legal or clinical, for why our model base case represents a “misinterpretation” of the label. This is more than an opinion in our view and implies a level of evidence that is absent. Stating that the manufacturer has misinterpreted its own marketing authorisation, especially in the circumstance where the medicine has not yet been launched into the NHS and its method of adaptation therein remains uncertain, is misleading.	Edited as suggested

	appropriate sensitivity analyses.”		
Section 1.3; page 19 Contradictory wording around NITs	Correct “Fibrosis staging in the MAESTRO-NASH trial relied on liver biopsy, which is unsuitable for routine care, while non-invasive tests lack the accuracy needed to determine fibrosis stage and cannot provide detailed information on MASH resolution.” To “Fibrosis staging in the MAESTRO-NASH trial relied on liver biopsy, which is unsuitable for routine care. NITs are expected to be used for fibrosis staging in the NHS, although MASH resolution is not definitively assessable by NIT.”		Edited as suggested

Issue 7 Repeated application of transition probabilities and short-term trial follow-up [EAG Issue 7]

Description of problem	Description of proposed amendment	Justification for amendment	EAG response
Section 1.3; Page 19 Incorrect cross-reference	Amend cross-reference in Section 1.3	The report refers to Sections 3.2.2.4 and 4.2.2 as relating to EAG Issue 7. However, Section 3.2.2.4 does not address the topic associated with Issue 7; instead, it discusses disease progression, not the specific methodological concern identified in Issue 7 Likewise section 4.2.2 does address some topics related to the model structure	These have been corrected.
Section 4.2.5; Page 76 Inaccurate representation of transitions applied in the economic model	Amend the paragraph to accurately describe the model structure and the analyses provided. For example, change text from: “The EAG has significant concerns regarding the repeated use of the same set of transition probabilities throughout the entire model time horizon. This assumption suggests that patients continuing treatment	The EAG state that the company’s approach “suggests that patients continuing treatment with resmetirom and SoC will lead to an increasing proportion of the modelled population achieving MASH resolution” and that this “implies that the likelihood of achieving MASH resolution is entirely independent of the duration of treatment, meaning your chance of resolution remains the same	Not a factual inaccuracy. The EAG considers this an accurate description of the model structure and the applied transition probabilities.

	with resmetirom and SoC will lead to an increasing proportion of the modelled population achieving MASH resolution; MASH resolution is fundamental to changes in fibrosis within the model and this assumption implies that the likelihood of achieving MASH resolution is entirely independent of the duration of treatment, meaning your chance of resolution remains the same whether you have never been treated before or have been on the same treatment for 30 years.” To: “The company model assumes time-homogeneous transition probabilities conditional on treatment status (on-resmetirom vs SoC/off-treatment) and fibrosis stage, based on MAESTRO-NASH. Over time, however, the proportion of patients receiving resmetirom decreases because of permanent and temporary treatment discontinuation and	whether you have never been treated before or have been on the same treatment for 30 years.” As currently drafted, the EAG text implies that: • transition probabilities are applied identically to all patients for the full time horizon, regardless of treatment discontinuation or stopping rules; and • no explicit exploration of treatment-effect waning or time-limited treatment was conducted. In fact, the model implements waning at the cohort level through empirically-based discontinuation and stopping rules, assumes no residual effect after stopping, and includes a scenario in which all patients discontinue after 2 years (consistent with TA875). Accurately reflecting these features is important for readers’ understanding of the structural assumptions, the extent to which long-term benefits may attenuate	

	stopping rules (patients stop resmetirom on regression to lower fibrosis stages < F2 or progression beyond F3). The cohort-average transition probabilities therefore gradually converge towards those for SoC, and no legacy treatment effect is assumed after discontinuation. The company explored alternative assumptions about durability, including a scenario in which all patients discontinue resmetirom after 2 years, consistent with NICE TA875. Nevertheless, in the base case, individuals who remain on treatment are assumed to retain the same probability of MASH resolution over time in the absence of longer-term data, which the EAG considers may overestimate long-term benefits.”	over time, and the robustness of the cost-effectiveness results to alternative waning assumptions. Moreover, the current EAG text does not accurately represent the mathematical structure of the company’s model and may mislead readers into believing that fixed transition probabilities are applied uniformly across the entire cohort for the full time horizon. The model incorporates: • patient-level discontinuation hazards (relatively high and constant), • treatment stopping rules, • a mixture-matrix formulation producing endogenous cohort-level waning, and • immediate reversion to SoC probabilities after stopping. Accurately reflecting these features is essential for understanding how long-term treatment effects evolve in the model, how waning is represented, and why the model	

		does not assume constant treatment benefit for 30 years.	

Issue 8 Misinterpretation of Singh et al (2015) [EAG Issue 8]

Description of problem	Description of proposed amendment	Justification for amendment	EAG response
Section 4.5.21; Page 77 Misrepresentation of how data from Singh et al. 2025 are used in the economic model	Amend: “Singh et al. (2015)³⁴ conducted a systematic review and a meta-analysis of paired-biopsy studies. As part of their analysis, they summarised transitions between fibrosis stages observed in the included studies. These studies followed patients for variable durations, though inclusion required a minimum follow-up of one year. This is not consistent with the way the data were used in the company’s model, where they informed the number of fibrosis stages a patient can transition through within a single annual model cycle.” To: “Singh et al. (2015) conducted a systematic review and meta-	The EAG state that Singh et al. (2015) were used “to inform the number of fibrosis stages a patient can transition through within a single annual model cycle.” This does not accurately describe how these data were implemented. In the company model, Singh et al. were used only to distribute patients who had already been classified as having fibrosis “improvement” or “worsening” across the available fibrosis stages (F0–F4), with the same distribution applied in both arms. The annual probabilities of improvement and worsening were parameterised from MAESTRO-NASH rather than directly from Singh et al.	For clarity, this has been edited to the following “This is not consistent with the way the data were used in the company’s model where they informed the number of fibrosis stages a patient can transition through in those who had already been categorised as improving or worsening fibrosis.”

	analysis of paired-biopsy studies. As part of their analysis, they summarised transitions between fibrosis stages observed over variable follow-up durations (minimum 1 year). In the company's model, these data were not used as annual transition probabilities but rather to distribute patients who had already been categorised as improving or worsening fibrosis across the fibrosis stages F0–F4, with the same distribution applied in both arms. The annual probabilities of improvement and worsening were based on MAESTRO-NASH data.”	This amendment is needed to accurately describe the role of Singh et al. (2015) in the economic model. As currently drafted, the text implies that Singh et al. were used directly as annual multi-stage transition probabilities, which is not the case and may mislead readers regarding the empirical basis for the model structure.	

Issue 9 Natural history of MASH and face validity of model progression rates [EAG Issue 9]

Description of problem	Description of proposed amendment	Justification for amendment	EAG response
Section 2.1; page 27 Section 3.2.2; Page 42 Section 4.1.3; Page 58	The EAG report fails to explain that MASLD evidence represents a broader metabolic liver disease population that is not directly applicable to the NICE-scoped population of	The EAG cites evidence and conclusions derived from MASLD cohorts, including patients with low fibrosis risk, to characterise progression rates and clinical trajectories relevant to the	We do not consider these sections to be factually inaccurate.

Inclusion of evidence from a broader patient cohort (MASLD) outside the scope of this decision problem (F2-F3 stage MASH fibrosis) to inform MASH-specific inputs	adults with MASH and F2–F3 fibrosis. All statements regarding progression rates, rapid progressors, long-term outcomes, or lifetime benefits should distinguish clearly between MASLD populations and the narrower, higher-risk MASH F2–F3 cohort and ensure wherever evidence that is based on MASLD patients or patients with earlier stages of fibrosis within MASH (F0, F1) has been appropriately caveated and cautioned to avoid overinterpretation considering the vast difference in prognosis, clinical profile and potential outcomes between these populations.	appraisal. However, the final NICE Scope defines the decision problem as adults with non-cirrhotic moderate to advanced liver fibrosis (F2–F3) caused by MASH. MASLD populations include a substantially broader and clinically heterogeneous group, most of whom do not have MASH and are at materially lower risk of progression and many of whom will never become eligible for treatment with resmetirom on the NHS. Using MASLD evidence to draw conclusions about progression rates, treatment effect duration, or long-term benefits does not align with the scoped population for decision-making and may significantly impact and bias decisions that should be based on clinical trial evidence. The proposed amendment is necessary to ensure that evidence is interpreted by Committee within the correct decision framework. MASLD populations differ substantially from MASH F2–F3 in	We do not consider MASH and broader MASLD to be equivalent, however we do think that the broader evidence on MASLD (e.g. in the MASLD-NASH-1 trial) is useful as some of those patients have MASH with fibrosis, and may more accurately represent typical patients who will not receive a liver biopsy to confirm MASH.

		baseline fibrosis severity, risk of progression, and event rates. As a result, MASLD-derived estimates — such as the low rates of liver-related mortality or slow natural progression which the EAG cites — are not directly generalisable to patients with moderate to advanced fibrosis, who are the focus of this appraisal.	

Issue 10 Limited justification for selected input parameters, poor referencing, and and lack of clarity regards how some input values are generated [EAG Issue 10]

Description of problem	Description of proposed amendment	Justification for amendment	EAG response
Section 4.2.5.2; Page 80 Omission of reference to supplied systematic reviews that informed the model approach and parameters	Amand: “The absence of a clear rationale for study selection raises concerns about potential cherry-picking. Furthermore, neither study includes UK patients, which may limit the generalisability of the findings to a UK setting, and event rates were small for some outcomes. For example, among patients with F3	The EAG’s wording implies widespread selective evidence use, whereas only a small number of transition parameters were queried. The most influential inputs in the model—including treatment effects, fibrosis transitions, cardiometabolic outcomes, and quality-of-life effects—are derived directly from the MAESTRO-NASH trial or from recent systematic literature reviews specifically conducted for this	Not a factual inaccuracy. It is clear that this issue concerns only a small number of transitions.

	fibrosis, only two HCC events were reported.” To: “The absence of further explanation of how these studies were selected make it unclear how parameters were derived. Studies used were identified through systematic literature reviews and transition values applied are consistent with those used in previous published economic evaluations. While neither study includes UK patients, which may limit generalisability to a UK setting, and event rates were small for some outcomes—for example, only two HCC events were reported among patients with F3 fibrosis.”	submission. In addition, all cost parameters were sourced from UK-relevant evidence (e.g., NICE NG49, Davidson et al.) to ensure applicability to the NHS setting. The transition values highlighted by the EAG represent a minor subset of inputs and have been used in previous published economic evaluations in MASLD/MASH.	

Issue 11 Appropriateness of modelled utility values and MASH resolution increment [EAG Issue 11]

Description of problem	Description of proposed amendment	Justification for amendment	EAG response
Section 4.2.6.; Page 89 Paragraph 1	Page 89: Amend “The EAG also considers the NG49	The EAG report is contradictory in that the EAG does not consider NG49 an appropriate source for	Edited as suggested

Resolve contradictory points	utility values to lack face validity.” To “The EAG also considers the NG49 utility values to lack face validity for some health states.” Page 89: Amend the statement “Given these limitations, the EAG does not consider NG49 to be an appropriate source of HRQoL values for the economic model.” To “Given these limitations, the EAG does not consider NG49 to be an appropriate source of HRQoL values for the economic model for F0-F4 health states.”	earlier health states but accepts its use for later health states, as noted on page 90, “For advanced liver disease health states (DCC, HCC, and LT), the company’s values appear reasonable.” Therefore, EAG should amend wording to avoid generalisation to NG49.	
Section 4.2.6.; Page 89 Paragraph 3	Amend “...reported that MASLD patients have lower HRQoL than matched healthy controls (0.77 vs 0.84; $P < 0.001$), but found minimal, non-significant differences between patients with and without advanced	The authors of this publication state, “However, all indices were significantly lower in cirrhotic (n=147) compared with non-cirrhotic	Edited to “... consistent with clinical advice received by the EAG”

	fibrosis (F0 vs F3: 0.777 vs 0.786; P = .570). The decline between F3 and F4 in this study was modest (0.79 vs 0.73; P < 0.032), which is more consistent with clinical expectations.” To “...reported that MASLD patients have lower HRQoL than matched healthy controls (0.768 [±0.273] vs 0.841 [±0.194]; P < 0.001), but found minimal, non-significant differences between patients with and without advanced fibrosis (F0 vs F3: 0.777 [±0.263] vs 0.786 [±0.267]; P = .570). The decline between F3 and F4 in this study was 0.787 (±0.264) vs 0.725 (±0.285; P = 0.032), which is more consistent with expectations from the clinicians we interviewed.”	(n=366) patients (Supplementary Table 2). Therefore, there was significant HRQoL impairment in all stages of NAFLD.” The authors do not comment about how “modest” or “large” the differences are, which is an interpretation of results by the EAG not supported by author conclusions. In addition, the authors consistently report standard deviations, which are lacking from the EAG report and may lead to misinterpretation of differences by the reader, but the standard deviations also incorporate quite a sizeable difference in point estimate (around 0.2 in utility) that exceeds the difference in utility values reported between F3 and F4 states in NG49 and that within the Papatheodoridi et al publication. These proposed edits also correct a typographical error regarding the p-value associated with the comparison of results between F3 and F4 patients.	

Section 4.2.6.; Page 89 Paragraph 3	Page 89: Amend “The NG49 values are also inconsistent with other UK evidence. Papatheodoridi et al. (2023), a UK study of 513 patients with MASLD, reported” To “The NG49 values are also inconsistent with other UK evidence. Papatheodoridi et al. (2023), a UK study of 513 patients with MASLD using EQ-5D-5L, reported...”	Papatheodoridi et al. (2023) is a study of MASLD patients using the EQ-5D-5L measure and utility values derived from this are not directly comparable to utility values calculated based on the EQ-5D-3L. It would be misleading to present this study as an alternative for use in the economic model without noting that this is using the -5L set and for recommending use of it without noting the need to convert values to 3L prior to use.	P 89 Edited as suggested
Section 4.2.6; Page 90 Paragraph 3	Page 90: Amend “The EAG’s preferred approach is therefore to use either the MAESTRO-NASH data or the values reported in Papatheodoridi et al. (2023) for health states F0–F3. For the compensated F4 health state, the EAG prefers to use the value from Papatheodoridi et al. (2023), as this better reflects clinical expectations and is more representative of the modelled population.”	As noted in the row above, the NICE health technology evaluations: the manual (Section 4.3.16) states: “If data was gathered using the EQ-5D-5L descriptive system, utility values in reference-case analyses should be calculated by mapping the 5L descriptive system data onto the 3L value set. If analyses use data gathered using both EQ-5D-3L and EQ-5D-5L descriptive systems, the 3L value set should be used to derive all utility values, with 5L mapped onto 3L when needed.”	P90. The EAG is not suggesting that these values be converted to EQ-5D-3L. This is not possible with the data available.

	To “The EAG’s preferred approach is therefore to use either the MAESTRO-NASH data or the values reported in Papatheodoridi et al. (2023) for health states F0–F3 after conversion to EQ-5D-3L For the compensated F4 health state, the EAG prefers to use the value from Papatheodoridi et al. (2023) after conversion to EQ-5D-3L, as this better reflects clinical expectations and is more representative of the modelled population.”		
Section 4.2.6.; Page 89 Paragraph 2 and 3	Amend the statement “There is no clear biological or clinical rationale for the large decline in HRQoL between F3 and F4 compensated cirrhosis implied by NG49.” To “The EAG do not believe there is justification for the magnitude in decline in utility value between F3 and F4 compensated cirrhosis stage as reported in NG49.”	The text in the second and third paragraph on this page is contradictory. If there was no biological or clinical rationale for a decline in HRQoL, there would not be a statistically significant change in HRQoL identified by Papatheodoridi et al between F3 and F4 health states. This is the interpretation of the EAG of a 0.12 change versus a 0.06 change between two different sources.	Not a factual inaccuracy The EAGs concern is the magnitude of the change, not whether one should exist at all.

		The HTA Lab report notes that progression to cirrhosis has impacts on both quality of life and survival, stating “MASH fibrosis is believed to be generally asymptomatic... Progression to decompensated cirrhosis represents a major reduction in health-related quality of life and is the stage that increases the likelihood of liver cancer and death.”	
Section 5.5; Page 111 The EAG interpretation of the utility evidence contains factual inaccuracies, including: (1) an incorrect EQ-5D-3L equivalent value for F4 derived from Paptheodoridi et al. (2023), (2) omission of NG49 as the NICE-endorsed UK source for utilities in progressive fatty-liver disease, and (3) omission of the statistically significant utility improvement associated	Amend the report to: (a) clarify that NG49 is the appropriate NICE-endorsed EQ-5D-3L utility source for fatty-liver disease; (b) update the F4 value from Paptheodoridi et al. (2023) using the correct Hernández (2022) EQ-5D-5L→3L crosswalk (0.64 rather than 0.725); (c) acknowledge the empirical MAESTRO-NASH utility improvement associated with MASH resolution; and (d) note that the company has implemented the EAG’s preferred MAESTRO-NASH	These corrections are needed to ensure factual accuracy. NG49 is the only NICE-endorsed, UK-relevant EQ-5D-3L utility set for progressive fatty-liver disease. Paptheodoridi et al. report EQ-5D-5L utilities from a NAFLD (not MASH) cohort, and the correct EQ-5D-3L equivalent using Hernández (2022) is 0.64, not 0.725. MAESTRO-NASH regression analyses show a statistically significant utility improvement for MASH resolution, supporting its inclusion. Applying the EAG-preferred fibrosis-stage utilities produced <6% change in incremental QALYs and the ICER, confirming that utilities are not a	Not a factual inaccuracy The EAG has made it very clear where the NG49 values come from and believes it has accurately reflected the issues at hand.

with MASH resolution observed in MAESTRO-NASH.	fibrosis-stage utilities (F0–F3 ± MASH resolution, plus F4 = 0.64).	major driver of cost-effectiveness and do not materially affect decision-making.	

Issue 14 Current and anticipated use of GLP-1 antagonists in the UK [EAG Issue 14]

Description of problem	Description of proposed amendment	Justification for amendment	EAG response
Section 1.4; page 23 Discrepancies between summary table versus body text	Correct “However, the EAG is concerned about excluding semaglutide.” To “The EAG accepts that semaglutide could not be reasonably made a direct comparator in this appraisal. However...” and then lead into the following text.	The report’s body text makes clear that while the EAG accepts the company’s reasons for excluding semaglutide in the CS, it nonetheless has concerns about semaglutide becoming a relevant comparator in the future. However, the summary table on page 19 is structured to convey that it is the company’s decision to exclude semaglutide which is the cause for concern.	We have amended the text of Issue 14 to clarify our position.
Section 2.3.5; page 32	Amend: “The EAG agrees that excluding these comparators is reasonable. However, we note that	The EAG comment in this table contradicts the EAG’s body text acknowledgement	We have amended the text about semaglutide in Table 2.

Table 2	that for the subset of patients with metabolic risk factors such as obesity and or type 2 diabetes, semaglutide should be considered as a comparator.” To: “The EAG agrees that excluding these comparators is reasonable and that it would not be reasonable to include semaglutide as a direct comparator in the submission for this appraisal. Patients with metabolic risk factors such as obesity and or type 2 diabetes may be eligible to receive semaglutide, which is anticipated to have its own marketing authorisation for MASH treatment in the future.”	that the CS could not have reasonably included semaglutide as a direct comparator.	
Section 1.4; Page 24	Change “The company submission did not reference the NICE HTA Innovation Lab report on MASLD treatments, despite its relevance in the NICE scope.” to “The company submission did not repeatedly reference the NICE HTA Innovation Lab report on MASLD treatments in developing the model design and approaches, despite its relevance in the NICE scope.”	The HTA Lab report is cited within the CS (reference # 22).	Edit to “The company submission made limited reference to the NICE HTA Innovation Lab report on MASLD treatments, despite its relevance in the NICE scope

Issue 15 Deviations for HTA Lab recommendations [EAG Issue 15]

Description of problem	Description of proposed amendment	Justification for amendment	EAG response
Section 4.1.3.1; Pages 59-61 The EAG states that the company did not adequately follow the recommendations set out in the NICE HTA Innovation Laboratory (HTA Lab) report. Table 10 of the EAG critique lists several areas where the company model is described as “diverging” from the HTA Lab guidance. The EAG suggests that the deviations undermine the consistency of the evaluation.	Amend the EAG report to clarify that the HTA Lab document provides advisory guidance rather than mandatory methodological requirements, and that the company model is aligned with the core structural recommendations (e.g., state-transition modelling, inclusion of hepatic and cardiometabolic outcomes). The wording should further indicate that several items listed in Table 10 represent optional or forward-looking enhancements that may be explored collaboratively during technical engagement if considered decision-relevant. Please see above rows related to EAG Issue 14. Amend Table 10 by removing the row “Stratification of	lems identified by the EAG as “deviations” in Table 10 primarily relate to areas that the HTA Lab document presents as potential future enhancements, rather than required components of a base-case model. For example: These subgroup analyses were not included in the final NICE scope and therefore fall outside the requirements of the current decision problem.	We have edited the text to make it clear that the HTA lab recommendations are not intended to be prescriptive.

	model population & subgroup analysis” and any text describing the company as diverging from HTA Lab recommendations in relation to BMI or hypertension subgroup modelling.		

Issue 16 Extrahepatic treatment effects [EAG Issue 16]

Description of problem	Description of proposed amendment	Justification for amendment	EAG response
Section 1.4; Page 25 Misinterpretation of clinical and epidemiological evidence around fibrosis and CVD	Amend “Regarding fibrosis, the model assumes advanced fibrosis increases CVD risk, based on the US HTA Agency (US ICER) assumptions. The EAG considers fibrosis a marker of cumulative cardiometabolic risk rather than a causal driver, and modelling it as directly influencing CVD events is unsupported by evidence.” To “Regarding fibrosis, the model assumes advanced fibrosis increases CVD risk, based on the US HTA Agency (US ICER) assumptions. The degree to which fibrosis stage	Liver fibrosis stage is an independent risk factor for cardiovascular events, separate to other cardiometabolic risk factors. This has been demonstrated in peer-reviewed studies, and it is factually incorrect for EAG to assert that fibrosis is only a marker of CVD rather than an evidence-backed predictor of CVD in its own right. We wish to point out that inclusion of CVD risk models and any changes to values	Not a factual inaccuracy. The EAG invites the company to present evidence to support the independent impact of fibrosis stage.

	independently promotes CVD risk should be further explored in sensitivity analysis as the EAG regards this as subject to uncertainty and its impact on the ICER should be quantified.”	derived from the trial data that in turn impact the risk calculations is in line with HTA Lab Report guidance.	
Section 1.4; Page 25 Misinterpretation of resmetirom’s mechanism of action	Change “For lipids, the model assumes the 12-month effects on LDL-C and HDL-C persist indefinitely, which is unrealistic given limited long-term data, the lack of statistically significant HDL-C changes, and inconsistent application of triglyceride effects.” To “For lipids, the model assumes the 12-month effects on LDL-C and HDL-C persist indefinitely, which is currently not assessed by long-term trial data.”	It is factually incorrect to say that an assumed persistent effect on lipids is “unrealistic”. It would be expected given the medicine’s mode of action. Lipid metabolism is the main pathway through which resmetirom protects the liver from further damage and facilitates regression of fibrosis. Returning lipids to baseline at 1 year is misrepresentative of the mechanism of action as it arbitrarily curtails a biological effect.	Not a factual inaccuracy. The EAG stands by the statements made in the report but is happy to consider evidence to the contrary.

Issue 17

Description of problem	Description of proposed amendment	Justification for amendment	EAG response
Section 2.3.5; Page 31 Section 2.3.5; page 125 EAG incorrectly states that Type II diabetes subgroup analyses were not done.	The EAG report should be amended to correctly note that a T2DM subgroup cost-effectiveness analysis was provided, and that a fibrosis-stage subgroup analysis was not feasible due to regulatory blinding constraints described in the CS.	The T2DM subgroup was analysed and reported (CS section 3.12.1). Fibrosis-stage analysis was not possible because the blinded progression-to-F4 data prevented reliable stratification. These constraints reflect data limitations rather than omissions in modelling (CS Section 3.3.2., page 110).	We have edited to correctly report that subgroup analysis was reported for the T2DM subgroup.

Issue 18

Description of problem	Description of proposed amendment	Justification for amendment	EAG response
Section 3.3.4 ; Page 48 Error in account of subgroup results provided in CS	Amend sentence “Subgroup analyses for key variables are referred to in section 2.8 (p. 82) of the CS, but no results are presented.” To “Subgroup analyses for key variables are referred to in section 2.8 (p. 82) of the CS,	Appendix C contained all subgroup analyses referenced in Section 2.8.	We have corrected Section 3.3.4 accordingly.

	and were presented as an appendix.”		

Issue 19

Description of problem	Description of proposed amendment	Justification for amendment	EAG response
Section 5.2.1; Page 105 Table 26 The EAG notes an apparent discrepancy between the proportion of patients with F3 fibrosis at baseline in the MAESTRO-NASH mITT population (n=966) and the proportion observed in the PLB-W52 paired-biopsy population (n=739). The EAG seeks clarification on whether the model uses baseline fibrosis distributions from the mITT cohort (W0) or those retrospectively	The model uses the baseline fibrosis distribution from the full mITT population, while the paired-biopsy subset is used exclusively for estimating transition probabilities. Although the paired-biopsy subset has different F2/F3 proportions from the full mITT cohort, this reflects the different roles	We can confirm that the model uses the baseline fibrosis distribution from the full mITT population (Table 9), ensuring that the simulated cohort reflects the entire randomised population to which treatment effects apply. The paired-biopsy population (Table 26) was used solely to estimate fibrosis transition probabilities because paired biopsies provide the most accurate observed evidence on progression and regression. We conducted balance assessments (as described in section B4 of clarification questions), which confirmed that the paired-biopsy subset is well balanced	Not a factual inaccuracy

linked from the Week-52 biopsy subset. The EAG also questions whether differences between Table 9 (mITT) and Table 26 (PLB-W52) indicate an inconsistency in the model's baseline population.	of the two datasets rather than any modelling inconsistency.	across treatment arms and suitable for transition estimation. We acknowledge that, methodologically, a more granular approach would be to estimate separate transition matrices for baseline F2 and F3 patients and those fibrosis specific transition probabilities applied to the model. However, this was not feasible due to regulatory blinding policies, which did not allow access to the necessary stratified transition information. For this reason, overall transition (F2 and F3) were applied in the model. Importantly, the paired-biopsy cohort was not used to define the model's baseline F2/F3 distribution; the model uses the full mITT distribution for baseline characteristics so that the simulated cohort aligns with the trial population.	

Issue 20 Typographical Errors

Description of problem	Description of proposed amendment	EAG response
Many sections of the document MAFLD (Metabolic Associated Fatty Liver Disease) was a proposed term used in some literature, but it is not the official name adopted by major liver societies.	Amend to use the current, internationally accepted term is MASLD (Metabolic dysfunction–Associated Steatotic Liver Disease).	MAFLD has been corrected to MASLD throughout.
Section 2.3.5; Page 32; Table 2, Comparator(s) row, EAG Comment column, paragraph 1	Amend typographic error in “considered to and add-ons to standard care or resmetirom”	This has been corrected
Section 2.3.5; Page 32; Table 2, Subgroups row, EAG Comment column, paragraph 1 and 2	Amend typographic errors in “resticted to primary outcomes and are not avaiambe” and Amend typographic error in paragraph 2 “remestirom”	This has been corrected
Section 3.2.2.1; Page 40 Paragraph 4 Typo	Correct typo in “The company declined to make results from these meetings available to the EAG (PfC response, QC6).” We believe the correct clarification response reference is QC5.	This has been corrected

Section 3.3.2; Page 45, paragraph 8 Typo	Correct typographic error in phrase “pared biopsy population”	This has been corrected

Single Technology Appraisal

Resmetirom for treating moderate to advanced liver fibrosis (without cirrhosis) caused by metabolic dysfunction-associated steatohepatitis [ID6529]

Technical engagement response form

As a stakeholder you have been invited to comment on the External Assessment Report (EAR) for this evaluation.

Your comments and feedback on the key issues below are really valued. The EAR and stakeholders' responses are used by the committee to help it make decisions at the committee meeting. Usually, only unresolved or uncertain key issues will be discussed at the meeting.

Information on completing this form

We are asking for your views on key issues in the EAR that are likely to be discussed by the committee. The key issues in the EAR reflect the areas where there is uncertainty in the evidence, and because of this the cost effectiveness of the treatment is also uncertain. The key issues are summarised in the executive summary at the beginning of the EAR.

You are not expected to comment on every key issue but instead comment on the issues that are in your area of expertise.

If you would like to comment on issues in the EAR that have not been identified as key issues, you can do so in the 'Additional issues' section.

If you are the company involved in this evaluation, please complete the 'Summary of changes to the company's cost-effectiveness estimates(s)' section if your response includes changes to your cost-effectiveness evidence.

Technical engagement response form

Resmetirom for treating moderate to advanced liver fibrosis (without cirrhosis) caused by metabolic dysfunction-associated steatohepatitis [ID6529]

Please do not embed documents (such as PDFs or tables) because this may lead to the information being mislaid or make the response unreadable. Please type information directly into the form.

Do not include medical information about yourself or another person that could identify you or the other person.

We are committed to meeting the requirements of copyright legislation. If you want to include journal articles in your submission you must have copyright clearance for these articles. We can accept journal articles in NICE Docs. For copyright reasons, we will have to return forms that have attachments without reading them. You can resubmit your form without attachments, but it must be sent by the deadline.

Combine all comments from your organisation (if applicable) into 1 response. We cannot accept more than 1 set of comments from each organisation.

Please underline all confidential information, and separately highlight information that is submitted as 'confidential [CON]' in turquoise, and all information submitted as 'depersonalised data [DPD]' in pink. If confidential information is submitted, please also send a second version of your comments with that information redacted. See [Health technology evaluations: interim methods and process guide for the proportionate approach to technology appraisals](#) (section 3.2) for more information.

The deadline for comments is **5pm on 12 February 2026**. Please log in to your NICE Docs account to upload your completed form, as a Word document (not a PDF).

Thank you for your time.

We reserve the right to summarise and edit comments received during engagement, or not to publish them at all, if we consider the comments are too long, or publication would be unlawful or otherwise inappropriate.

Comments received during engagement are published in the interests of openness and transparency, and to promote understanding of how recommendations are developed. The comments are published as a record of the comments we received, and are not endorsed by NICE, its officers or advisory committees.

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Resmetirom for treating moderate to advanced liver fibrosis (without cirrhosis) caused by metabolic dysfunction-associated steatohepatitis [ID6529]

About you

Table 1. About you

Your name	Carl Gibbons, Head of Market Access UK
Organisation name: stakeholder or respondent (if you are responding as an individual rather than a registered stakeholder, please leave blank)	Madrigal Pharmaceuticals UK Limited
Disclosure Please disclose any funding received from the company bringing the treatment to NICE for evaluation or from any of the comparator treatment companies in the last 12 months [Relevant companies are listed in the appraisal stakeholder list.] Please state: • the name of the company • the amount • the purpose of funding including whether it related to a product mentioned in the stakeholder list • whether it is ongoing or has ceased.	N/A
Please disclose any past or current, direct or indirect links to, or funding from, the tobacco industry	N/A

Technical engagement response form

Resmetirom for treating moderate to advanced liver fibrosis (without cirrhosis) caused by metabolic dysfunction-associated steatohepatitis [ID6529]

Key issues for engagement

Table 2 Key issues

Key issue	Does this response contain new evidence, data or analyses?	Response
Issue 1: The trial population does not match the population in scope.	Yes	Company Response The EAG's concerns around this issue noted, in particular: • the use of liver biopsy for trial inclusion, • the high proportion of patients with advanced fibrosis (F3), • the apparent severity of metabolic comorbidity relative to UK real-world data. Our response explores why differences were observed, why the MAESTRO-NASH (M-NASH) trial population provides the most relevant efficacy data for those patients likely to be offered resmetirom in NHS practice, and lends support and context for Committee discussion around the 'fast progressor phenotype' as the target for resmetirom, also discussed under Issues 2 and 9. 1. Alignment with Decision Problem Resmetirom utilisation in UK secondary care will be in patients who have been referred via a non-invasive test (NIT)-driven community pathway (essentially aligned with NICE NG49 [1] or EASL-EASO-EASD consensus guidance [2]) that by design enriches for moderate to advanced fibrosis (i.e., the resmetirom eligible population). The MASH population seen in NHS secondary care is reflective of enrichment via NG49 [1] or an equivalent pathway (typically involving two-step testing: first step, FIB-4; second step, a fibrosis NIT). Through our budget impact modelling research, we already know that these community pathways enrich for populations similar to M-NASH; data we have gathered from several UK centres so far clearly showed clinics that had identified patients with high-risk fibrosis and suspected MASH using existing pathways, with no additional need for community diagnostic capacity.

Technical engagement response form

Resmetirom for treating moderate to advanced liver fibrosis (without cirrhosis) caused by metabolic dysfunction-associated steatohepatitis [ID6529]

Therefore, we consider that the Decision Problem population and M-NASH study population are both aligned to comprise adults with non-cirrhotic MASH and moderate to advanced fibrosis (F2–F3).

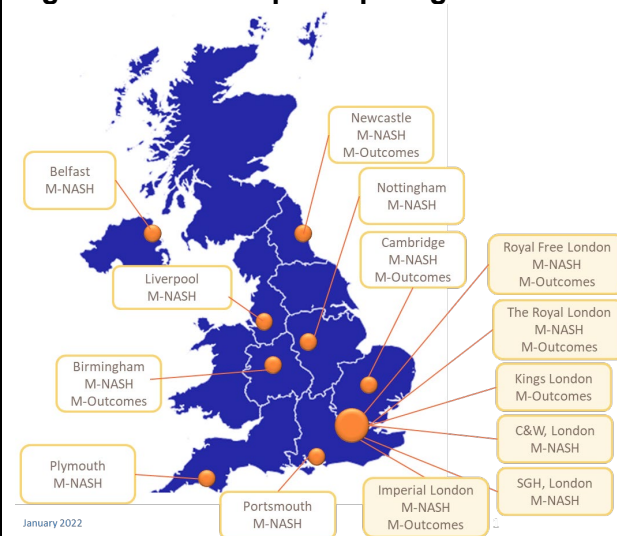
M-NASH enrolled a sample of patients with approximately 60% of patients having F3 fibrosis and ~33% with F2 fibrosis. This distribution reflects the intended treatment population under ID6529, rather than the broader population with MASLD or early-stage disease.

The trial's enrichment for F3 disease should not be interpreted as a lack of generalisability, but rather as appropriate alignment with the clinically prioritised population under the NICE scope that is most likely to be offered resmetirom in practice – bearing in mind that diagnosis and treatment decisions will occur in secondary care under specialist management.

2. International trial conduct and UK relevance

Although M-NASH was multinational, thirteen UK NHS sites were included and the biological drivers of MASH progression (fibrosis severity and metabolic dysfunction) are not country-specific (Figure 1).

Figure 1. UK sites participating in M-NASH



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		UK-based epidemiological analyses confirm that: • excess mortality and morbidity in MASLD/MASH are driven primarily by fibrosis stage; • cardiovascular and extrahepatic cancer outcomes dominate at earlier stages, and; • these patterns are consistent across UK and international cohorts. As such, there is no evidence that the international nature of M-NASH materially limits applicability to UK clinical practice. 3. Use of liver biopsy in M-NASH Liver biopsy was used for trial eligibility and endpoint assessment in M-NASH. This methodology was required by regulators and was not intended to serve as a proxy for UK diagnostic practice. In UK clinical practice: • Identification of eligible patients relies on NITs such as FIB-4, ELF, and transient elastography. • These tools, when used in two-step community pathways that align with NG49 [1] and other guidance (EASL, BSG, BASL Quality Standards [3]), are specifically intended to enrich for the same high-risk F2–F3 population included in M-NASH. UK outcome data based on NIT-defined MASLD/MASH populations demonstrate fibrosis-dependent risk gradients for mortality and clinical events that are directionally and quantitatively consistent with histology-defined cohorts. Thus, while biopsy enhances internal validity, it does not undermine external validity, and the trial population remains applicable to the anticipated, NIT-defined NHS treatment population. 4. Differences between M-NASH and UK real-world population analyses – methodological origin The apparent mismatch between M-NASH patient characteristics and UK real-world analyses primarily reflects methodological differences in how populations were defined and captured, rather than a lack of representativeness. The M-NASH clinical trial design required that patients have three or more metabolic risk factors to be eligible. Meanwhile, most UK population-based datasets (e.g., Davidson et al. 2025 [4], Morgan et al. 2021 [5]) were designed to estimate disease prevalence across the full MASLD spectrum and therefore include large numbers of individuals with early or non-progressive disease. These datasets dilute the observed clinical and metabolic severity, compared to patients who progress to specialist care and would be considered for pharmacotherapy. Clinical expert opinion and local data suggest that UK patients referred through NIT-driven community pathways to secondary care are enriched for cardiometabolic risk factors. This observation is seen even when there is no specific requirement for additional or fixed numbers of CMRFs as part of initial referral criteria. This is substantiated by the fact that M-NASH successfully screened and recruited participants at multiple UK clinical sites. Therefore, the baseline M-NASH

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		population, including presence of a range of independent CMRFs, is reflective of the population referred to secondary care. Hence, the number of CMRFs to be eligible for M-NASH is not unrepresentative of UK secondary care populations. It would be considered unequitable to require a specific number of CMRFs for initial screening in a community pathway, referral to secondary care or for consideration of eligibility for resmetirom. UK Biobank study – new evidence Metabolic characteristics observed in M-NASH (mean BMI ~35–36 kg/m², T2DM ~67%, hypertension ~78%, dyslipidaemia ~71%) resemble an “at risk MASH” subgroup that was defined within a recent analysis of the UK Biobank dataset [6]. This study found that: • at-risk MASH constitutes a small but clinically critical subgroup (~2.2% of steatotic liver disease cases), • this subgroup has the highest BMI, greatest inflammatory burden, most severe metabolic dysfunction, and • it is explicitly identified as the population likely to be eligible for pharmacological therapies. The UK Biobank study utilized cT1₁≥875ms (a marker of fibro-inflammation) to define at-risk MASH. This cohort showed the highest levels of liver enzymes (ALT and AST) and the highest median liver fat on MRI (22.2%), corresponding closely with the high baseline NAFLD activity scores (≥5) seen in 83.5% of the M-NASH trial participants [6]. The demographic profiles were broadly similar between M-NASH and the UK Biobank “at risk MASH” cohort (respectively: mean age 56.6 vs 61 years; 56.3% vs 49% female; 89.3% vs 95.3% White ethnicity). Both the UK Biobank cohort and M-NASH populations had significant obesity (respectively, mean BMI 35.7 in M-NASH and median BMI 33.4 in UK Biobank). The UK Biobank's at-risk MASH subgroup had the "most severe metabolic and inflammatory profiles" of the entire SLD population, despite being defined independently of any CMRF-related criteria [6]. Resmetirom targets patients with F2 and F3 fibrosis, the stages most likely to progress to costly and fatal end-stage liver disease (ESLD). In the UK, stages F2 and F3 account for roughly 33.7% of the MASH population. By recruiting a population where 93.4% of participants were at stage F2 or F3, the resmetirom trial enriched its study population for the exact same cohort which will be prioritised for treatment in the NHS.
Issue 2: Reliance on Surrogate Endpoints	Yes	Fibrosis stage is a well-established prognostic factor in MASH, consistently observed across populations, study designs, and follow-up durations. The existing evidence base extends beyond cross-sectional correlations and can now able to demonstrate that changes in fibrosis stage are associated with corresponding changes in clinical risks of end-stage liver disease, major adverse liver outcomes (MALO) and death.

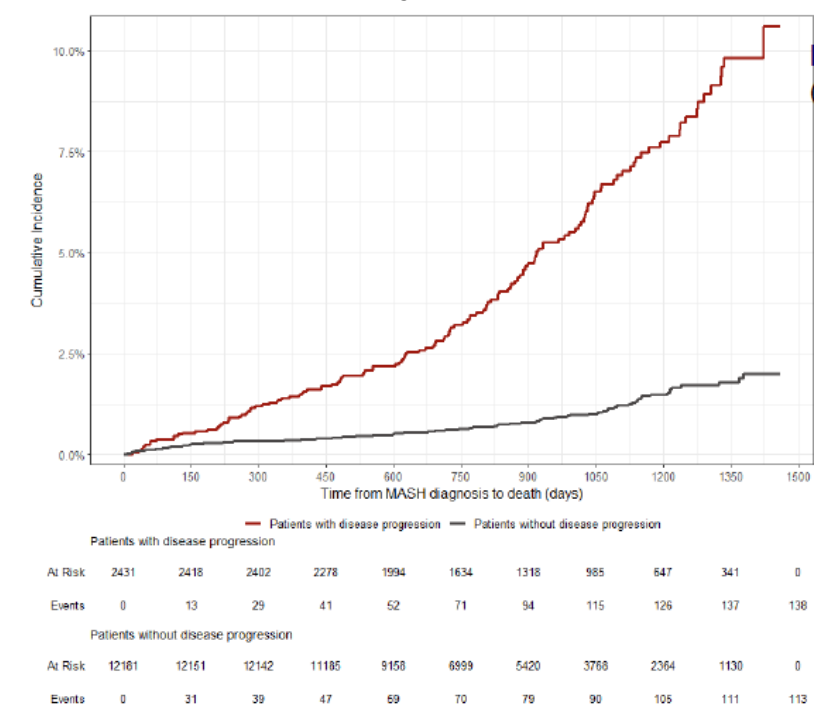
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Resmetirom for treating moderate to advanced liver fibrosis (without cirrhosis) caused by metabolic dysfunction-associated steatohepatitis [ID6529]

		Regression to lower fibrosis stages has also been associated with reduced risks of hepatic decompensation, MALO, and mortality, supporting ≥ 1-stage fibrosis improvement as movement along a validated prognostic pathway. This section presents additional evidence supporting these statements. Risks of severe disease and death based on fibrosis: Barritt et al 2025 [7] A systematic literature review and meta-analysis by Barritt et al. 2025 [7] of studies in patients with MASH (N=7 unique studies) $\pm$ MASLD (N=25 unique studies) showed that (all hazard ratios below are pooled adjusted HRs) instantaneous risk of later stage events increases with increasing fibrosis stage: • Patients with F3–F4 vs F0–F2 fibrosis have: ○ ~10-fold higher risk of hepatic decompensation (HR:10.93; 95% CI: 6.31, 18.92) ○ ~6-fold higher risk of MALO (HR: 6.66; 95% CI: 4.04, 10.99) ○ ~3-fold higher risk of all-cause mortality (HR: 3.36; 95% CI: 2.37-4.75) • Importantly, risk gradients are preserved between adjacent stages (e.g., F3 vs F2; F4 vs F3), supporting fibrosis stage as a continuous prognostic continuum, not a binary threshold: ○ F3 vs F2 for cirrhosis: ~2 fold higher risk (HR: 2.05; 95% CI: 1.45; 2.90) ○ F4 vs F3 for MALO: >3-fold risk (HR: 3.27; 95% CI: 1.98, 5.41) ○ F4 vs F3 for all-cause mortality: HR=2.13 (95% CI: 1.10, 4.10) Risk of death based on fibrosis progression: Kim et al 2025 [8] Recent analysis of a large U.S. adult MASH cohort (retrospective cohort of MASH patients from Optum's® De-identified Market Clarity Data [January 1, 2019, to December 31, 2024]; N=21,894) found that of patients without end-stage liver disease at baseline (n=14,612), those who experienced disease progression (n=2,431/14,612) had nearly 5-times higher incidence of all-cause mortality versus those who did not experience disease progression over a short follow-up period (median around 2 years) [8]. Figure 2 shows the cumulative incidence plot of mortality for all observations. Among patients without ESLD at baseline, 2,431 (16.6%) progressed during follow-up: 467 (19.2%) to CC, 1,902 (78.2%) to DC, 48 (2.0%) to HCC, 14 (0.6%) to LT.

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Figure 2. Cumulative incidence of death by progression status among patients with MASH without ESLD at baseline in the Optum® study from Kim et al. 2025 [8]



Risks of severe liver disease and death based on fibrosis stage: Hagström et al 2017 [9]

Hagström et al. 2017 [9] conducted a retrospective cohort study of 646 biopsy-proven NAFLD patients (matched for age, sex and municipality) with a mean follow up of 20 years (range 0-40). Comparing to control population without NAFLD, the authors estimated hazard ratios for severe liver disease risk, by fibrosis stage. The HR estimates markedly increased with fibrosis stage, with significant results found for:

- F2 (HR 5.48; 95% CI 3.10–9.70; $p < 0.001$),
- F3 (HR 14.28; 95% CI 7.90–25.80; $p < 0.001$), and

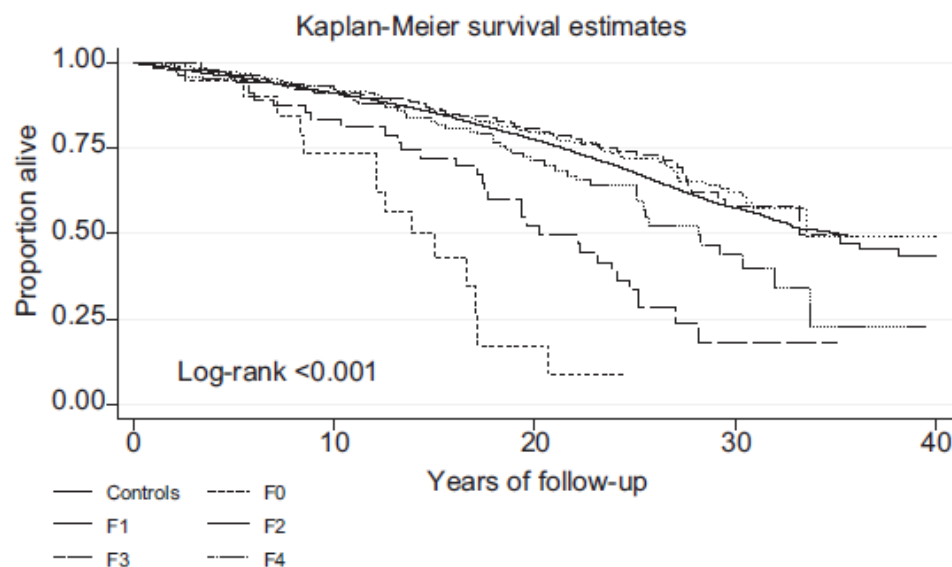
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- F4 (HR 104.52; 95% CI 57.20–191.10; $p < 0.001$).

Similarly, Hagström et al. 2017 [9] found an increasing trend of mortality by fibrosis stage versus controls. Notably, in this study F0 and F1 patients showed no statistical significance versus controls, highlighting the importance to focus treatment on patients with higher-risk disease:

- F2 (HR 1.36; 95% CI 1.02–1.80; $p = 0.03$),
- F3 (HR 2.54; 95% CI 1.79–3.60; $p < 0.001$), and
- F4 (HR 5.19, 95% CI 3.06–8.79, $p < 0.001$).

Figure 3. Overall mortality stratified on fibrosis stage compared to matched controls (log-rank test $p < 0.001$) from Hagström et al 2017 [9]



Risks of severe liver disease and death based on fibrosis stage and fibrosis changes: Roden et al 2025 [10]

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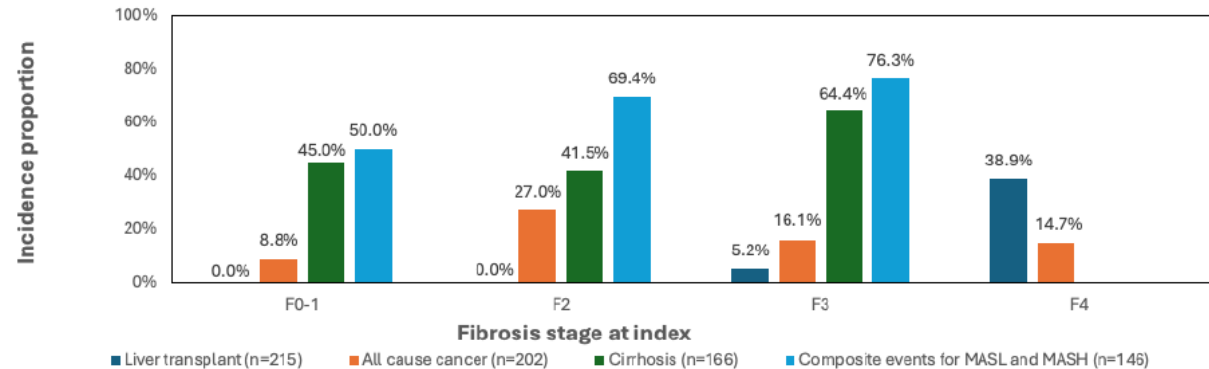
Resmetirom for treating moderate to advanced liver fibrosis (without cirrhosis) caused by metabolic dysfunction-associated steatohepatitis [ID6529]

		Roden et al. 2025 [10] published an analysis investigating the relationship between change in fibrosis stage and incidence of clinical outcomes based on TARGET-NASH (an ongoing longitudinal observational study with over 6,000 patients with MASLD receiving standard of care therapy in the US. In this study, a biopsy cohort (N=215) was drawn that included participants with two liver biopsies and who were classified as stable/improved or worsened based on changes in fibrosis stage between biopsies. Clinical outcomes in the study included progression to cirrhosis, decompensation, all-cause mortality, and other adverse events, and were stratified by index fibrosis stage and subgroups. Demographics of the biopsy cohort were: median age 52 years, BMI 33 (IQR: 29-38) kg/m², 65% female, and 67% with T2DM). At all timepoints, compared with patients at F0-F1 fibrosis, patients with stage F3 had a two-fold higher risk of cirrhosis (HR: 2.0, 95% CI: 1.3-3.1), and those with stage F4 had a four-fold higher risk of decompensation (HR: 4.1, 95% CI: 2.2–7.8), after adjusting for other covariates. Patients with T2DM had about a 2-fold increase in risk at any time for cirrhosis (HR: 2.1, 95% CI: 1.4-3.2) compared to patients without. As shown in Figure 4, incidence of liver transplant, cirrhosis, and composite liver events (cirrhosis, decompensation, HCC, MELD score change, liver transplant, CV event, all-cause mortality or cancer) was higher for F3 patients versus F2 or F1 patients. The incidence of liver transplant was substantially higher for F4 patients (n=14; 38.9%) than for F3 patients (n=3; 5.2%), with a reported median time to liver transplant of 3.3 years and 7.5 years, respectively. Higher fibrosis stage at index was associated with a higher probability of developing decompensation at any time during follow-up (HRs versus F0/F1: F2=0.5, F3=1.4, F4=4.1). Figure 4. Incidence of clinical outcomes by fibrosis stage at index date in the TARGET-NASH biopsy cohort from Roden et al 2025. [10]

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Resmetirom for treating moderate to advanced liver fibrosis (without cirrhosis) caused by metabolic dysfunction-associated steatohepatitis [ID6529]

a. Clinical incidence proportions by fibrosis stage



Note: Composite events includes progression to cirrhosis, decompensation, HCC, MELD score change, LT, CV event, all-cause mortality, or cancer.
b. Clinical incidence proportions by disease progression

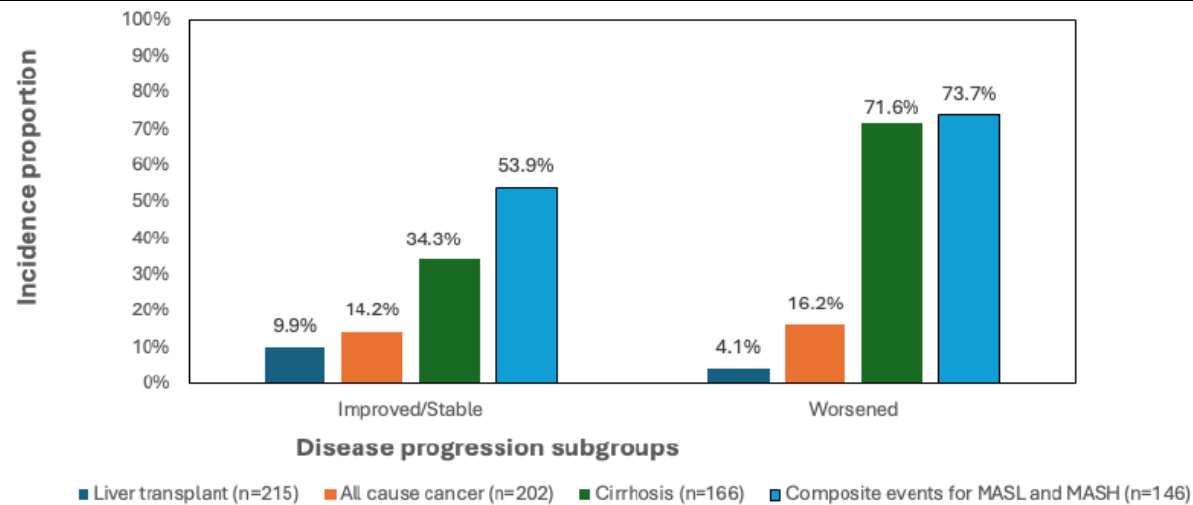
In addition, when compared with patients with improved/stable disease (Figure 5), patients whose disease worsened had a much higher incidence of cirrhosis (71.6% vs 34.3%; $p<0.0001$) and composite events (73.7% versus 53.9%), while liver transplants and all cause cancer were slightly higher for improved/stable disease patients. The authors reported that among patients with F0-F3 fibrosis, the incidence rate of a composite event after index was highest among index F3 patients followed by index F2 patients (incidence rate per 100 person years=13.4 and 9.67, respectively).

These results highlight an important need for a therapy to reduce progression of MASH from F2 to F3 stages to later stages of fibrosis and advanced liver disease.

Figure 5. Incidence of clinical outcomes by disease progression status at index date in the TARGET-NASH biopsy cohort from Roden et al 2025. [10]

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Resmetirom for treating moderate to advanced liver fibrosis (without cirrhosis) caused by metabolic dysfunction-associated steatohepatitis [ID6529]



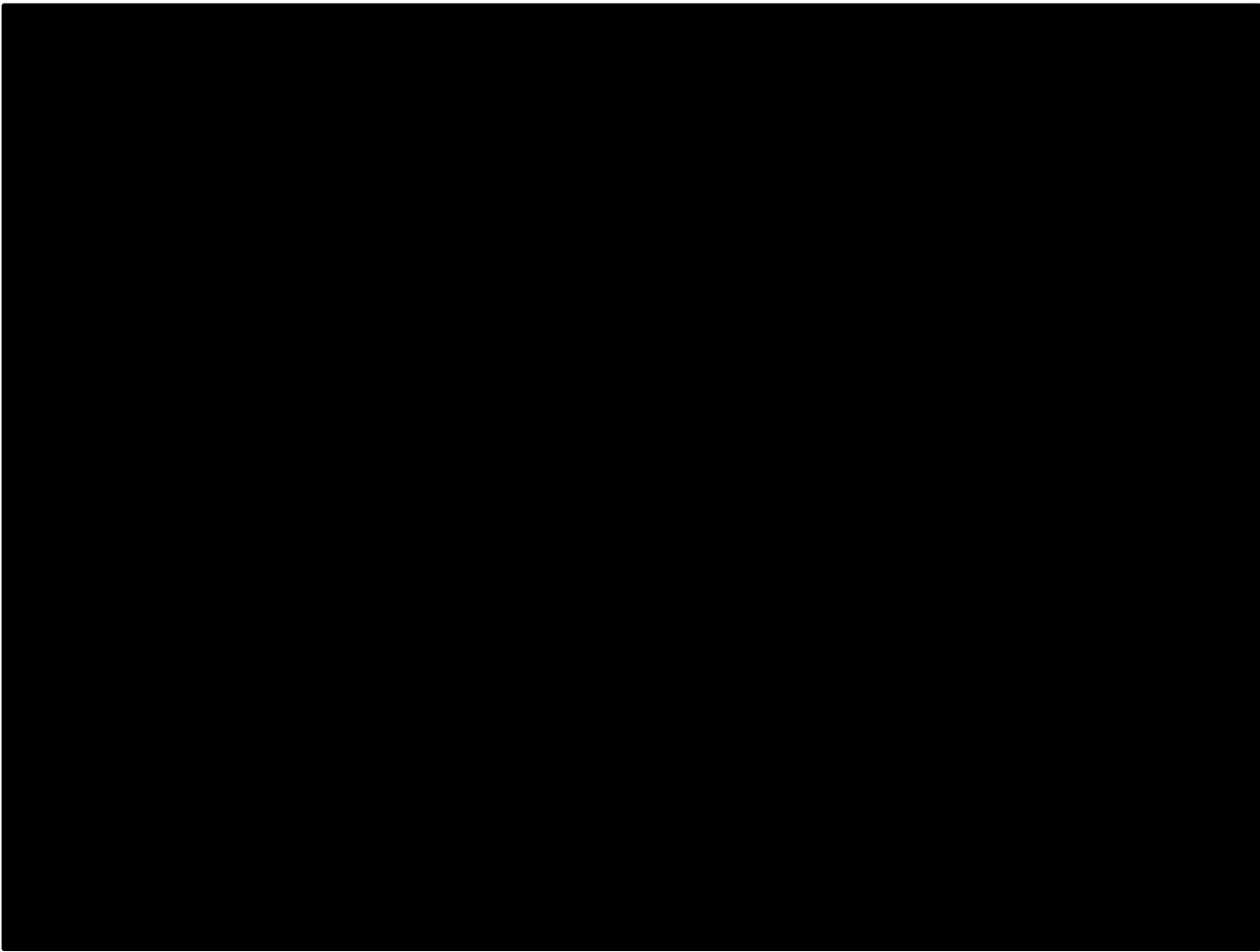
Risks of severe liver disease and death based on fibrosis: Sanyal et al 2026 (unpublished, AIC) [11]

A further analysis of the TARGET-NASH dataset (manuscript currently in preparation by Sanyal et al. [11]; expected submission late-Feb 2026) highlighted the surrogate relationship of fibrosis stage with events (including death). As seen in Figure 6, when pooling F2-F3 patients (as per this decision problem), at any time, the risk of cirrhosis at any time is [REDACTED] fold higher than F0-F1 fibrosis (HR: [REDACTED]; 95% CI: [REDACTED]). Similarly, higher fibrosis stage was associated with increased risk of decompensation events at any time: F4 patients had nearly a [REDACTED]-fold higher risk than F0/F1 (HR: [REDACTED]; 95% CI: [REDACTED]) and F2-F3 patients had about a [REDACTED]-fold higher risk versus patients with early fibrosis (F0-F1; HR: [REDACTED]; 95% CI: [REDACTED]).

This directional increase of event risk at any time with increasing fibrosis stage was also observed for an event of death (all-cause): HR for F4 patients vs F0/F1=[REDACTED] (95% CI: [REDACTED]); HR for F2-F3 patients vs F0-F1=[REDACTED] (95% CI: [REDACTED]).

Figure 6. Progression to cirrhosis, decompensated events, and death stratified by index fibrosis stage category from the TARGET-NASH biopsy cohort in Sanyal et al. [11] (manuscript in preparation; same cohort as Roden et al. 2025 [10])

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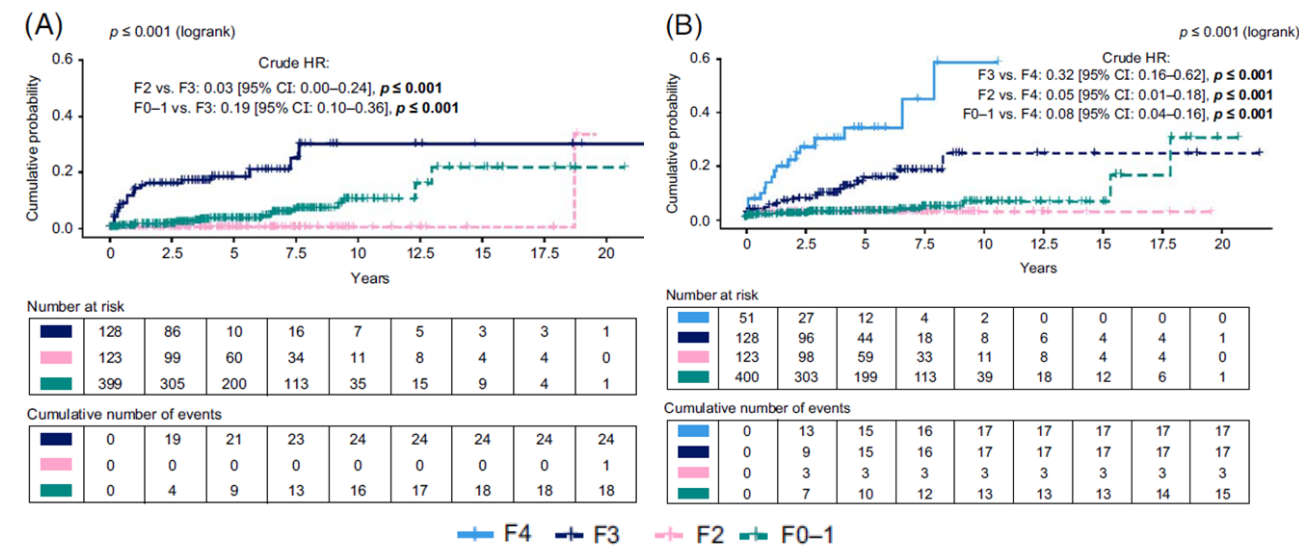
Resmetirom for treating moderate to advanced liver fibrosis (without cirrhosis) caused by metabolic dysfunction-associated steatohepatitis [ID6529]

Risks of severe liver disease based on fibrosis: Younossi et al. 2024 [12]

The rapid onset of cirrhosis events and surrogacy between outcomes and fibrosis stage was also observed in a study by Younossi et al. 2024 [12] based on the a separate real-world cohort of adults (N = 702) recorded on Vanderbilt University Medical Center’s Synthetic Derivative database (1984–2021) with evidence of MASH on liver biopsy, who were followed from the first biopsy until the first clinical event or last database entry (median: 4.7 y). Baseline characteristics of this cohort were as follows: 70% female, median age: 50 years (IQR: 42-58), 80% obese, 72% with hypertension, 54% with dyslipidaemia, and 51% of patients with T2DM (highest in patients with F4 at baseline: 63%).

In this analysis, lower fibrosis stages consistently reduced risk of cirrhosis or liver-related outcomes, consistent with the Roden et al. 2025 [10] and Sanyal et al. [11] TARGET-NASH studies. Patients with F3 fibrosis had 4.5 times greater risk of cirrhosis at any time versus patients with F0-F1 fibrosis (HR for F0-1 vs F3: 0.22; 95% CI: 0.12-0.42), and significantly higher risks of liver-related outcomes for patients with F4 (HR for F0-1 vs F4: 0.12; 95% CI: 0.05-0.25), representing over an 8-fold increase (excluding cirrhosis; Figure 7).

Figure 7. Cumulative probability plots and HRs for (A) cirrhosis, (B) liver-related outcomes in Younossi et al. 2024 [12]



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		Regulatory support We also note that regulators have accepted the endpoints in the MAESTRO-NASH study as valid surrogate endpoints (US Food and Drug Administration [13]) and intermediate endpoints (European Medicines Agency; EMA [14]) The EMA has stated that the MAESTRO-NASH study's co-primary endpoints are acceptable as intermediate endpoints in clinical studies of shorter duration, due to the feasibility issues associated with capturing longer-term outcomes and the existing unmet medical need in MASH. Summary Regarding the EAG's recommendation to follow TSD 20 in exploring the available evidence, we found insufficient data to conduct a multivariate meta-analysis specifically for patients with MASH and advanced fibrosis (stages F2 and F3). However, the relationship of liver-related outcomes with fibrosis stage – whether absolute or relative changes over time – has been established clearly in the literature, if not definitively quantified. The importance of delaying or reversing fibrosis for MASH patients is reinforced, as it reduces liver-related and all-cause mortality for MASH patients. Our long-term outcomes trial continues to gather data on 'hard' outcomes for resmetirom versus SoC, and we appreciate the difficulty in creating an evidence base which allows us to accurately quantify their links with short-term response data. But in the interim we would suggest that the M-NASH study exists in an environment of growing consensus about the urgency to treating advanced fibrosis as a means of preventing later adverse liver outcomes. We may not know the precise extent, but we know that the outcomes are severe, and can manifest quickly in high-risk individuals.
Issue 3: Differences between the ITT population and paired liver biopsy population	Yes	The EAG notes a concern about possible differences between the PLB-W52 F2/F3 subpopulation from M-NASH (n=739), which we use to calculate transition probabilities for MASH resolution and fibrosis changes, versus the study's main analysis dataset mITT-LB-W52 (n=766), which our microsimulation samples to generate the modelled population at baseline. PLB-W52 was a selective sample that excluded patients without complete biopsy records: they had to have readable biopsy slides at baseline and week 52, all biopsies had to have dual radiologist-reader agreement, and these requirements also automatically led to exclusion of patients discontinuing the study for any reason. EAG's concern is that by excluding patients with incomplete data (in contrast to automatically coding them as 'non responders', as the published analyses of the mITT-LB-W52 dataset did) the PLB-W52 sample might unfairly bias efficacy estimates in favour of resmetirom via attrition and/or selection bias. The EAG states it is unclear whether biopsy data were missing completely at random as our modelling assumes, so any imbalance in the reasons for discontinuation between arms could lead to an under- or over-estimation of resmetirom's effect. We believe the EAG's chief concern is around over-estimation of effect, based on its comparison of discontinuation rates between study arms and the apparently higher efficacy estimates derived from PLB-W52 compared to mITT-LB-W52.

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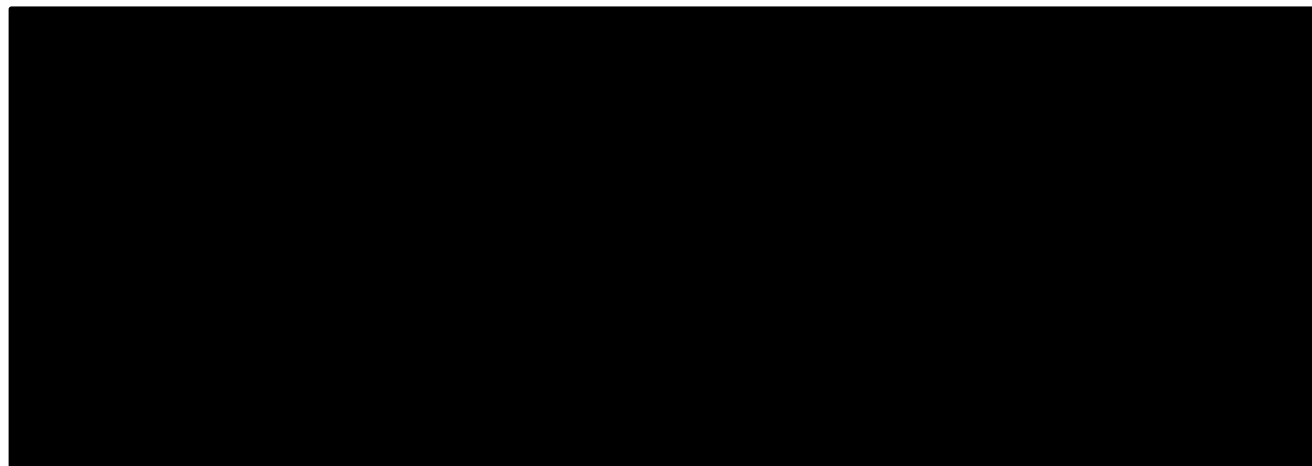
Resmetirom for treating moderate to advanced liver fibrosis (without cirrhosis) caused by metabolic dysfunction-associated steatohepatitis [ID6529]

		Having sought additional clinical expert input and reviewed the M-NASH study's statistical design, we consider it highly unlikely that the PLB-W52 data's restrictions have unfairly favoured resmetirom by excluding missing data. Missing second biopsies, which were excluded from PLB-W52 instead of being counted as 'non response' outcomes like they were in mITT-LB-W52, have several plausible clinical reasons for missingness – not all point to a loss of response or adverse events that would favour resmetirom if dropped from analysis. In a double-blinded design, patient or investigator belief in response vs non-response can both influence decisions to discontinue or not carry out a biopsy. Risk of breaking the blinding (bearing in mind the study is intended to carry on blinded for several years) may have led to reluctance for a week 52 liver biopsy. The risk of a patient or investigator attributing response or non-response status to resmetirom prior to 52-week biopsy is considered low as the mechanism of action is liver-directed (i.e., requires investigations to assess) rather than a non-hepatic mode of action on an underlying cardiometabolic risk factor (i.e., observable weight change for patients and investigators), but psychological factors may have acted to influence such occurrences. We cannot compute the true balance of discontinuation or biopsy missingness due to the ongoing study blinding, however there is not a strong justification for automatically assuming an exclusion of missing data would overstate resmetirom's benefit – discontinuation rate data in themselves are insufficient to back up this assumption. During Clarification, we referred the EAG to a robust prespecified sensitivity analysis within the M-NASH protocol (it is summarised in the online supplement to M-NASH's primary publication [15] and in our CSR) and provided a brief summary of it, however we acknowledge that its relevance to this Issue may not have been adequately communicated before. To summarise, the M-NASH statistical sensitivity analysis tested whether different missing data approaches (namely multiple imputation, tipping point and general estimating equation) affected efficacy outcomes or conclusions when applied to mITT-LB-W52. This approach, the best possible given the absence of precise unblinded information about discontinuation reasons, found a consistent estimated treatment effect regardless of data approach, suggesting no significant imbalance in reasons for missingness between study arms. This stability was replicated in all major sub-groups, justifying our approach of treating missing data as 'missing at random' [15]. <u>More background to the PLB-W52 population</u> The PLB-W52 population is numerically smaller than the mITT-LB-W52 population, but demographic and comorbid conditions are consistent among the samples. However, after removing the F1B patients there was a slightly higher proportion of F3 patients in the modelled population as shown in Figure 8.

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Figure 8. Summary Baseline Characteristics by population (mITT-W52 vs. PLB-W52)



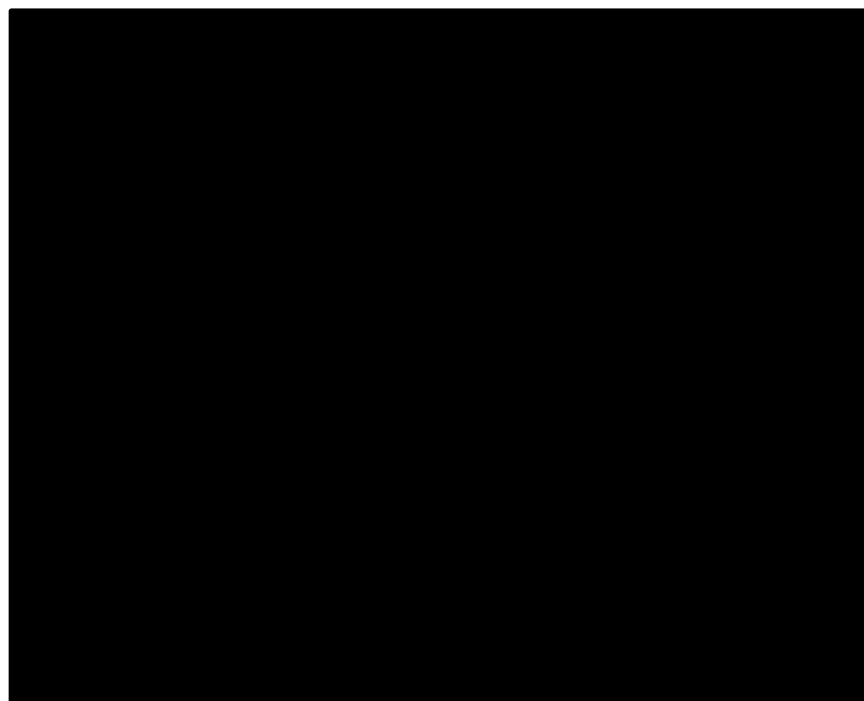
Statistical comparisons of PLB-W52 vs mITT-LB-W52

Standardised mean difference (SMD) analyses demonstrated very close alignment between the PLB-W52 and mITT-LB-W52 populations across age, sex, BMI, baseline fibrosis stage and type 2 diabetes, with all SMDs well below commonly used thresholds (Figure 9). These results were shared during Clarification, suggest only marginal differences in demographics and clinical profile.

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Figure 9. Standardised mean differences between mITT population (n = 966) and PLB-W52 (n = 781)



Scenario analyses

Per the EAG's suggestion, we have included a scenario in the new model's Excel Master Input dashboard (see Issue #4 for more details) which allows the relative treatment effects for MASH resolution from mITT-LB-W52 population analysis to be applied in microsimulation, whilst continuing to model fibrosis progression using PLB-W52. Results from this scenario analysis had a modest impact on the ICER, increasing it without altering overall conclusions. This result is to be expected given that the mITT-LB-W52 analysis automatically assumed all patients with missing data did not achieve MASH resolution.

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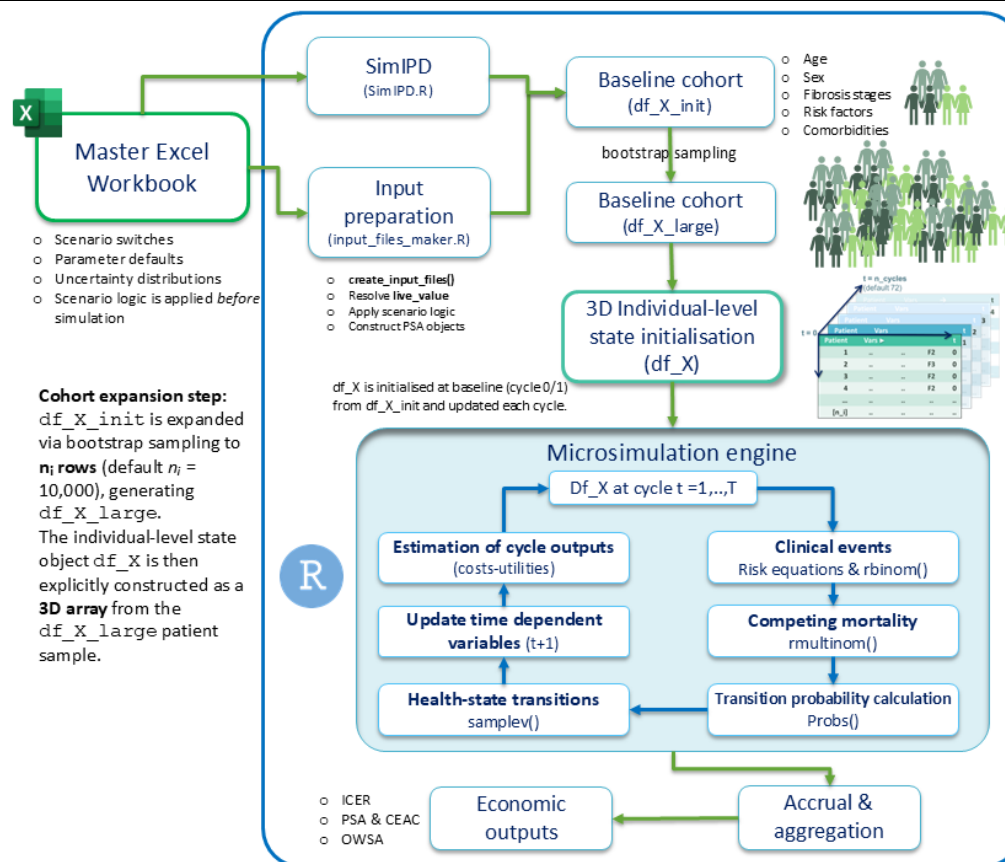
		<table><tr><th>Technologies</th><th>Total costs (£)</th><th>Total LYG</th><th>Total QALYs</th><th>Incremental costs (£)</th><th>Incremental LYG</th><th>Incremental QALYs</th><th>ICER (£/QALY)</th></tr><tr><td>SoC</td><td>████</td><td>████</td><td>████</td><td>NA</td><td>NA</td><td>NA</td><td>NA</td></tr><tr><td>Resmetirom</td><td>████</td><td>████</td><td>████</td><td>████</td><td>████</td><td>████</td><td>40,318</td></tr></table> To explore the potential influence of missing Week-52 biopsy data in PLB-W52, we developed a complementary exploratory scenario having the following positive assumptions around missing data or discontinuation: • patients without a Week-52 biopsy experience MASH resolution benefit comparable to those with observed paired biopsies, reflecting the fact that missing biopsy data do not imply a lack of biological response, consistent with observed improvements in non-invasive biomarkers among patients who discontinued early; • patients who discontinue treatment experience a MASH resolution treatment response consistent with the placebo arm. In other words, missing biopsy outcomes are not assumed to represent ‘no change’ in fibrosis but rather patients are allowed to worsen or improve according to the same likelihoods as patients receiving SoC. <table><tr><th>Technologies</th><th>Total costs (£)</th><th>Total LYG</th><th>Total QALYs</th><th>Incremental costs (£)</th><th>Incremental LYG</th><th>Incremental QALYs</th><th>ICER (£/QALY)</th></tr><tr><td>SoC</td><td>████</td><td>████</td><td>████</td><td>NA</td><td>NA</td><td>NA</td><td>NA</td></tr><tr><td>Resmetirom</td><td>████</td><td>████</td><td>████</td><td>████</td><td>████</td><td>████</td><td>35,806</td></tr></table> Discussion Taken together, the above scenario analyses indicate that our model results are unlikely to be biased by the selective inclusion criteria of the PLB-W52 population. Instead, our base-case estimate lies between more and less conservative values depending on the assumptions taken as to missing data. We hope that this information will provide reassurance that potential bias related to missing biopsies has been explicitly explored, is bounded, and should not materially impact Committee’s ability to interpret cost-effectiveness on this issue.	Technologies	Total costs (£)	Total LYG	Total QALYs	Incremental costs (£)	Incremental LYG	Incremental QALYs	ICER (£/QALY)	SoC	████	████	████	NA	NA	NA	NA	Resmetirom	████	████	████	████	████	████	40,318	Technologies	Total costs (£)	Total LYG	Total QALYs	Incremental costs (£)	Incremental LYG	Incremental QALYs	ICER (£/QALY)	SoC	████	████	████	NA	NA	NA	NA	Resmetirom	████	████	████	████	████	████	35,806
Technologies	Total costs (£)	Total LYG	Total QALYs	Incremental costs (£)	Incremental LYG	Incremental QALYs	ICER (£/QALY)																																											
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Resmetirom	████	████	████	████	████	████	35,806																																											
Issue 4: Validation of the company model	Yes	In response to the EAG’s observations during Clarification and Technical Engagement, we have taken the following key steps to improve the model’s ease of use and transparency:																																																

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and programming complexity		• Amend R typo regarding the estimation of LYs identified during ‘black box tests’ related to life-years calculation (this did not affect ICERs previously presented) and streamline coding in several domains as recommended by EAG. • Prepare a Model Mapping document that outlines the flow of data through the R code, at a level of detail about named matrices, dataframes and vectors that we hope is sufficient to allow EAG reviewers to more readily track the computations of the microsimulation. The key model flow summary from this document is shown in Figure 10. Figure 10. Key model flow summary

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- **Combine all input data**, formerly stored in separate Excel files and accessed through multiple read procedures in the R code, into a single common Master Input Parameters Excel workbook with a single corresponding read procedure in R. This Excel workbook includes:
 - a single sheet for all inputs (excepting individual patient-level data [IPD], life tables and risk equations)

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		○ a Dashboard allowing quick user selection of scenarios and settings requested by EAG during Clarification or TE; selections made in this sheet automatically change values in the inputs sheet – alternatively users may manually enter values directly into the Inputs sheet ○ dedicated tabs laying out the calculation and estimation of key input parameters, for example conversion of M-NASH patient cross-tabulations into transition probabilities ○ a Front Page with general user instructions ○ two tabs allowing the specification and creation of a fully synthetic model population (generated IPD) per the suggestion in EAR section 5.2.1.3. ○ a Black Box test sheet setting out all items in the TECH-VER checklist and enabling their run through our R model, with appropriate caveats noted against some tests which will not generate exact results per TECH-VER specifications due to the stochastic nature of the microsimulation. (Please note, the EAGs assertion in its FAC response that the use of a common random seed should eliminate stochastic differences in incremental results between treatment arms does not hold in our model, because SoC and resmetirom arms each use a different number of stochastic functions per cycle: resmetirom patients have two additional rbinom() operations to estimate drug discontinuation, meaning that SoC and resmetirom arms are immediately thrown out of sync with regards to which values in the random seed vector they are calling, even if they both start by referring to the same one). ▪ (Results from a full TECH-VER check of our new base case model are also presented in this sheet) • Seek advice from TECH-VER checklist authors regarding how to pragmatically implement that list's 'black box' items on a microsimulation. These comments have been taken on board and can be viewed in the Excel implementation of Black Box tests. We also copy our correspondence with the two authors below. Original Text sent on behalf of Madrigal: “Dear XXX, I am writing to seek your guidance on a specific methodological point regarding the TECH-VER checklist, for which you were...[an] author. We greatly value this work and its role in promoting good verification practice in health economic modelling. In a current NICE appraisal, the checklist has been applied to an individual-level stochastic microsimulation model. A particular issue has arisen around verification tests that expect exactly zero incremental differences under certain extreme

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	scenarios (e.g., identical inputs across arms). In a microsimulation framework, small non-zero differences can occur due to stochastic sampling, even when the model is correctly implemented. I would be very grateful for your view on whether such tests were intended to be interpreted differently for stochastic microsimulation models, or whether some tolerance or adaptation is implied when exact deterministic equivalence (zero differences) is not theoretically guaranteed. Any brief guidance you could share on this point would be greatly appreciated! With kind regards, Amir” Response from Prof. Maureen Rutten – van Molken, TECH-VER checklist publication author (reproduced with permission): “Dear Amir, Thank you for your questions about TECHVER. We discussed them extensively; please find my answers below. <u>1. Applicability of TECH-VER to individual-level microsimulation models</u> In general, the TECH-VER checklist is not intended to be applied directly and uniformly to individual-level microsimulation (ILM) models. TECH-VER was developed as a black-box technical verification checklist, with an implicit default assumption of deterministic or cohort-based model behaviour. Thus, some of its tests rely on expectations such as: • exact equality of outcomes under equal effects, • exact reversal of incremental results when effects are swapped, • deterministic state accounting (e.g., given the same inputs, the model will always produce exactly the same state counts and outcomes). In ILM models, outcomes are stochastic realisations, not deterministic quantities. As a result: • exact equality (e.g., exactly zero incremental effects under equal effects assumption) is not necessarily required, • small deviations can be expected and accepted (even under fixed seeds), and • arm-specific or path-dependent logic can legitimately break deterministic symmetry.

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		Thus, for ILM models, TECH-VER tests should be interpreted in terms of: • convergence (e.g., incremental outcomes converging to zero under equal effects assumptions), • directionality (e.g., sign reversal when effects are swapped), • monotonic behaviour (e.g. stronger effects producing larger expected gains), and • explainability of differences based on documented structural logic. In conclusion, TECH-VER, in its original form, still provides a valuable framework, but several tests require adaptation or careful interpretation when applied to non-cohort models, particularly where deterministic expectations are replaced by stochastic behaviour. <u>2. Availability of microsimulation-specific verification or validation guidance</u> I am not aware of a TECH-VER-equivalent checklist specifically tailored to ILM models. Validation of ILMs therefore relies on adapting general frameworks and checklist, as explained above. I do know that colleagues from Groningen University have done some preliminary work on this topic (not published yet) and that they intend to follow up on it. Kind regards, Maureen Rutten-van Mölken, PhD Full Professor of Economic Evaluation of Innovations for Health Head of the HTA department Scientific Director of the Institute for Medical Technology Assessment W Erasmus School of Health Policy & Management (ESHPM) W Institute for Medical Technology Assessment (IMTA) W Erasmus Centre for Health Economics Rotterdam (EsCHER) W Erasmus Choice Modelling Centre (ECMC)” Response from Dr Maiwenn AI, senior author on TECH-VER checklist publication (reproduced with permission): “Dear Amir, ...

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	You ask me a very interesting question...When we developed the TECH-VER, we had cohort models in mind, thus allowing checks like you mentioned, ie some difference being exactly 0, for instance. And indeed, this does not work for a microsimulation model (though I can think of a specific set up of the simulation model that would give the exact same result for both arms, but is not the norm in microsimulation modelling). As you suggested, a way to deal with this would be to set some level of tolerance, so that the test is passed when the difference is smaller than this value. Of course, now the problem becomes what level of tolerance to use, as it should neither be too large or too small. In general, the larger the population that you are simulating, the smaller the difference between the 2 arms if indeed they are the same, so you could increase the population size from e.g. 1000 to 100,000 and see if the difference is now so small that you can confidently assume it to be 0. But the computational time might be a problem here. But you could also try 5,000 or 2,500, maybe that is already enough. Alternatively, instead of just looking at the mean over the whole population, you could compare the histograms of all patients for both arms, because if the 2 arms are now the same, the histograms should be the same as well. And besides visual inspection, this could also be checked using some statistical test. And if you remain uncertain with your population size of 1,000 now an increase to e.g. 5,000 might be enough to come to a conclusion. So, to summarize: 1. compare means and check if the difference becomes smaller if you increase the size of the population you simulate (maybe apply statistical test for difference of means, eg Student T-test or Mann-Whitney test) 2. Compare whole distribution of outcomes in population, not just means. By looking at whole distribution you might not need to increase the population as much as for option 1. You can test for differences using Kolmogorov-Smirnov test Let me know how this worked out for you! Best wishes, Maiwenn AI, PhD Maiwenn Model Validation" In relation to Issue #4 we have also carried out additional analyses to verify our model's predicted rates of advanced liver disease and mortality against external sources. These are provided in full in Appendix BA document. In short, although many of the external data sources we consulted did not allow a direct comparison on the key events, we found a good

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		level of agreement between several published estimates of long-term progression relevant to this disease area, and the rates our model predicts for advanced liver disease complications and death. For example, using a hazard ratio from the study of the UK Biobank data (Feng et al. 2026 [16]) and applying it to UK Life tables (2022–2024) [17] the predicted life expectancy (13.42 discounted life years) aligned closely with the life expectancy produced in our model (13.17 discounted life years). We found a similar concordance when comparing our model's predicted rates of progression to compensated cirrhosis, decompensated cirrhosis, liver transplantation, or hepatocellular carcinoma with those reported in a large claims study by Loomba et al. 2020 [18] (at 8 years, the model predicts 26.8% of patients progress to compensated cirrhosis (F4), 1.4% develop decompensated cirrhosis, 1.4% have hepatocellular carcinoma, 2.2% undergo liver transplantation, and 7.4% experience liver-related mortality – total 39%; compared to Loomba et al. 2020 [18] which reported an aggregate total for these outcomes of 39% at 8 years).
Issue 5: Response to treatment not captured by the current model structure AND Issue 6: Stopping rules and discontinuation of resmetirom treatment	Yes	We have combined our responses to Issues 5 and 6 into a single item. To address these issues, we sought the advice of clinical experts via an advisory board meeting held on 9 December 2025 in London. One aim of the meeting was to develop a clearer set of suggestions for how resmetirom might be started, suspended and discontinued in NHS practice using the NITs currently available, at thresholds which balance safety with clinical priority. As summarised under Issue 1, community MASLD pathways in the UK routinely use two-step sequential testing to stratify patients for risk of significant fibrosis. The first step uses a validated NIT with high negative predictive value (e.g., FIB-4 score) to risk assess for clinically significant liver fibrosis in a low prevalence community setting. If the value is high or intermediate, a second discriminatory NIT (e.g., VCTE, ELF) is frequently used, with hepatology referral recommended if greater than a threshold suggestive of moderate to advanced fibrosis (e.g., LSM >8 kPa). Hence, patients referred to secondary care specialist services are characterised and enriched as at-risk MASH (moderate-advanced fibrosis), compared to the community population (low risk patients are not routinely referred). Therefore, and as discussed earlier, the enriched patient population already in specialist care are those who are potentially eligible for resmetirom. There is extensive evidence from clinical studies and routine NHS utilisation that NITs, like VCTE or equivalent, perform well in characterising a moderate to advanced fibrosis risk population, consistent with that identified by liver histology (LSM ≥8,10 kPa; ≥F2,3). This evidence underpins a broad range of professional, consensus or expert recommendations for the characterisation of at-risk MASH patients and the NIT thresholds (consistent with F-stage) for the initiation, monitoring and response evaluation for resmetirom in NHS patients. The mapping of NIT thresholds to the resmetirom STA economic model is based on the above rationale, including the basis of how histological response can be confidently evaluated with NITs in routine care.

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		The mapping and clinical algorithm below synthesises current evidence and is informed by clinical input from the Madrigal UK ad board and expert opinion. Liver stiffness measures from VCTE have been outlined, although equivalent thresholds for other available validated NITs can be considered. Individual patient characteristics must be considered when evaluating resmetirom eligibility and response. <u>Initiation of Resmetirom (consistent with regulatory indication)</u> • Patients are initiated on Resmetirom ○ Historical or existing biopsy with F2/3 ▪ Ensure baseline NIT prior to starting resmetirom to allow for annual response evaluation ○ NITs consistent with F2-3, (aligned to evidence and consensus) ▪ LSM 10-20 kPa ▪ Or, equivalent or emerging thresholds for other NITs • Exclusion - patients with clinical evidence of cirrhosis ○ Historical or existing biopsy with F4 ○ NITs consistent with F4, cirrhosis (aligned to evidence and consensus) ▪ LSM >15 kPa and Plt <150,000 (CSPH) or LSM >20 kPa ▪ Or, equivalent or emerging thresholds for other NITs <u>NIT response evaluation (annual assessment) and stopping rules</u> • Non-Response – progression, consistent with cirrhosis (F4) ○ Clinical evaluation, including NITs consistent with progression to cirrhosis (aligned to evidence and consensus) ▪ LSM >15 kPa and Plt <150,000 (CSPH) or LSM >20 kPa ▪ ≥ 25-30% worsening in LSM (compared to baseline) and value consistent with cirrhosis ▪ Or, equivalent thresholds and changes for other NITs ▪ If there is clinical uncertainty, repeat after short interval for validation of prior NIT evaluation ○ Stop Resmetirom ▪ Ongoing routine management as per UK clinical practice • Response Stable - consistent with F2/3

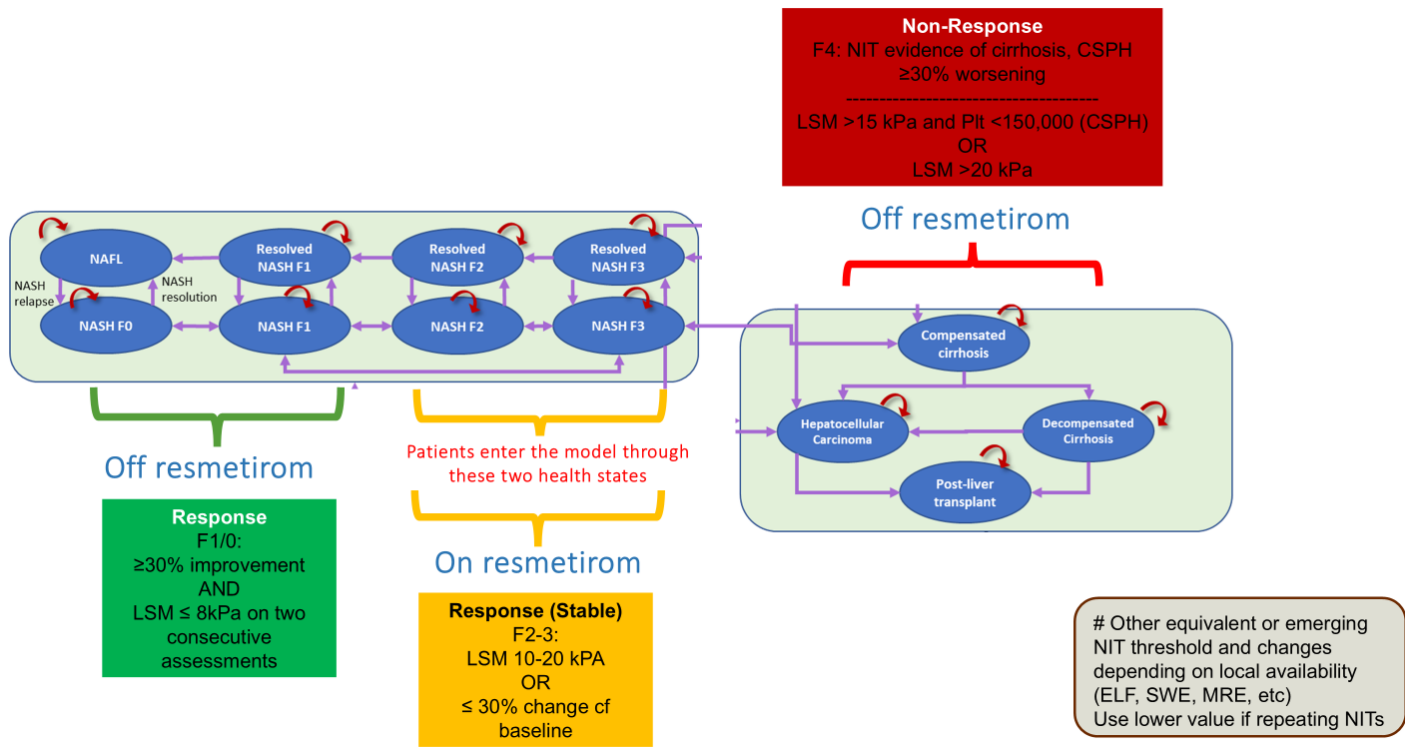
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		○ NITs remain consistent with F2-3 (regulatory indication) ▪ LSM 10-20 kPa ▪ ≤ 25-30% change in LSM compared to baseline ▪ Or, equivalent thresholds and changes for other NITs ○ Continue Resmetirom – evaluate in 12 months ▪ NIT changes are always compared to baseline value from initiation • Response Improver (fibrosis improved, consistent with F0/1) ○ NITs improvement consistent with F0/1 ▪ ≥ 25-30% improvement in LSM (compared to baseline) and LSM ≤ 8 kPa ▪ Or, equivalent thresholds and changes for other NITs ▪ Repeat after interval (i.e. 3 months) for data validation of prior NIT assessment (i.e. LSM values remain consistent with response improver) ○ Stop Resmetirom ▪ Clinical evaluation supports sustained improvement ○ Stop resmetirom ○ Repeat NIT evaluation on an annual basis ▪ Restart resmetirom if annual evaluation suggests worsening while off therapy ○ ≥ 25-30% worsening in LSM (compared to last stop value) ○ LSM consistent with F2-3 (i.e., ≥ 10kPa)

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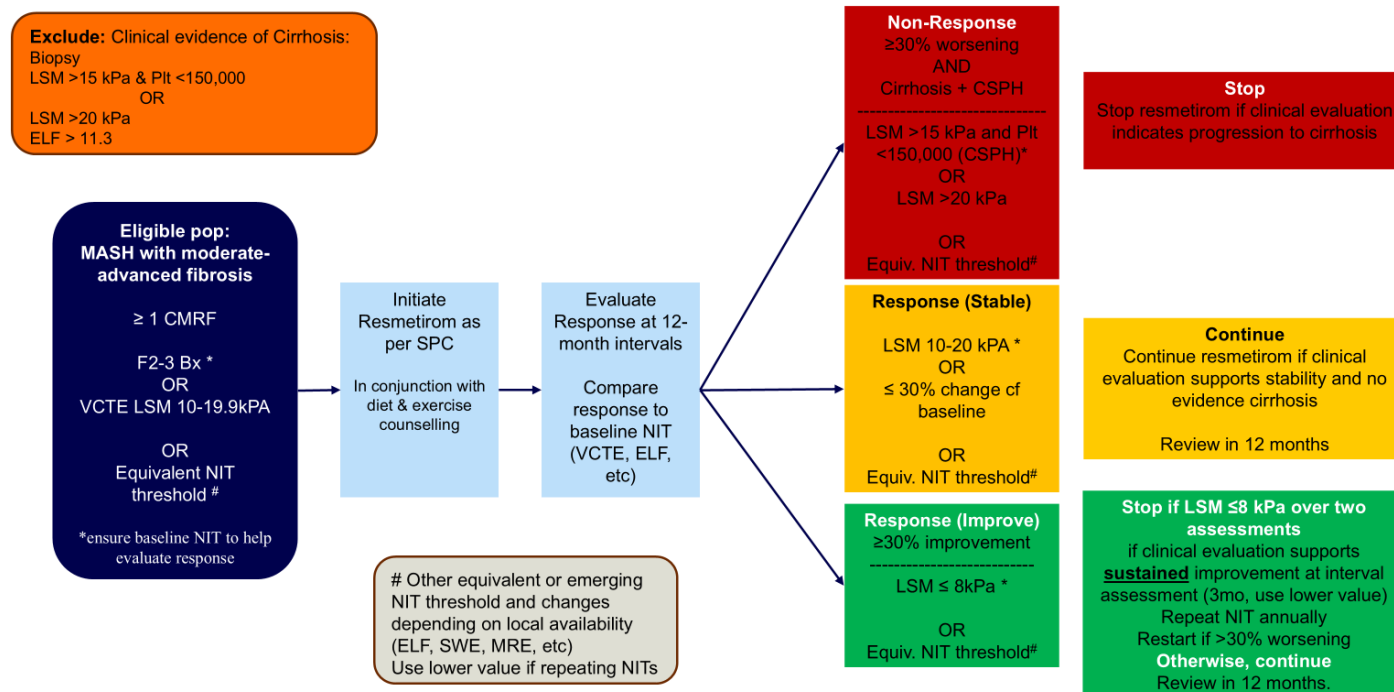
Figure 11. Mapping VCTE thresholds to resmetirom STA model structure



The treatment initiation, response evaluation and stopping rules outlined above are consistent with the resmetirom model structure (Figure 11) and current evidence or recommendations. These rules can be implemented in NHS clinical practice with the below suggested algorithm, aligning with the current standard of care clinical for annual clinical evaluation, including with NITs. There is limited additional diagnostic or clinical service requirement to implement a clinical algorithm similar to in Figure 12.

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Figure 12. Clinical algorithm for initiating, evaluating response, and discontinuation of resmetirom



Permanent discontinuation of resmetirom in NHS routine care is expected to align to NHS clinical practice recommendations, such as those suggested above. Therefore, most specialists would be expected to discontinue resmetirom at an annual assessment if the clinical evaluation indicated non-response and progression to cirrhosis. A small proportion of specialists may consider repeat evaluation after a short interval (LSM data validation) before stopping due to non-response and cirrhosis.

Suspending or stopping resmetirom in patients with robust clinical evidence of response improvement consistent with F0-1. In this circumstance, the majority of specialists are likely to repeat an NIT evaluation for reassurance and data validation after an interval. This interval can be as short as that for repeating in non-response, but may be extended given

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the last VCTE evaluation indicated response improvement. Most repeat evaluations are likely to be completed between 3-6 months, after which 'fibrosis improver' patients could stop resmetirom. A small fraction of specialists may extend the repeat interval for longer before stopping resmetirom.

Stopping rule scenarios in new economic model

Our economic model Excel Input sheet now enables exploration of the cost impact of implementing the above stopping and discontinuation rules; it can also model other stopping rule combinations which the EAG or NICE technical team have formally requested or expressed interest in during Clarification or Technical Engagement. Via the Excel input dashboard (see screenshot below), users can select which fibrosis stages are to be treated with resmetirom and configure the model to add the cost of either 3 or 6 months' additional resmetirom to reflect the extra time required to perform confirmatory tests prior to discontinuation, as well as the cost of an additional confirmatory outpatient Fibroscan. These additional cost options can be applied separately to permanent discontinuation after non-response (works only if F4 is deselected), or temporary discontinuation due to improvement.

Figure 13. Portion of user interface where stopping rules can be implemented in the model

Stopping rules

Click the relevant button to select or unselect

Based on fibrosis stages (liver biopsy)

F0 F1 F2 F3 F4

Extra resmetirom costs

1 Extra FibroScan cost

Total extra costs +£0 +£0 +£0

Stop resmetirom Continue resmetirom

Scenario analyses

We have used this new functionality to calculate ICER values for the stopping rule scenarios we believe to be most relevant in the table below. As there are no effectiveness estimates associated with these scenarios, only costs and the ICERs are presented:

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		Scenario	SoC total cost (£)	Resmetirom total cost (£)	Incremental cost (£)	ICER (£/QALY)
		1 Stopping at F1 or better, with 3 months' additional resmetirom cost and one extra outpatient FibroScan assessment	██████	██████	██████	38,771
		2 Stopping at F1 or better, with 6 months' additional resmetirom cost and one extra outpatient FibroScan assessment	██████	██████	██████	41,505
		3 Permanent discontinuation at F4, with 3 months' additional resmetirom cost and one extra outpatient FibroScan assessment	██████	██████	██████	36,553
		4 Permanent discontinuation at F4, with 6 months' additional resmetirom cost and one extra outpatient FibroScan assessment	██████	██████	██████	37,144
		5 Scenarios 1 and 3 combined	██████	██████	██████	39,382
		6 Scenarios 2 and 4 combined	██████	██████	██████	42,706
Issue 7: Repeated application of transition probabilities and short-term trial follow-up	Yes	We acknowledge that M-NASH provides short-term (12-month) trial data and that clinical advice to EAG has led to a questioning of whether MASH resolution rates observed at month 12 could reasonably be expected to persist over time. We believe there are biological, clinical, and empirical grounds supporting the plausibility of using Month-12 transition probabilities for MASH resolution as constant annual rates in long-term microsimulation models for MASH. Since THR-β belongs to the nuclear hormone receptor superfamily, a wide range of effects are expected through gene expression and its master regulator role on lipid metabolism. Stimulation of THR-β in the liver improves mitochondrial function and lipid metabolism, and increases fatty acid βoxidation, thereby reducing lipotoxic liver fat, inflammation and liver fibrosis. Resmetirom's liver directed THR-β agonism on a nuclear receptor level, and therefore gene expression, is central to reducing the drivers of steatohepatitis through reducing lipotoxic liver fat and inflammation. Therefore, the beneficial biologic effects on steatohepatitis and fibrosis persist with continuing resmetirom exposure through ongoing activation of the THR-β master regulatory pathway. Similar to other therapies in chronic disease, ongoing drug exposure and pathway activation leads to continuing biologic effect and disease modification that manifests as ongoing clinical				

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	effect. There is no expectation that there would be treatment effect waning from a gradual decline in resmetirom’s efficacy or benefit over time given the activation of a core hormonal pathway and the biological rationale outlined. All major population and economic models of MASH, including those specific to the UK, rely on constant or piecewise-constant transition probabilities due to the underlying biology and lack of evidence for non-linear long-term dynamics. In UK-focused modelling: • Transition probabilities were calibrated using obesity and T2DM prevalence and applied uniformly across annual cycles to project disease burden. • Models explicitly acknowledge that fibrosis progression is driven by persistent metabolic exposure, which may not biologically “reset” over time. Importantly, these UK models have underpinned policy-level decision making and implicitly validate the methodological acceptability of constant annual rates in the absence of contradictory evidence [15,19,20]. The EAG correctly notes uncertainty; however: • There is no empirical evidence supporting alternative time-dependent functional forms. • NICE methodological guidance accepts constant or piecewise-constant hazards where disease biology is chronic and progressive and where data are limited. Scenario analysis options provided In response to EAG’s suggested alternative scenarios, our amended model’s Master Inputs Excel interface allows EAG to manually specify percentage changes (positive or negative) in years 2 through 5+ to treatment effects of resmetirom and SoC for the following clinical outcomes: • MASH resolution efficacy; • Fibrosis improvement rate; • Fibrosis worsening rate. In response to the EAG’s requested scenario, we have run a scenario where MASH resolution is set to zero for both arms from year 2 onwards in the model: <table><tr><th>Technologies</th><th>Total costs (£)</th><th>Total LYG</th><th>Total QALYs</th><th>Incremental costs (£)</th><th>Incremental LYG</th><th>Incremental QALYs</th><th>ICER (£/QALY)</th></tr><tr><td></td><td></td><td></td><td></td><td></td><td></td><td></td><td></td></tr></table>	Technologies	Total costs (£)	Total LYG	Total QALYs	Incremental costs (£)	Incremental LYG	Incremental QALYs	ICER (£/QALY)								
Technologies	Total costs (£)	Total LYG	Total QALYs	Incremental costs (£)	Incremental LYG	Incremental QALYs	ICER (£/QALY)										

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		SoC	████	████	████	NA	NA	NA	NA	
		Resmetirom	████	████	████	████	████	████	38,726	
Issue 8: Misinterpretation of Singh et al (2015)	Yes	To address this issue, the EAG recommended that “Evidence of multistate progressions should ideally be generated from the [M-NASH] trial. If this data cannot be provided, a more appropriate data source should be selected.” We agree with the EAG that the M-NASH study [15] would be the most appropriate source for this submission. However, in the original CS model, we utilised Singh et al. 2015 [21] to inform what proportions of patients with ‘fibrosis improvement’ or ‘fibrosis worsening’ would experience 1- or 2-stage changes to their fibrosis scores. Contrary to the clinical advice received by EAG, two-stage improvement in fibrosis within one year is clinically plausible and a common endpoints in MASH trials: M-NASH measured it (Harrison et al. 2024 [15] and CS section 2.6.2, Table 18) and found that 8.3% and 10.1% of patients in 80mg and 100mg resmetirom arms respectively achieved a 2-stage reduction in fibrosis at week 52 with no worsening of NAS score, compared with 2.8% of placebo arm patients. It would have been ideal to source all fibrosis regression and progression statistics directly from M-NASH, but as explained in the CS and at Clarification, fibrosis worsening cannot be fully disaggregated for F2 and F3 patients, as it would involve per-arm disclosure of patients becoming cirrhotic (F4) in the study, which jeopardises our regulatory commitment to maintain double-blinding. Concerns over this regulatory restriction are why we initially used Singh et al. 2015 [21] data to have a single source informing the proportions of patients making such transitions (in both directions) in the model. Upon reflection of the limitations highlighted by the EAG in using Singh et al. 2015 [21], we have revisited the issue and our approach to develop analyses exploring the impact that multi-stage fibrosis transitions (or their removal) have on the estimated cost-effectiveness of resmetirom. Scenario analyses developed We amended the model to utilise M-NASH data directly for fibrosis regression amounts, which we have confirmed does not involve per-arm disclosure of crucial outcomes, maintaining our regulatory commitments. This reduces the model’s dependence on Singh et al. 2015 [21] in line with the suggestion by the EAG and allows selection of alternative assumptions regarding maximum rates of annual fibrosis progression and regression. We have provided multiple additional options for the EAG in scenario analyses. These scenarios can be accessed via the “Annual fibrosis changes pattern” option drop-down in the Master Inputs Excel file and are summarised below: 1. Fibrosis progression and regression both restricted to a maximum 1 of stage per year								

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2. Progression and regression maximum 2 stages per year: fibrosis regression statistics come from M-NASH IPD, fibrosis progression statistics come from Singh et al. 2015 [21] as per original CS technique
3. Fibrosis progression limited to 1 stage per year, regression sourced from M-NASH IPD and allowed to be multi-stage per year if trial patients achieved it (**used in new base case**)

We have run scenario 1 above as requested by EAG, in which fibrosis progression (and regression) are both limited to a maximum of one stage per year. Results of this scenario are shown here; they were found to have a marginal impact on the ICER:

Technologies	Total costs (£)	Total LYG	Total QALYs	Incremental costs (£)	Incremental LYG	Incremental QALYs	ICER (£/QALY)
SoC	████	████	████	NA	NA	NA	NA
Resmetirom	████	████	████	████	████	████	36,763

Running scenario 2 described above produces results as follows:

Technologies	Total costs (£)	Total LYG	Total QALYs	Incremental costs (£)	Incremental LYG	Incremental QALYs	ICER (£/QALY)
SoC	████	████	████	NA	NA	NA	NA
Resmetirom	████	████	████	████	████	████	29,766

New base case (Scenario 3 above)

To reduce the impact of uncertainty around using Singh et al. 2015 [21] in our model, we also amended our base case to use scenario 3 above by default – thus fibrosis worsening is restricted to a maximum of one stage per annual cycle and not dependent on Singh et al. 2015 [21], and stage-to-stage regression in fibrosis is directly mapped from M-NASH IPD. Results from this amendment are summarised in the “base case changes” table at the end of this response document.

Issue 9: Natural history of MASH	Yes	In the EAR, the EAG has interpreted MASH natural history papers to mean that fibrosis progression slows down as disease advances. However, this does not correctly reflect the observed risks of MASH patients with advanced fibrosis, as

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and face validity of model progression rates	both arms of the M-NASH study demonstrated. Multiple clinical expert advisers familiar with the risk profiles of MASH patients eligible for resmetirom have communicated to us that the EAR interpretation of the available data is not correct for such patients. We believe this has probably been caused by a misunderstanding of the two meta-analyses cited by EAG (Le et al. 2023 [22] and Singh et al. 2015 [21]). In developing our response and the requested scenario analyses, we reconsidered the available data in detail, searched for newly-published evidence and revisited the apparent core assumptions of the EAG in relation to this issue. Slow progression and interpretation of Singh et al. 2015 [21] The EAR asserts in several places that the resmetirom trial results and our model appear “<i>inconsistent with the findings of Le et al. (2023)³³ and Singh et al. (2014), which indicate that progression to ALD typically occurs only after a prolonged period.</i>” It is indeed true that MASH can be a slow-moving disease for many patients, but as the M-NASH study demonstrated, and as emerging guidelines and consensus statements are suggesting, there are patients with advanced disease in whom the risk of progression is higher and in whom rapid identification and treatment are urgent. The EAG report stated, “<i>The EAG also notes that the findings of Le et al. (2023)³³ are consistent with earlier work by Singh et al. (2014), which similarly shows that the annual fibrosis progression rate decreases with increasing baseline fibrosis stage.</i>” However, the Singh et al. 2015 [21] publication also explicitly stated – and we believe this point may have been missed by EAG – “<i>...we were unable to estimate the FPR [fibrosis progression rate] for patients with intermediate and advanced fibrosis at baseline.</i>” The authors further noted: “<i>It also is likely that patients who progressed from advanced fibrosis to decompensated cirrhosis were not advised to repeat a histologic examination, potentially underestimating the rate of fibrosis progression [for these patients]. To overcome this limitation, we specifically estimated the FPR in patients with stage 0 fibrosis.</i>” We feel the average FPR reported in Singh et al. 2015 [21] (which is explicitly developed for MASH patients initially identified with stage 0 fibrosis at baseline) was misinterpreted as having relevance to the entire fibrosis spectrum, including those with baseline F2 and F3 in the decision problem. MASH is an area with relatively sparse data for the kinds of high-risk patients likely to be offered resmetirom (excepting the M-NASH study). The HTA Lab Report highlighted these challenges: • “<i>Given the heterogeneity of the MASH population... accurately reflecting the progression of MASH in economic models may potentially pose a challenge. There is also a lack of published high-quality data to inform estimated of the natural history of the condition.</i>”

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		• “While long-term data on the effectiveness of the treatments in the pipeline may be available for other indications, there is currently limited data on their effectiveness for MASH. So, modelling the lifetime effects of treatments in terms of quality and length of life will require long-term extrapolation from short-term outcomes observed in the trials.” However, to fulfil our commitment to equip our R microsimulation with all model scenarios requested in TE, we investigated how to develop scenarios whereby SoC patients’ fibrosis progression is informed by a ‘natural’ external reference population, and RR statistics are used to subsequently map resmetirom’s efficacy gains on top of SoC. The intent is not dissimilar to the approach used in NICE STAs of primary biliary cholangitis medicines (obeticholic acid, elafibranor and seladelpar) where UK-PBC registry cohort data were calibrated to align to placebo arm data from respective medicines’ RCTs before applying RR statistics for the intervention of interest. The first study we considered, per the EAG’s suggestion was Le et al. 2023 [22]. Reliability and applicability of Le et al 2023 [22] in the requested scenario The EAR states “The company’s rationale for rejecting Le et al. is that the results are clinically implausible, as they suggest that progression slows with advancing fibrosis (see Table 31 of the CS).” To be clear, our rejection of Le et al. 2023 [22] as a natural history data source was not decided only because its results went in the opposite direction to what we considered clinically plausible. It was also because we observed rapid progression of fibrosis in M-NASH’s advanced fibrosis population. Furthermore, UK clinical expert feedback received at several points during this STA has directly contradicted the EAG’s characterisation of “slowing” progression with increasing fibrosis level. Over ten expert hepatologists, gastroenterologists and endocrinologists have commented to us in this regard, indicating that patients with suspected MASH, advanced fibrosis and comorbid conditions are an urgent priority to treat because they have limited time left to avoid progression to cirrhosis: increasing fibrosis severity exacerbates the risk of risk of further progression or cirrhosis – it does not attenuate it. Pooled progression rates from published natural history studies such as Le et al. 2023 [22], are not representative of these patients because they mix results from patients with vastly different risk profiles and baseline disease stages. With a view to designing a scenario analysis, we attempted to probe the source RCT data extracted by Le et al. 2023 [22] to see if these might contain sufficient subgroup information to allow some form of calibration to match the placebo arm of MAESTRO-NASH. Unfortunately, while investigating the source papers from Le et al. 2023 [22], we identified anomalous estimates as well as substantive flaws in the paper’s analyses, including transcription errors, inconsistent calculation methods and inclusion of heterogeneous and partially unreported population characteristics. These are provided in a separate Appendix BB. One anomalous finding bears summarising here as it would have a material impact on results when used in scenario analysis:

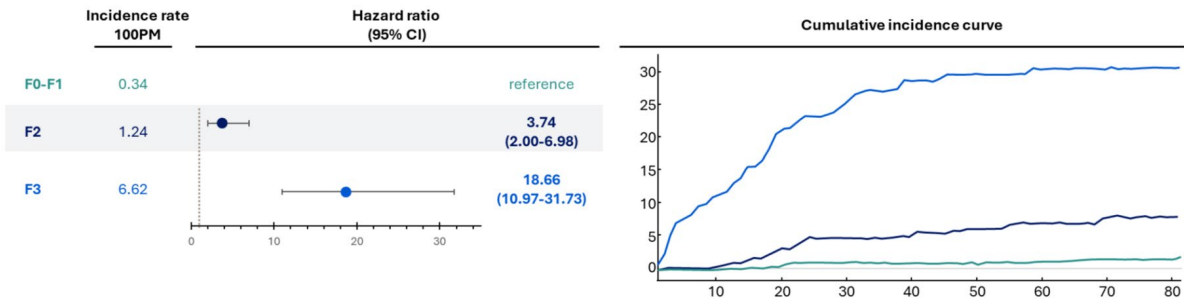
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Le et al. 2023 [22] estimated that F3 patients had a much higher incidence of **regression** to F2 fibrosis (i.e. their livers spontaneously improving) than of **progression** to F4 (the F3 to F2 rate was 17.7 per 100 patient-years [95% CI: 13.2-23.6] versus the F3 to F4 rate of 8.4 per 100 person-years [95% CI: 4.96-14.3]). These two transition estimates represent an inverse relationship compared to all other stages calculated in Le et al. 2023 [22], wherein incidence of progression typically exceeded regression.

We were unable to find risk-based publications corroborating this pattern; most appear to contradict this position by showing that the hazard of cirrhosis increases with increasing fibrosis stage, for example see Figure 14 [23]. We are aware that the EAR currently rejects Luthra et al. 2025 [23] as evidence of higher fibrosis stages being associated with faster progression – suggesting that it can only associate higher fibrosis stages with “worse outcomes” (Page 77, section 4.2.5) without informing progression speed. We hope that the visual comparison of cumulative incidence curves over time (in months; Figure 14) from this publication might help to illustrate that increasing fibrosis stage – particularly F3 – increases relative hazard of cirrhosis in both time and frequency domains.

Figure 14. Incidence rates and cumulative incidence for progression to cirrhosis among patients with non-cirrhotic MASH stratified by disease severity. From Luthra et al. 2025 [23]



Incidence rates are reported per 100PM. Forest plots display hazard ratios and the dashed line depicts $x = 1$. Hazard ratios shown in bold are statistically significant. Cumulative incidence curves are displayed as a function of time in months. Cumulative incidence curves are displayed as follows: F0–F1 solid green line, F2 solid dark blue line, F3 solid blue line. 100PM 100 person-months, CI confidence interval, F0–F1 fibrosis stage 0 or 1, F2 fibrosis stage 2, F3 fibrosis stage 3, MASH metabolic dysfunction-associated steatohepatitis

As discussed in Issue 2, and equally relevant to this issue around natural history, Roden et al. 2025 [10] analysed the TARGET-NASH registry to establish the increased risk of cirrhosis for F3 patients and decompensation for F4 patients

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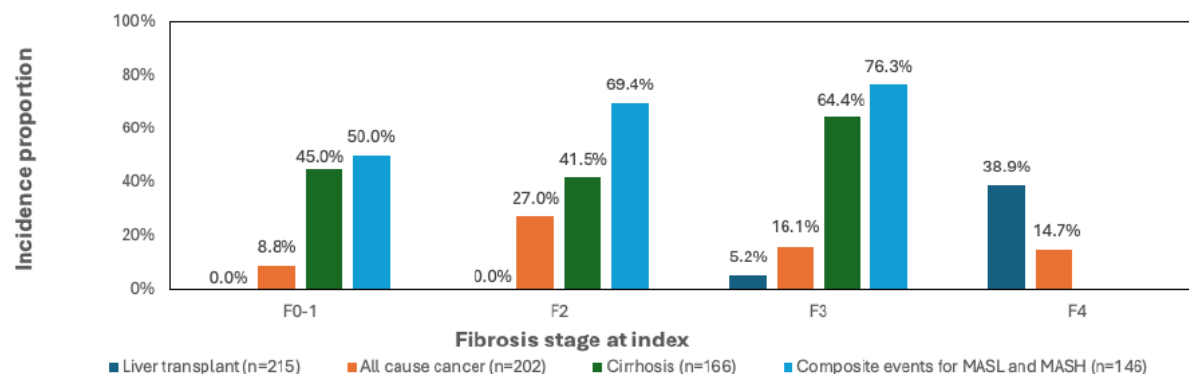
versus patients with early-stage fibrosis (F0-F1) and a higher risk at any time for cirrhosis for patients with T2DM versus those without T2DM.

As shown in Figure 4 in Issue 2 (also Figure 15 below), the incidence of liver transplant, cirrhosis, and composite liver events was higher for F3 patients versus F2 or F1 patients. The incidence of liver transplant was substantially higher for F4 patients (n=14; 38.9%) than for F3 patients (n=3; 5.2%), with a reported median time to liver transplant of 3.3 years and 7.5 years, respectively. As discussed in issue 2, higher fibrosis stage at index was also associated with a higher probability of developing decompensation at any time during follow-up (HRs versus F0/F1: F2=0.5, F3=1.4, F4=4.1).

If the disease were to 'slow' with increasing fibrosis per the anomalous result for F3 in Le et al, then the instantaneous risk of experiencing such events and the incidence of these events would not be higher with increasing fibrosis stages [10].

Figure 15. Incidence of clinical outcomes by fibrosis stage at index date in the TARGET-NASH biopsy cohort from Roden et al. 2025. [10]

a. Clinical incidence proportions by fibrosis stage



Note: Composite events includes progression to cirrhosis, decompensation, HCC, MELD score change, LT, CV event, all-cause mortality, or cancer.

b. Clinical incidence proportions by disease progression

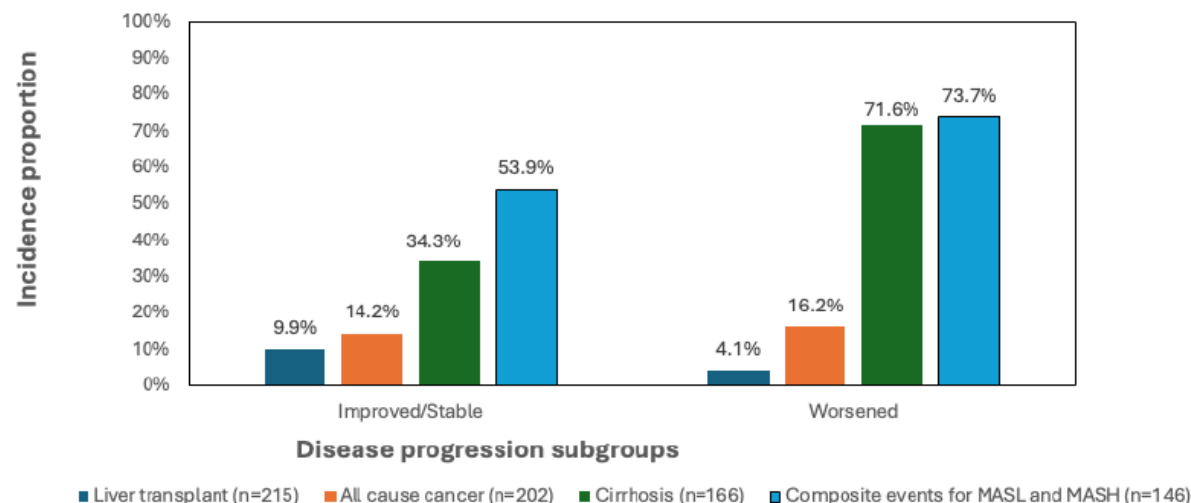
Progression of fibrosis itself also had an association with the incidence of advanced liver disease: compared to those without progression, patients with progressed or "worsened" liver disease had a much higher incidence of cirrhosis (71.6% vs 34.3%; $p < 0.0001$) and composite events (73.7% versus 53.9%, as detailed below; Figure 16). The authors also reported that among patients with F0-F3 fibrosis, the incidence rate of a composite event after index was highest among index F3 patients followed by index F2 patients (incidence rate per 100 person years=13.4 and 9.67, respectively) [10].

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The results from this study support the clinical expert opinion we received that in MASH, disease does not slow with worsening fibrosis progression, contradicting specifically the F3 category results in Le et al. 2023 [22].

Figure 16. Incidence of clinical outcomes by disease progression status at index date in the TARGET-NASH biopsy cohort from Roden et al. 2025. [10]



Scenario analyses

EAG suggested

Taken together, the Le et al. 2023 paper's [22] shortcomings made it impossible to calibrate or adjust for factors which would make a model based on its estimates more applicable to the resmetirom-eligible population. Therefore, the scenario analysis we have developed involving Le et al. 2023 RCT data (from Table 2 in Le et al. 2023 [22]) is unadjusted: it converts stage-to-stage fibrosis incidence rates from RCT data in Le et al. 2023 [22] directly into annual probabilities for use with SoC; resmetirom's additional treatment benefit is modelled by applying a RR statistic as previously described. MASH resolution outcomes remain informed by M-NASH as suggested by EAG.

As an alternative to the Le et al. 2023 publication [22], we considered other meta-analyses of placebo arm data (Ng et al. 2022 [24]) and TARGET-NASH (Luthra et al. 2025 [23]) to inform SoC natural history. However, when attempting to calculate transition probabilities from Luthra et al. 2025 [23], we identified an error in the calculation of all incidence rates

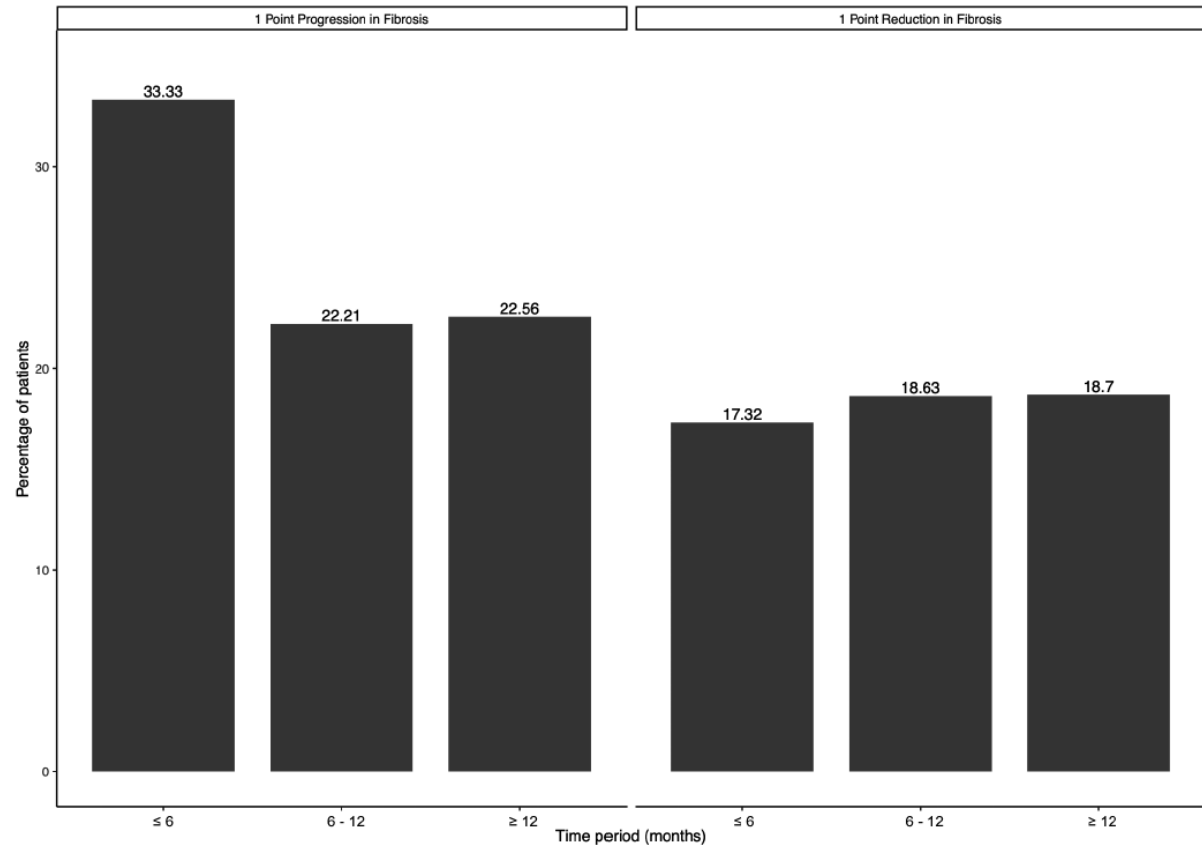
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		in the publication. The authors did not respond to questions about this error; therefore, we did not use Luthra et al. 2025 [23] as an alternative natural scenario but instead focussed on Ng et al 2022 [24]. <u>Alternative natural history source: Ng et al. 2022 [24] meta-analysis of placebo arms from NASH RCTs</u> The meta-analysis by Ng et al. 2022 [24] considered placebo arms from NASH (MASH) RCTs, with the primary outcomes of (1) the resolution of NASH without worsening of fibrosis, (2) a two-point reduction in NAS without worsening of fibrosis, and (3) at least one point reduction in fibrosis, all of which are common efficacy endpoints in RCTs for this disease area. Secondary outcomes of interest included other histological endpoints from liver biopsy (i.e., at least a one-point reduction and progression in steatosis, ballooning, and inflammation) and change in mean NAS score. The authors also assessed change in biochemical parameters. A total of 29 studies were included in the meta-analysis of at least one point reduction in fibrosis, representing 1522 patients, of which 18.82% (95% CI: 15.65%-22.4%) experienced a one-point reduction (Figure 17). This was lower than the effect size of at least one point progression in fibrosis calculated from 14 studies with 965 patients (22.74%; 95% CI: 19.63%-26.17%). The authors also looked at subgroup analyses based on duration of measurement (≤ 6 months, 6-12 months, and ≥ 12 months), but values for reduction were similar irrespective of time point, meaning that across studies, approximately 1/5 of patients experienced progression in a similar time frame as observed in the M-NASH study (12 months). Figure 17. Placebo effects on at least one-point reduction and progression in fibrosis from Ng. et al 2022 [24] by time period assessed

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Additional Scenarios

Ng et al was used in combination with Le et al to develop additional scenarios for modelling SoC natural history, resulting in a total of four scenarios addressing Issue #9:

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1. **Le et al 2023 [22] unadjusted:** converts stage-to-stage fibrosis transitions from RCT data in Le et al. 2023 [22] into annual probabilities for use with SoC; transitions used are shown below.

Table 2. Annual fibrosis stage-to-stage transition probabilities for SoC derived from Le et al 2023 [22]

Le et al.	F0	F1	F2	F3	F4
F0	0.7452765	0.1767469	0.077977	0	0
F1	0.1192663	0.6564255	0.148361	0.075947	0
F2	0.0357261	0.1273315	0.648338	0.167849	0.020756
F3	0	0.0669044	0.095316	0.757211	0.080569
F4	0	0	0	0.086069	0.913931

2. **Ng et al. 2022 [24] unadjusted:** use 12-month '1 Point Progression in Fibrosis' and '1 Point Regression in Fibrosis' outcomes (shown in Figure 17) as a source for transitions at each fibrosis stage. Since Ng et al. 2022 [24] did not specify the stage-magnitude of such changes, this analysis allows a maximum of one fibrosis stage change per year in either direction. Transitions are summarised below.

Table 3. Annual fibrosis transition probabilities by stage for SoC derived from Ng et al. 2022 [24]

Ng et al.	Progression	Regression
F0	0.199164723	
F1	0.199164723	0.16997545
F2	0.199164723	0.16997545
F3	0.199164723	0.16997545
F4		0.16997545

3. **Le et al. 2023 [22] and Ng et al. 2022 [24] combined (1 stage max):** same as scenario 1 but replace F3 transition probabilities with those from Ng et al. 2022 [24], to counter the anomalous F3 progression/regression balance observed. To match Ng et al. outcomes, allow a maximum of one fibrosis stage change per year in either direction.

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Table 4. Annual fibrosis transition probabilities by stage used for SoC in Ng & Le combination scenario (1 stage per year max)

Le & Ng et al.	Progression	Regression	Source
F0	0.254723509		Le et al. 2023 [22]
F1	0.224308198	0.11926633	Le et al. 2023 [22]
F2	0.188604764	0.16305758	Le et al. 2023 [22]
F3	0.199164723	0.16997545	Ng et al. 2022 [24]
F4		0.08606881	Le et al. 2023 [22]

4. **Le et al. 2023 [22] and Ng et al. 2022 [24] combined (2 stages max):** same as scenario 3 but assume that patients in stages other than F3 can transition by the same number of fibrosis stages as estimated in Le et al. 2023 [22].

Table 5. Annual fibrosis stage-to-stage transition probabilities used for SoC in Ng & Le combination scenario (2 stages per year max)

Le & Ng et al.	F0	F1	F2	F3	F4	Source
F0	0.745276491	0.25472351	0	0	0	Le et al. 2023 [22]
F1	0.119266327	0.65642547	0.224308	0	0	Le et al. 2023 [22]
F2	0	0.16305758	0.648338	0.188605	0	Le et al. 2023 [22]
F3	0	0	0.169975	0.63086	0.199165	Ng et al. 2022 [24]
F4	0	0	0	0.086069	0.913931	Le et al. 2023 [22]

Derivation of all above transition probabilities from publication values is transparently shown and can be reviewed by EAG in the “**NH – data**” tab of the Excel Master Inputs file.

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Running the four scenarios as above produces the following results:

1. Le et al. 2023 [22] unadjusted:

Technologies	Total costs (£)	Total LYG	Total QALYs	Incremental costs (£)	Incremental LYG	Incremental QALYs	ICER (£/QALY)
SoC	████	████	████	NA	NA	NA	NA
Resmetirom	████	████	████	████	████	████	161,514

2. Ng et al. 2022 [24] unadjusted:

Technologies	Total costs (£)	Total LYG	Total QALYs	Incremental costs (£)	Incremental LYG	Incremental QALYs	ICER (£/QALY)
SoC	████	████	████	NA	NA	NA	NA
Resmetirom	████	████	████	████	████	████	124,377

3. Le et al. 2023 [22] and Ng et al. 2022 [24] combined (1 stage max):

Technologies	Total costs (£)	Total LYG	Total QALYs	Incremental costs (£)	Incremental LYG	Incremental QALYs	ICER (£/QALY)
SoC	████	████	████	NA	NA	NA	NA
Resmetirom	████	████	████	████	████	████	108,958

4. Le et al. 2023 [22] and Ng et al. 2022 [24] combined (2 stages max):

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		Technologies	Total costs (£)	Total LYG	Total QALYs	Incremental costs (£)	Incremental LYG	Incremental QALYs	ICER (£/QALY)
		SoC	██████	██████	██████	NA	NA	NA	NA
		Resmetirom	██████	██████	██████	██████	██████	██████	95,735
		Although potentially informative as sensitivity analyses showing how the model reacts under a “external data for SoC + treatment RR” design, we do not consider the estimates informing this scenario – which come from aggregate data in heterogeneous and MASH populations, many of them lower-risk – to reflect the anticipated incremental treatment costs or benefits of resmetirom in the patients covered in scope. These findings emphasise the need for greater clarity and consensus that are highlighted in the EAR, concerning how to characterise MASH patients who are ‘at risk’ of experiencing rapid progression. <u>Concept of ‘fast progressors’ – support in literature</u> On page 25 in section 2.1 of the EAR, clinical advice to EAG was summarised: “<i>there could be some patients whose fibrosis stage progresses rapidly (rapid progressors) and clinical advice to the EAG indicates this depends on comorbidities and the stage of disease at diagnosis.</i>” By contrast, page 40 in section 3.2.2.4 stated, “<i>one of the advisers did not recognise the phenomenon of the ‘rapid progressor’ in clinical practice</i>” and page 77 in section 4.2.5 noted “<i>evidence supporting a clinical phenotype of fast progressors is, however, still emerging, and clinical advice received by the EAG confirms that there is no universal consensus on a definitive phenotype. Moreover, even if such a phenotype exists, the company does not demonstrate that all (or even the majority) of patients eligible for resmetirom fall into this category.</i>” We hope that the clinical feedback summarised in Issues 5 and 6 regarding identification of patients eligible for resmetirom may go some way to illustrating how patients considered at high risk for progression might be identified in clinical practice. However, we recognise that MASH is a heterogeneous disease and that many studies have estimated the association of various risk factors, including comorbidities but also fibrosis level and other biomarkers, with advanced liver disease-related events. Therefore, we have provided a summary of literature to further support this concept, although we recognise that this cannot necessarily be used to generate guidance.							

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	As discussed in the CS, Singh et al. 2015 [21] identified of a subset of patients with NASH (MASH; 18.2% of total) who experienced rapid disease progression from early disease stages to advanced fibrosis stages (baseline stage 0 patients who progressed to stage 3 or 4 fibrosis over a mean follow-up period of 5.9 [$\pm$3.7] years). This phenomenon was also observed in NAFLD and NAFL with similar proportions of patients. The authors concluded that approximately 1 in 5 patients will be a “rapid progressor”, which has also been supported by numerous subsequent publications subsequent to Singh et al. 2015 [24–27] and is not a new concept introduced by the company. Sanyal et al. 2019 [26] reported results from simtuzumab trials (in MASH patients with F3 or F4 fibrosis), which conducted biopsies at baseline, 48 weeks and 96 weeks, after which the trial was terminated due to lack of efficacy. The authors reported that 22% (n=48/217) of F3 patients progressed to cirrhosis with an incidence rate of 10.6 events per 100 person-years (95% CI, 8.0-14.0), and median time to progression reported as 10.9 months (IQR: 8.6-12.3 months). In the cohort of patients with cirrhosis, 19% (n=50/258) of patients experienced liver-related clinical events (decompensation event, MELD score 15, liver transplantation, or death). In this study, 8.6% of cirrhosis patients and 21% of patients with bridging fibrosis (with repeat liver biopsies) had experienced a $\geq$1 stage reduction in NASH CRN fibrosis stage. These results highlight the importance of <i>preventing progression</i> of F3 patients to cirrhosis, especially for the subset of patients who would experience rapid progression. We agree with the EAG’s assessment that there currently “<i>there is no validated tool to differentiate rapid progressors in the MASH population</i>” (EAG report, p. 25), although a number of recent studies have been researching MASH with the aim of identifying key factors associated with rapid progression. Some of these studies were conducted in the UK (Imperial College Healthcare NHS Trust, and using the UK Biobank data). A study by Jambulingam et al. 2023 [25] included all consecutive new referrals to the specialist NAFLD clinic at St. Mary’s Hospital in London between 2011 and 2019. Authors found that fast progressors, as based on changes in liver stiffness measurements, represented 23.8% of patients in the study (N=189), and they were able to identify several metabolites and lipoproteins that could identify fast progressors. The interest to identify rapid progressor patients remains high, particularly given the prioritisation which will be required when rolling out the first wave of pharmacotherapies for MASH in the NHS. Schattenberg et al. 2024 [27] conducted a study using Optum electronic health records from 2007 to 2018 where patients were classified according to their time to progression to cirrhosis or HCC from time of earliest observable disease (NAFLD or NASH): fast (0.5-3 years), intermediate (>3 to 6 years) and standard (>6-10 years). As presented in Figure 18, fast progressors represented 24% of all patients (n= 951/4013). The authors also observed that a higher proportion of patients among the fast progressors had obesity at index date (24% vs 18%, $p<.01$) and higher comorbidity load at index date, with 25% of fast progressors having a Charlson comorbidity index (CCI) score of 3 or higher vs 12% of standard progressors (Figure 19).

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Figure 18. Cohort classification of patients based on time of progression from index date to the date of cirrhosis or hepatocellular as presented in Schattenberg et al. 2024 [27]

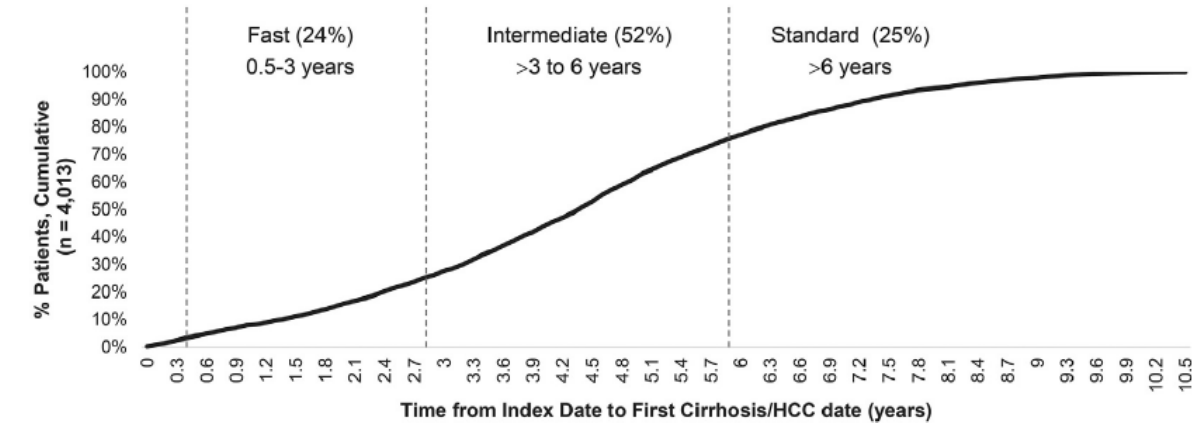
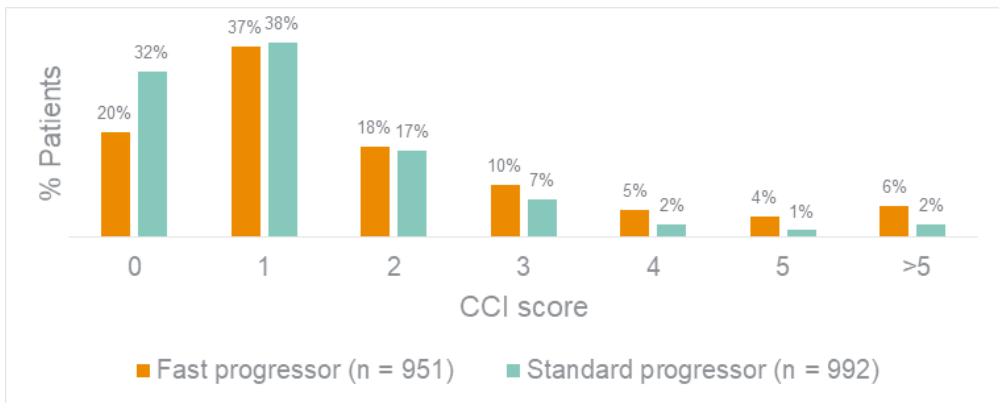


Figure 19. Comparison of Charlson Comorbidity Index between fast and standard progressors at the index date (Schattenberg et al. 2024 supplemental Figure 1 [27])



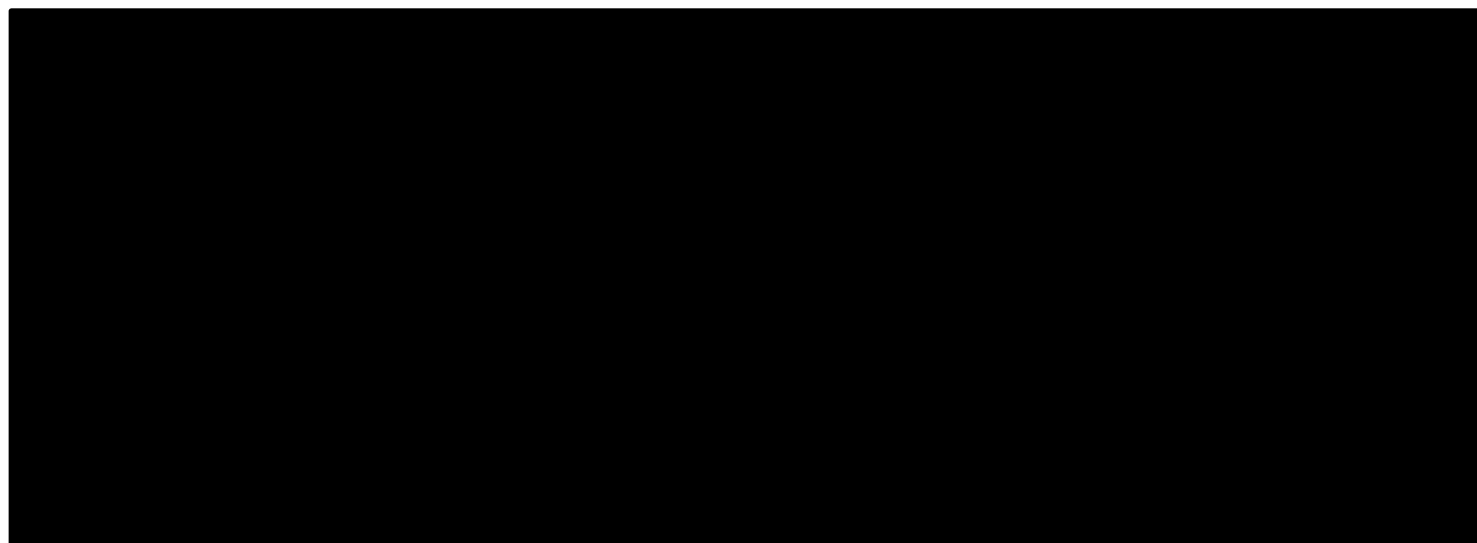
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		We appreciate that the characterisation and identification of rapid progressors within the heterogeneous MASH population is an evolving area of research, with no definitive definitions or thresholds available at this point. Nevertheless, two recent studies, using different methodologies and approaches, have independently found two distinctive subtypes of MASLD – one that is confined to the liver and is associated with more aggressive/rapid progressive liver disease, and a systemic/cardiometabolic-driven type that results in a higher risk of cardiometabolic disease. Raverdy et al. 2024 [28] conducted clustering using a simple algorithm based on six widely available traits: age, BMI, HbA1c, ALT, LDL cholesterol and triglycerides and validated this with European cohorts. Jamialahmadi et al. 2024 [29] developed two partitioned polygenic risk scores based on the presence of lipoprotein retention in the liver. A further analysis of the TARGET-NASH dataset (as previously discussed in issue 2 from the manuscript in preparation by Sanyal et al. 2026 [11]) highlighted the surrogate relationship of fibrosis stage with events (including death), but it also shows that the cumulative incidence of events rises quickly for [REDACTED] fibrosis stage patients for the outcomes of cirrhosis (F2-F3 vs F0-F1) and decompensation (F4 vs F2-F3 vs F0-1). This highlights the rapid onset of events in a subset of patients in the TARGET-NASH registry with higher fibrosis stage at index. As seen in <i>Figure 20</i>, (originally presented in issue 2), when pooling F2-F3 patients (as per this decision problem), the cumulative incidence of cirrhosis is nearly [REDACTED]% by year 2 (24 months) and the cumulative risk of decompensation for F4 patients is nearly [REDACTED]% by year 3 (36 months), highlighting a rapid onset of progression for a subset of these patients to later disease stages.

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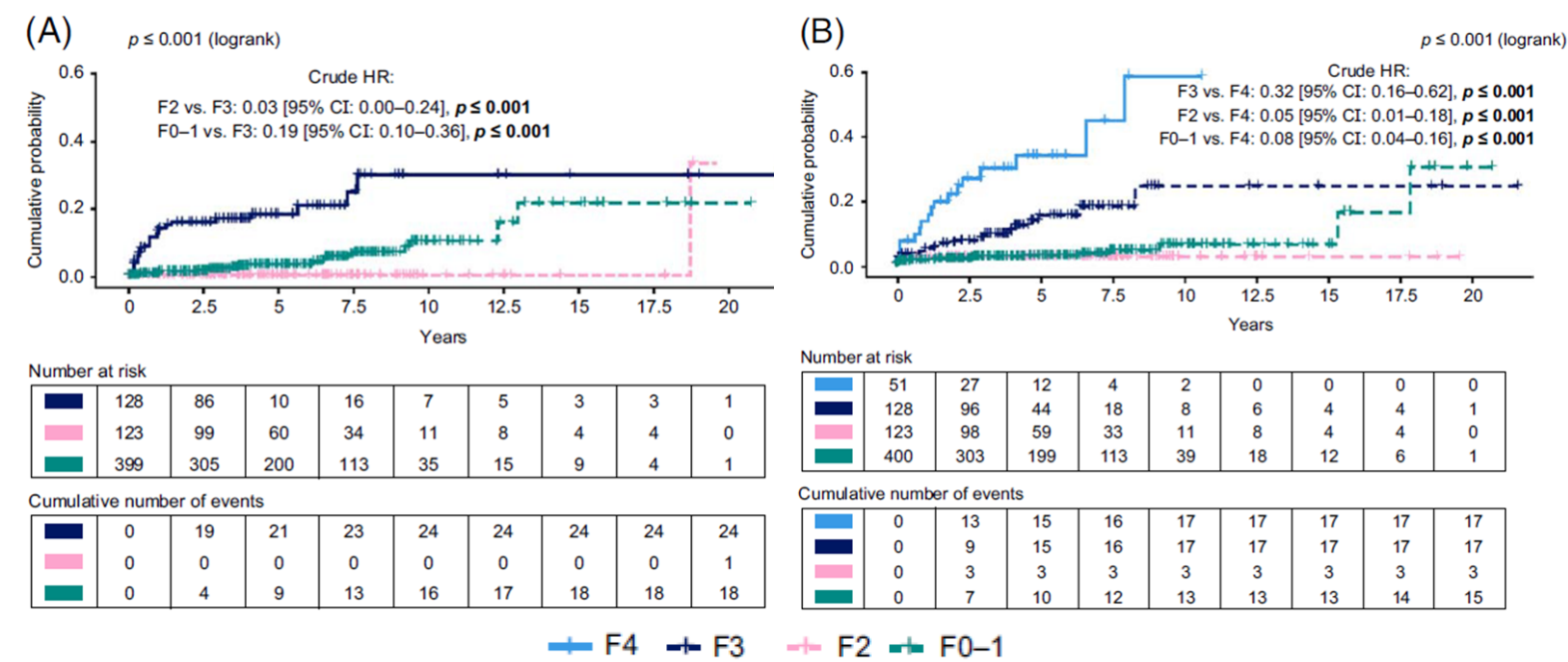
Figure 20. Progression to cirrhosis, decompensated events, and death stratified by index fibrosis stage category from the TARGET-NASH biopsy cohort in Roden et al. 2025 [10] and Sanyal et al. 2026 (manuscript in preparation) [11]



The rapid onset of cirrhosis events and surrogacy between outcomes and fibrosis stage was also observed in a separate observational study by Younossi et al. 2024 [12], presented earlier in this response (Issue 2). As mentioned, Younossi et al. 2024 [12] reported that, at any time, patients with F3 had substantially higher risk of cirrhosis than lower fibrosis stages and patients with F4 had higher risk than lower fibrosis stages of liver-related outcomes (excluding cirrhosis; Figure 21). And, as seen in Figure 21, of patients who had events, the majority experienced them early. Of F3 patients who had an event of cirrhosis, 79.2% of all events happened in the first 2.5 years (n=19/24 total events) of follow-up. Similarly, for patients who experienced liver-related outcomes, these happened rapidly for F4 and F3 patients: 76.5% of events (n=13/17) and 52.9% (n=9/17) happened within the first 2.5 years of follow-up for the two fibrosis groups, respectively. This shows that a subset of “rapid progressor” MASH patients exist and it is important to prevent progression to later stages of disease.

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Figure 21. Cumulative probability plots for (A) cirrhosis, (B) liver-related outcomes in Younossi et al. 2024 [12]



Whilst the scope of some of these new studies falls outside of this decision problem, we feel it is worth recognising that a subset of MASH patients with elevated risk of rapid progression does exist. At this time, it is difficult to define and this makes the use of external ‘control’ datasets to model natural history problematic, since most of the sources we have located do not disaggregate and independently estimate progression in ‘fast progressor’ patients, instead reporting averages from broader or milder disease populations, limiting the value of such an analysis. However, we were able to locate another data source with explicit transition rates to use as a contrast with Le et al. within our ‘natural history’ modelling scenario.

On the role of cardiometabolic risk factors

A growing body of contemporary evidence indicates that cardiometabolic risk factors, particularly T2DM and hypertension, are among the strongest drivers of fibrosis severity, progression, and liver-related outcomes in MASLD/MASH, sometimes

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		exceeding the influence of fibrosis stage alone. These factors are therefore central to understanding disease trajectories in patients referred for specialist care. In a large, multi-cohort analysis spanning the United States, South Korea, and the United Kingdom, Park et al. 2025 [30] demonstrate a strong and graded relationship between cardiometabolic risk burden and significant fibrosis. Across cross-sectional cohorts assessed using elastography, fibrosis severity increased monotonically with the accumulation of cardiometabolic risk factors. When individual risk factors were examined, impaired fasting glucose and T2DM emerged as the dominant determinants of significant fibrosis, with effect sizes exceeding those associated with obesity, dyslipidaemia, or hypertension considered in isolation. Hypertension was identified as the second most important contributor to fibrosis risk. Crucially for NICE decision-making, Park et al. 2025 [30] also evaluated long-term outcomes in a large UK Biobank cohort with extended follow-up. In this population, glucose dysregulation was associated with the highest adjusted hazard ratios for liver-related events, hepatocellular carcinoma, and liver-related mortality, with risk increasing progressively from impaired fasting glucose to overt T2DM. Across outcomes, patients with dysglycaemia experienced approximately two- to four-fold higher risks of liver-related events compared with those without glucose abnormality—magnitudes comparable to carrying multiple cardiometabolic risk factors simultaneously. These findings underscore that patients with T2DM represent a distinct, higher-risk MASH phenotype, rather than a marginal subgroup. Complementary UK-based evidence further supports the clinical importance of hypertension. In the study by Zhou et al. 2026 [31], hypertension was independently associated with adverse clinical outcomes after multivariable adjustment, even after excluding very high-progressor subgroups. This reinforces that elevated blood pressure is not merely a background comorbidity but an independent contributor to liver disease risk and progression. Taken together, these data indicate that T2DM and hypertension are not incidental characteristics, but core features shaping the natural history of MASH in patients seen in specialist care.
Issue 10: Limited justification for selected input parameters, poor referencing, and lack of clarity	Yes	Per the EAG's suggestion, each of the themed tabs in our Master Inputs Excel file (for example, "HSUV & Adv liver disease" tab for utilities and advance liver disease transitions) now provides transparent, tabular summaries of evidence sources and calculation methods for input values where it was not previously clear how or why a value was sourced and/or calculated. Update to transition data used for advanced liver disease EAG's comments regarding transparency, generalisability, and derivation of transition probabilities applied in particular to advanced liver complications where multiple sources were used and sometimes with a variety of calculation methods.

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regards how some input values are generated	Accordingly, we have carried out new, targeted supplementary searches to seek more appropriate and clear sources relating to end-stage liver disease and liver-related mortality, where the EAG requested further clarification on source selection and derivation. These targeted searches focused on identifying longitudinal studies reporting stage-specific risks of decompensation, hepatocellular carcinoma, liver transplantation, and liver-related death. The final values selected can be found on the “HSUV & Adv liver disease” tab of the Master Inputs Excel file and are also reproduced in this section. Evidence from both the original review and the targeted supplementary searches was prioritised using a structured hierarchy, consistent with NICE expectations for informing long-term outcomes and transition probabilities: 1. Large, well-characterised longitudinal cohort studies with clear fibrosis staging, enabling estimation of stage-specific risks of advanced liver outcomes and mortality. 2. Population-based observational studies, including those reflective of UK or comparable healthcare settings, to support external validity and face validity of the estimates. 3. Pooled analyses and meta-analyses, used where individual studies did not provide sufficient precision, with heterogeneity explicitly considered. 4. Established real-world registries and prior health technology assessments, used to support consistency with previously accepted modelling approaches and to inform sensitivity analyses. This hierarchy was applied consistently across all hepatic transition and mortality parameters. Where non-UK data were used, this reflected limitations in the available UK-specific evidence for advanced liver disease outcomes rather than selective study choice. While the original submission relied on established benchmarks used in prior economic evaluations—including those underpinning NICE NG49 [1], models from the Institute for Clinical and Economic Review (ICER) for MASH, [32–34] and widely cited cost-effectiveness studies (e.g., Javanbakht et al. 2023 [35], Chhatwal 2022 [36]; Gal 2023 [37])—the re-review undertaken here, incorporating newly published evidence available in the months following the original submission, was used to refine the transition parameters for advanced liver disease. Table 6 below summarizes the updates made to the incidence probabilities for advanced liver disease and associated comorbidities. Additional details on source selection and value calculations are provided in the Appendix BC and laid out in Excel Master Input file.

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Table 6 Annual transition probabilities for advanced liver complications and mortality

Transition	Original values and sources		Updated values and sources	
Health state transition	Mean probability	Source	Mean probability	Source
F3 with MASH to DCC	0.004	Vilar-Gomez et al. 2018 [38]	0.029	Davidson et al. 2025 [4]
F3 with resolved MASH to DCC	0.004	Assumed equivalent to patients with MASH	0.029	Assumed equivalent to patients with MASH
F3 with MASH to HCC	0.003	Vilar-Gomez et al. 2018 [38]	0.002	Vilar-Gomez et al. 2018 [38] Sanyal et al. 2021 [19]
F3 with resolved MASH to HCC	0.003	Assumed equivalent to patients with MASH	0.002	Assumed equivalent to patients with MASH
F4 with MASH to DCC	0.019	Vilar-Gomez et al. 2018 [38]	0.076	Davidson et al. 2025 [4]
F4 with resolved MASH to DCC	0.019	Assumed equivalent to patients with MASH	0.076	Assumed equivalent to patients with MASH
F4 with MASH to HCC	0.014	Vilar-Gomez et al. 2018 [38]	0.057	Shang et al. 2026 [39]
F4 with resolved MASH to HCC	0.014	Assumed equivalent to patients with MASH	0.057	Assumed equivalent to patients with MASH
DCC to HCC	0.026	Ascha et al. 2010 [40]	0.043	Shang et al. 2026 [39]
DCC to liver transplant 1st year	0.43	Vilar-Gomez et al. 2018 [38]	0.018	Shang et al. 2026 [39]
DCC to liver transplant 2nd year	0.008	Vilar-Gomez et al. 2018 [38] - Calibrated	0.014	Shang et al. 2026 [39]
DCC to liver transplant 3rd year	0.008	Vilar-Gomez et al. 2018 [38] - Calibrated	0.014	Shang et al. 2026 [39]

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		DCC to liver transplant 4th year	0.008	Vilar-Gomez et al. 2018 [38] - Calibrated	0.014	Shang et al. 2026 [39]
		DCC to liver transplant +5th year	0.008	Vilar-Gomez et al. 2018 [38] - Calibrated	0.014	Shang et al. 2026 [39]
		HCC to liver transplant 1st year	0.557	Vilar-Gomez et al. 2018 [38] - Calibrated	0.375	Faulkes et al. 2025 [41]
		HCC to liver transplant 2nd year	0.017	Vilar-Gomez et al. 2018 [38] - Calibrated	0.014	Assumption: equal to DCC - Shang et al. 2026 [39]
		HCC to liver transplant 3rd year	0.017	Vilar-Gomez et al. 2018 [38] - Calibrated	0.014	Assumption: equal to DCC - Shang et al. 2026 [39]
		HCC to liver transplant 4th year	0.017	Vilar-Gomez et al. 2018 [38] - Calibrated	0.014	Assumption: equal to DCC - Shang et al. 2026 [39]
		HCC to liver transplant +5th year	0.017	Vilar-Gomez et al. 2018 [38] - Calibrated	0.014	Assumption: equal to DCC - Shang et al. 2026 [39]
		F4 to death	0.021	Pearson et al. 2016 [32] Ascha et al. 2010 [40]	0.054	Shang et al. 2026 [39]
		DCC to death	0.130	Pearson et al. 2016 [32] Ascha et al. 2010 [40]	0.052	Shang et al. 2026 [39]
		HCC to death year 1	0.144	Thuluvath et al. 2019 [42]	0.234	Faulkes et al. 2025 [41]
		HCC to death year 2	0.044	Thuluvath et al. 2019 [42]	0.173	Faulkes et al. 2025 [41]
		HCC to death year 3	0.012	Thuluvath et al. 2019 [42]	0.173	Faulkes et al. 2025 [41]
		HCC to death year 4	0.009	Thuluvath et al. 2019 [42]	0.112	Faulkes et al. 2025 [41]

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		HCC to death year 5+	0.008	Thuluvath et al. 2019 [42]	0.112	Faulkes et al. 2025 [41]																				
		LT to death	0.098	Lidgren et al. 2007 [43]	0.049	Faulkes et al. 2025 [41]																				
		PLT to death	0.057	Lidgren et al. 2007 [43]	0.067	Faulkes et al. 2025 [41]																				
		Updated Baseline Probabilities for Key Diabetes-Related Complications The original model inputs for baseline prevalence of diabetic complications—namely ischaemic heart disease (IHD), congestive heart failure (CHF), diabetic retinopathy, and diabetic foot ulcer—were based on placeholder or hard-coded values not derived from specific epidemiological data. Following internal review, these parameters have been updated to reflect the most appropriate evidence available for patients with type 2 diabetes mellitus (T2DM) in the UK. The updated values are:																								
		<table><tr><th>Parameter</th><th>Previous Value</th><th>Updated Value</th><th>Source Basis</th></tr><tr><td>Retinopathy</td><td>0.028</td><td>0.123</td><td>Haider et al. 2021 [44]</td></tr><tr><td>CHF</td><td>0.107</td><td>0.034</td><td>NHS National Diabetes Audit, 2017-18 [45]</td></tr><tr><td>IHD</td><td>0.181</td><td>0.354</td><td>Lautsch et al. 2019 [46]</td></tr><tr><td>Diabetic Foot Ulcer</td><td>0.009</td><td>0.017</td><td>Scottish Diabetes Survey 2020 [47]</td></tr></table>	Parameter	Previous Value	Updated Value	Source Basis	Retinopathy	0.028	0.123	Haider et al. 2021 [44]	CHF	0.107	0.034	NHS National Diabetes Audit, 2017-18 [45]	IHD	0.181	0.354	Lautsch et al. 2019 [46]	Diabetic Foot Ulcer	0.009	0.017	Scottish Diabetes Survey 2020 [47]				
Parameter	Previous Value	Updated Value	Source Basis																							
Retinopathy	0.028	0.123	Haider et al. 2021 [44]																							
CHF	0.107	0.034	NHS National Diabetes Audit, 2017-18 [45]																							
IHD	0.181	0.354	Lautsch et al. 2019 [46]																							
Diabetic Foot Ulcer	0.009	0.017	Scottish Diabetes Survey 2020 [47]																							
		The updated values are based on UK real-world data sources specific to type 2 diabetes populations, ensuring relevance to the NHS setting and suitability as point prevalence estimates for baseline risk in an individual patient-level model (IPD). These changes were necessary because the MAESTRO-NASH trial population did not report baseline prevalence of these diabetes-specific comorbidities which are necessary for UKPDS risk equation, and thus could not be used to parameterize background complication rates within the model. In line with these adjustments, we also assumed that patients with eGFR <60 ml/min/1.73m ² (NICE NG203 [48]) are classified as having chronic kidney disease (CKD), which was not included in the previous model version (see Section 03.3, line 328 in the main .rmd file). The updated inputs allow the model to more accurately reflect the initial health state risk of T2DM patients prior to disease progression or intervention.																								

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Issue 11: Appropriateness of modelled utility values and MASH resolution increment	Yes	The company has agreed with the EAG’s suggestion for an alternative approach to address this issue and have changed the health utility values in the model for F0-F3 health states to use M-NASH (with and without MASH resolution, using the fibrosis-stage–specific estimates derived from the M-NASH trial) and the F4 utility to that from Papatheodoridi et al. 2023 [49] for the compensated cirrhosis health state. As noted during FAC, Papatheodoridi et al. 2023 [49] reports EQ-5D-5L data, which differs from NICE guidance in the health technology evaluations manual (Section 4.3.16). NICE advises mapping EQ-5D-5L descriptive data to the EQ-5D-3L value set. To align with NICE methods—and consistent with the EQ-5D-3L analysis of M-NASH HRQoL data—the company applied the established University of Sheffield mapping approach to convert the Papatheodoridi et al. values to the 3L value set (method available at: https://sheffield.ac.uk/nice-dsu/methods-development/mapping-eq-5d-5l-3l) [50]. Using this method, the EQ-5D-3L utility for compensated cirrhosis is 0.64 (0.642 for males and 0.638 for females), rather than 0.725 under the 5L value set. Together with the M-NASH utilities, these values remain below general population norms and align with the EAG’s expectations for face validity and real-world disease burden across the spectrum. Regarding the MASH-resolution utility increment, regression analyses presented in the CS (Section 3.4.3) and clarification responses (Section B16) demonstrate a statistically significant improvement in utility for patients with MASH resolution. This provides empirical support for the increment used. The impact of this change on the base case ICER (versus the old base case) is presented later in this document where we detail changes for the new base case. Table 7. Utility values applied in the model in line with the EAG request <table><tr><th>Fibrosis stage</th><th>Nash Resolution</th><th>Mean 52W EQ-5D score</th><th colspan="3">95% CL</th><th>Source</th></tr><tr><td rowspan="2">F1</td><td>No</td><td>0.64</td><td>0.63</td><td>0.65</td><td>0.64</td><td rowspan="6">MAESTRO-NASH RCT</td></tr><tr><td>Yes</td><td>0.64</td><td>0.63</td><td>0.65</td><td>0.64</td></tr><tr><td rowspan="2">F2</td><td>No</td><td>0.64</td><td>0.63</td><td>0.65</td><td>0.64</td></tr><tr><td>Yes</td><td>0.64</td><td>0.63</td><td>0.65</td><td>0.64</td></tr><tr><td rowspan="2">F3</td><td>No</td><td>0.64</td><td>0.63</td><td>0.65</td><td>0.64</td></tr><tr><td>Yes</td><td>0.64</td><td>0.63</td><td>0.65</td><td>0.64</td></tr></table>	Fibrosis stage	Nash Resolution	Mean 52W EQ-5D score	95% CL			Source	F1	No	0.64	0.63	0.65	0.64	MAESTRO-NASH RCT	Yes	0.64	0.63	0.65	0.64	F2	No	0.64	0.63	0.65	0.64	Yes	0.64	0.63	0.65	0.64	F3	No	0.64	0.63	0.65	0.64	Yes	0.64	0.63	0.65	0.64
Fibrosis stage	Nash Resolution	Mean 52W EQ-5D score	95% CL			Source																																					
F1	No	0.64	0.63	0.65	0.64	MAESTRO-NASH RCT																																					
	Yes	0.64	0.63	0.65	0.64																																						
F2	No	0.64	0.63	0.65	0.64																																						
	Yes	0.64	0.63	0.65	0.64																																						
F3	No	0.64	0.63	0.65	0.64																																						
	Yes	0.64	0.63	0.65	0.64																																						

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		F4	NA				Papatheodoridi et al. 2023 [49] converted to EQ-5D-3L
Table 8. GLM regression results for EQ-5D utility at 52 weeks (miTT population), using Beta dist. and identity link function							
term				Estimate	Std.error	Statistic	P.value
(Intercept)							
TRT01PMGL-3196 100 mg							
TRT01PMGL-3196 80 mg							
AGE							
SEX							
NASH RES. Yes							
(phi)							

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Issue 12: Health state costs and the interpretation of the Davidson study	Yes	In the updated model, costs for non-cirrhotic disease (F0–F3) and compensated cirrhosis (F4) are anchored to the published annualised values reported by Davidson et al. 2025 [4], in line with the EAG’s recommendation to prioritise peer-reviewed UK evidence. Davidson et al. 2025 [4] provides real-world estimates of MASH-related healthcare resource use in England and represents an appropriate foundation for early and moderate disease states. Because Davidson does not report fibrosis-stage-specific costs within the non-cirrhotic group, these costs were apportioned across F0–F3 using relative gradients informed by Younossi et al. 2025 [51], preserving the Davidson cost envelope while allowing costs to increase plausibly with disease severity. For advanced liver disease states beyond compensated cirrhosis (DCC and HCC), the company prioritised Younossi et al. 2025 [51] to inform secondary-care costs. Younossi was selected because it provides a state-based, event-anchored representation of healthcare utilisation, in which outpatient care, diagnostics, procedures and, critically, hospitalisations are modelled by disease severity and calibrated to country-specific incidence of advanced liver outcomes, including decompensated cirrhosis, hepatocellular carcinoma and liver transplantation. These advanced events are the dominant drivers of NHS secondary-care expenditure, and anchoring costs to their observed incidence improves face validity for both the level and ordering of costs across health states. Importantly, Younossi includes UK-relevant calibration, supporting its applicability to the NHS setting once costs are converted to GBP and inflated to the model price year using standard methods. By contrast, Morgan et al. 2021 [5] – recommended by EAG – estimated UK health-system costs using a cost-of-illness framework in which secondary care costs are derived indirectly from previous models, guideline pathways and expert opinion. While valuable for understanding aggregate burden, this approach does not as directly link to hospital event incidence and provides limited disaggregation of inpatient versus outpatient components, reducing the accuracy for NHS secondary-care costing within a NICE decision model. For this reason, Morgan was considered less suitable than Younossi for informing the magnitude and distribution of secondary-care costs in advanced disease states, although it remains informative as a comparator. To ensure transparency and to facilitate independent exploration by the EAG, the revised model has been structured to allow three explicit cost scenarios to be examined: 1. Davidson (up to F4) & Morgan – applying published Davidson costs to F0–CC and Morgan costs to DCC and HCC (requested by the EAG) <table><tr><th>Technologies</th><th>Total costs (£)</th><th>Total LYG</th><th>Total QALYs</th><th>Incremental costs (£)</th><th>Incremental LYG</th><th>Incremental QALYs</th><th>ICER (£/QALY)</th></tr><tr><td></td><td></td><td></td><td></td><td></td><td></td><td></td><td></td></tr></table>	Technologies	Total costs (£)	Total LYG	Total QALYs	Incremental costs (£)	Incremental LYG	Incremental QALYs	ICER (£/QALY)								
Technologies	Total costs (£)	Total LYG	Total QALYs	Incremental costs (£)	Incremental LYG	Incremental QALYs	ICER (£/QALY)											

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		SoC	████	████	████	NA	NA	NA	NA
		Resmetirom	████	████	████	████	████	████	37,294
		2. Davidson (up to CC) & Younossi – applying published Davidson costs to F0–CC and Younossi costs to DCC and HCC (new company base case)							
		3. Younossi et al. (2025) [51] only – applying Younossi costs across all liver health states							
		Technologies	Total costs (£)	Total LYG	Total QALYs	Incremental costs (£)	Incremental LYG	Incremental QALYs	ICER (£/QALY)
		SoC	████	████	████	NA	NA	NA	NA
		Resmetirom	████	████	████	████	████	████	36,489
		This structure enables the EAG and Committee to assess the sensitivity of results to alternative, while preserving consistency between disease severity, event incidence, and secondary-care resource use.							
		Finally, costs for liver transplantation and post-transplant follow-up have been revised in line with NICE guidance and NHS reference costs, addressing the EAG’s concerns regarding interpretation of NG49 [1] and avoiding inappropriate annualisation of one-off procedural costs. Costs for cardiovascular and diabetes-related complications have also been updated using more recent UK-relevant sources where appropriate.							
		In response to the EAG’s comments on cardiovascular event costs, the model has been updated to reflect more recent UKPDS84-based estimates where appropriate, while retaining UK-relevant sources and standard inflation methods. Costs associated with diabetes-related complications were unchanged, as the EAG indicated these were appropriate and consistent with NICE guidance.							
		Overall, these revisions address the EAG’s concerns regarding transparency and justification of cost inputs, restore clinically plausible ordering of costs across liver disease states, and provide a clear framework for scenario analysis without privileging any single cost source as definitive.							

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Resmetirom for treating moderate to advanced liver fibrosis (without cirrhosis) caused by metabolic dysfunction-associated steatohepatitis [ID6529]

Additional issues

All: Please use the table below to respond to additional issues in the EAR that have not been identified as key issues. Please do **not** use this table to repeat issues or comments that have been raised at an earlier point in this evaluation (for example, at the clarification stage).

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Resmetirom for treating moderate to advanced liver fibrosis (without cirrhosis) caused by metabolic dysfunction-associated steatohepatitis [ID6529]

Table 9. Additional issues from the EAR

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Resmetirom for treating moderate to advanced liver fibrosis (without cirrhosis) caused by metabolic dysfunction-associated steatohepatitis [ID6529]

Issue from the EAR	Relevant section(s) and/or page(s)	Does this response contain new evidence, data or analyses?	Response

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Resmetirom for treating moderate to advanced liver fibrosis (without cirrhosis) caused by metabolic dysfunction-associated steatohepatitis [ID6529]

Issue 13: Differences in dosing of resmetirom between trial and clinical practice	1.4; 2.3.2; 4.2.4	Yes	The dosing strategy used in the M-NASH trial differs from the weight-based dosing described in the SmPC for clinical practice. This reflects standard trial design considerations, where fixed doses are sometimes used to preserve randomisation and enable clear estimation of treatment effects, rather than an inconsistency in the evidence base. As a result, some translation was required when applying trial findings to anticipated NHS use. In the company’s original base case, treatment effects were aligned to SmPC dosing to reflect anticipated clinical use, with efficacy and discontinuation parameters drawn from the 80 mg or 100 mg trial arms as appropriate. We recognise the EAG’s concern that this approach does not fully address the underlying inconsistency between trial dosing and real-world prescribing and may implicitly over-interpret dose–response relationships in a trial that was not stratified by body weight. We agree with the EAG that pooling the 80 mg and 100 mg trial arms represents a pragmatic and methodologically defensible alternative. The Excel Master Input dashboard now has an option (see “Resmetirom treatment effect estimates based on...” drop-down) whereby transition probabilities, discontinuation rates and treatment effects are derived from combined 80 mg and 100 mg trial arms. Results from this scenario are shown below – the impact on ICER value was around 0.01%. <table><tr><th>Technologies</th><th>Total costs (£)</th><th>Total LYG</th><th>Total QALYs</th><th>Incremental costs (£)</th><th>Incremental LYG</th><th>Incremental QALYs</th><th>ICER (£/QALY)</th></tr><tr><td>SoC</td><td>██████</td><td>██████</td><td>██████</td><td>NA</td><td>NA</td><td>NA</td><td>NA</td></tr><tr><td>Resmetirom</td><td>██████</td><td>██████</td><td>██████</td><td>██████</td><td>██████</td><td>██████</td><td>36,128</td></tr></table> The original “separate arms” configuration was retained for the company’s base-case analysis, as it reflects the primary modelling approach and preserves the integrity of the trial-specific dosing structure. However, we do not disagree with the EAG’s pragmatic considerations around this point and have made the ‘pooled’ configuration available in the Excel Master Inputs dashboard should this be a preferred scenario for additional analyses.	Technologies	Total costs (£)	Total LYG	Total QALYs	Incremental costs (£)	Incremental LYG	Incremental QALYs	ICER (£/QALY)	SoC	██████	██████	██████	NA	NA	NA	NA	Resmetirom	██████	██████	██████	██████	██████	██████	36,128
Technologies	Total costs (£)	Total LYG	Total QALYs	Incremental costs (£)	Incremental LYG	Incremental QALYs	ICER (£/QALY)																				
SoC	██████	██████	██████	NA	NA	NA	NA																				
Resmetirom	██████	██████	██████	██████	██████	██████	36,128																				

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Issue 14 Current and anticipated use of GLP-1 antagonists in the UK	1.4; 2.3.3; 3.2.2.1; 4.2.4	No	The EAG commented that clinicians may be reluctant to prescribe resmetirom alongside successful GLP-1 receptor agonist therapy and suggested that semaglutide may therefore represent a relevant comparator. However, the EAR also acknowledged that our submission could not reasonably have included semaglutide. At present, besides expert clinical opinion there is little evidence that can be used to further inform decision-making regarding resmetirom in context with GLP-1 RAs, save to emphasise that prior or current GLP-1 RA exposure was not an exclusion criterion in M-NASH, and we would not expect resmetirom and GLP-1 therapies to be used to absolute mutual exclusion in MASH patients. We noted that on page 39 of the EAR, two clinical advisers to EAG <i>“had indicated they would not, or would be hesitant to, prescribe resmetirom concomitantly to patients successfully losing weight with a GLP-1 RA.”</i> This wording at face value suggests that to the two clinicians consulted, successful weight loss alone might be sufficient grounds to avoid or delay concomitant resmetirom for MASH – however we feel that this observation probably needs further contextualising given the current community pathways that specifically identify and refer patients with evidence of advanced fibrosis and suspected high-risk MASH. We also feel that perhaps the observation was made under the broader, inaccurate assumption inherent in the EAR that many patients eligible for resmetirom have mild, slow-progressing disease for which there is no urgency to treat. We raised Issue 14 at the UK ad board, and in response a question was raised about what ‘successful’ GLP-1 therapy for MASH would look like in terms of: • which factors should be measured to determine a successful MASH response (Weight loss? Fibrosis stabilisation? Other markers?); • what thresholds and timeframes should apply, how urgent is the need to reverse fibrosis; • what criteria for GLP-1 dose titration and patient adherence should be met in respect of MASH treatment. The only other information we can offer here is a recap of the therapeutic particulars of resmetirom: it is a liver-directed therapy that acts directly on hepatic thyroid hormone receptor-β to reduce liver fat, inflammation, and downstream fibrosis. By contrast, semaglutide is a

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			systemic cardiometabolic therapy that primarily targets weight and glycaemic control. Current clinical guidance recognises that: • GLP-1 receptor agonists may improve metabolic risk factors and reduce liver fat, but • they are not established or authorised as antifibrotic therapies, and their effects on fibrosis progression remain under investigation. Accordingly, semaglutide and resmetirom are mechanistically complementary rather than substitutive, and their concurrent use would, in our view, be clinically plausible in patients with both metabolic disease and MASH.
Issue 15: Deviations from HTA Lab recommendations	1.4; 4.1.3.1	Yes (provided under scenarios in relevant issues)	We do not believe this issue has a material impact on the Committee's ability to make an informed decision on this HTA. Where possible and informed by data or in line with the NICE scope, our submission met the recommendations of the HTA lab. The HTA Lab document provides advisory guidance, rather than mandatory methodological requirements, and the company model is aligned with all core structural recommendations (e.g., state-transition modelling, inclusion of hepatic and cardiometabolic outcomes). Furthermore, additional scenarios mentioned in the HTA Lab report that are related to other issues within this Technical Engagement have been provided as above/below, and a user-friendly interface has been constructed enabling the EAG to change elements within the model to further explore any outstanding issues. We have given further detail about how the economic model meets the HTA Lab report recommendations point-by-point in the form of responses to items in Table 10 from the EAG's report in the Appendix BD of this technical engagement. We have also provided a figure reporting liver-related outcomes with the base case results as suggested by the EAG (Figure 22 later in this document).

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Resmetirom for treating moderate to advanced liver fibrosis (without cirrhosis) caused by metabolic dysfunction-associated steatohepatitis [ID6529]

Issue 16 Extrahepatic treatment effects	1.4; 4.2.5.3	Yes	THR-β agonists, like with resmetirom, improve metabolic function within and outside the liver [52,53]. THR-β stimulation improves mitochondrial function and lipid metabolism in the liver. THRβ agonistic action leads to decreased liver fat, increased fatty acid beta oxidation and autophagy, and leads to increased insulin sensitivity, reduction of serum lipids, including LDL-C. The beneficial effect on lipid metabolism was demonstrated in the resmetirom clinical development programme. Resmetirom reduces blood low density lipoprotein (LDL) cholesterol, apolipoprotein B, lipoprotein (a) and triglyceride levels. Reductions in all lipid endpoints were observed initially after 4 weeks and sustained at 24 and through 52 weeks of treatment. Resmetirom reduced lipid and lipoprotein particles to a greater extent than placebo. At week 24, resmetirom significantly reduced LDL-C, the key secondary endpoint of M-NASH, at both studied doses. It is expected that this will lead to reduced atherosclerosis and improved cardiovascular outcomes in the long-term. Regarding how our model is characterised in the EAR, we would like to clarify that the model changes assumed LDL-C or HDL-C levels over time. As detailed in Tables 15, 17, and 19 of the clarification response, trial-based percentage changes in LDL-C, HDL-C, and triglycerides observed in M-NASH are applied for one cycle only ($n\_cycles\_risk\_factor\_effect = 1$). From Year 2 onwards, lipid values evolve according to long-term background trends informed by external epidemiological data (Domanski et al. 2020 [54]), with LDL-C increasing by +0.1 mg/dL per year and HDL-C decreasing by -0.1 mg/dL per year. Triglycerides are conservatively assumed to revert fully to baseline from Year 2 onwards. Accordingly, the statement that lipid treatment effects are assumed to persist over the entire model time horizon does not reflect the model implementation. This approach was explicitly described during the clarification phase and was designed to maintain a conservative approach to these outcomes. Considering our clarification above, we do not consider the concern regarding internal inconsistency between lipid assumptions to apply. All lipid parameters follow a consistent structure: a short-term trial-based effect followed by long-term background physiological trends. The assumption that triglycerides revert fully to baseline from Year 2 reflects a deliberately conservative choice where long-term evidence is most limited and most likely underestimates a sustained benefit. These assumptions and their parameterisation were clearly documented in the Clarification response.

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			BMI evolves annually in the model based on age- and sex-specific background trends derived from NHS Digital population data, combined with modest treatment effects observed in M-NASH while patients remain on therapy. Weight is recalculated deterministically from BMI each cycle. This structure does not impose indefinite or unbounded weight loss but allows trajectories to stabilise over time through the interaction of background trends, treatment effects, and model caps. In response to the EAG's concerns regarding the durability of weight-related effects, the company implemented an alternative scenario in which both lifestyle-related changes in the standard-of-care arm and treatment-related effects in the resmetirom arm are applied for one year only. From Year 2 onwards, BMI and weight follow UK general population trends without any ongoing treatment or lifestyle modification effect. This scenario was implemented in the model to allow exploration of the impact of more conservative assumptions on long-term outcomes, and the results were shared during the clarification process. Modelling CVD events CVD risk in the microsimulation is driven primarily by established risk equations (QRISK3 for first events in non-diabetics; UKPDS in diabetes; Framingham for recurrent events), which already incorporate key cardiometabolic predictors. The fibrosis-stage relative risks (RRs) are implemented only as multipliers on these baseline risks. Consistent with this, the model does not apply any excess CVD risk in early fibrosis stages (F0–F2) or in fibrosis regression states. A modest uplift is applied only in limited circumstances: • F3 with active MASH: RR = 1.10 • F3 without MASH: RR = 1.00 (no additional risk) • Compensated cirrhosis (F4): RR = 1.20 • Advanced clinical liver states (DCC, HCC, liver transplant): RR = 1.50 This structure is intentionally conservative, avoiding the attribution of broad cardiovascular effects to early histological changes and limiting risk increases largely to patients with advanced liver disease and/or ongoing inflammatory activity.

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Recent UK Biobank evidence reported by Shen et al. 2026 [55] provides a useful external benchmark. In this large population-based cohort, increasing MASLD fibrosis severity defined using validated non-invasive fibrosis risk scores) was associated with materially higher risks of major adverse cardiovascular events and cardiovascular mortality, even after adjustment for conventional cardiometabolic risk factors.

Notably, the hazard ratios reported for individuals with high or advanced fibrosis risk substantially exceed the modest uplifts applied in the model for advanced fibrosis and cirrhosis.

Scenario analysis

To help the Committee explore the sensitivity of our model to assumptions regarding fibrosis, we present a sensitivity scenario in which the fibrosis-stage CVD multipliers are removed entirely (i.e., all RR_CVD parameters set to 1.0). This scenario directly reflects the EAG’s position that fibrosis stage should be treated as a marker rather than an independent determinant of CVD outcomes, while preserving the remainder of the model structure predicting CVD events (including QRISK3/UKPDS/Framingham-based risk prediction).

Technologies	Total costs (£)	Total LYG	Total QALYs	Incremental costs (£)	Incremental LYG	Incremental QALYs	ICER (£/QALY)
SoC				NA	NA	NA	NA
Resmetirom							35,784

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Summary of changes to the company's cost-effectiveness estimate(s)

Important note: Besides the addition of an Excel Master Inputs interface and modifications to the R code to work with this, the model also incorporates a minor structural change relating to Issue 8, which was necessary to allow apportionment of fibrosis stage-changes per study arm: previously values from Singh et al. 2015 [21] were used as a **common source for all patients** when informing proportions of 1- or 2-stage fibrosis changes after 'worsening' or 'improvement' – the new structure allows the model to draw upon **treatment-specific patient-level data** in M-NASH to inform proportions of 1- or 2- stage fibrosis changes after 'improvement'. This structural change means that when the "Old Base Case" button is used on the Excel Master Input dashboard, all inputs and assumptions are set to old values from original CS, but the final ICER produced is slightly different (around 5% less favourable to resmetirom) from that presented in the original CS, due to the way microsimulation apportions transitions and competing risks under the new structure.

Table 10. Changes to the company's cost-effectiveness estimate

Key issue(s) in the EAR that the change relates to	Company's base case before technical engagement	Change(s) made in response to technical engagement	Impact on the company's base-case incremental cost-effectiveness ratio (ICER in £/QALY)
Issue 10: Clarity and justification of sources Natural history and Advanced liver disease (ALD) transition probabilities	ALD transitions derived from mixed sources using varied methods.	Conducted an updated targeted literature review to further strengthen the evidence base for ALD transitions. Selected transition probabilities were updated using more recent longitudinal and registry-based evidence.	Old ICER: 21,422 New ICER: 22,762
Issue 10: Clarity and justification of sources Baseline probabilities for key diabetes-related complications	Placeholder or hard-coded prevalence values not based on UK epidemiological evidence.	Updated baseline prevalence of IHD, CHF, retinopathy, and diabetic foot ulcer using UK real-world data sources specific to T2DM populations. Incorporated CKD definition consistent with NICE guidance. To be used in the UKPDS equation	Old ICER: 21,422 New ICER: 21,635

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Issue 11: Utilities	Utilities primarily sourced from NICE NG49 (2016)[1], particularly for non-advanced fibrosis stages (F0–F3 and F4).	M-NASH trial data for F0-F3 stages and Papatheodoridi et al. 2023 [49] for F4	Old ICER: 21,422 New ICER: 25,213
Issue 12: Health state costs	Davidson 2025 pre-publication values and NG-49 [1]	Davidson et al. 2025 published values [4] & Younossi et al. 2024 [12]	Old ICER: 21,422 New ICER: 33,947

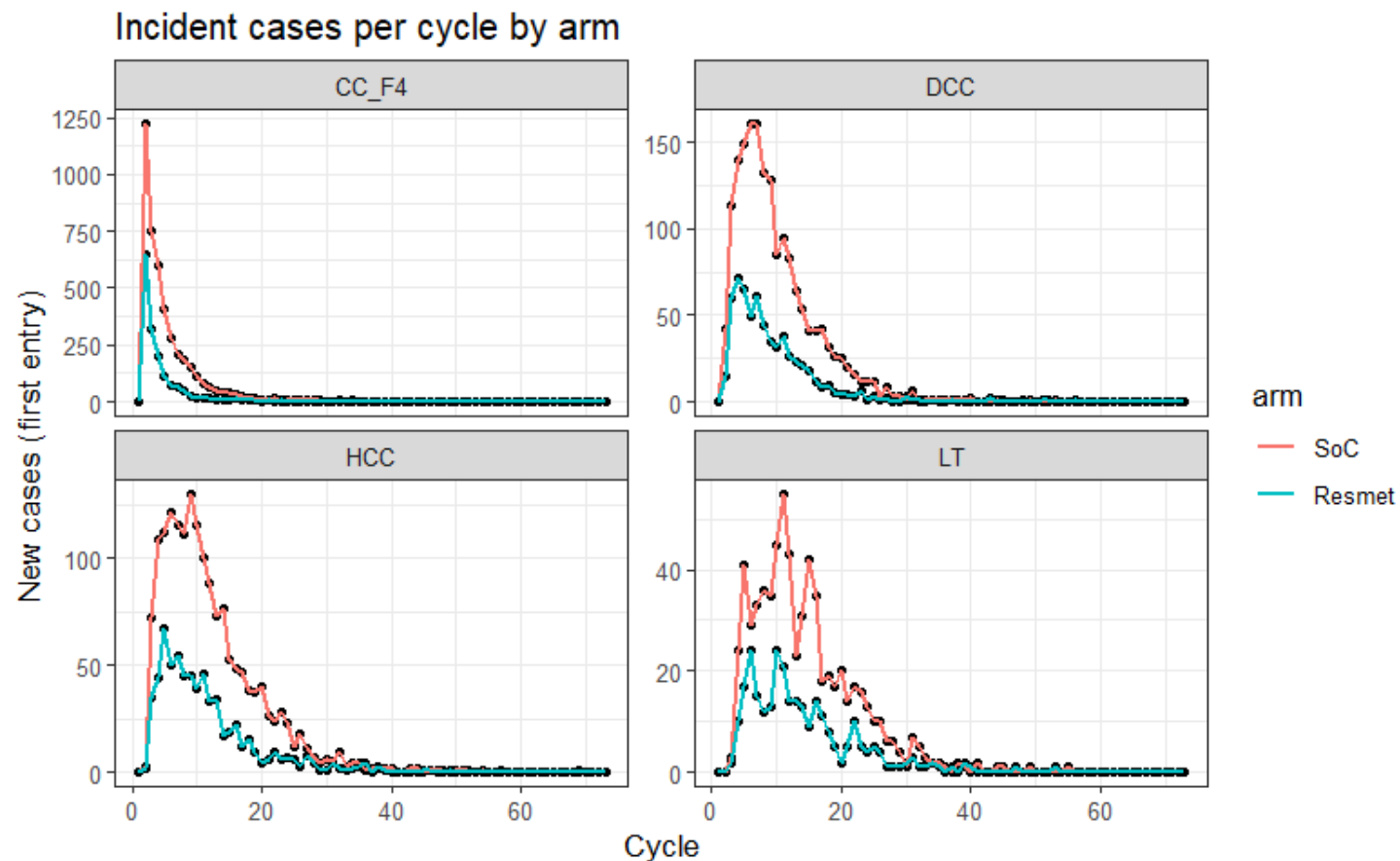
Revised base case for Technical Engagement (all above changes applied):

Technologies	Total costs (£)	Total LYG	Total QALYs	Incremental costs (£)	Incremental LYG	Incremental QALYs	ICER (£/QALY)
SoC	██████	██████	██████	NA	NA	NA	NA
Resmetirom	██████	██████	██████	██████	██████	██████	35,943

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Resmetirom for treating moderate to advanced liver fibrosis (without cirrhosis) caused by metabolic dysfunction-associated steatohepatitis [ID6529]

Figure 22. Revised Base Case: Incident cases of liver-related outcomes (CC, DCC, HCC, and liver transplant) by model arm and cycle



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Resmetirom for treating moderate to advanced liver fibrosis (without cirrhosis) caused by metabolic dysfunction-associated steatohepatitis [ID6529]

Sensitivity analyses around revised base case

PSA and OWSA have been provided. Original scenarios from CS have been replicated on the new base case.

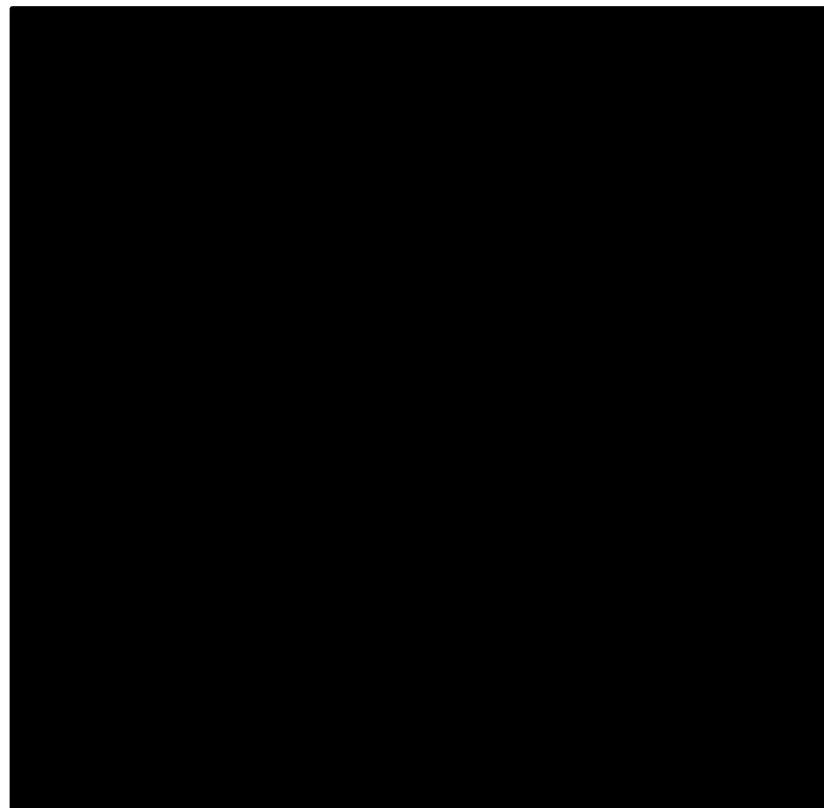
Probabilistic base-case results for resmetirom vs. SoC – Base case analysis based on 10,000 sampled patients and 1,500 model iterations

Technologies	Total costs (£)	Total LYG	Total QALYs	Incremental costs (£)	Incremental LYG	Incremental QALYs	ICER (£/QALY)
SoC	██████	██████	██████	NA	NA	NA	NA
Resmetirom	██████	██████	██████	██████	██████	██████	35,506

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Figure 23. Cost-effectiveness plane for resmetirom vs. SoC – Base case analysis



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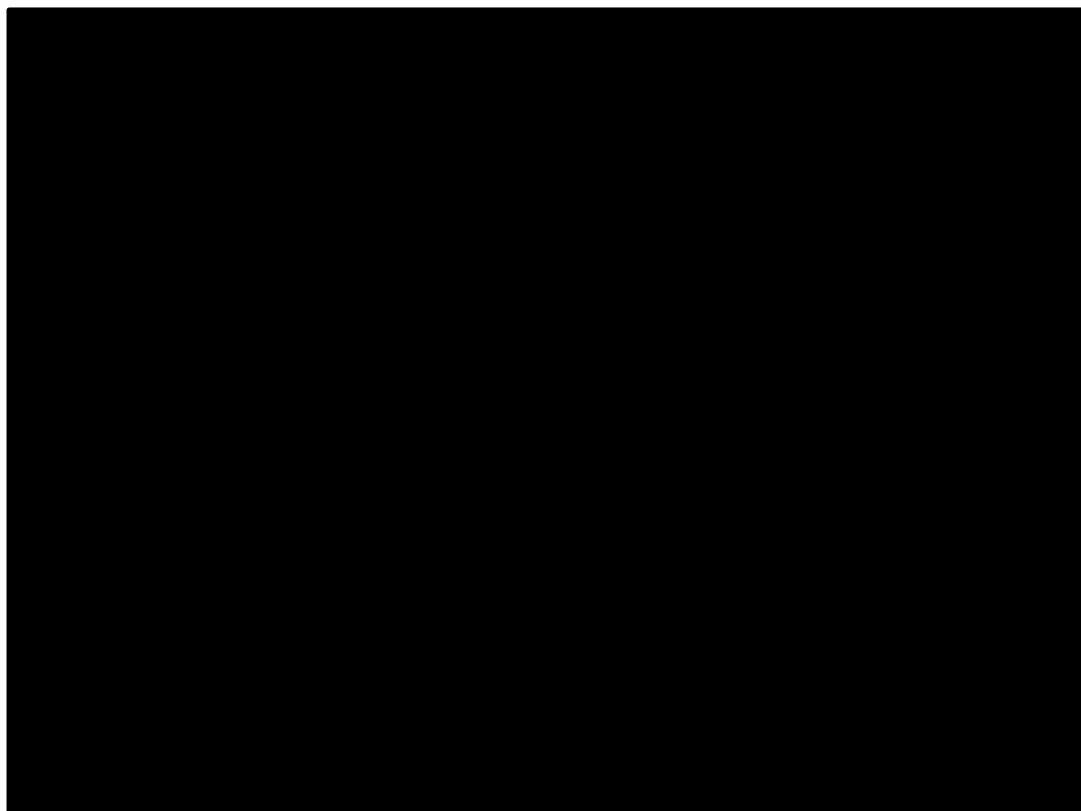
Figure 24. CEAC for resmetirom vs. SoC – Base case analysis



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Figure 25. One way sensitivity analysis for resmetirom vs SoC – base case analysis (10,000 Sampled patients)



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Resmetirom for treating moderate to advanced liver fibrosis (without cirrhosis) caused by metabolic dysfunction-associated steatohepatitis [ID6529]

Scenario analyses on revised base case for scenarios presented in original CS that remain relevant:

• 1- Scenario 1: excluding CVD as a comorbidity

Technologies	Total costs (£)	Total LYG	Total QALYs	Incremental costs (£)	Incremental LYG	Incremental QALYs	ICER (£/QALY)
SoC	████	████	████	NA	NA	NA	NA
Resmetirom	████	████	████	████	████	████	33,166

• 2- Scenario 2: excluding CVD and T2DM as comorbidities

Technologies	Total costs (£)	Total LYG	Total QALYs	Incremental costs (£)	Incremental LYG	Incremental QALYs	ICER (£/QALY)
SoC	████	████	████	NA	NA	NA	NA
Resmetirom	████	████	████	████	████	████	32,876

• Scenario 6: Exclude the application of age- and sex-specific utility decrements

Technologies	Total costs (£)	Total LYG	Total QALYs	Incremental costs (£)	Incremental LYG	Incremental QALYs	ICER (£/QALY)
SoC	████	████	████	NA	NA	NA	NA
Resmetirom	████	████	████	████	████	████	32,523

• Scenario 7: 50% reduction in discontinuation for resmetirom (80 mg and 100 mg)

Technologies	Total costs (£)	Total LYG	Total QALYs	Incremental costs (£)	Incremental LYG	Incremental QALYs	ICER (£/QALY)
SoC	████	████	████	NA	NA	NA	NA

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Resmetirom for treating moderate to advanced liver fibrosis (without cirrhosis) caused by metabolic dysfunction-associated steatohepatitis [ID6529]

Resmetirom							37,506

Subgroup analysis - Diabetic population

Results of microsimulation – 10,000 sampled patients (base case using T2DM subpopulation)

Technologies	Total costs (£)	Total LYG	Total QALYs	Incremental costs (£)	Incremental LYG	Incremental QALYs	ICER (£/QALY)
SoC				NA	NA	NA	NA
Resmetirom							46,255

Probabilistic base-case results for resmetirom vs. SoC – T2DM subpopulation

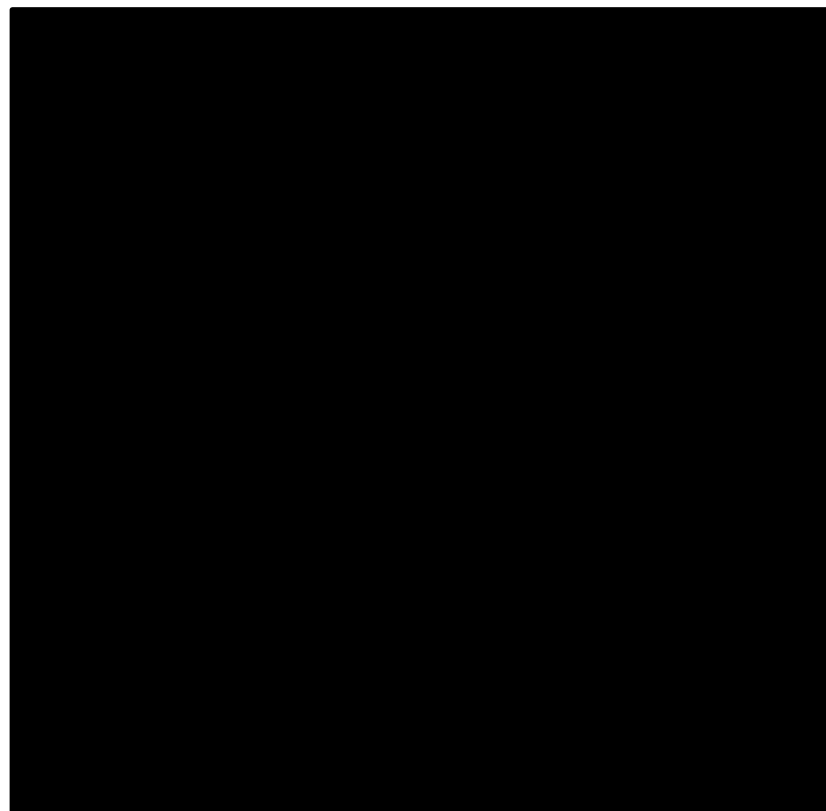
Based on 10,000 sampled patients and 1,500 model iterations

Technologies	Total costs (£)	Total LYG	Total QALYs	Incremental costs (£)	Incremental LYG	Incremental QALYs	ICER (£/QALY)
SoC				NA	NA	NA	NA
Resmetirom							44,599

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Resmetirom for treating moderate to advanced liver fibrosis (without cirrhosis) caused by metabolic dysfunction-associated steatohepatitis [ID6529]

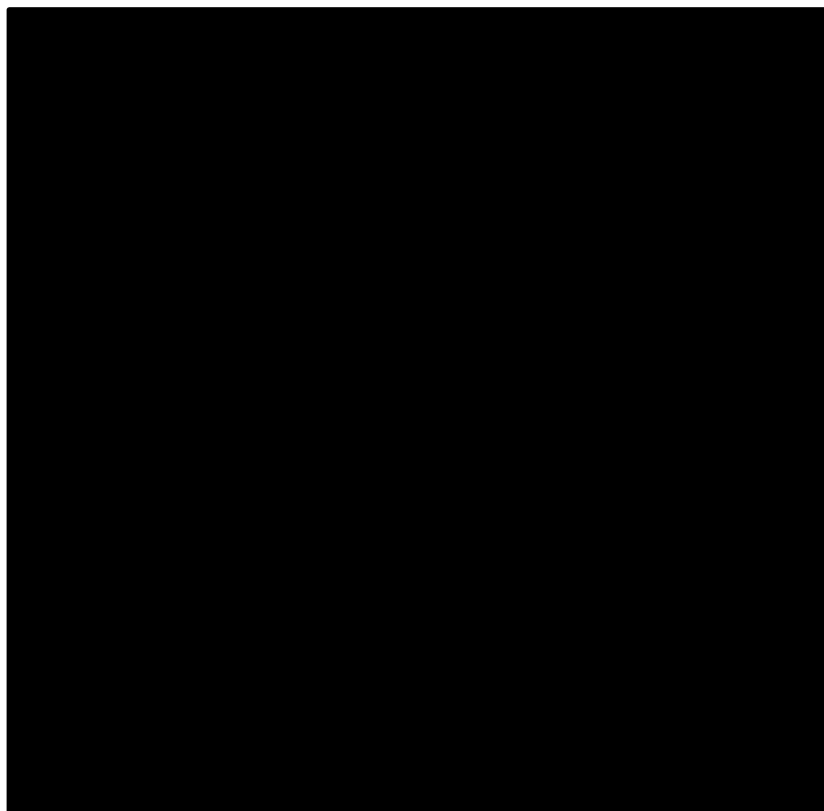
Figure 26. Cost-effectiveness plane for resmetirom vs. SoC – T2DM subpopulation analysis



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Resmetirom for treating moderate to advanced liver fibrosis (without cirrhosis) caused by metabolic dysfunction-associated steatohepatitis [ID6529]

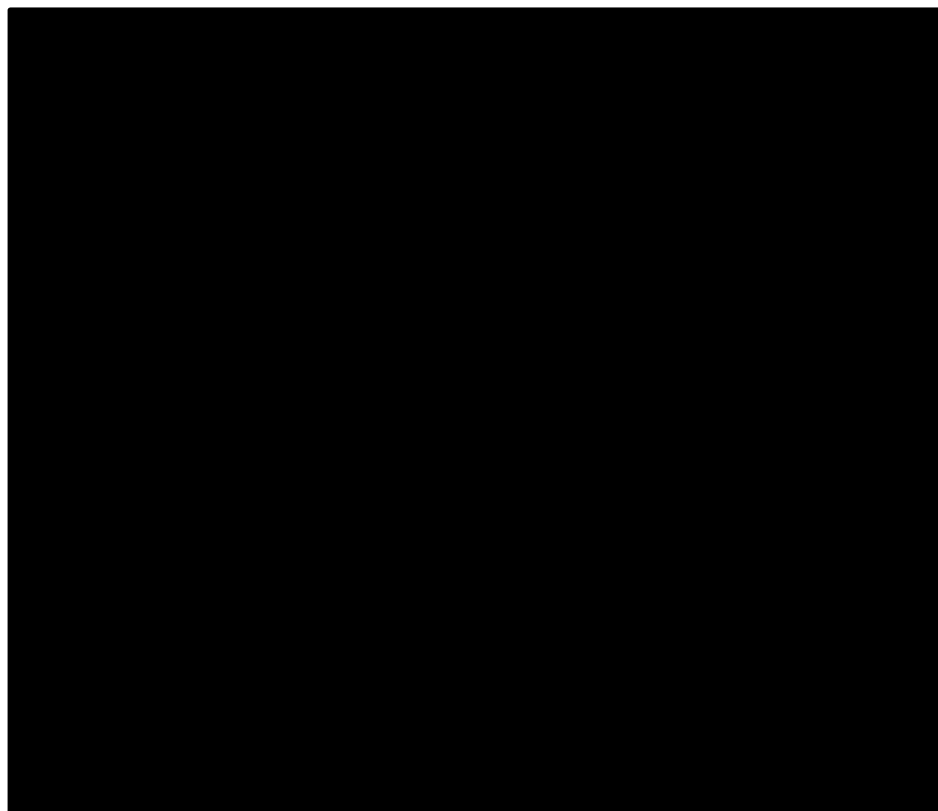
Figure 27. CEAC for resmetirom vs. SoC – T2DM subpopulation



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Resmetirom for treating moderate to advanced liver fibrosis (without cirrhosis) caused by metabolic dysfunction-associated steatohepatitis [ID6529]

Figure 28. One way sensitivity analysis for resmetirom vs SoC – T2DM subpopulation analysis (10,000 Sampled patients)



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Resmetirom for treating moderate to advanced liver fibrosis (without cirrhosis) caused by metabolic dysfunction-associated steatohepatitis [ID6529]

NATIONAL INSTITUTE FOR HEALTH AND CARE EXCELLENCE

Single technology appraisal

**Resmetirom for treating moderate to advanced
liver fibrosis (without cirrhosis) caused by
metabolic dysfunction-associated
steatohepatitis [ID6529]**

Clarification questions – Technical engagement response

February 2026

File name	Version	Contains confidential information	Date
		Yes	5/03/2026

Section A: Clarification on effectiveness data

A1. Priority question. The Company has proposed eligibility criteria defined by a liver stiffness measure (LSM) of 10–20 kPa, or equivalent thresholds using alternative non-invasive tests (NITs), including any emerging criteria. Please provide subgroup analyses from the MAESTRO-NASH trial restricted to patients who meet these proposed eligibility criteria.

Company Response: To prepare the requested subgroup analysis, we first developed a dataset based on the MAESTRO-NASH mITT population that only included patients with baseline liver stiffness measurement (LSM) values between 10 kPa and 20 kPa. The mITT population from which this dataset was drawn included patients with fibrosis stages F1B, F2, and F3, to ensure all individuals with LSM values meeting the criterion would be included.

From the 966 patients in the mITT population, [REDACTED] patients met the LSM eligibility criterion (at baseline), comprising [REDACTED] patients in the placebo arm, [REDACTED] patients in the resmetirom 80 mg arm, and [REDACTED] patients in the resmetirom 100 mg arm. The baseline characteristics for mITT patients meeting the LSM eligibility criterion are summarised in Table 1, following the approach taken in our base case wherein baseline characteristics of simulated patients are informed by the mITT population.

To facilitate identification of this subgroup in modelling, the amended individual patient data (IPD) file in our model folder “MGL-3196-

11_HEcon_Baseline_Listing.xlsx” now includes a new variable, **LSM_eligible**, indicating eligibility status (0 = does not meet the criterion; 1 = meets the criterion). The Excel **master_input_parameters.xlsx** file has been updated to allow selection of an “LSM eligible” population for analysis.

Table 1: Baseline characteristics of patients meeting the LSM eligibility criterion (10–20 kPa VCTE)

Characteristic	Placebo (N=181)	Resmetirom 80 mg (N=182)	Resmetirom 100 mg (N=185)
F1B			
F2			
F3			
Type 2 diabetes			
Hypertension			
Mean BMI			
Mean LDL (mg/dL)			
Had a missing Week 52 VCTE			

To provide a suitable adjunct to our base-case analysis (which uses the paired-liver biopsy [PLB-W52] population for efficacy) we cross-tabulated key endpoints for the “LSM-eligible” PLB-W52 population only in Table 2. This population contains a total of ■■■ patients (placebo, n=■■■; resmetirom 80 mg and 100 mg, n=■■■ in both arms).

Table 2: Efficacy outcomes in the LSM-eligible PLB-W52 population

	MASH resolution						
	Yes			No			
	Fibrosis No change	with Fibrosis improvement	with Fibrosis worsening	Fibrosis No change	with Fibrosis improvement	with Fibrosis worsening	Sum
Placebo							
Resmetirom 100mg							
Resmetirom 80mg							

In line with Technical Engagement Issue 3, we also provide the main efficacy outcomes for the mITT “LSM-eligible” population, presented by MASH resolution and fibrosis change in Table 3. As previously mentioned in CS, at clarification, and in TE, patients with missing data for the W52 biopsy in the mITT population are assumed per protocol to have had no fibrosis stage changes and no MASH resolution. In this analysis, a total of ■■■ LSM-eligible patients across treatment arms had missing biopsy data versus the LSM-eligible mITT population. It is important to consider using the LSM-eligible mITT data as a conservative approach, given the proportions of patients with fibrosis improvement (or worsening) and MASH resolution observed

between the resmetirom and placebo arms in the biopsy-confirmed PLB-W52 population (Table 2). More patients with missing biopsy data in the resmetirom arms were included in the ‘Fibrosis no change’ with ‘No’ for MASH resolution status than in the placebo arms (n=■ and n=■ in the LSM-eligible mITT population for resmetirom 80 mg and 100 mg, respectively, versus n=■ in each arm in the LSM-eligible PLB-W52 population, and n=■ for placebo in the LSM-eligible mITT population versus n=■ for placebo in the LSM-eligible PLB-W52 population). This difference translates to an impact on results presented in response to question B1 below.

Table 3: Efficacy outcomes in the LSM-eligible mITT population

	MASH resolution						
	Yes			No			
	Fibrosis No change	with Fibrosis improvement	with Fibrosis worsening	Fibrosis No change	with Fibrosis improvement	with Fibrosis worsening	Sum
Placebo							181
Resmetirom 100mg							185
Resmetirom 80mg							182

Changes in cardiometabolic risk factors from baseline were also estimated for the “LSM-eligible” mITT population and stratified by age band and treatment arm (Table 4). These estimates were used as population-level inputs for the economic model where relevant.

Table 4: Changes in cardiometabolic risk factors from baseline in the LSM-eligible population by age groups and treatment arm

TG	Age Groups	SoC	Resmetirom 80mg	Resmetirom 100mg
	0-39	■	■	■
	40-49	■	■	■
	50-59	■	■	■
	60-69	■	■	■
	70+	■	■	■
LDLC	Age Groups	SoC	Resmetirom 80mg	Resmetirom 100mg
	0-39	■	■	■
	40-49	■	■	■
	50-59	■	■	■
	60-69	■	■	■
	70+	■	■	■

HDLC	Age Groups	SoC	Resmetirom 80mg	Resmetirom 100mg
	0-39			
	40-49			
	50-59			
	60-69			
	70+			
BMI	Age Groups	SoC	Resmetirom 80mg	Resmetirom 100mg
	0-39			
	40-49			
	50-59			
	60-69			
	70+			

The number of “LSM-eligible” patients achieving ≥ 2 -stage fibrosis improvement is summarised below. (Note, cell counts are identical for both mITT and PLB-W52 populations, since achieving this outcome is conditional on having biopsies both at baseline and Week 52).

Table 5: Number of patients with ≥ 2 -stage fibrosis improvement in the LSM-eligible population (mITT and PLB-W52)

Treatment arm	Patients with ≥ 2 -stage fibrosis improvement
Placebo	
Resmetirom 80 mg	
Resmetirom 100 mg	

Section B: Clarification on cost-effectiveness data

B1.Priority question. Please integrate the subgroup analysis requested in A1 into the economic analysis. The subgroup should be reflected in both the patient characteristics and the treatment effect estimates.

Company Response: Updating our base case model to use “LSM-eligible” subgroup data (i.e. sampling the new IPD as a basis for simulated population and using crosstab data from Table 2 to inform fibrosis & MASH transitions) resulted in a modest improvement in cost-effectiveness:

Table 6: Revised cost-effectiveness results for base case - LSM-eligible subpopulation

Technologies	Total costs (£)	Total LYG	Total QALYs	Incremental costs (£)	Incremental LYG	Incremental QALYs	ICER (£/QALY)
SoC	██████	██████	██████	NA	NA	NA	NA
Resmetirom	██████	██████	██████	██████	██████	██████	33,975

As we presented in A1, to help link into discussions raised under Issue 3 of Technical Engagement, we also estimated “LSM-eligible” subgroup ICERs using IPD and efficacy cross-tabulations (see Table 3) for the wider mITT population. This resulted in a minor increase to ICER values as expected, since the mITT population assumed per protocol that patients with missing W52 biopsies had no MASH response and no fibrosis change. Results are shown in Table 7 below.

Table 7: Revised cost-effectiveness results for mITT population scenario (per TE Issue 3) - LSM-eligible subpopulation

Technologies	Total costs (£)	Total LYG	Total QALYs	Incremental costs (£)	Incremental LYG	Incremental QALYs	ICER (£/QALY)
SoC	██████	██████	██████	NA	NA	NA	NA
Resmetirom	██████	██████	██████	██████	██████	██████	43,270

Overall, we consider that the findings from this restricted subgroup broadly align with those in our base case analysis and follow the same direction in response to data selection between PLB-W52 and mITT populations.

B2. Priority question. The scenario analyses presented in response to Issue 9 (natural history) do not appear to function using the Excel model provided.

- a) Please provide an updated version of the model in which these scenarios can be implemented as described, or alternatively, provide clear step-by-step instructions on how they should be implemented within the current version of the model.
- b) Please provide additional detail on: i) which specific parameters are being modified in these scenarios; ii) how the changes relate to the

**natural history data/transition probabilities reported in your response;
and how relative treatment effects are applied within each scenario?**

Company Response: a) We thank the EAG for highlighting this issue and apologise for any inconvenience caused. The natural history (NH) scenarios are functional in the current Excel model version; however, the required helper file was missing from the model we submitted.

The helper file **df_NASH_outcome_M-NASH_mITT.csv** is now located in the main model folder (i.e., the same directory as the .rmd file), uploaded via NICE Docs in response to Clarification.

An amendment to **master_input_parameters.xlsx** was also necessary regarding natural history scenarios (see our comments for sub-question **b** for an explanation).

To run or re-run natural history scenarios, please proceed as follows:

1. Reset the model to Base Case configuration

- In the master input Excel file, ensure that all model inputs are set to the **Base Case** values before implementing any scenario.

2. Setting up Natural History Scenarios from our TE response in the Master Input Excel sheet:

Scenario 1: Le et al. 2023 – RCT data

- For “SoC arm based on”, select:
“Le et al. 2023 – RCTs”
- For “Annual fibrosis changes pattern”, select:
“2-stages reg. & prog. Le et al.”

Scenario 2: Ng et al. 2022 data

- For “SoC arm based on”, select:
“Ng et al. 2022”
- For “Annual fibrosis changes pattern”, select:
“Only one stage prog. & reg.”

Scenario 3: Le & Ng combined data (1 stage max)

- For “SoC arm based on”, select:
“Le & Ng combined”
- For “Annual fibrosis changes pattern”, select:
“Only one stage prog. & reg.”

Scenario 4: Le & Ng combined data (2 stages max)

- For “SoC arm based on”, select:
“Le & Ng combined”
- For “Annual fibrosis changes pattern”, select:
“2-stages reg. & prog. Le et al”

After selecting the relevant options, the model will automatically update the transition probabilities used in the state-transition framework.

- b) Our response to TE Issue 9 set out our rationale for NH data collection and general considerations around the issue. This clarification response aims to link the statistics presented in our TE response for Issue 9, with their implementation into the model.

The model develops transition probabilities based on NH data in the following order:

- Disregard MASH resolution:** since Le et al and Ng et al present fibrosis statistics irrespective of MASH resolution, this pathway is disabled within the four “Natural History” scenarios and fibrosis is the only driver of health states.
- MAESTRO-NASH (PLB-W52) is used to calculate relative risks (RRs) for resmetirom 80mg and 100mg vs. placebo:** this was done for fibrosis improvement and fibrosis worsening (also referred to as “regression” and “progression”). The same RR values are used in every natural history scenario. The RR table can be viewed in the Excel file **master_input_parameters.xlsx**, sheet: “M-NASH Pop&efficacy” Range C10:K17.

Amendment to model RRs

For our TE response on 12 February 2026, we calculated RRs using patient-level data for patients having “no MASH resolution” (range H12:H15 in sheet “M-NASH Pop&efficacy”).

However, we acknowledge that a more appropriate approach would have been to calculate these RRs irrespective of NASH resolution status, to reflect the presentation of estimates in Le and Ng. These revised RRs have been applied in the new version of

master_input_parameters.xlsx and can be viewed in the range

K12:K15 in sheet “M-NASH Pop&efficacy”. RR values are summarised below:

Comparison	Outcome	RR
Resmetirom 100mg vs Pbo	Improvement	
Resmetirom 100mg vs Pbo	Worsening	
Resmetirom 80mg vs Pbo	Improvement	
Resmetirom 80mg vs Pbo	Worsening	

This correction has the impact of reducing the ICERs reported for each of the natural history scenario results in our original TE response (see revised tables at end of document) but does not materially impact the assessment of these ICER values relative to NICE thresholds.

- iii. **Calculate annual probability of fibrosis progression and regression:** we used relevant published estimates (Le et al., Ng et al., or a combination of both) to derive these probabilities for SoC and then calculated SoC x RR to derive probabilities for resmetirom arms (see master_input_parameters.xls sheet “NH - data” Rows 12-16 for SoC and Rows 35–47 for resmetirom – the application of RRs can be traced via formulae).
- iv. **Apportion ‘progressing’ or ‘regressing’ patients to 1 or 2 fibrosis stage-changes, using published data:** the approach here depends on the selected scenario and level of detail available in each publication (all calculations on sheet “NH – data” and the final resulting probabilities of stage-to-stage fibrosis transition for SoC are shown in sheet “NH - data” Rows 28-32):
 - **Scenario 1 using Le et al:** proportions worsening or improving by 1 or 2 fibrosis stages are informed by the Le et al publication (sheet “NH - data”, range K28:O32). Company response to TE Issue 9 - Table 2 showed the resulting stage-to-stage transitions for SoC.
 - **Scenario 2 using Ng et al:** assume maximum 1 stage/year regression or progression, per Ng et al publication. Our TE response Table 3 showed SoC transitions.

- **Scenario 3 using Le & Ng combined:** progression / regression derived from Le or Ng per description in TE response but allow maximum 1 stage/year regression or progression. Table 4 in our TE response showed SoC transitions.
- **Scenario 4 using Le & Ng combined:** as per Scenario 3, but among any patients progressing or regressing, apportion them between 1 or 2 fibrosis stage-changes using relative proportions from Le et al (sheet “NH - data”, range K28:O32). This apportionment mechanism applies for **all** fibrosis stages - our TE response on 12/2/2026 incorrectly implied that F3 patients were still limited to 1 stage progression/regression and summary table 5 – showing stage-to-stage transitions for SoC – was erroneously repeating Scenario 3 numbers. It should have read as:

Le & Ng et al.	F0	F1	F2	F3	F4
F0	0.745276	0.176747	0.077977	0	0
F1	0.119266	0.656425	0.148361	0.075947	0
F2	0.035726	0.127331	0.648338	0.167849	0.020756
F3	0	0.070103	0.099873	0.63086	0.199165
F4	0	0	0	0.086069	0.913931

(the above table comes from “NH - data” Range AR27:AW32 in the updated Excel input file).

- The probabilities of NASH resolution for SoC and resmetirom arms were set to zero; therefore, transitions through the NASH resolution pathway were disabled within these scenarios.

Below are presented updated NH scenario results, using revised RRs as described previously:

Table 8. Natural history scenario 1. Le et al. 2023

Technologies	Total costs (£)	Total LYG	Total QALYs	Incremental costs (£)	Incremental LYG	Incremental QALYs	ICER (£/QALY)
SoC	██████	██████	██████	NA	NA	NA	NA
Resmetirom	██████	██████	██████	██████	██████	██████	161,514

Table 9. Natural history scenario 2. Ng et al. 2022

Technologies	Total costs (£)	Total LYG	Total QALYs	Incremental costs (£)	Incremental LYG	Incremental QALYs	ICER (£/QALY)
SoC	██████	██████	██████	NA	NA	NA	NA
Resmetirom	██████	██████	██████	██████	██████	██████	124,377

Table 10. Natural history scenario 3. Le et al. 2023 and Ng et al. 2022 combined (1 stage max)

Technologies	Total costs (£)	Total LYG	Total QALYs	Incremental costs (£)	Incremental LYG	Incremental QALYs	ICER (£/QALY)
SoC	██████	██████	██████	NA	NA	NA	NA
Resmetirom	██████	██████	██████	██████	██████	██████	108,958

Table 11. Natural history scenario 4. Le et al. 2023 and Ng et al. 2022 combined (2 stages max):

Technologies	Total costs (£)	Total LYG	Total QALYs	Incremental costs (£)	Incremental LYG	Incremental QALYs	ICER (£/QALY)
SoC	██████	██████	██████	NA	NA	NA	NA
Resmetirom	██████	██████	██████	██████	██████	██████	95,735

Single Technology Appraisal

Resmetirom for treating moderate to advanced liver fibrosis (without cirrhosis) caused by metabolic dysfunction-associated steatohepatitis [ID6529]

Clinical expert statement and technical engagement response form

Thank you for agreeing to comment on the external assessment report (EAR) for this evaluation, and for providing your views on this technology and its possible use in the NHS.

You can provide a unique perspective on the technology in the context of current clinical practice that is not typically available from the published literature. The EAR and stakeholder responses are used by the committee to help it make decisions at the committee meeting. Usually, only unresolved or uncertain key issues will be discussed at the meeting.

Information on completing this form

In [part 1](#) we are asking for your views on this technology. The text boxes will expand as you type.

In [part 2](#) we are asking for your views on key issues in the EAR that are likely to be discussed by the committee. The key issues in the EAR reflect the areas where there is uncertainty in the evidence, and because of this the cost effectiveness of the treatment is also uncertain. The key issues are summarised in section 1.3 of the executive summary at the beginning of the EAR. You are not expected to comment on every key issue but instead comment on the issues that are in your area of expertise.

A clinical perspective could help either:

- resolve any uncertainty that has been identified OR
- provide missing or additional information that could help committee reach a collaborative decision in the face of uncertainty that cannot be resolved.

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In [part 3](#) we are asking you to provide 5 summary sentences on the main points contained in this document.

Please do not embed documents (such as a PDF) in a submission because this may lead to the information being mislaid or make the submission unreadable. Please type information directly into the form.

Do not include medical information about yourself or another person that could identify you or the other person.

We are committed to meeting the requirements of copyright legislation. If you want to include **journal articles** in your submission you must have copyright clearance for these articles. We can accept journal articles in NICE Docs. For copyright reasons, we will have to return forms that have attachments without reading them. You can resubmit your form without attachments, but it must be sent by the deadline.

Combine all comments from your organisation (if applicable) into 1 response. We cannot accept more than 1 set of comments from each organisation.

Please underline all confidential information, and separately highlight information that is submitted as 'confidential [CON]' in turquoise, and all information submitted as 'depersonalised data [DPD]' in pink. If confidential information is submitted, please also send a second version of your comments with that information redacted. See [Health technology evaluations: interim methods and process guide for the proportionate approach to technology appraisals](#) (section 3.2) for more information.

Please note, part 1 can be completed at any time. We advise that **part 2** is completed after the expert engagement teleconference (if you are attending or have attended). At this teleconference we will discuss some of the key issues, answer any specific questions you may have about the form, and explain the type of information the committee would find useful.

The deadline for your response is **5pm** on **<insert deadline>**. Please log in to your NICE Docs account to upload your completed form, as a Word document (not a PDF).

Thank you for your time.

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We reserve the right to summarise and edit comments received during engagement, or not to publish them at all, if we consider the comments are too long, or publication would be unlawful or otherwise inappropriate.

Comments received during engagement are published in the interests of openness and transparency, and to promote understanding of how recommendations are developed. The comments are published as a record of the comments we received, and are not endorsed by NICE, its officers or advisory committees.

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Part 1: Treating moderate to advanced liver fibrosis (without cirrhosis) caused by metabolic dysfunction-associated steatohepatitis and current treatment options

Table 1 About you, aim of treatment, place and use of technology, sources of evidence and equality

1. Your name	Professor Quentin Anstee
2. Name of organisation	Newcastle University, UK
3. Job title or position	Pro-Vice-Chancellor – Faculty of Medical Sciences Ruth & Lionel Jacobson Chair of Personalised Medicine Honorary Consultant Hepatologist
4. Are you (please tick all that apply)	☐ An employee or representative of a healthcare professional organisation that represents clinicians? ☒ A specialist in the treatment of people with moderate to advanced liver fibrosis (without cirrhosis) caused by metabolic dysfunction-associated steatohepatitis ? ☒ A specialist in the clinical evidence base for moderate to advanced liver fibrosis (without cirrhosis) caused by metabolic dysfunction-associated steatohepatitis or technology? ☐ Other (please specify):
5. Do you wish to agree with your nominating organisation's submission? (We would encourage you to complete this form even if you agree with your nominating organisation's submission)	☐ Yes, I agree with it ☐ No, I disagree with it ☒ I agree with some of it, but disagree with some of it ☐ Other (they did not submit one, I do not know if they submitted one etc.)
6. If you wrote the organisation submission and/or do not have anything to add, tick here.	☐ Yes

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(If you tick this box, the rest of this form will be deleted after submission)	
7. Please disclose any past or current, direct or indirect links to, or funding from, the tobacco industry.	No links to or funding from the tobacco industry at any time. I have the following other Disclosures (included here as I can't find any other place on form to put them): Research Grant Funding: Coordinator of the EU IMI-2 LITMUS consortium, which is funded by the EU Horizon 2020 programme and EFPIA. AstraZeneca, Boehringer Ingelheim, Intercept. Consultancy on behalf of Newcastle University: Alimentiv, Akero, AstraZeneca, Axcella, 89Bio, Boehringer Ingelheim, Bristol Myers Squibb, Corcept, Echosens, Enyo Pharma, Galmed, Genfit, Genentech, Gilead, GlaxoSmithKline, Hanmi, HistoIndex, Intercept, Inventiva, Ionis, IQVIA, Janssen, Madrigal, Medpace, Merck, Metadeq, NGMBio, North Sea Therapeutics, Novartis, Novo Nordisk, PathAI, Pfizer, Pharmanest, Poxel, Prosciento, Resolution Therapeutics, Roche, Ridgeline Therapeutics, RTI, Shionogi, Terns. Speaker: Fishawack, Integrity Communications, Kenes, Novo Nordisk, Madrigal, Medscape, Springer Healthcare. Royalties: Elsevier Ltd.
8. What is the main aim of treatment for moderate to advanced liver fibrosis (without cirrhosis) caused by metabolic dysfunction-associated steatohepatitis? (For example, to stop progression, to cure the condition, or prevent progression or disability)	MASLD/MASH is a chronic condition that should be considered analogous to long-term cardiometabolic conditions like hypertension, dyslipidaemia or type 2 diabetes (T2DM) where the goal is to control the disease over the long term, not achieve a “cure” <i>per se</i>. The long-term aim is therefore to prevent MASLD/MASH progression to cirrhosis, and so avoid hepatic decompensation, primary liver cancer (hepatocellular carcinoma, HCC) and liver-related death.
9. What do you consider a clinically significant treatment response?	The FDA and EMA define Reasonably Likely Surrogate Endpoints (RLSE) histologically [1, 2]. These are either (or both of): a. MASH resolution without worsening of fibrosis (with ballooning score zero on the NASH-CRN Scoring

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(For example, MASH resolution, regression in liver fibrosis stage, or a reduction in disease activity by a certain amount)	system [3]); b. Fibrosis improvement by at least one histological stage without worsening of MASH. Natural history studies demonstrate that long-term outcomes align most closely with fibrosis stage [4, 5]. This holds true whether fibrosis is measured histologically or with non-invasive tests [6, 7]. Therefore, in my opinion, the most important treatment response is evidence of regression of fibrosis by at least one histological stage. If this is corroborated with evidence of improvement in relevant biomarkers (eg elastography by Fibroscan VCTE, or biomarkers of extracellular matrix turnover such as ELF or PROC3) this is even more persuasive [8]. It could be argued that preventing progression, i.e. holding fibrosis steady at early stages such as F2, might also be a clinically significant response given that liver-related adverse outcomes tend to occur in patients with cirrhosis (F4) [9, 10]. Evidence of MASH resolution is also an important finding as pathophysiology is based on the understanding that steatohepatitis activity drives fibrosis progression [11], and so MASH resolution is thought likely to halt disease progression. Although there is less direct evidence to link steatohepatitis grade with outcomes independent of fibrosis (likely because this takes too long to read through yet in existing cohorts) [5, 12], there are good data demonstrating that change in grade of steatohepatitis is associated with progression/regression of fibrosis, which is in turn linked to outcomes [13].
10. In your view, is there an unmet need for patients and healthcare professionals in moderate to advanced liver fibrosis (without cirrhosis) caused by metabolic dysfunction-associated steatohepatitis?	Yes, unreservedly.
11. How is moderate to advanced liver fibrosis (without cirrhosis) caused by metabolic dysfunction-	Despite the presence of clinical guidelines, their adoption and the management of MASLD/MASH is highly variable between clinicians and regions of the UK

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associated steatohepatitis currently treated in the NHS? • Are any clinical guidelines used in the treatment of the condition, and if so, which? • Is the pathway of care well defined? Does it vary or are there differences of opinion between professionals across the NHS? (Please state if your experience is from outside England.) • What impact would the technology have on the current pathway of care?	(and internationally) [14]. There are however exemplars of good practice around the UK [15]. • Main clinical guidelines: ○ EASL-EASD-EASO (most widely used in Europe and UK by specialists) [16] ○ AASLD [17, 18] ○ A BSG quality standards consensus statement was published in 2022 [19]. • At present, in the absence of a licenced drug therapy, treatment is based upon treating the metabolic syndrome to optimise cardiovascular disease risk, lifestyle change (diet/exercise to effect weight loss – very difficult for individual patients to implement and sustain so frequently unsuccessful), and monitoring for complications of the disease so that they can be “caught” and treated when they occur [16]. • As above, there is a relatively good understanding of what an effective care pathway should be but this is inconsistently applied across the UK [15]. • The presence of a licenced drug therapy for MASLD would be important to address a pervasive view amongst some clinicians that there is no need to diagnose this progressive liver disease because there is no specific therapy beyond lifestyle advice. This view means that many patients are only identified late in the disease natural history when the liver decompensates (fails) or liver cancer occurs. Access to efficacious drug therapy would help to address this and would give clinicians an effective pharmacological treatment to offer patients that complements lifestyle change and reduces/prevents progression of disease.
12. Will the technology be used (or is it already used) in the same way as current care in NHS clinical practice?	The technology being assessed (Resmetriom) will prove a valuable pharmacological therapy that may be prescribed to selected patients alongside lifestyle change (as above) to reverse disease progression. This agent has already been licenced for use in Europe and the USA for non-cirrhotic

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• How does healthcare resource use differ between the technology and current care? • In what clinical setting should the technology be used? (for example, primary or secondary care, specialist clinic) • What investment is needed to introduce the technology? (for example, for facilities, equipment, or training)	MASH and offers an important treatment option for a highly prevalent condition that at present is underserved by the NHS, with substantial consequences for patients, their families and society. Given the progressive nature of MASLD/MASH, the requirement to identify pre-cirrhotic patients with significant fibrosis, and the need to monitor for disease progression in the event of non-response, this drug should be used in the secondary/tertiary setting (at least initially). There would be a need for clear clinical guidelines within the NHS to standardise access and prescribing of the drug and provide guidance to clinicians on which patients to treat, how to assess treatment response/non-response, and when to consider discontinuing treatment. A package of lifestyle modification (diet and exercise) alongside the pharmacological therapy would be the optimum approach.
13. Do you expect the technology to provide clinically meaningful benefits compared with current care? • Do you expect the technology to increase length of life more than current care? • Do you expect the technology to increase health-related quality of life more than current care?	Yes. The evidence for histological improvement over a relatively short period of time in clinical trials gives confidence that this agent is likely to translate into long-term outcome benefit for patients. Although as yet there is no trial evidence of improved long-term outcomes for MASLD with any drug therapy, trials are ongoing to address this. The evidence for fibrosis improvement and MASH resolution, and the consequent likely benefits on liver-related morbidity and mortality are apparent (see Part 1, Q9). We and others have published on the health-related quality of life impacts of MASLD/MASH, which are substantial [20-23]. There are a number of validated patient reported outcome measures that have been used to address this (NASH-CHECK [21, 24, 25], and CLDQ/CLDQ-NASH [26]). Studies have shown that improvement of MASH is linked with improvement of health-related quality of life, both with Resmetirom [27] and with other pharmacological agents [28]. Given the barriers encountered in delivering and sustaining meaningful

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	lifestyle change/weight loss [29-31], it is likely that pharmacological therapy will offer benefits beyond those achieved with current standard of care.
14. Are there any groups of people for whom the technology would be more or less effective (or appropriate) than the general population?	I am not aware that there is evidence as yet to support this view, but it is conceivable that data will support a more tailored/personalised approach to medicines in the future based on, for example, genomic profiles. Given that MASLD/MASH is most common and often more severe in patients with multiple features of the metabolic syndrome (and especially type 2 diabetes), it may be that these groups should be prioritised initially for case identification. This does not however necessarily link to drug efficacy.
15. Will the technology be easier or more difficult to use for patients or healthcare professionals than current care? Are there any practical implications for its use? (For example, any concomitant treatments needed, additional clinical requirements, factors affecting patient acceptability or ease of use or additional tests or monitoring needed)	Easier to use – oral medication, much easier than trying to effect lifestyle change alone, which is resource intensive to deliver and often unsuccessful/difficult to sustain for long enough to change disease natural history. Based on trial evidence and real-world experience, the drug is generally well tolerated [32, 33].
16. Will any rules (informal or formal) be used to start or stop treatment with the technology? Do these include any additional testing?	Yes – use of non-invasive biomarkers will be needed to guide patient selection and detect presence or absence of treatment response during follow-up. Formalised guidance on this will need to be developed. An example of how this may be applied has been published by clinicians in USA [34], although this should not necessarily be precisely adopted in UK.
17. Do you consider that the use of the technology will result in any substantial health-related benefits that are unlikely to be included in the quality-adjusted life year (QALY) calculation? Do the instruments that measure quality of life fully capture all the benefits of the technology or have some	The technical details of QALY calculation are outside my scope of expertise so I am unable to respond to this question but happy to discuss and provide clinical perspective during the meeting.

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been missed? For example, the treatment regimen may be more easily administered (such as an oral tablet or home treatment) than current standard of care	
18. Do you consider the technology to be innovative in its potential to make a significant and substantial impact on health-related benefits and how might it improve the way that current need is met? - Is the technology a 'step-change' in the management of the condition? - Does the use of the technology address any particular unmet need of the patient population?	Yes. This is a new class of drugs and would be the first drug licenced in the UK to treat MASLD/MASH, a condition that carries a substantial health-economic burden and societal burden. We and others have published evidence derived from real-world datasets of some of these impacts in various populations, including work-productivity [35],
19. How do any side effects or adverse effects of the technology affect the management of the condition and the patient's quality of life?	Drug is generally well tolerated [32, 33]. Data on quality of life have also been reported [27].
20. Do the clinical trials on the technology reflect current UK clinical practice? - If not, how could the results be extrapolated to the UK setting? - What, in your view, are the most important outcomes, and were they measured in the trials? - If surrogate outcome measures were used, do they adequately predict long-term clinical outcomes? - Are there any adverse effects that were not apparent in clinical trials but have come to light subsequently?	The biological relevance of the trials is high, but the operational generalisability is more limited in terms of how care is delivered in the UK. I address this in more detail below (Part 2 Q1) but the key differences are: UK practice is largely based on use of non-invasive tests whilst MAESTRO-NASH trial was histologically based. The use of histology is a consequence of the regulatory framework that requires use of histological surrogate endpoints rather than NITs to demonstrate efficacy. - The trials exclude certain comorbidities and significant alcohol intake and apply protocol stability requirements—this tends to produce a cleaner, more adherent, more intensively monitored population than routine NHS care. - To extrapolate to the UK population would require a non-invasive definition of pre-cirrhotic MASH that identifies a population with similar disease to the population recruited in the trial. This is something that has been addressed by professional societies like AASLD and EASL in their

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	guidelines and could be adapted for use in the NHS to provide a tractable way forward [16-18]. The most important outcomes are how a patient “feels, functions and survives”. These aspects are addressed in the ongoing MAESTRO-NASH trials and further data on survival will be available in the future, but that is some time off. The evidence of efficacy at this time is based on the regulatory (EMA/FDA) defined histological surrogate endpoints outlined above. Based on a range of publications it is believed that these are “reasonably-likely” to predict improved outcomes. Trials are ongoing that will validate these results. I am not aware of new, unexpected adverse events for Resmetirom that have come to light since the trials were published. A recent publication summarises experience from the first year of use in the USA based on the FDA Adverse Event Reporting System (FAERS) database [33].
21. Are you aware of any relevant evidence that might not be found by a systematic review of the trial evidence?	No
22. How do data on real-world experience compare with the trial data?	Limited data currently available, largely from USA although the drug has recently been licenced for use in Europe.
23. NICE considers whether there are any equalities issues at each stage of an evaluation. Are there any potential equality issues that should be taken into account when considering this condition and this treatment? Please explain if you think any groups of people with this condition are particularly disadvantaged. Equality legislation includes people of a particular age, disability, gender reassignment, marriage and civil	Not that I am aware of.

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partnership, pregnancy and maternity, race, religion or belief, sex, and sexual orientation or people with any other shared characteristics.

Please state if you think this evaluation could

- exclude any people for which this treatment is or will be licensed but who are protected by the equality legislation
- lead to recommendations that have a different impact on people protected by the equality legislation than on the wider population
- lead to recommendations that have an adverse impact on disabled people.

Please consider whether these issues are different from issues with current care and why.

More information on how NICE deals with equalities issues can be found in the [NICE equality scheme](#).

[Find more general information about the Equality Act and equalities issues here.](#)

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Part 2: Technical engagement questions for clinical experts

We welcome your comments on the key issues below, but you may want to concentrate on issues that are in your field of expertise. If you think an issue that is important to clinicians or patients has been missed in the EAR, please also advise on this in the space provided at the end of this section.

The text boxes will expand as you type. Your responses to the following issues will be considered by the committee and may be summarised and presented in slides at the committee meeting.

For information: the professional organisation that nominated you has also been sent a technical engagement response form (a separate document) which asks for comments on each of the key issues that have been raised in the EAR. These will also be considered by the committee.

Table 2 Issues arising from technical engagement

Issue 1: The trial population does not match the population in scope.	<i>We would be grateful if you could answer the following questions related to this key issue:</i> <i>What diagnostic tools are used to identify people with MASH with liver fibrosis in clinical practice? Do you expect any changes to diagnostic tools or methods if resmetirom becomes available as a treatment option?</i> Steatohepatitis is a histological diagnosis and there are few if any high performing non-invasive diagnostic tests for grading steatohepatitis [36]. In the UK and internationally, most pathways do not try to diagnose MASH per se in primary care. Instead, they risk-stratify for clinically significant/advanced fibrosis (ie Fibrosis stage F2+ and F3+ respectively, out of 4 stages) in people with MASLD/MASH risk factors such as T2DM, then refer/select for specialist review. A stepwise approach to non-invasive testing is recommended in most clinical guidelines (eg FIB4 followed by Fibroscan VCTE or ELF) [16, 19, 37]. This leverages the high negative predictive value of FIB4 to rule out many patients with mild disease, so improving the pre-test probability for the second line test to identify those patients most likely to have clinically significant/advanced disease. It should be noted however that no testing strategy is

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	perfect [36, 38]. However, repeated FIB4 testing annually is an effective way to mitigate against “missed cases” and to monitor disease progression/outcome risk [39]. In routine practice, biopsy is typically reserved for diagnostic uncertainty, suspected competing aetiologies, or where precise staging/activity would change management—rather than routine confirmation for all patients. Because Resmetirom’s trial evidence of efficacy is currently for non-cirrhotic MASH with F2–F3 fibrosis (“At-Risk MASH”) [32, 40], there may be a change towards identifying cases that meet treatment/staging criteria. Likely consequences (assuming liver biopsy is not mandated for drug prescribing): • Greater emphasis on accurate F2–F3 ascertainment, not just “advanced fibrosis” (≥F3) as now. However, there will remain a need to identify those patients with F4 (cirrhosis) as they require specialist monitoring for HCC, etc • More structured, auditable NIT algorithms (e.g., FIB-4 → ELF and/or VCTE; sometimes VCTE + ELF concordance) to approximate F2–F3 and exclude cirrhosis. This direction aligns with EASL–EASD–EASO guidance endorsing initial use of simple blood-based biomarkers (FIB-4) followed by direct collagen biomarkers (ELF) or elastography (VCTE) for fibrosis detection. • Inclusion of NIT based assessment as part of annual review for patients with relevant comorbidities that increase risk of MASLD/MASH (eg T2DM) <i>What are likely to be the appropriate criteria for identifying people eligible for resmetirom in clinical practice?</i> The target group for treatment should be non-cirrhotic MASH with F2–F3 fibrosis (“At-Risk MASH”). However, widespread routine use of liver biopsy would be impractical, resource intensive and carries an unacceptable level of risk as well as poor patient acceptability and so non-invasive tests will be used to identify patients suitable for treatment [41]. This uses a stepwise process such as: • Evidence of MASLD/MASH phenotype (metabolic risk factors, steatosis on imaging, exclusion of significant alcohol/other liver diseases), consistent with guideline definitions.

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	• Fibrosis stage consistent with F2–F3 using VCTE and/or ELF, possibly seeking concordance of more than one test (e.g., FIB-4 indeterminate/high + ELF high and/or VCTE elevated). • Specialist confirmation (hepatology/metabolic liver clinic) to: ○ exclude alternative aetiologies, ○ assess cirrhosis risk/portal hypertension, ○ optimise cardiometabolic management, ○ check drug–drug interactions and monitoring. Note: Analysis of data from UK centres derived from the European MASLD Registry [42] may assist in defining/modelling non-invasive thresholds. • <i>How does the patient population likely to be eligible for resmetirom in clinical practice differ from that in the MAESTRO-NASH trial?</i> The trial population in MAESTRO-NASH was positively defined by the presence of specific metabolic comorbidities (≥ 3 metabolic risk factors), non-invasive test enrichment criteria (evidence of increased hepatic fat content and VCTE ≥ 8.5 kPa) and then histological features (NAS (NAFLD Activity Score) ≥ 4 plus Fibrosis stage F1B, F2, or F3 [majority F2–F3]) [32, 40]. These were complemented with a number of standard exclusion criteria such as high alcohol consumption, etc. [32, 40]. In clinical practice, the main differences would be: • Broader comorbidity and concomitant therapy • No liver biopsy, instead non-invasively defined treatment population, and therefore no histological confirmation of MASH activity and likely a different fibrosis stage mix.

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	However, there is an important caveat that needs to be remembered: liver biopsy/histology is not a perfect assessment of the severity of liver disease. Liver disease tends to be heterogenous across the liver parenchyma and so the biopsy procedure inevitably introduces sampling error and may not be representative of the wider state of disease [43]. Furthermore, histological interpretation is subject to substantial inter- and intra-observer variation, even with expert histopathologists – a situation that is especially evident is detecting histological features of MASH such as hepatocyte ballooning [44]. • <i>What are the implications of the differences between the appropriate criteria in clinical practice and the eligibility criteria of the MAESTRO-NASH trial for the generalisability of the trial data?</i> As above, liver biopsy should not be considered a perfect measure of the “ground truth” of disease severity. The gap between the trials and UK clinical practice based on NITs will depend largely on diagnostic misclassification, leading to variation in fibrosis stage mix. • In practice (treating some patients without true F2–F3 MASH, and missing some who do have it) could dilute observed treatment benefit versus the RCT (because some treated patients cannot benefit as much), and/or create apparently “variable” responses across sites if a single set of guidelines is not implemented to guide patient selection. Conversely, specialist pathways could be used to preferentially select higher-risk phenotypes, which could increase apparent benefit on clinical outcomes (for example, if true F3 enriched, although that is speculation). • If some early/occult F4 cases were selected for treatment prior to trials confirming safety/efficacy in cirrhosis this could have drug safety/pharmacodynamics implications. Sampling error between F3 and F4 is also a potential issue with biopsy and so should not be held as a limitation in selection of patients for any specific therapy using NITs. Existing real-world datasets where cases are histologically characterised and have broad non-invasive biomarker coverage could assist in modelling how best to bridge this diagnostic gap. These include the European MASLD Registry, hosted at Newcastle University, UK [42].
Issue 2: Reliance on Surrogate Endpoints	<i>We would be grateful if you could answer the following question related to this key issue:</i>

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	<i>Please comment on the plausibility and validity of MASH resolution and fibrosis stage as predictors of comorbid events, liver-related events and mortality.</i> See comments above (Part 1, Q9). The pathophysiological view of MASLD natural history is that steatohepatitis drives fibrosis progression – higher grade of steatohepatitis, fibrosis more likely to progress to cirrhosis and vice versa. Natural history studies support this view [13]. We and others have also published data to show that long-term outcomes align most closely with fibrosis stage [4, 5]. Reversal of cirrhosis is also associated with better outcomes [8]. This holds true whether fibrosis is measured histologically or with non-invasive tests [6, 7]. Whilst it is biologically plausible that both MASH grade (or MASH resolution) and Fibrosis stage are predictive of outcomes, the data are stronger for the later.
Issue 3: Differences between the ITT population and paired liver biopsy population	Happy to discuss and provide clinical perspective during the meeting.
Issue 4: Validation of the company model and programming complexity	This is outside my scope of expertise but happy to discuss and provide clinical perspective during the meeting.
Issue 5: Response to treatment not captured by the current model structure	<i>We would be grateful if you could answer the following questions related to this key issue:</i> <i>How are changes in fibrosis stage assessed in clinical practice?</i> Routine clinical practice employs non-invasive testing (simple scores like FIB4, elastography [VCTE Fibroscan, etc] and extracellular matrix biomarkers like ELF). Liver biopsy is uncommon and serial liver biopsy is now unusual outside clinical trials and tertiary care settings. Changes in fibrosis are therefore assessed by increase/decrease in non-invasive biomarkers.

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	• <i>How do you anticipate resmetirom will be used in clinical practice?</i> Already covered above – imitate treatment in pre-defined MASLD populations using non-invasive biomarkers of fibrosis (eg VCTE/ELF, etc), monitor treatment response at annual intervals, define stopping rules if response not apparent after a biologically plausible period of time (for example >52-weeks, likely 96-weeks). • <i>Do you anticipate that resmetirom will be used based on a response assessment? How do you anticipate this response assessment would work in practice?</i> ◦ <i>Would it be based on non-invasive tests (NITs)? If so, please specify the NITs.</i> See above, likely VCTE and/or ELF. Change needs to be greater than the established coefficient of variation of each test and assessed at a biologically plausible time point to establish meaningful change or lack thereof. ◦ <i>How frequently would these NITs be administered?</i> Annually, following a biologically plausible period for drug to work. ◦ <i>What decision criteria do you anticipate would be applied to inform treatment discontinuation decisions?</i> Time/meaningful change or absence, whether drug has additional extra-hepatic benefits beyond those on MASLD that should also be considered before discontinuation (eg weight loss, cardiovascular risk reduction, etc). This is an important topic to discuss at the meeting.

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Issue 6: Stopping rules and discontinuation of resmetirom treatment	<i>We would be grateful if you could answer the following questions related to this key issue:</i> <i>Would it be appropriate to stop resmetirom treatment when fibrosis regresses without MASH resolution?</i> This needs careful consideration and discussion. Given that treatment will be based on non-invasive tests to select for treatment/monitor response, and that there are no widely available, high performing tests for MASH that are truly independent of fibrosis, this scenario is unlikely to occur in clinical practice. The grade of steatohepatitis in the liver parenchyma is heterogeneous and waxes/wanes so the histological phenomenon of fibrosis regression in the absence of improved MASH is likely to be driven by biopsy sampling artefact and/or variations in biopsy interpretation (see [43, 44]). For these reasons, the apparent disconnect between fibrosis and MASH described is unlikely to be relevant in clinical decision making. A more relevant question is whether treatment should be discontinued if the fibrosis regresses. Here, one needs to consider if the underlying drivers of disease remain or have been addressed through lifestyle change/weight loss. The analogy of stopping treatment of other cardiometabolic diseases like hypertension or diabetes simply because the BP readings are normal or the HBA1c has fallen within the desired range may be helpful – normal practice would be to consider these indicators of effective disease control, not cure. The same rationale would likely apply to MASLD/MASH if the fundamental drivers of disease (insulin resistance, obesity, etc) have not been removed. <i>Is progression to F4 compensated cirrhosis more likely to reflect treatment failure or insufficient treatment?</i> Treatment failure - given that all drugs for which phase 3 trial data are available show no more than approx. 20% response rates over placebo.

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	• <i>Would it be appropriate to stop resmetirom treatment when people progress to advanced liver disease including compensated cirrhosis?</i> There remains the question of whether the agent has offered some marginal benefit (ie slowed progression) however at present we do not have sufficient data to support such a claim and do not know if there is evidence for efficacy in reversal of cirrhosis or safety in a cirrhotic population (trials ongoing). Until such data are available, stopping drug would be the prudent course - <i>primum non nocere</i>.
Issue 7: Repeated application of transition probabilities and short-term trial follow-up	<i>We would be grateful if you could answer the following questions related to this key issue:</i> • <i>Please comment on the biological plausibility of the assumption that people have the same probability of resolving MASH throughout the entire time horizon</i> There are very limited data to support or refute this. My personal view is that MASH resolution would tend to happen within the first year of treatment however fibrosis improvement would be slower and so may take some time to occur as the liver remodels, this could be over a number of years. This is based on the observation that markers of disease like hepatic fat accumulation (eg MR-PDFF) and activity (eg ALT, AST and even some markers of collagen deposition) tend to drop rapidly within the first few months of treatment in the trials across multiple agents/MOAs and then plateau or slow their decline. • <i>Please comment on the plausibility of the assumption that all people having resmetirom or standard of care (SoC) experience a continuous decline in weight (and BMI) throughout the entire time horizon.</i>

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	In my experience the weight of patients with MASLD/MASH tends to fluctuate. There are considerable barriers to sustained lifestyle change and, although some are able to lose weight, in practice many find it difficult to sustain and weight tends to creep back up. <i>Please comment on the assumption that people having resmetirom experience a faster decline in weight than people receiving SoC.</i> I am not aware of the basis for this assumption.
Issue 8: Misinterpretation of Singh et al (2015)	It is not clear what the question is here. Happy to discuss and provide clinical perspective during the meeting.
Issue 9: Natural history of MASH and face validity of model progression rates	<i>We would be grateful if you could answer the following questions related to this key issue:</i> <i>How long does it typically take for people to progress by one or two liver fibrosis stage(s)?</i> Highly variable. Estimates in unselected natural history studies vary. <i>To what extent is progression between liver fibrosis stages heterogeneous?</i> Yes, it is heterogeneous. <i>What factors are associated with more rapid progression?</i>

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	Presence of more features of the metabolic syndrome (or development of new features of the metabolic syndrome), carriage of certain genetic variants (eg PNPLA3), etc. are associated with more advanced disease. • <i>Are some people 'rapid progressors', and can these people be identified in clinical practice?</i> That hypothesis has been proposed. It is probably an over simplification to binarise disease progression rate, which is likely to be a continuous variable. It is however true that some people appear to progress more rapidly than others and that some experience advanced liver disease at a younger age than others. • <i>How plausible and how common is multi-stage fibrosis stage progression within 1 year?</i> It is uncommon to progress more than one stage in fibrosis in a single year in MASLD/MASH. As discussed above, liver disease distribution (steatohepatitis and fibrosis) is heterogenous within the liver parenchyma and this can lead to substantial sampling variability with liver biopsy [43]. This study also showed that 35% (of 51 patients undergoing two transcutaneous biopsies to different parts of the liver on the same day) exhibited substantial variation in fibrosis stage, ranging from F3 to F0/1 (and that 41% had at least a 1 stage discordance between the biopsies). In my opinion very large changes in histologically assessed fibrosis stage over a short period of time are more likely to be due to sampling variation and disease heterogeneity.
Issue 10: Limited justification for selected input parameters, poor referencing, and lack of clarity regards how some input values are generated	It is not clear what the question is here. Happy to discuss and provide clinical perspective during the meeting.

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Issue 11: Appropriateness of modelled utility values and MASH resolution increment	<i>We would be grateful if you could answer the following questions related to this key issue:</i> • <i>Please comment on the face validity of the health state utility values from NICE guideline NG49 (presented in Table 17 of the EAG report and Table 37 of the company submission).</i> • <i>Please comment on the face validity of the health state utility values from the MAESTRO-NASH trial (presented in Table 38 of the company submission).</i> • <i>How would you expect health-related quality of life to change from progression between F3 and F4 compensated cirrhosis?</i> ○ <i>How do you expect this change to compare with the change in health-related quality of life from progression between F4 compensated cirrhosis and decompensated cirrhosis</i> • <i>To what extent would you expect an improvement in health-related quality of life from MASH resolution?</i> Some of this already answered above. Happy to discuss and provide clinical perspective during the meeting.
Issue 12: Health state costs and the interpretation of the Davidson study	Heath state costs are outside my scope of expertise but happy to discuss and provide clinical perspective during the meeting.
Issue 13: Differences in dosing of resmetirom between trial and clinical practice	It is not clear what the question is here. Happy to discuss and provide clinical perspective during the meeting.
Issue 14 Current and anticipated use of	<i>We would be grateful if you could answer the following questions related to this key issue:</i>

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GLP-1 antagonists in the UK	For people with MASH already having a GLP-1 agonist for overweight, obesity or T2DM, would you prescribe resmetirom alongside GLP-1 therapy? Resmetirom and GLP-1 agonists have different mechanisms of action. GLP-1 agonists like Semaglutide act predominantly through inducing weight loss (there are no GLP-1 receptors on hepatocytes) whereas Resmetirom is thought to have direct effects on hepatocyte metabolism. These mechanisms of action could be considered complementary. In terms of efficacy, both Semaglutide and Resmetirom have Phase 3 trial evidence of their ability to induce improvement of steatohepatitis and fibrosis. Recent data (secondary analysis of MAESTRO-NASH) does not suggest that efficacy of Resmetirom is adversely affected by prior stable treatment with GLP-1 agonists [45]. However, this does not necessarily imply that there would not be an added benefit of combination therapy in some patients. It should be noted that patients screened for MAESTRO-NASH were not excluded if they were on GLP-1 agonists but were required to be on stable doses of GLP-1 at trial entry. Semaglutide is reported as showing resolution of MASH without worsening of fibrosis in 62.9% of patients in the semaglutide group and in 34.3% in the placebo group (estimated difference, 28.7 percentage points; 95% confidence interval [CI], 21.1 to 36.2; $P < 0.001$) and a reduction in liver fibrosis without worsening of steatohepatitis was reported in 36.8% of the patients in the semaglutide group and in 22.4% of those in the placebo group after 96 weeks (estimated difference, 14.4 percentage points; 95% CI, 7.5 to 21.3; $P < 0.001$) [46]. The cases entering MAESTRO-NASH were therefore presumably amongst the “GLP-1 non-responders” as they had evidence of persistent active MASH with fibrosis despite established GLP-1 therapy and stable weight. Further research is required to prospectively address this point, but concomitant use of both agents may, theoretically, be beneficial for some patients. Relevant aspects to consider in practice are whether both agents should be started simultaneously or sequentially if the intent is to treat the liver disease, and in the event of combination therapy whether the same stopping rules should be applied to both agents given the potential for extra-hepatic benefits.
Issue 15: Deviations from HTA Lab recommendations	It is not clear what the question is here. Happy to discuss and provide clinical perspective during the meeting.
Issue 16 Extrahepatic treatment effects	It is not clear what the question is here. Happy to discuss and provide clinical perspective during the meeting.

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Are there any important issues that have been missed in EAR?	Not at this time.

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Part 3: Key messages

In up to 5 sentences, please summarise the key messages of your statement:

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Resmetirom for treating moderate to advanced liver fibrosis (without cirrhosis) caused by metabolic dysfunction-associated steatohepatitis [ID6529]

Single Technology Appraisal

Resmetirom for treating moderate to advanced liver fibrosis (without cirrhosis) caused by metabolic dysfunction-associated steatohepatitis [ID6529]

Clinical expert statement and technical engagement response form

Thank you for agreeing to comment on the external assessment report (EAR) for this evaluation, and for providing your views on this technology and its possible use in the NHS.

You can provide a unique perspective on the technology in the context of current clinical practice that is not typically available from the published literature. The EAR and stakeholder responses are used by the committee to help it make decisions at the committee meeting. Usually, only unresolved or uncertain key issues will be discussed at the meeting.

Information on completing this form

In [part 1](#) we are asking for your views on this technology. The text boxes will expand as you type.

In [part 2](#) we are asking for your views on key issues in the EAR that are likely to be discussed by the committee. The key issues in the EAR reflect the areas where there is uncertainty in the evidence, and because of this the cost effectiveness of the treatment is also uncertain. The key issues are summarised in section 1.3 of the executive summary at the beginning of the EAR. You are not expected to comment on every key issue but instead comment on the issues that are in your area of expertise.

A clinical perspective could help either:

- resolve any uncertainty that has been identified OR
- provide missing or additional information that could help committee reach a collaborative decision in the face of uncertainty that cannot be resolved.

Clinical expert statement

Resmetirom for treating moderate to advanced liver fibrosis (without cirrhosis) caused by metabolic dysfunction-associated steatohepatitis [ID6529]

In [part 3](#) we are asking you to provide 5 summary sentences on the main points contained in this document.

Please do not embed documents (such as a PDF) in a submission because this may lead to the information being mislaid or make the submission unreadable. Please type information directly into the form.

Do not include medical information about yourself or another person that could identify you or the other person.

We are committed to meeting the requirements of copyright legislation. If you want to include **journal articles** in your submission you must have copyright clearance for these articles. We can accept journal articles in NICE Docs. For copyright reasons, we will have to return forms that have attachments without reading them. You can resubmit your form without attachments, but it must be sent by the deadline.

Combine all comments from your organisation (if applicable) into 1 response. We cannot accept more than 1 set of comments from each organisation.

Please underline all confidential information, and separately highlight information that is submitted as 'confidential [CON]' in turquoise, and all information submitted as 'depersonalised data [DPD]' in pink. If confidential information is submitted, please also send a second version of your comments with that information redacted. See [Health technology evaluations: interim methods and process guide for the proportionate approach to technology appraisals](#) (section 3.2) for more information.

Please note, part 1 can be completed at any time. We advise that **part 2** is completed after the expert engagement teleconference (if you are attending or have attended). At this teleconference we will discuss some of the key issues, answer any specific questions you may have about the form, and explain the type of information the committee would find useful.

The deadline for your response is **5pm** on **<insert deadline>**. Please log in to your NICE Docs account to upload your completed form, as a Word document (not a PDF).

Thank you for your time.

Clinical expert statement

Resmetirom for treating moderate to advanced liver fibrosis (without cirrhosis) caused by metabolic dysfunction-associated steatohepatitis [ID6529]

We reserve the right to summarise and edit comments received during engagement, or not to publish them at all, if we consider the comments are too long, or publication would be unlawful or otherwise inappropriate.

Comments received during engagement are published in the interests of openness and transparency, and to promote understanding of how recommendations are developed. The comments are published as a record of the comments we received, and are not endorsed by NICE, its officers or advisory committees.

Clinical expert statement

Resmetirom for treating moderate to advanced liver fibrosis (without cirrhosis) caused by metabolic dysfunction-associated steatohepatitis [ID6529]

Part 1: Treating moderate to advanced liver fibrosis (without cirrhosis) caused by metabolic dysfunction-associated steatohepatitis and current treatment options

Table 1 About you, aim of treatment, place and use of technology, sources of evidence and equality

1. Your name	Dr Richard Aspinall
2. Name of organisation	NHS England
3. Job title or position	National Specialty Advisor and CRG Chair – Hepatobiliary & Pancreas
4. Are you (please tick all that apply)	☐ An employee or representative of a healthcare professional organisation that represents clinicians? ☒ A specialist in the treatment of people with moderate to advanced liver fibrosis (without cirrhosis) caused by metabolic dysfunction-associated steatohepatitis ? ☐ A specialist in the clinical evidence base for moderate to advanced liver fibrosis (without cirrhosis) caused by metabolic dysfunction-associated steatohepatitis or technology? ☐ Other (please specify):
5. Do you wish to agree with your nominating organisation's submission? (We would encourage you to complete this form even if you agree with your nominating organisation's submission)	☒ Yes, I agree with it ☐ No, I disagree with it ☐ I agree with some of it, but disagree with some of it ☐ Other (they did not submit one, I do not know if they submitted one etc.)
6. If you wrote the organisation submission and/or do not have anything to add, tick here. (If you tick this box, the rest of this form will be deleted after submission)	☐ Yes

Clinical expert statement

Resmetirom for treating moderate to advanced liver fibrosis (without cirrhosis) caused by metabolic dysfunction-associated steatohepatitis [ID6529]

7. Please disclose any past or current, direct or indirect links to, or funding from, the tobacco industry.	None.
8. What is the main aim of treatment for moderate to advanced liver fibrosis (without cirrhosis) caused by metabolic dysfunction-associated steatohepatitis? (For example, to stop progression, to cure the condition, or prevent progression or disability)	The main evidence-based aims are to reduce liver fibrosis and resolve inflammation. In the longer term, we would aim to see a reduction in clinical events (cirrhosis development, hepatic decompensation, death or liver transplantation) but data on these endpoints are not yet available for this technology.
9. What do you consider a clinically significant treatment response? (For example, MASH resolution, regression in liver fibrosis stage, or a reduction in disease activity by a certain amount)	Improvement in fibrosis staging or resolution of inflammation without worsening of fibrosis.
10. In your view, is there an unmet need for patients and healthcare professionals in moderate to advanced liver fibrosis (without cirrhosis) caused by metabolic dysfunction-associated steatohepatitis?	Yes. There are currently no licensed, effective pharmacological therapies for this group of patients.
11. How is moderate to advanced liver fibrosis (without cirrhosis) caused by metabolic dysfunction-associated steatohepatitis currently treated in the NHS? - Are any clinical guidelines used in the treatment of the condition, and if so, which? - Is the pathway of care well defined? Does it vary or are there differences of opinion between professionals across the NHS? (Please state if your experience is from outside England.) - What impact would the technology have on the current pathway of care?	Currently, most patients are managed using “lifestyle” interventions designed to tackle obesity such as weight loss through improved diet or increased physical activity. Some patients may have other characteristics that qualify them for bariatric surgery or incretin-based pharmacotherapies. However, these interventions are not currently NICE-approved for purely the treatment of MASLD/MASH. Clinical guidelines are available from a number of sources. The NICE NG49 guideline is now 10 years old and is in the process of being revised. The British Society of Gastroenterology and British Association for the Study of the Liver jointly published agreed quality standards for clinical management in 2022.

Clinical expert statement

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	The European Association for the Study of the Liver (EASL) have recently published revised guidelines (in association with EASD and EASO) that include the role of resmetirom in settings where it is licensed and available. With regards to pathways of care, serial publications have shown that large areas of England currently do not have clear community pathways for the diagnosis and staging of liver disease (most recently surveyed by Jarvis H et al <i>BJGP Open</i> 2025). In those areas with established pathways, many deploy a two-stage process, using an indirect liver fibrosis risk score (eg FIB-4, NAFLD Fibrosis Score) with a high negative predictive value to risk-stratify in the community. High risk patients would usually be seen in secondary care, whereas people with an indeterminate risk score would usually be offered a second fibrosis test such as transient elastography or Enhanced Liver Fibrosis (ELF) testing. Where results remain indeterminate or equivocal, liver biopsy may have been offered to selected patients for accurate staging or to allow consideration for clinical trial recruitment. Historically, the net result of these triages would have been to return most people with early-intermediate fibrosis to primary care, with only those having likely F3-F4 kept in secondary care. However, the potential availability of effective pharmacotherapies for MASLD/MASH with F2-F3 fibrosis would require a shift in emphasis with these grades of fibrosis requiring assessment for treatment.
12. Will the technology be used (or is it already used) in the same way as current care in NHS clinical practice? • How does healthcare resource use differ between the technology and current care? • In what clinical setting should the technology be used? (for example, primary or secondary care, specialist clinic)	As per the MAESTRO phase 3 clinical trial design and in keeping with the European authorisation for resmetirom, the technology should be provided in conjunction with support regarding appropriate diet and exercise. The availability of such support outside of clinical trial settings is variable and may need to become more formalised. However, wider NHS initiatives regarding the management of obesity and type 2 diabetes are likely to prove helpful.

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What investment is needed to introduce the technology? (for example, for facilities, equipment, or training)	Given the moves towards more non-invasive testing of fibrosis and access to the necessary tests, it is likely that evaluation for resmetirom and its initial prescription would take place in secondary care, under the supervision of a hepatology service. As per the broader NHS England submission, enabling access to the technology will require improvements in access to non-invasive fibrosis testing.
13. Do you expect the technology to provide clinically meaningful benefits compared with current care? - Do you expect the technology to increase length of life more than current care? - Do you expect the technology to increase health-related quality of life more than current care?	It is difficult to give a definitive answer regarding longevity. Current data is based on the trial endpoints. The MAESTRO programme has an extended data collection study which aims to gather data on clinical milestones. Given the strong associations between liver fibrosis and liver-related events (as well as all-cause mortality) one could speculate that reductions in liver fibrosis may lead to improved survival but we currently do not have this data. Similarly, HRQOL is known to be impaired in people living with MASLD and there are adverse impacts on economic status and work productivity with progression of liver disease. Data from the MAESTRO programme has shown improved QoL in people treated with resmetirom who met histological endpoints (Younossi ZM et al <i>Hepatology</i> 2025) but longer term data is awaited.
14. Are there any groups of people for whom the technology would be more or less effective (or appropriate) than the general population?	Data is not available on several groups as per the MAESTRO trial exclusions. I would also highlight the technology would not be appropriate (on current evidence) for people with cirrhosis (F4 liver fibrosis) or for those consuming excess alcohol.
15. Will the technology be easier or more difficult to use for patients or healthcare professionals than current care? Are there any practical implications for its use? (For example, any concomitant treatments needed, additional clinical requirements, factors affecting patient	Many patients will already be processed through MASLD clinical pathways and will also be receiving treatments for comorbidities. Given the potential scale of the eligible population, it will not be desirable or practical to rely on liver biopsy to routinely select patients for treatment nor to assess response. There will need to be some upscaling of non-invasive fibrosis testing.

Clinical expert statement

Resmetirom for treating moderate to advanced liver fibrosis (without cirrhosis) caused by metabolic dysfunction-associated steatohepatitis [ID6529]

acceptability or ease of use or additional tests or monitoring needed)	
16. Will any rules (informal or formal) be used to start or stop treatment with the technology? Do these include any additional testing?	Both the American Association for the Study of Liver Disease (AASLD) and the European Association for the Study of the Liver (EASL) have issued guidance based on non-invasive fibrosis tests. There are some subtle but important differences in the range of values advocated by the societies. The MASLD Special Interest Group of the British Association for the Study of the Liver (BASL) is developing guidance in this area.
17. Do you consider that the use of the technology will result in any substantial health-related benefits that are unlikely to be included in the quality-adjusted life year (QALY) calculation? Do the instruments that measure quality of life fully capture all the benefits of the technology or have some been missed? For example, the treatment regimen may be more easily administered (such as an oral tablet or home treatment) than current standard of care	Not applicable, given current lack of pharmacological therapy.
18. Do you consider the technology to be innovative in its potential to make a significant and substantial impact on health-related benefits and how might it improve the way that current need is met? - Is the technology a 'step-change' in the management of the condition? - Does the use of the technology address any particular unmet need of the patient population?	Resmetirom would be the first effective, licensed, disease-specific pharmacological therapy in this area. It would be particularly advantageous for people with F3 liver fibrosis who are at risk of progression to cirrhosis.
19. How do any side effects or adverse effects of the technology affect the management of the condition and the patient's quality of life?	In MAESTRO, resmetirom was overall well tolerated in terms of safety. Diarrhoea was reported more commonly with resmetirom (80 mg, 27.0%; 100 mg, 33.4%) compared with placebo (15.6%). There were no major differences among serious adverse events seen between resmetirom and placebo.

Clinical expert statement

Resmetirom for treating moderate to advanced liver fibrosis (without cirrhosis) caused by metabolic dysfunction-associated steatohepatitis [ID6529]

20. Do the clinical trials on the technology reflect current UK clinical practice? • If not, how could the results be extrapolated to the UK setting? • What, in your view, are the most important outcomes, and were they measured in the trials? • If surrogate outcome measures were used, do they adequately predict long-term clinical outcomes? • Are there any adverse effects that were not apparent in clinical trials but have come to light subsequently?	As per the MAESTRO trial exclusion criteria, there are certain groups who were excluded including significant comorbidities, recent changes in medications and poorly controlled type 2 diabetes mellitus. People with type 1 diabetes were excluded. The trial used surrogate endpoints but these are accepted as the current standards for evaluating potential therapies in MASLD. Longer term follow-up studies are in progress to gather data on “hard” clinical outcomes.
21. Are you aware of any relevant evidence that might not be found by a systematic review of the trial evidence?	No.
22. How do data on real-world experience compare with the trial data?	Emerging data are compatible with the trial.
23. NICE considers whether there are any equalities issues at each stage of an evaluation. Are there any potential equality issues that should be taken into account when considering this condition and this treatment? Please explain if you think any groups of people with this condition are particularly disadvantaged. Equality legislation includes people of a particular age, disability, gender reassignment, marriage and civil partnership, pregnancy and maternity, race, religion or belief, sex, and sexual orientation or people with any other shared characteristics. Please state if you think this evaluation could	Obesity and MASLD disproportionately affect people in deprived socioeconomic groups. There are potential weaknesses of some non-invasive liver fibrosis tests in certain age groups – particularly the under 35s and the over 65s. In the MAESTRO trial, women of childbearing potential were required to maintain two highly effective methods of contraception and so this may have discouraged some from participating.

Clinical expert statement

Resmetirom for treating moderate to advanced liver fibrosis (without cirrhosis) caused by metabolic dysfunction-associated steatohepatitis [ID6529]

- exclude any people for which this treatment is or will be licensed but who are protected by the equality legislation
- lead to recommendations that have a different impact on people protected by the equality legislation than on the wider population
- lead to recommendations that have an adverse impact on disabled people.

Please consider whether these issues are different from issues with current care and why.

More information on how NICE deals with equalities issues can be found in the [NICE equality scheme](#).

[Find more general information about the Equality Act and equalities issues here.](#)

Clinical expert statement

Resmetirom for treating moderate to advanced liver fibrosis (without cirrhosis) caused by metabolic dysfunction-associated steatohepatitis [ID6529]

Part 2: Technical engagement questions for clinical experts

We welcome your comments on the key issues below, but you may want to concentrate on issues that are in your field of expertise. If you think an issue that is important to clinicians or patients has been missed in the EAR, please also advise on this in the space provided at the end of this section.

The text boxes will expand as you type. Your responses to the following issues will be considered by the committee and may be summarised and presented in slides at the committee meeting.

For information: the professional organisation that nominated you has also been sent a technical engagement response form (a separate document) which asks for comments on each of the key issues that have been raised in the EAR. These will also be considered by the committee.

Table 2 Issues arising from technical engagement

Issue 1: The trial population does not match the population in scope.	<i>We would be grateful if you could answer the following questions related to this key issue:</i> <i>What diagnostic tools are used to identify people with MASH with liver fibrosis in clinical practice? Do you expect any changes to diagnostic tools or methods if resmetirom becomes available as a treatment option?</i> Currently, fibrosis assessment is a two-stage process with an initial triage using an indirect fibrosis risk score (FIB-4, NFS) with a high negative predictive value. People with an indeterminate risk score would be offered second line testing with either transient elastography or ELF. If the results remained equivocal, liver biopsy may be deployed but this is impractical for large numbers of people outside of a clinical trial setting. The availability of resmetirom would not change the type of testing used but it would require some expansion in capacity. <i>What are likely to be the appropriate criteria for identifying people eligible for resmetirom in clinical practice?</i> Exclusion of cirrhosis. Identification of F2-F3 liver fibrosis based on non-invasive testing.

Clinical expert statement

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	• <i>How does the patient population likely to be eligible for resmetirom in clinical practice differ from that in the MAESTRO-NASH trial?</i> Potentially more people with comorbidities and poorer diabetes control. Fewer certainties regarding appropriate dietary and exercise support. • <i>What are the implications of the differences between the appropriate criteria in clinical practice and the eligibility criteria of the MAESTRO-NASH trial for the generalisability of the trial data?</i> Trial criteria were broadly in line with clinical practice. There may need to be a greater focus on accurately assessing baseline alcohol intake in “real world” settings.
Issue 2: Reliance on Surrogate Endpoints	<i>We would be grateful if you could answer the following question related to this key issue:</i> • <i>Please comment on the plausibility and validity of MASH resolution and fibrosis stage as predictors of comorbid events, liver-related events and mortality.</i> Consistent data from longitudinal studies show the grade of liver fibrosis correlates with longer term liver-related outcomes as well as all-cause mortality. Data on MASH resolution is less strong but the open label extension of the MAESTRO programme is designed to study these questions. Data from other liver conditions have shown convincing links between histological improvements and reductions in liver-related events.
Issue 3: Differences between the ITT population and paired liver biopsy population	
Issue 4: Validation of the company model and programming complexity	

Clinical expert statement

Resmetirom for treating moderate to advanced liver fibrosis (without cirrhosis) caused by metabolic dysfunction-associated steatohepatitis [ID6529]

Issue 5: Response to treatment not captured by the current model structure	<i>We would be grateful if you could answer the following questions related to this key issue:</i> • <i>How are changes in fibrosis stage assessed in clinical practice?</i> Generally, fibrosis assessment is a two-stage process with an initial triage using an indirect fibrosis risk score (FIB-4, NFS) with a high negative predictive value. People with an indeterminate risk score would be offered second line testing with either transient elastography or ELF. If the results remained equivocal, liver biopsy may be deployed but this is impractical for large numbers of people outside of a clinical trial setting. The availability of resmetirom would not change the type of testing used but it would require some expansion in capacity. • <i>How do you anticipate resmetirom will be used in clinical practice?</i> I expect the initial patient selection and prescription will at least be supervised by secondary care hepatologists, perhaps utilising clinical nurse specialists. • <i>Do you anticipate that resmetirom will be used based on a response assessment? How do you anticipate this response assessment would work in practice?</i> ○ <i>Would it be based on non-invasive tests (NITs)? If so, please specify the NITs.</i> We are currently awaiting UK-specific guidance from BASL but the AASLD's October 2024 Updated MASLD Practice Guideline has proposed evaluating treatment response after 12 months using a combination of transient elastography and blood tests. Based on non-invasive criteria, a "traffic light" triage would classify patients as having no response, a beneficial response or an uncertain response (see Chen VL et al. <i>Hepatology</i> 2025). ○ <i>How frequently would these NITs be administered? As above, AASLD have advised safety assessments at 3, 6 and 12 months with a response evaluation at 12 months.</i> ○ <i>What decision criteria do you anticipate would be applied to inform treatment discontinuation decisions? As per the AASLD guidance above, this would be based on blood tests and non-invasive fibrosis testing such as transient elastography.</i>

Clinical expert statement

Resmetirom for treating moderate to advanced liver fibrosis (without cirrhosis) caused by metabolic dysfunction-associated steatohepatitis [ID6529]

Issue 6: Stopping rules and discontinuation of resmetirom treatment	<i>We would be grateful if you could answer the following questions related to this key issue:</i> • <i>Would it be appropriate to stop resmetirom treatment when fibrosis regresses without MASH resolution?</i> We currently lack data on longer term impact beyond the published trials. It would make sense to continue therapy pending updates from the long term MAESTRO programme. • <i>Is progression to F4 compensated cirrhosis more likely to reflect treatment failure or insufficient treatment?</i> I would suggest treatment failure but it is a very difficult question to answer for an individual patient. • <i>Would it be appropriate to stop resmetirom treatment when people progress to advanced liver disease including compensated cirrhosis?</i> In my opinion, yes. Resmetirom is currently contraindicated in decompensated cirrhosis. There are ongoing clinical trials to assess safety and efficacy in compensated cirrhosis.
Issue 7: Repeated application of transition probabilities and short-term trial follow-up	<i>We would be grateful if you could answer the following questions related to this key issue:</i> • <i>Please comment on the biological plausibility of the assumption that people have the same probability of resolving MASH throughout the entire time horizon</i> MASLD is a complex, multiorgan syndrome affecting a diverse range of people who have different comorbidities and metabolic risk factors. In addition, we know that rate of deposition and resolution of liver fibrosis differs between individuals. Consequently, there is likely to be considerable inter-individual variation. • <i>Please comment on the plausibility of the assumption that all people having resmetirom or standard of care (SoC) experience a continuous decline in weight (and BMI) throughout the entire time horizon.</i> For the reasons given above, there is likely to be considerable variation in individuals, particularly outside of clinical trial settings. We would expect some plateauing of weight loss over time. • <i>Please comment on the assumption that people having resmetirom experience a faster decline in weight than people receiving SoC.</i> MAESTRO trial data at week 52 showed minor reductions in weight across all groups including placebo.

Clinical expert statement

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Issue 8: Misinterpretation of Singh et al (2015)	
Issue 9: Natural history of MASH and face validity of model progression rates	<i>We would be grateful if you could answer the following questions related to this key issue:</i> • <i>How long does it typically take for people to progress by one or two liver fibrosis stage(s)?</i> A 2015 meta-analysis of paired liver biopsy studies suggested an average 7 year interval to progress from one stage to the next (Singh S et al. <i>Clin Gastro Hepatol</i> 2015). However, more advanced fibrosis may progress in a non-linear fashion. In patients with MASH and F3 fibrosis, 22% developed cirrhosis after a mean of 29 months (Sanyal A et al. <i>Hepatology</i> 2019). • <i>To what extent is progression between liver fibrosis stages heterogeneous?</i> There is considerable heterogeneity. The meta-analysis by Singh et al listed above found fibrosis only progressed in around 30% of paired biopsies but there was a small group of rapid fibrosers who progressed quickly. • <i>What factors are associated with more rapid progression?</i> Higher BMI, presence of type 2 diabetes, hypertension, elevated AST/ALT. • <i>Are some people ‘rapid progressors’, and can these people be identified in clinical practice?</i> Yes, as above. However, they cannot currently be easily identified beyond the clinical risk factors. • <i>How plausible and how common is multi-stage fibrosis stage progression within 1 year?</i> It is unusual but recognised.
Issue 10: Limited justification for selected input parameters, poor referencing, and lack of clarity regards	

Clinical expert statement

Resmetirom for treating moderate to advanced liver fibrosis (without cirrhosis) caused by metabolic dysfunction-associated steatohepatitis [ID6529]

how some input values are generated	
Issue 11: Appropriateness of modelled utility values and MASH resolution increment	<i>We would be grateful if you could answer the following questions related to this key issue:</i> • <i>Please comment on the face validity of the health state utility values from NICE guideline NG49 (presented in Table 17 of the EAG report and Table 37 of the company submission).</i> • <i>Please comment on the face validity of the health state utility values from the MAESTRO-NASH trial (presented in Table 38 of the company submission).</i> • <i>How would you expect health-related quality of life to change from progression between F3 and F4 compensated cirrhosis?</i> ○ <i>How do you expect this change to compare with the change in health-related quality of life from progression between F4 compensated cirrhosis and decompensated cirrhosis</i> We know that there is a step-change in impairment of quality of life when liver disease progresses to compensated cirrhosis and, particularly, to decompensation. There are additional impacts on household socioeconomic values, occupational aspects and a significant caregiver burden for close relatives. • <i>To what extent would you expect an improvement in health-related quality of life from MASH resolution?</i>
Issue 12: Health state costs and the interpretation of the Davidson study	
Issue 13: Differences in dosing of resmetirom between trial and clinical practice	
Issue 14 Current and anticipated use of GLP-1 antagonists in the UK	<i>We would be grateful if you could answer the following questions related to this key issue:</i> • <i>For people with MASH already having a GLP-1 agonist for overweight, obesity or T2DM, would you prescribe resmetirom alongside GLP-1 therapy?</i>

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Resmetirom for treating moderate to advanced liver fibrosis (without cirrhosis) caused by metabolic dysfunction-associated steatohepatitis [ID6529]

	Potentially, yes – although (as per the MAESTRO trial) the GLP-1 agonist dosage would need to have been stabilised for at least 24 weeks. MASLD is part of a complex disease with multiple potential therapeutic targets.
Issue 15: Deviations from HTA Lab recommendations	
Issue 16 Extrahepatic treatment effects	
Are there any important issues that have been missed in EAR?	

Clinical expert statement

Resmetirom for treating moderate to advanced liver fibrosis (without cirrhosis) caused by metabolic dysfunction-associated steatohepatitis [ID6529]

Part 3: Key messages

In up to 5 sentences, please summarise the key messages of your statement:

Click or tap here to enter text.

Click or tap here to enter text.

Click or tap here to enter text.

Click or tap here to enter text.

Click or tap here to enter text.

Thank you for your time.

Your privacy

The information that you provide on this form will be used to contact you about the topic above.

☐ **Please tick this box** if you would like to receive information about other NICE topics.

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Clinical expert statement

Resmetirom for treating moderate to advanced liver fibrosis (without cirrhosis) caused by metabolic dysfunction-associated steatohepatitis [ID6529]

Single Technology Appraisal

Resmetirom for treating moderate to advanced liver fibrosis (without cirrhosis) caused by metabolic dysfunction-associated steatohepatitis [ID6529]

Patient expert statement and technical engagement response form

Thank you for agreeing to give us your views on this treatment and its possible use in the NHS.

Your comments and feedback on the key issues below are really valued. You can provide a unique perspective on conditions and their treatment that is not typically available from other sources. The external assessment report (EAR) and stakeholder responses are used by the committee to help it make decisions at the committee meeting. Usually, only unresolved or uncertain key issues will be discussed at the meeting.

Information on completing this form

In [part 1](#) we are asking you about living with moderate to advanced liver fibrosis (without cirrhosis) caused by metabolic dysfunction-associated steatohepatitis or caring for a patient with moderate to advanced liver fibrosis (without cirrhosis) caused by metabolic dysfunction-associated steatohepatitis. The text boxes will expand as you type.

In [part 2](#) we are asking for your views on key issues in the EAR that are likely to be discussed by the committee. The key issues in the EAR reflect the areas where there is uncertainty in the evidence, and because of this the cost effectiveness of the treatment is also uncertain. The key issues are summarised in section 1.3 of the executive summary at the beginning of the EAR.

A patient perspective could help either:

- resolve any uncertainty that has been identified OR

Patient expert statement

Resmetirom for treating moderate to advanced liver fibrosis (without cirrhosis) caused by metabolic dysfunction-associated steatohepatitis [ID6529]

- provide missing or additional information that could help committee reach a collaborative decision in the face of uncertainty that cannot be resolved.

You are not expected to comment on every key issue but instead comment on the issues that are in your area of expertise. We have given guidance on the issues in which we expect this to be the case and advice on what you could consider when giving your response.

In [part 3](#) we are asking you to provide 5 summary sentences on the main points contained in this document.

Help with completing this form

If you have any questions or need help with completing this form please email the public involvement (PIP) team at pip@nice.org.uk (please include the ID number of your appraisal in any correspondence to the PIP team).

Please use this questionnaire with our [hints and tips for patient experts](#). You can also refer to the [Patient Organisation submission guide](#). **You do not have to answer every question** – they are prompts to guide you. There is also an opportunity to raise issues that are important to patients that you think have been missed and want to bring to the attention of the committee.

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Your response should not be longer than 15 pages.

Please note, **part 1** can be completed at any time. We advise that **part 2** is completed after the expert engagement teleconference (if you are attending or have attended). At this teleconference we will discuss some of the key issues, answer any specific questions you may have about the form, and explain the type of information the committee would find useful.

Patient expert statement

Resmetirom for treating moderate to advanced liver fibrosis (without cirrhosis) caused by metabolic dysfunction-associated steatohepatitis [ID6529]

Please log in to your NICE Docs account to upload your completed form, as a Word document (not a PDF).

Thank you for your time.

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Patient expert statement

Resmetirom for treating moderate to advanced liver fibrosis (without cirrhosis) caused by metabolic dysfunction-associated steatohepatitis [ID6529]

Part 1: Living with this condition or caring for a patient with moderate to advanced liver fibrosis (without cirrhosis) caused by metabolic dysfunction-associated steatohepatitis

Table 1 About you, moderate to advanced liver fibrosis (without cirrhosis) caused by metabolic dysfunction-associated steatohepatitis, current treatments and equality

1. Your name	Vanessa Hebditch
2. Are you (please tick all that apply)	☐ A patient with moderate to advanced liver fibrosis (without cirrhosis) caused by metabolic dysfunction-associated steatohepatitis? ☐ A patient with experience of the treatment being evaluated? ☐ A carer of a patient with moderate to advanced liver fibrosis (without cirrhosis) caused by metabolic dysfunction-associated steatohepatitis? ☒ A patient organisation employee or volunteer? ☐ Other (please specify):
3. Name of your nominating organisation	British Liver Trust
4. Has your nominating organisation provided a submission? (please tick all options that apply)	☐ No (please review all the questions and provide answers when possible) ☒ Yes, my nominating organisation has provided a submission ☐ I agree with it and do not wish to complete a patient expert statement ☒ Yes, I authored / was a contributor to my nominating organisations submission ☐ I agree with it and do not wish to complete this statement ☐ I agree with it and will be completing

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5. How did you gather the information included in your statement? (please tick all that apply)	☐ I am drawing from personal experience ☒ I have other relevant knowledge or experience (for example, I am drawing on others' experiences). Please specify what other experience: The British Liver Trust regularly supports and gathers insight from people with lived experience of MASLD/MASH. This includes gathering feedback and insight from our services (helpline, online forum with over 40,000 members, support groups); feedback when undertaking co-creation of patient materials, focus groups, patient experience survey with 606 MASH patients and 93 family members of MASH patients. This includes over 500 qualitative statements, Individual telephone interviews with patients, feedback forms from social media and on the website. I have not completed much of the first part of the form as it seemed repetition of the submission document. ☒ I have completed part 2 of the statement after attending the expert engagement teleconference. ☐ I have completed part 2 of the statement but was not able to attend the expert engagement teleconference ☐ I have not completed part 2 of the statement
6. What is your experience of living with moderate to advanced liver fibrosis (without cirrhosis) caused by metabolic dysfunction-associated steatohepatitis? If you are a carer (for someone with moderate to advanced liver fibrosis (without cirrhosis) caused by metabolic dysfunction-associated steatohepatitis) please share your experience of caring for them	See above
7a. What do you think of the current treatments and care available for moderate to advanced liver fibrosis	There are extremely limited treatment options. The main treatment option is lifestyle advice – changed to diet and exercise and losing weight.

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(without cirrhosis) caused by metabolic dysfunction-associated steatohepatitis on the NHS? 7b. How do your views on these current treatments compare to those of other people that you may be aware of?	
8. If there are disadvantages for patients of current NHS treatments for moderate to advanced liver fibrosis (without cirrhosis) caused by metabolic dysfunction-associated steatohepatitis (for example, how they are given or taken, side effects of treatment, and any others) please describe these	
9a. If there are advantages of resmetirom over current treatments on the NHS please describe these. For example, the effect on your quality of life, your ability to continue work, education, self-care, and care for others? 9b. If you have stated more than one advantage, which one(s) do you consider to be the most important, and why? 9c. Does resmetirom help to overcome or address any of the listed disadvantages of current treatment that you have described in question 8? If so, please describe these	There is a lack of treatment options currently available. Patients say “this feels like a direct answer to a problem that until now had only lifestyle and risk-factor management.” Patients also see it as potentially disease-modifying rather than just symptom control.
10. If there are disadvantages of resmetirom over current treatments on the NHS please describe these. For example, are there any risks with resmetirom? If you are concerned about any potential side effects you have heard about, please describe them and explain why	

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11. Are there any groups of patients who might benefit more from resmetirom or any who may benefit less? If so, please describe them and explain why Consider, for example, if patients also have other health conditions (for example overweight, obesity, type 2 diabetes) that affect the suitability of different treatments	
12. Are there any potential equality issues that should be taken into account when considering moderate to advanced liver fibrosis (without cirrhosis) caused by metabolic dysfunction-associated steatohepatitis and resmetirom? Please explain if you think any groups of people with this condition are particularly disadvantaged Equality legislation includes people of a particular age, disability, gender reassignment, marriage and civil partnership, pregnancy and maternity, race, religion or belief, sex, and sexual orientation or people with any other shared characteristics More information on how NICE deals with equalities issues can be found in the NICE equality scheme Find more general information about the Equality Act and equalities issues here.	
13. Are there any other issues that you would like the committee to consider?	Data from the Office for Health Improvement and Disparities highlights that premature mortality rates for fatty liver disease are now 6.4 times higher in the most deprived areas of England compared to the most affluent. It is also a disease that affects people when they are relatively young – often of working age.

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Part 2: Technical engagement questions for patient experts

Issues arising from technical engagement

The issues raised in the EAR are listed in [table 2](#). We welcome your comments on the issues, but you do not have to provide a response to every issue, such as the ones that are technical, that is, cost effectiveness-related issues. We have added a comment to the issues where we consider a patient perspective would be most relevant and valuable. If you think an issue that is important to patients has been missed in the EAR, please let us know in the space provided at the end of this section.

For information: the patient organisation that nominated you has also been sent a technical engagement response form (a separate document) which asks for comments on each of the key issues that have been raised in the EAR, the patient organisation responses will also be considered by the committee.

Table 2 Issues arising from technical engagement

Issue 1: The trial population does not match the population in scope.	Cannot comment
Issue 2: Reliance on Surrogate Endpoints	Cannot comment
Issue 3: Differences between the ITT population and paired liver biopsy population	Patients do not like liver biopsies and we don't think they should be required to determine treatment eligibility. There is a close association between MASH and fibrosis and non invasive technologies are able to indicate moderate-to-advanced fibrosis in the context of metabolic risk.
Issue 4: Validation of the company model	Cannot comment

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and programming complexity	
Issue 5: Response to treatment not captured by the current model structure	Cannot comment
Issue 6: Stopping rules and discontinuation of resmetirom treatment	Could the clinician repeat the non-invasive marker (i.e. ELF or Fibroscan) after 6 months or a year to see if treatment is working?
Issue 7: Repeated application of transition probabilities and short-term trial follow-up	Cannot comment
Issue 8: Misinterpretation of Singh et al (2015)	Cannot comment
Issue 9: Natural history of MASH and face validity of model progression rates	Clinicians better placed to answer
Issue 10: Limited justification for selected input	Cannot comment

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parameters, poor referencing, and lack of clarity regards how some input values are generated	
Issue 11: Appropriateness of modelled utility values and MASH resolution increment	From a patient perspective, the move from Fibrosis 3 to Fibrosis 4 represents a noticeable shift in day-to-day life. Some patients are often unaware of what stage they are at but when the stages are explained to them they can pinpoint when their lives started to change. Patients with earlier stage disease often report fluctuating fatigue, reduced stamina, and a need to pace themselves. However, many can still maintain work, family responsibilities, and social activities—albeit with increasing effort. When the disease progresses, people frequently describe a step-change in how they feel. Fatigue becomes more intrusive. Patients talk about “hitting a wall” earlier in the day, needing long rest periods, or being unable to complete tasks they previously managed. Many patients report being unable to carry out normal daily activities. Physical functioning also declines. Activities such as climbing stairs, carrying shopping, or walking at a normal pace become more difficult. People often describe feeling “slower” or “heavier,” even without visible swelling. Some patients report that their cognitive symptoms become more noticeable. Many carers, partners or family members describe increased forgetfulness, difficulty concentrating, or “brain fog,” which can affect confidence at work or in social settings. Patients when diagnosed often feel very frightened about their future.. Patients describe feeling as though they have “crossed a line,” with greater anxiety about liver failure, hospitalisation, or the need for a transplant. Social and family life is affected. People report withdrawing from social activities because they are too tired, worried about symptoms, or embarrassed by reduced stamina. Parents describe struggling to keep up with children; working-age adults often reduce hours or change roles. Patients often express that this stage feels like “losing ground”—not yet severely ill, but no longer able to live life on their own terms. Even without decompensation, the combination of physical limitations, cognitive changes, and emotional strain leads to a meaningful decline in quality of life. At the British Liver Trust we also often hear from carers who describe how they feel they have “lost their partner or loved one” and they are “no longer the same person”. Carers often struggle with families being affected

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	financially as people have to stop working or need time off due to hospital appointments, severe fatigue or “not being able to keep up with their job”. Even though the person with MASH may still appear outwardly well, carers frequently report that life becomes more structured around managing fatigue, monitoring symptoms and providing day-to-day support. Carers frequently report changes in family dynamics and often reduce their own social activities because the person they care for is too tired to participate or because they feel uncomfortable leaving them alone for long periods. For people living with MASH, the move from F3 to decompensated cirrhosis is often described as a dramatic and life-changing shift. While compensated cirrhosis already brings fatigue, reduced stamina and emotional strain, most people can still manage a degree of independence. Once decompensation occurs—through ascites, jaundice, variceal bleeding, or episodes of hepatic encephalopathy—quality of life typically deteriorates sharply. Tasks they previously managed with difficulty become impossible without help. Examples include needing assistance to get dressed because of weakness or abdominal swelling or being unable to walk far due to breathlessness or muscle wasting and having to rely on others for cooking, cleaning and shopping People frequently say they feel as though their body has “given up on them. Fatigue becomes overwhelming and constant. Patients describe sleeping for long periods but never feeling rested and being unable to stay awake during the day and feeling completely “drained” after even minimal activity This level of exhaustion often forces people to stop working entirely. Decompensation brings symptoms that are not only uncomfortable but frightening: • Ascites can cause pressure, severe discomfort, difficulty breathing and a sense of “carrying a heavy weight.” • Jaundice affects appearance and can lead to stigma or embarrassment. It can also cause nausea and general malaise, tiredness • Hepatic encephalopathy causes confusion, memory loss and personality changes that patients often find deeply distressing.

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	People at this stage have frequent hospital visits for fluid drainage, bleeding episodes or encephalopathy management. This disrupts family life, work, and social connections. Patients describe living with a constant fear of the next emergency. The toll on family members increases. The emotional toll is also profound. People commonly report that they are frightened of dying and some feel depressed and guilty about the burden placed on family members. Because of fatigue, symptoms and hospital visits, people often withdraw from social life. They may stop working, reduce contact with friends, and lose the ability to participate in family activities. People describe heartbreak at being unable to care for or play with their children or grandchildren. Resolution of the disease—meaning the inflammation and liver injury settle—would be expected to bring a meaningful and noticeable improvement in day-to-day quality of life. Many of the symptoms that people find most limiting are directly linked to active liver inflammation, fatigue, and the emotional burden of living with a progressive condition. When MASH resolves, patients often describe feeling as though “a weight has lifted.” Resolution of MASH would lead to a clear, meaningful and life-enhancing improvement in quality of life. People feel better physically, think more clearly, participate more fully in daily life, and experience a significant reduction in fear and uncertainty. Even when not all symptoms disappear, the shift from active disease to stability is often described as transformative.
Issue 12: Health state costs and the interpretation of the Davidson study	Cannot comment
Issue 13: Differences in dosing of resmetirom between trial and clinical practice	Cannot comment
Issue 14 Current and anticipated use of	Cannot comment

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GLP-1 antagonists in the UK	
Issue 15: Deviations from HTA Lab recommendations	Cannot comment
Issue 16 Extrahepatic treatment effects	Cannot comment
Are there any important issues that have been missed in EAR?	Cannot comment

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Part 3: Key messages

In up to 5 sentences, please summarise the key messages of your statement:

- Click or tap here to enter text.
- Click or tap here to enter text.
- Click or tap here to enter text.
- Click or tap here to enter text.
- Click or tap here to enter text.

Thank you for your time.

Your privacy

The information that you provide on this form will be used to contact you about the topic above.

☐ **Please tick this box** if you would like to receive information about other NICE topics.

For more information about how we process your personal data please see [NICE's privacy notice](#).

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Single Technology Appraisal

Resmetirom for treating moderate to advanced liver fibrosis (without cirrhosis) caused by metabolic dysfunction-associated steatohepatitis [ID6529]

Patient expert statement and technical engagement response form

Thank you for agreeing to give us your views on this treatment and its possible use in the NHS.

Your comments and feedback on the key issues below are really valued. You can provide a unique perspective on conditions and their treatment that is not typically available from other sources. The external assessment report (EAR) and stakeholder responses are used by the committee to help it make decisions at the committee meeting. Usually, only unresolved or uncertain key issues will be discussed at the meeting.

Information on completing this form

In [part 1](#) we are asking you about living with moderate to advanced liver fibrosis (without cirrhosis) caused by metabolic dysfunction-associated steatohepatitis or caring for a patient with moderate to advanced liver fibrosis (without cirrhosis) caused by metabolic dysfunction-associated steatohepatitis. The text boxes will expand as you type.

In [part 2](#) we are asking for your views on key issues in the EAR that are likely to be discussed by the committee. The key issues in the EAR reflect the areas where there is uncertainty in the evidence, and because of this the cost effectiveness of the treatment is also uncertain. The key issues are summarised in section 1.3 of the executive summary at the beginning of the EAR.

A patient perspective could help either:

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- resolve any uncertainty that has been identified OR
- provide missing or additional information that could help committee reach a collaborative decision in the face of uncertainty that cannot be resolved.

You are not expected to comment on every key issue but instead comment on the issues that are in your area of expertise. We have given guidance on the issues in which we expect this to be the case and advice on what you could consider when giving your response.

In [part 3](#) we are asking you to provide 5 summary sentences on the main points contained in this document.

Help with completing this form

If you have any questions or need help with completing this form please email the public involvement (PIP) team at pip@nice.org.uk (please include the ID number of your appraisal in any correspondence to the PIP team).

Please use this questionnaire with our [hints and tips for patient experts](#). You can also refer to the [Patient Organisation submission guide](#). **You do not have to answer every question** – they are prompts to guide you. There is also an opportunity to raise issues that are important to patients that you think have been missed and want to bring to the attention of the committee.

Please do not embed documents (such as a PDF) in a submission because this may lead to the information being mislaid or make the submission unreadable. Please type information directly into the form.

We are committed to meeting the requirements of copyright legislation. If you want to include **journal articles** in your submission you must have copyright clearance for these articles. We can accept journal articles in NICE Docs. For copyright reasons, we will have to return forms that have attachments without reading them. You can resubmit your form without attachments, but it must be sent by the deadline.

Your response should not be longer than 15 pages.

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Please note, **part 1** can be completed at any time. We advise that **part 2** is completed after the expert engagement teleconference (if you are attending or have attended). At this teleconference we will discuss some of the key issues, answer any specific questions you may have about the form, and explain the type of information the committee would find useful.

The deadline for your response is **5pm** on **<insert deadline>**. Please log in to your NICE Docs account to upload your completed form, as a Word document (not a PDF).

Thank you for your time.

We reserve the right to summarise and edit comments received during engagement, or not to publish them at all, if we consider the comments are too long, or publication would be unlawful or otherwise inappropriate.

Comments received during engagement are published in the interests of openness and transparency, and to promote understanding of how recommendations are developed. The comments are published as a record of the comments we received, and are not endorsed by NICE, its officers or advisory committees.

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Part 1: Living with this condition or caring for a patient with moderate to advanced liver fibrosis (without cirrhosis) caused by metabolic dysfunction-associated steatohepatitis

Table 1 About you, moderate to advanced liver fibrosis (without cirrhosis) caused by metabolic dysfunction-associated steatohepatitis, current treatments and equality

1. Your name	Sara Harding
2. Are you (please tick all that apply)	☐ A patient with moderate to advanced liver fibrosis (without cirrhosis) caused by metabolic dysfunction-associated steatohepatitis? ☐ A patient with experience of the treatment being evaluated? ☐ A carer of a patient with moderate to advanced liver fibrosis (without cirrhosis) caused by metabolic dysfunction-associated steatohepatitis? ☐ A patient organisation employee or volunteer? ☒ Other (please specify): A relative of a patient deceased by decompensated liver cirrhosis caused by metabolic dysfunction-associated steatohepatitis
3. Name of your nominating organisation	British Liver Trust
4. Has your nominating organisation provided a submission? (please tick all options that apply)	☐ No (please review all the questions and provide answers when possible) ☒ Yes, my nominating organisation has provided a submission ☐ I agree with it and do not wish to complete a patient expert statement ☐ Yes, I authored / was a contributor to my nominating organisations submission ☐ I agree with it and do not wish to complete this statement

Patient expert statement

	☒ I agree with it and will be completing
5. How did you gather the information included in your statement? (please tick all that apply)	☒ I am drawing from personal experience ☐ I have other relevant knowledge or experience (for example, I am drawing on others' experiences). Please specify what other experience: ☐ I have completed part 2 of the statement after attending the expert engagement teleconference ☐ I have completed part 2 of the statement but was not able to attend the expert engagement teleconference ☐ I have not completed part 2 of the statement
6. What is your experience of living with moderate to advanced liver fibrosis (without cirrhosis) caused by metabolic dysfunction-associated steatohepatitis? If you are a carer (for someone with moderate to advanced liver fibrosis (without cirrhosis) caused by metabolic dysfunction-associated steatohepatitis) please share your experience of caring for them	We only learnt of my dad's diagnosis of end stage cirrhosis four months before he passed away and as such unable to provide any insight living with moderate to advanced liver fibrosis.
7a. What do you think of the current treatments and care available for moderate to advanced liver fibrosis (without cirrhosis) caused by metabolic dysfunction-associated steatohepatitis on the NHS? 7b. How do your views on these current treatments compare to those of other people that you may be aware of?	My understanding from volunteering with the British Liver Trust is that the current treatments are lifestyle led heavily reliant upon diet and exercise. From personal experience my dad who was told he had a fatty liver for over a decade was routinely told to not to worry about it as he had a healthy diet and lifestyle. If my dad had received an earlier diagnosis this treatment could have potentially saved his life. As such it would have prevented his suffering, stopped numerous hospital admissions, ICU stay, stress of a transplant assessment and ultimately his untimely death.

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8. If there are disadvantages for patients of current NHS treatments for moderate to advanced liver fibrosis (without cirrhosis) caused by metabolic dysfunction-associated steatohepatitis (for example, how they are given or taken, side effects of treatment, and any others) please describe these	From my personal experience there is a lack of knowledge at a local level for patients living with a liver condition, its only when they are under the care of a specialist team such as liver nurses or consultant that appropriate support is provided. This is worrying given the nature of liver disease being asymptomatic in its earliest stages – the stages in which the early intervention is must key.
9a. If there are advantages of resmetirom over current treatments on the NHS please describe these. For example, the effect on your quality of life, your ability to continue work, education, self-care, and care for others? 9b. If you have stated more than one advantage, which one(s) do you consider to be the most important, and why? 9c. Does resmetirom help to overcome or address any of the listed disadvantages of current treatment that you have described in question 8? If so, please describe these	First treatment of its kind and as such could change the landscape of how patients treated, literally give them a lifeline and stop their illness progressing like my dads did. If left undiagnosed, untreated lives will be lost just as my dads was.
10. If there are disadvantages of resmetirom over current treatments on the NHS please describe these. For example, are there any risks with resmetirom? If you are concerned about any potential side effects you have heard about, please describe them and explain why	
11. Are there any groups of patients who might benefit more from resmetirom or any who may benefit less? If so, please describe them and explain why	

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Consider, for example, if patients also have other health conditions (for example overweight, obesity, type 2 diabetes) that affect the suitability of different treatments	
12. Are there any potential equality issues that should be taken into account when considering moderate to advanced liver fibrosis (without cirrhosis) caused by metabolic dysfunction-associated steatohepatitis and resmetirom? Please explain if you think any groups of people with this condition are particularly disadvantaged Equality legislation includes people of a particular age, disability, gender reassignment, marriage and civil partnership, pregnancy and maternity, race, religion or belief, sex, and sexual orientation or people with any other shared characteristics More information on how NICE deals with equalities issues can be found in the NICE equality scheme Find more general information about the Equality Act and equalities issues here.	
13. Are there any other issues that you would like the committee to consider?	St Helens where my dad lived has the highest rate of liver disease deaths in England (43.5 per 100,000) and the second highest rate of deaths from fatty liver disease/MASLD.

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Part 2: Technical engagement questions for patient experts

Issues arising from technical engagement

The issues raised in the EAR are listed in [table 2](#). We welcome your comments on the issues, but you do not have to provide a response to every issue, such as the ones that are technical, that is, cost effectiveness-related issues. We have added a comment to the issues where we consider a patient perspective would be most relevant and valuable. If you think an issue that is important to patients has been missed in the EAR, please let us know in the space provided at the end of this section.

For information: the patient organisation that nominated you has also been sent a technical engagement response form (a separate document) which asks for comments on each of the key issues that have been raised in the EAR, the patient organisation responses will also be considered by the committee.

Table 2 Issues arising from technical engagement

Issue 1: The trial population does not match the population in scope.	Cannot comment
Issue 2: Reliance on Surrogate Endpoints	Cannot comment
Issue 3: Differences between the ITT population and paired liver biopsy population	Cannot Comment
Issue 4: Validation of the company model	Cannot Comment

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and programming complexity	
Issue 5: Response to treatment not captured by the current model structure	Cannot comment
Issue 6: Stopping rules and discontinuation of resmetirom treatment	Cannot Comment
Issue 7: Repeated application of transition probabilities and short-term trial follow-up	Cannot comment
Issue 8: Misinterpretation of Singh et al (2015)	Cannot comment
Issue 9: Natural history of MASH and face validity of model progression rates	Cannot comment
Issue 10: Limited justification for selected input	Cannot comment

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parameters, poor referencing, and lack of clarity regards how some input values are generated	
Issue 11: Appropriateness of modelled utility values and MASH resolution increment	This is my dads story and what happens if MASH is left untreated. My dad Ste was diagnosed with MASLD in January 2024 , and decompensated cirrhosis in March 2024 and given a 50 percent chance of surviving a year, he died four months later at 62 years of age. He was our everything, had a problem call dad, unsure of something call dad, need something fixing call dad. He wasn't a drinker, but he was type two diabetic for over twenty years but this was well controlled with diet and he led a healthy lifestyle loving cycling and walks in the Lakes. Dad was told for years by his GP practice within his appointments that he had a fatty liver but not to worry as he was living a healthy lifestyle, he last had a routine scan on his liver in 2016. He had a history of deranged LFTs but was never referred or a second opinion given on his liver health. In April 2023 he was feeling really lethargic which his doctors thought was an iron deficiency and prescribed tablets. By September Dad was quite withdrawn, forgetful, slurring his words, and kept going back to bed. The doctors were doing lots of tests and thought it might be something neurological, but still weren't looking at his liver.

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	By December my dad was like a zombie and I thought could it be depression as he was really not himself. If only we had known then that they were mild HE episodes and signs of how poorly he actually was. In January 2024 he went into hospital with a painful hernia and without that I don't think they would ever have found the MASLD. He was diagnosed with cirrhosis in March and as soon as I heard that word I went onto the British Liver Trust's website. The doctors said it might be compensated – I asked if they were sure it wasn't decompensated due to dad's symptoms. They came back and agreed and my dad was given a 50 per cent mortality within 12 months. We were devastated and in utter shock. Upon diagnosis myself and my dad's wife agreed that she would care for dad's everyday needs and I would look after the medical side – attending appointments with them, asking questions to the doctors, researching what we needed to do to get dad a transplant. I had a four-month-old baby at the time and wasn't getting much sleep, so all I'd do at night was research. The 'Questions to ask your consultant' page on the British Liver Trust website became my Bible. This research equipped me to have quality conversations and ask questions to his consultant be proactive in this fight for dad's life. I told the consultant that my dad had had these HE episodes since at least November and he asked if I was from a medical background. I told him I wasn't but had done a lot of reading on the British Liver Trust's website. Dad was fast tracked to a consultant and put under the liver team at our local hospital who were amazing. "You do know you're dying, don't you?" the consultant said to my dad when we first saw him in April 2024. I wanted to know what we could do to help, and the consultant said at least 10,000 steps a day to get dad fit enough for the transplant assessment. That was the goal, to be fit

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	enough for a liver transplant in Leeds. He was also given Lactulose and Rifaximin to help manage his HE episodes and also put on insulin to give him a good shot at a transplant. Dad smashed his transplant assessment, looked fitter and brighter than he had for weeks. The transplant team were due to talk about him at the next MDT meeting and discuss listing him but lesions were found on dad's liver so he needed a scan to rule anything out. He had to wait for a scan but in the days weeks following his assessment dad's health started to dip and we noticed the HE symptoms creeping back in. We knew it was a race against time for the transplant. On the Monday morning of 1st July we called an ambulance because of how dad was presenting and were worried he could go into a coma due to the HE. The same Monday he was due to go to Leeds for a scan to rule out anything sinister with the lesions. He kept having fits and the consultant was worried they were seizures so they did a CCG. It didn't show anything in his brain, so they monitored him for 24 hours and again nothing showed up, so it had to be HE. The consultant said he'd never seen it so bad. HE took everything from my dad. My dad was put in an induced coma for a few days and it took two weeks for him to get out of ICU. There were signs of improvement when he went onto a ward and we got a private physio in to work with him because he couldn't have a transplant unless he was walking the transplant team had advised. He fought and fought but dad wasn't improving. I pleaded with the consultant saying: "He's dying but give him a chance with a transplant even if he dies while you're trying". The consultant explained dad wouldn't make it through the operation and that he couldn't do anything further but gave us credit as a family for fighting so hard for him. He died 31st July 2024.

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	HE in decompensated cirrhosis took everything from my dad. In his last year of life he was a shadow of himself, he was unable to hold a conversation, drive, dress himself and on some days unable to recognise who I was. His wife became his full-time carer as she was determined he wouldn't lose his dignity as well as his independence. She didn't want carers coming into their home, strangers seeing dad at his most vulnerable unable to wash himself, dress himself or use the bathroom. It became unsafe for dad to sleep upstairs as he was at risk of falling (on the better days when he could stand) and so we bought a bed for downstairs and him and his wife slept together downstairs as she couldn't leave his side as he may fall out of bed and needed help going to the toilet several times throughout the night. Some nights she carried him across the room to his commode. In the mornings she would wash him downstairs with a baby bath and sponge as he was unable to walk upstairs and unable to wash himself. She would hold his straw and drink to his mouth and feed him as he could not feed himself. She had no experience of caring and no idea the strain and impact this would have on her. Seeing her prior fit and able, hands-on husband decline before her eyes was torture. She wasn't able to leave dad alone and so I would come and sit with dad whilst she went to get shopping or pick up his medication. I would try to help dad with flash cards to prompt his memory. It was like we lost dad before we lost him. Looking back its heartbreaking as he knew he was losing himself and no one should have to suffer like he did. I would drive him to appointments, slumped in the passenger seat, unable to keep his eyes open, unable to fasten his own seat belt and sit down unaided. This was a man who loved rally driving in his younger years, was happiest behind the steering wheel of his newest car but now couldn't sit safely in a passenger seat.

Patient expert statement

Resmetirom for treating moderate to advanced liver fibrosis (without cirrhosis) caused by metabolic dysfunction-associated steatohepatitis [ID6529]

	As a family we were given no support upon diagnosis other than a leaflet with the number for our local team that went straight through to a voicemail and you would receive a call back within two days. Not ideal when you are living with liver disease and you need immediate advice. NHS 111 and paramedics had no knowledge of HE and couldn't help. Had I not googled MASLD and discovered the British Liver Trust we wouldn't have any information about Dad's illness. There is simply no other help or advice available for families who have been told their loved one is terminally ill with MASLD and we had to just get on with it and learn with the support of British Liver Trust. No family should find themselves in this awful situation. A situation where they're googling to find out if what they're doing for their loved one is all they can do, where they're learning how to be a carer for this illness from a website and second guessing themselves at every turn. This drug would prevent this situation for many families who suddenly find themselves thrust into the role of carer with nothing but a leaflet and an answering machine for support. This ordeal has taken a huge toll on our mental health as a family. I'd spend countless nights researching Dad's illness whilst caring for a young baby, I spent endless hours in the hospital watching my dad suffer and still to this day wonder why my dad was failed so badly. I'm not the same person that I was with before dad died, my life has been changed forever. I will never be the same wife, mother, sister that I was before due to the trauma we have lived through. My dad's widow is now left to live a life without him, all their plans for the future and life as they knew it gone.

Patient expert statement

Resmetirom for treating moderate to advanced liver fibrosis (without cirrhosis) caused by metabolic dysfunction-associated steatohepatitis [ID6529]

	Not only faced with a mental and emotional toll of dad's illness he had numerous hospital admissions and length stays that we needed to support. As a family we drove to the hospital twice a day for months to ensure he was never alone at visiting. In the last month of his life his wife stayed at the hospital 24/7. It was only on the day dad died we were told that as he was palliative we qualified for free parking and discount at the hospital canteen. He died hours later. As a family we were able to fund the costs of parking, transport to and from the hospitals, meals from the canteen but not all families are in this position. Both my sister and I had to take unpaid leave from work to support dad and our family at this time. In total I took 12 months off from working from dad's diagnosis, his death four months later and then me feeling able to go back to work following weekly counselling to support my return to work. This treatment is needed as there is no cure for liver disease, the only option being for end stage like my dada a transplant. However, bearing in mind you must be poorly enough to warrant the transplant but well enough to make it through the surgery. Transplants are costly, complex and ultimately there are not enough livers available for each patient. Transplant care isn't just the surgeon and what happens on the day but the assessments, the clinic visits, the quarterly blood check-ups, the back and forth to one of the specialist liver centres in the country ours of which was over a two hour round trip from our house. How are families expected to travel back and forth when their loved ones are ill and under such mental strain. This is a preventable condition. Both my sister and I had attended the British Liver Trusts Love your Liver Roadshow in the November after our dads death. Their roadshows offer liver fibroscans to identify potential damage as 9 in 10 cases are preventable. We both has scans which showed signs of fatty liver and stiffness. A year later we have both reversed our fatty liver and our scans are showing normal and level stiffness has significantly reduced by adapting our lifestyle slightly, cutting down on chocolate and doing more exercise. However, we were only captured as we attended the Roadshow. If we hadn't, we wouldn't have made those changes, we did not have the typical contributors of MASH other than our

Patient expert statement

Resmetirom for treating moderate to advanced liver fibrosis (without cirrhosis) caused by metabolic dysfunction-associated steatohepatitis [ID6529]

	genetics and dad's history. If left ours would have progressed and we know only too well the heartache this brings. This treatment could help others at later stage and help prevent progression. We were fortunate, we were scanned and were able to make changes. But unfortunately for us and for Dad his diagnosis was just too late for treatment but that doesn't have to be the case. All that pain, loss and suffering could be prevented.
Issue 12: Health state costs and the interpretation of the Davidson study	Cannot comment
Issue 13: Differences in dosing of resmetirom between trial and clinical practice	Cannot comment
Issue 14 Current and anticipated use of GLP-1 antagonists in the UK	Cannot comment
Issue 15: Deviations from HTA Lab recommendations	Cannot comment
Issue 16 Extrahepatic treatment effects	Cannot comment
Are there any important issues that	Cannot comment

Patient expert statement

have been missed in EAR?	

Patient expert statement

Resmetirom for treating moderate to advanced liver fibrosis (without cirrhosis) caused by metabolic dysfunction-associated steatohepatitis [ID6529]

Part 3: Key messages

In up to 5 sentences, please summarise the key messages of your statement:

- This medicine could reduce mortality and save lives. My dad was just 62 years of age and had everything to live for
- Quality of life. My dad could no longer drive, a thing he loved, care for himself and at times recognise his family.
- Prevent HE and other complications – pain and suffering to the individual that could be prevented
- The toll this illness takes on families is horrendous with little to no support for families
- There is a severe lack of knowledge of MASLD and HE within the NHS, specialist care is needed and often is received too late

Thank you for your time.

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Patient expert statement

Resmetirom for treating moderate to advanced liver fibrosis (without cirrhosis) caused by metabolic dysfunction-associated steatohepatitis [ID6529]

Single Technology Appraisal

Resmetirom for treating moderate to advanced liver fibrosis (without cirrhosis) caused by metabolic dysfunction-associated steatohepatitis [ID6529]

Technical engagement response form

As a stakeholder you have been invited to comment on the External Assessment Report (EAR) for this evaluation.

Your comments and feedback on the key issues below are really valued. The EAR and stakeholders' responses are used by the committee to help it make decisions at the committee meeting. Usually, only unresolved or uncertain key issues will be discussed at the meeting.

Information on completing this form

We are asking for your views on key issues in the EAR that are likely to be discussed by the committee. The key issues in the EAR reflect the areas where there is uncertainty in the evidence, and because of this the cost effectiveness of the treatment is also uncertain. The key issues are summarised in the executive summary at the beginning of the EAR.

You are not expected to comment on every key issue but instead comment on the issues that are in your area of expertise.

If you would like to comment on issues in the EAR that have not been identified as key issues, you can do so in the 'Additional issues' section.

If you are the company involved in this evaluation, please complete the 'Summary of changes to the company's cost-effectiveness estimates(s)' section if your response includes changes to your cost-effectiveness evidence.

Technical engagement response form

Resmetirom for treating moderate to advanced liver fibrosis (without cirrhosis) caused by metabolic dysfunction-associated steatohepatitis [ID6529]

Please do not embed documents (such as PDFs or tables) because this may lead to the information being mislaid or make the response unreadable. Please type information directly into the form.

Do not include medical information about yourself or another person that could identify you or the other person.

We are committed to meeting the requirements of copyright legislation. If you want to include journal articles in your submission you must have copyright clearance for these articles. We can accept journal articles in NICE Docs. For copyright reasons, we will have to return forms that have attachments without reading them. You can resubmit your form without attachments, but it must be sent by the deadline.

Combine all comments from your organisation (if applicable) into 1 response. We cannot accept more than 1 set of comments from each organisation.

Please underline all confidential information, and separately highlight information that is submitted as 'confidential [CON]' in turquoise, and all information submitted as 'depersonalised data [DPD]' in pink. If confidential information is submitted, please also send a second version of your comments with that information redacted. See [Health technology evaluations: interim methods and process guide for the proportionate approach to technology appraisals](#) (section 3.2) for more information.

The deadline for comments is **5pm** on  **<insert deadline>**. Please log in to your NICE Docs account to upload your completed form, as a Word document (not a PDF).

Thank you for your time.

We reserve the right to summarise and edit comments received during engagement, or not to publish them at all, if we consider the comments are too long, or publication would be unlawful or otherwise inappropriate.

Comments received during engagement are published in the interests of openness and transparency, and to promote understanding of how recommendations are developed. The comments are published as a record of the comments we received, and are not endorsed by NICE, its officers or advisory committees.

Technical engagement response form

Resmetirom for treating moderate to advanced liver fibrosis (without cirrhosis) caused by metabolic dysfunction-associated steatohepatitis [ID6529]

About you

Table 1 About you

Your name	[REDACTED]
Organisation name: stakeholder or respondent (if you are responding as an individual rather than a registered stakeholder, please leave blank)	Chair, BSG/BASL MASLD Special Interest Group
Disclosure Please disclose any funding received from the company bringing the treatment to NICE for evaluation or from any of the comparator treatment companies in the last 12 months [Relevant companies are listed in the appraisal stakeholder list.] Please state: - the name of the company - the amount - the purpose of funding including whether it related to a product mentioned in the stakeholder list - whether it is ongoing or has ceased.	[REDACTED] [name of nominator in 'Your name' above]: Madrigal: c. £2000 for speaker fees and advisory board meeting in 2025 related to resmetirom. No further consultancy/ad board or speaker engagements booked or planned NovoNordisk: c. £500 consultancy 2025. No further consultancy/ad board or speaker engagements booked or planned. BASL: Madrigal Pharmaceuticals (company) – BASL received £38,600 in sponsorship funding towards their annual conference and a MASLD special interest group symposium in 2025. No signed contracts in place for 2026. Novo Nordisk Ltd (comparator) – BASL received £48,000 in sponsorship funding through a Partnership agreement towards their annual meeting and other educational events in 2025. N signed contracts in place for 2026.
Please disclose any past or current, direct or indirect links to, or funding from, the tobacco industry	Nil

Technical engagement response form

Resmetirom for treating moderate to advanced liver fibrosis (without cirrhosis) caused by metabolic dysfunction-associated steatohepatitis [ID6529]

Key issues for engagement

All: Please use the table below to respond to the key issues raised in the EAR.

Table 2 Key issues

Key issue	Does this response contain new evidence, data or analyses?	Response
Issue 1: The trial population does not match the population in scope.	No	In practice, the majority of patients with a diagnosis of MASLD/MASH and moderate to advanced liver fibrosis will have ≥ 3 cardiometabolic risk factors (e.g. overweight/obese, hypertension (or on treatment), dyslipidaemia (or on treatment), type 2 diabetes or impaired glucose tolerance) as these risk factors are associated with more advanced liver disease severity.
Issue 2: Reliance on Surrogate Endpoints	No	The lack of data on hard clinical endpoints to date is acknowledged, but severity of liver fibrosis is a strong predictor of liver-related and all cause mortality. It is not yet known whether treatment to reduce fibrosis stage will translate to reduced harm. UK clinical consensus recommendations from the BASL MASL SIG (manuscript in revision with Lancet Gastroenterology and Hepatology) suggests: MASH is a histological diagnosis Fibrosis staging F0-F4 is an ordinal histological classification, but non-invasive tests can be used to estimate fibrosis stage

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		3. Pragmatically, "at risk MASH" can be expected to be present in people with MASLD who have elevated fibrosis markers 4. A diagnosis of MASLD and non-invasive markers consistent with clinically significant fibrosis but not cirrhosis can be used to identify a population likely to have stage F2-3 fibrosis 5. Where non-invasive markers of fibrosis and/or imaging are equivocal, liver biopsy can be used 6. If a label does not specify histology, patients should not have to undergo biopsy solely to determine eligibility for treatment 7. If a label specifies histological MASH, then a historic biopsy is sufficient providing there is non-invasive evidence of persistent steatosis and fibrosis at the time of treatment 8. All patients considered for treatment should have had a minimum of a two-tier, non-invasive assessment of fibrosis in keeping with current guidance (e.g. FIB-4 followed by VCTE or ELF) 9. Where liver biopsy is not used, treatment eligibility should be based on at least two independent and concordant NITs

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		indicative of advanced fibrosis (in absence of evidence of cirrhosis) 10. Eligibility should be based on NITs performed within 6-months of starting therapy 11. Eligibility with NITs may be reassessed at a clinically-appropriate interval 12. Prescribers should individualise treatment based on clinical factors but specific histological and NIT cut-offs should be used to determine minimum thresholds for eligibility 13. Treatment should not be considered where liver stiffness <10kPa, unless histological assessment provides an indication for therapy 14. Where the label states F2-F3 fibrosis, treatment should not be prescribed in people with evidence of cirrhosis
Issue 3: Differences between the ITT population and paired liver biopsy population	Yes/No	Please provide your response to this key issue, including any new evidence, data or analyses

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Issue 4: Validation of the company model and programming complexity	Yes/No	Please provide your response to this key issue, including any new evidence, data or analyses
Issue 5: Response to treatment not captured by the current model structure	Yes/No	UK clinical consensus recommendations from the BASL MASL SIG (manuscript in revision with Lancet Gastroenterology and Hepatology) suggests: 1. Further assessment should occur at 12 months and annually 2. LSM should be part of regular patient monitoring every 12 months 3. Hepatological response to a medication should be assessed after a minimum of 12 months, with the first time point considered to be the day of dose optimisation (i.e. reaching recommended dose for MASLD treatment, if escalation is required). 4. Response can be assessed with non-invasive markers of fibrosis 5. A verified or repeated $\geq 30\%$ decrease in liver stiffness would indicate response to therapy 6. A verified or repeated $\geq 30\%$ increase in liver stiffness would indicate non-response to therapy

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		7. Non-invasive markers of fibrosis should be repeated before determining non-response 8. Evidence indicating lack of progression of liver fibrosis may be considered response to therapy 9. In those patients with histology at baseline, liver biopsy can be considered to determine response or non-response 10. Histologically, response may be defined as resolution of steatohepatitis without worsening of fibrosis or improvement in fibrosis without worsening of steatohepatitis 11. Histologically, progression of liver fibrosis (increase in fibrosis stage) is considered non-response to treatment 12. Progression to cirrhosis should be excluded at annual review 13. Non-response can be determined if blood tests and/or imaging suggest progression to cirrhosis (assuming the patient does not have cirrhosis at baseline)

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Issue 6: Stopping rules and discontinuation of resmetirom treatment	No	In addition to the statements from the MASL SIG, above, UK clinical consensus recommendations from the BASL MASL SIG (manuscript in revision with Lancet Gastroenterology and Hepatology) suggests: <i>1. Discontinuation of treatment should be considered in those with non-response to therapy</i> <i>2. Patients' comorbidities and functional status should be considered when considering treatment discontinuation</i> <i>3. Treatment should be discontinued in the event of a probable or definite drug-induced liver injury to the agent</i> <i>4. Treatment should be discontinued in the event of development of hepatic decompensation, HCC, or evidence of clinically significant portal hypertension</i>
Issue 7: Repeated application of transition probabilities and short-term trial follow-up	Yes/No	Please provide your response to this key issue, including any new evidence, data or analyses
Issue 8: Misinterpretation of Singh et al (2015)	Yes/No	Please provide your response to this key issue, including any new evidence, data or analyses

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Issue 9: Natural history of MASH and face validity of model progression rates	Yes/No	Please provide your response to this key issue, including any new evidence, data or analyses
Issue 10: Limited justification for selected input parameters, poor referencing, and lack of clarity regards how some input values are generated	Yes/No	Please provide your response to this key issue, including any new evidence, data or analyses
Issue 11: Appropriateness of modelled utility values and MASH resolution increment	Yes/No	Please provide your response to this key issue, including any new evidence, data or analyses
Issue 12: Health state costs and the interpretation of the Davidson study	Yes/No	Please provide your response to this key issue, including any new evidence, data or analyses

Technical engagement response form

Additional issues

All: Please use the table below to respond to additional issues in the EAR that have not been identified as key issues. Please do **not** use this table to repeat issues or comments that have been raised at an earlier point in this evaluation (for example, at the clarification stage).

Feedback above is included, where relevant, from a Delphi exercise to collate expert clinical opinion for use of MASH-targeted therapies. It represents new data on clinical opinion, but not new primary data.

Technical engagement response form

Resmetirom for treating moderate to advanced liver fibrosis (without cirrhosis) caused by metabolic dysfunction-associated steatohepatitis [ID6529]

Table 3 Additional issues from the EAR

Issue from the EAR	Relevant section(s) and/or page(s)	Does this response contain new evidence, data or analyses?	Response
Issue 13: Differences in dosing of resmetirom between trial and clinical practice	1.4; 2.3.2; 4.2.4	Yes/No	Please include your response, including any new evidence, data or analyses, and a description of why you think this is an important issue for decision making
Issue 14 Current and anticipated use of GLP-1 antagonists in the UK	1.4; 2.3.3; 3.2.2.1; 4.2.4	Yes/No	Please include your response, including any new evidence, data or analyses, and a description of why you think this is an important issue for decision making
Issue 15: Deviations from HTA Lab recommendations	1.4; 4.1.3.1	Yes/No	Please include your response, including any new evidence, data or analyses, and a description of why you think this is an important issue for decision making
Issue 16 Extrahepatic treatment effects	1.4; 4.2.5.3	Yes/No	Please include your response, including any new evidence, data or analyses, and a description of why you think this is an important issue for decision making

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Resmetirom for treating moderate to advanced liver fibrosis (without cirrhosis) caused by metabolic dysfunction-associated steatohepatitis [ID6529]

EAG ADDENDUM

Review of the company's response to Technical Engagement: Resmetirom for treating moderate to advanced liver fibrosis (without cirrhosis) caused by metabolic dysfunction-associated steatohepatitis MIDC5001

Produced by

York Technology Assessment Group, University of York, Heslington, York, YO10 5DD

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None

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Rider on responsibility for report

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1 OVERVIEW

This addendum to the External Assessment Report (EAR) report presents the External Assessment Group's (EAG) critique of the additional evidence provided by the company in their response to several key issues that were raised by the EAG in its report, which were discussed at technical engagement.

The technical engagement covered 16 key issues. In response, the company submitted substantive new evidence on several points, alongside a revised economic analysis and updated base case. Following review, the EAG considers that issues 8, 12, 13 and 15 are resolved, with agreement between the EAG and the company on the appropriate modelling assumptions, or where new evidence has sufficiently addressed the underlying uncertainty. Issues 3, 4, 10 and 11 are considered partly resolved: although additional evidence has reduced uncertainty, differences remain in the interpretation of evidence and/or in the assumptions applied. All other issues remain unresolved. A summary of the issues the EAG considers to be resolved, partly resolved or unresolved is provided in Table 1.

Table 1: Summary of the key issues

#	Issue	Resolved?
1	The trial population does not match the population in scope.	No
2	Reliance on Surrogate Endpoints	No
3	Differences between the ITT population and paired liver biopsy population	Partly
4	Validation of the company model and programming complexity	Partly
5	Response to treatment not captured by the current model structure	No
6	Stopping rules and discontinuation of resmetirom treatment	No
7	Repeated application of transition probabilities and short-term trial follow-up	No
8	Misinterpretation of Singh et al (2015)	Yes
9	Natural history of MASH and face validity of model progression rates	No
10	Limited justification for selected input parameters, poor referencing, and lack of clarity regard how some input values are generated	Partly
11	Appropriateness of modelled utility values and MASH resolution increment	Partly
12	Health state costs and the interpretation of the Davidson study	Yes
13	Differences in dosing of resmetirom between trial and clinical practice	Yes
14	Current and anticipated use of GLP-1 antagonists in the UK	No
15	Deviations from HTA Lab recommendations	Yes
16	Extrahepatic treatment effects	No

2 DESCRIPTION AND CRITIQUE OF ADDITIONAL EVIDENCE

2.1 *Issue 1: Trial population does not match the population in scope*

2.1.1 **Issue 1a: Need for liver biopsy**

The company reiterates that eligibility of patients with Metabolic Dysfunction-Associated Steatohepatitis (MASH) for resmetirom will be based on non-invasive testing (NIT) in the NHS. They consider the MAESTRO-NASH trial sample of patients with fibrosis stage 2 or 3, selected based on liver biopsy results, to be representative of the NIT-defined NHS treatment population.

The EAG's response

Clinical experts, including those consulted by the EAG and those who responded to the technical engagement, unequivocally endorse the use of NITs to identify NHS patients suitable for resmetirom, rather than relying on routine liver biopsy.

The EAG agrees with the company that NITs are likely to be the primary method for identifying patients eligible for resmetirom. However, diagnostic criteria for determining eligibility have not yet been established in routine practice, although several alternatives have been proposed in the literature. As discussed in the EAR, while NITs can estimate the probability of clinically significant fibrosis, they do not directly assess histological fibrosis stage. They cannot distinguish fibrosis stages with the same accuracy as a liver biopsy. Only [REDACTED] of the trial population meets the criteria proposed at the BASL MASLD SIG consensus meeting (unpublished; reported in clarification response QA15). The EAG therefore does not consider the trial population to be fully aligned with the population in scope.

Given the outlined limitations of NITs, the EAG considers it inevitable that NITs will both miss some eligible patients (as defined by liver biopsy) and incorrectly identify some ineligible patients. In the technical engagement response, clinical expert Prof Anstee noted that the treatment effect observed in the trial could be diluted in clinical practice (compared to the MAESTRO-NASH trial) if a proportion of patients without fibrosis stage 2 or 3 are treated. In additional clarification questions, the EAG requested the company provide an additional subgroup analysis restricting the population to only patients who meet the proposed NIT based eligibility criteria. These analyses demonstrate that the outcomes in this restricted population are similar to those of the whole population. Additional scenario analysis integrating this subgroup analysis into the economic model demonstrates a modest reduction in the ICER in accordance with the somewhat greater rates of MASH resolution observed in the subgroup analysis.

This subgroup analysis provides some reassurance that treatment effects do not differ substantively in a population defined by NIT-based eligibility criteria. However, it only partially addresses the

uncertainty, as outcome assessments remain based on histologically defined endpoints rather than NIT-based outcomes, which would be used in clinical practice. NITs have well-recognised limitations: they cannot reliably distinguish between intermediate fibrosis stages (for example, F1 versus F2) and do not provide detailed information on MASH resolution. As a result, it remains unclear how the use of NIT-based assessment would affect the estimation of treatment effects. Substantial uncertainty therefore remains.

2.1.2 Issue 1b: Trial requirement for 3 metabolic risk factors

Eligibility criteria for MAESTRO-NASH included the presence of three or more cardiometabolic risk factors (CMRFs). The company provides additional evidence from the UK Biobank study,¹ which shows that cardiometabolic risk factors CMRFs are common in an ‘at risk’ MASH cohort. The evidence presented does not estimate the proportion of patients with ‘at risk’ MASH who have three or more CMRFs.

The EAG’s response

The EAG agrees that patients eligible for resmetirom are likely to have multiple cardiometabolic risk factors (CMRFs), reflecting the nature of the condition. Clinical expert testimony from Prof Anstee indicated that most patients with MASLD/MASH and moderate-to-advanced liver fibrosis have three or more CMRFs. However, the NICE scope does not restrict inclusion to patients with CMRFs, and while the evidence and expert opinion suggest many patients meet this threshold, some eligible NHS patients will likely have fewer than three CMRFs and are therefore not represented in the trial population. This further limits the generalisability of the trial evidence.

2.2 Issue 2: Reliance on surrogate endpoints

The company provides a review of the literature describing the relationship between fibrosis stage and liver-related morbidity and mortality. The company outlines that fibrosis stage is a well-established prognostic factor in MASH, with higher stages consistently associated with increased risk of severe liver disease, major adverse liver outcomes, and mortality.

The company further highlights that regulatory agencies (FDA, EMA) accept improvements in fibrosis as valid surrogate or intermediate endpoints for MASH clinical trials, acknowledging the practical challenges of capturing long-term outcomes.

The EAG’s response

The EAG agrees with the company that progression in fibrosis stage is associated with adverse liver-related outcomes, including severe liver disease and mortality, making it plausible that delaying progression through resmetirom could improve outcomes. However, the current evidence demonstrates associations rather than causal relationships. There is no direct evidence that

improvements in fibrosis stage lead to better clinical outcomes, and no pharmacotherapy trials have shown that treatment-induced fibrosis regression reduces liver-related events or mortality.

As part of the technical engagement response, Prof Anstee considered that surrogate outcomes are ‘reasonably likely’ to predict improved longer-term outcomes, and similar views were expressed by the EAG’s clinical advisers. However, changes in such outcomes would occur beyond the MAESTRO-NASH trial horizon, and there is, at present, no validated surrogate relationship between fibrosis stage and liver-related morbidity and mortality. The EAG’s position remains that there is no direct evidence to support the plausible claim that treatment-induced regression in fibrosis improves future clinical outcomes.

As part of technical engagement, Prof. Anstee concludes that “it is not yet known whether treatment to reduce fibrosis stage will translate to reduced harm.” All experts who provided comments point to the importance of longer-term follow-up data to establish causal relationships between treatment and long-term morbidity and mortality.

The EAG notes that the risk profile of a person at, for example, fibrosis stage F1 through natural disease progression is unlikely to be the same as that of a person who has regressed to F1 from F3 as a result of treatment. It is possible that improvements in fibrosis stage, or slower worsening of fibrosis, partially but not fully reduce the risk of future morbidity and mortality, for example, due to architectural damage, microvascular changes, and persistent metabolic drivers of disease. In this case, patients would not shift onto the natural history curve of the fibrosis stage obtained through treatment and remain at increased risk of morbidity and mortality.

2.3 Issue 3: Modelled population

The company has presented several arguments to support the validity of relative treatment effects derived from the paired liver biopsy week 52 (PLB-W52) population rather than the modified intention to treat liver biopsy week 52 (mITT-LB-W52). They note that missingness is not always attributable to adverse events or loss of response, and that the requirement for histological assessment combined with the blinded trial design makes discontinuation due to perceived loss of response unlikely to be a major contributor to missing data. They also highlight that a positive treatment effect for resmetirom is observed consistently across pre-specified subgroups and appears robust to alternative approaches for handling missing data. In addition, the demographic and baseline characteristics of the PLB-W52 and mITT-LB-W52 populations are broadly comparable, supporting the validity of cross-population comparisons.

The EAG's response

The EAG considers the clinical evidence derived from the mITT-LB–W52 population to be the most appropriate for inclusion in the base-case economic model, as it reflects the pre-specified primary analysis and, as such reflects the most unbiased estimate of treatment effect across the intended trial population. This analysis also underpins the regulatory decision regarding effectiveness.

While the EAG acknowledges that the company has explored the robustness of results using different imputation methods, these additional analyses do not resolve the concern that missing data may have influenced the magnitude of the treatment effect. Tables 7 and 8 of the EAR (pp. 43–44) indicate that estimates of relative treatment effects are more favourable for resmetirom when data from patients with clinician disagreements in biopsy interpretation are removed.

The EAG considers post-hoc analyses, including those employing alternative imputation approaches, to be more appropriately presented as scenario analyses, with the mITT-LB–W52 results retained in the EAG base case.

2.4 Issue 4: Validation of the company model and programming complexity

The company submitted a revised model with corrections to life year calculations, along with a completed TECH-VER checklist. All input data used in the model were combined into a single input parameters workbook, which simplified the corresponding read procedure in R. The R code in the main Rmd file was streamlined, and detailed documentation summarising the model workflow and a log of changes to the model were provided. These have improved ease of use and model transparency. During the clarification and technical engagement stage, the company added options for scenario analysis, created a synthetic data generation mechanism, and further updated the model to correct an error in cost calculation.

The EAG's response

The EAG appreciates the company's modifications to the R model, including a detailed guide to the model's workflow and corrections to errors identified during black-box testing. The validation of the model using the TECH-VER checklist and other updates (e.g., centralised random seed, relocation of codes, improved sequencing of input loading, and enhanced code hygiene) have improved the model's run time, usability, and transparency. The EAG recognises the limited data available for modelling individual biomarker and risk profile trajectories (e.g., weight and lipid profiles), but raises concerns about the face validity of some of these projections over time, such as changes in weight and lipids.

The company provided codes to generate simulated individual patient-level data. Although the functional form of data generation for some risk factors was provided in the spreadsheet, it was not

clear how this was implemented in R, as the codes contained very few annotations. Although the code generates values for a synthetic population, it lacks correlation between variables

The EAG notes that, although the revised model is an improvement, it still contained some errors when the EAG received it. It also adds several thousand lines of R code to the original model. The EAG have therefore not been able to fully check the model and, although it appears to work correctly, the EAG cannot be certain as to whether there may be unidentified errors remaining that impact the results.

2.5 Issues 5: Response to treatment not captured by the current model structure, and Issue 6: Stopping rules and discontinuation of resmetirom treatment

The company sought clinical advice to develop a set of NIT-based criteria to inform initiation, suspension and discontinuation of treatment. The proposed criteria are principally based on liver stiffness measurement (LSM) assessed via vibration-controlled transient elastography (VCTE) or other relevant testing approaches. Where appropriate, LSM thresholds are supplemented by the presence of clinically significant portal hypertension, as indicated by platelet count. Details of the specific criteria are reported in the company response.

The company outlines that NITs would be used in place of biopsy, and that histological assessment of fibrosis stage would therefore not be required, although it could be used to determine eligibility where available. However, the NIT criteria are not incorporated into the economic analysis; the model structure remains unchanged, which is based on histologically assessed fibrosis stage, in line with the design of the MAESTRO-NASH trial. The proposed criteria therefore function as a proxy for histologically assessed fibrosis stage.

As per the company's original base case, treatment is initiated in patients with F2 or F3 fibrosis. A gated stopping rule is applied, whereby patients who regress to F0 or F1 discontinue treatment but are assumed to resume treatment if they subsequently progress to F2 or F3. Progression to F4 compensated cirrhosis (CC), decompensated cirrhosis (DCC) or hepatocellular carcinoma (HCC) results in permanent discontinuation. Fibrosis assessment is assumed to occur annually using a single NIT. However, as suggested by the EAG, the company explores scenarios in which repeat testing is used to assess treatment response, reflecting the limitations of NITs in accurately staging fibrosis. Under these scenarios, additional costs are incorporated, including further resmetirom acquisition and administration costs, repeat VCTE testing and an additional consultation visit. These scenarios consider repeat testing after 3 months or after a further 6 months.

The EAG's response

Use of NITs to establish eligibility

As outlined in Issue 1, the EAG agrees that in clinical practice, NITs will play a critical role in determining treatment eligibility and assessing response. The EAG, however, has several concerns regarding the specific criteria proposed by the company. As noted in Issue 1, applying the MAESTRO-NASH trial criteria would result in the inclusion of only [REDACTED] of the population, raising concerns about the generalisability of the trial population to the likely treated population and the suitability of these criteria.

Advice from clinical advisors also raised concerns regarding the number of patients who would be eligible for treatment under these criteria, suggesting that hundreds of thousands of patients could be eligible if the criteria were applied, and that many would be at low risk of subsequent disease. This is supported by evidence from several large cohort studies^{2, 3} demonstrating that the risk of cirrhosis and other clinically significant events is low in many patients with a liver stiffness measurement (LSM) of greater than 10 kPa. The EAG is therefore concerned that these criteria could lead to overtreatment of many patients.

Additionally, clinical expert Dr Aspinall stated in the technical engagement response that improvements in access to non-invasive fibrosis testing will be required to implement resmetirom in practice, which may require investment in current service provision. Importantly, all three clinical experts (Prof Anstee, Dr Aspinall, and Prof. Anstee) indicated that determining eligibility for treatment to help reduce errors in the selection of patients. These costs have not been included in the company's economic analysis. The EAG therefore presents additional analysis in Section 3 to explore the impact of these potential additional costs.

Integration of NIT into the economic model

The proposed NIT criteria are not integrated into the economic analysis, which remains based on histologically assessed fibrosis stage. While the EAG accepts that the design of the MAESTRO-NASH trial is based on histological outcomes, there are substantive concerns regarding the mismatch between the population proposed for clinical practice and that evaluated within the economic model.

The proposed NIT criteria are effectively assumed to correspond directly to fibrosis stage. However, as discussed in Issue 1, NITs have important limitations, and it is unclear whether outcomes assessed using NITs would replicate those observed based on histological assessments of MASH resolution and fibrosis stage. This issue is not limited to differences in measurement, but reflects a structural misalignment between the model and clinical practice. The model defines health states, treatment response, and disease progression using histologically assessed outcomes, whereas in practice, patients will be assessed and managed using NITs.

As NITs cannot reliably distinguish between intermediate fibrosis stages and do not directly capture MASH resolution, the correspondence between modelled health states and those observed in practice is uncertain. This has implications not only for the identification of the target population, but also for the estimation of treatment effects and disease progression. Consequently, it is unclear whether the model's predictions, which are based on histological endpoints, are representative of outcomes that would be realised in a clinical setting where NITs are used.

Moreover, given these limitations, the EAG considers it likely that repeat NIT testing would be required for clinicians to confidently implement the company's proposed stopping rules. Patients discontinuing treatment would therefore incur additional resmetirom acquisition costs while NIT results are confirmed, alongside additional testing and consultation costs. Although these costs were explored in scenario analyses provided during technical engagement, they are not reflected in the company's updated base case.

Appropriateness of modelled stopping rules

Although the EAG accepts that the incremental benefit of continued resmetirom treatment may be more limited in patients whose fibrosis has substantially improved, uncertainty remains as to whether the proposed stopping rule is clinically appropriate. The summary of product characteristics (SmPC) does not specify a fibrosis regression-based discontinuation criterion, and stakeholder opinion provided during technical engagement did not demonstrate strong support for introducing such a rule. Two of the three clinical submissions indicated that treatment should be continued, a position consistent with the views of the EAG's clinical advisers.

The EAG also has concerns regarding the feasibility of implementing such a stopping rule in clinical practice, as NITs have limited ability to reliably distinguish between adjacent fibrosis stages and do not provide detailed information on MASH resolution, raising the possibility that treatment could be discontinued in patients in whom the underlying disease process remains active. Further, clinical expert advice indicated that patients with early-stage fibrosis (F0/F1) would normally be discharged to primary care, which may not be possible if patients require persistent monitoring.

The company's economic analysis also proposes treatment discontinuation upon progression to advanced liver disease (ALD), including F4/CC. The EAG agrees that discontinuation of treatment upon progression to DCC or (HCC) is appropriate and notes the general clinical consensus reflected in stakeholder responses. However, uncertainty remains regarding treatment continuation in patients with CC. As noted in the EAR, no fibrosis-stage-based stopping rule was imposed in the MAESTRO-NASH study. Furthermore, the ongoing MAESTRO-NASH-OUTCOMES⁴ trial is evaluating resmetirom in patients with well-compensated cirrhotic disease. Stakeholder submissions were notably equivocal regarding treatment continuation in these patient groups, with several references

made to the ongoing trial. Accordingly, the EAG considers it plausible that patients with CC may continue treatment in practice; however, real-world implementation is likely to be influenced by the results of the MAESTRO-NASH-OUTCOMES study.

2.6 Issue 6: Stopping rules and discontinuation of resmetirom treatment

Issue 6 is considered in combination with Issue 5.

2.7 Issue 7: Repeated application of transition probabilities and short-term trial follow-up

The company acknowledges that the MAESTRO-NASH provides 12-month follow-up data only. They consider the repeated application of transition probabilities generated from a 12-month follow-up throughout the model time horizon to be biologically justified.

The company further notes that published population and economic models of MASH, including UK-focused models, commonly apply constant or piecewise-constant transition probabilities in the absence of long-term empirical data. It therefore considers this modelling approach consistent with standard practice in chronic disease modelling.

In response to EAG queries, the amended model allows scenario analyses in which treatment effects from year 2 onwards can be varied.

The EAG's response

The EAG remains concerned by the repeated application of the same transition probabilities across the entire model time horizon. While the EAG acknowledges the biological rationale presented by the company, this rationale requires several assumptions that are not empirically established.

First, the company assumes that continuous THR- β pathway activation will lead to continued reductions in steatohepatitis over time. This assumes that the pathway remains equally active and that the treatment effect does not wane. However, waning may plausibly occur for a variety of reasons, including receptor adaptation, behavioural drift (e.g. weight gain or metabolic deterioration), or other aspects of disease biology. Importantly, the possibility of a maximal treatment effect and plateau in response is not acknowledged in the company's response.

Second, the company's reasoning assumes that reductions in steatohepatitis will inevitably result in MASH resolution. However, reductions in inflammatory activity do not necessarily equate to complete histological resolution; partial improvement may occur, with residual ballooning or low-grade inflammation persisting.

Further, pharmacodynamic data from the MAESTRO-NASH trial show that reductions in liver fat occur rapidly, within 16 weeks. This suggests that resmetirom produces an early biological effect on hepatic fat content. A more plausible interpretation is therefore that long-term treatment maintains early responders rather than progressively converting non-responders at a constant annual rate. This interpretation is consistent with clinical advice received by the EAG, which anticipated diminishing returns over time and an eventual plateau in the proportion of patients achieving MASH resolution.

Given that trial evidence extends only to 12 months, it is not possible to establish the proportion of patients who might achieve MASH resolution beyond the first year. While it is plausible that some additional patients could achieve resolution with longer exposure, it is unlikely that the probability of resolution remains constant and independent of treatment duration. The company's base-case assumption, therefore, represents an optimistic extrapolation of short-term evidence. In the absence of empirical evidence supporting sustained annual conversion, the EAG considers it more appropriate to assume that MASH resolution occurs only within the first cycle of the model.

The EAG acknowledges that alternative specifications, such as treatment effect waning after 2, 3 or 5 years, could be explored. However, there is no empirical evidence to inform the timing, rate, or functional form of any waning effect. As such, selecting between alternative waning assumptions would be inherently arbitrary and would introduce additional structural uncertainty without improving the evidence base. In contrast, assuming that MASH resolution occurs within the first cycle avoids imposing unsupported assumptions about long-term treatment dynamics. The EAG therefore considers this to be a more transparent and grounded approach, given the current evidence limitations.

2.8 Issue 8: Misinterpretation of Singh *et al* (2015)

This issue concerns the transition probabilities applied in the economic model, specifically the assumption that individual patients may either regress or progress by more than one fibrosis stage within a single annual cycle.

In its response, the company expresses broad agreement with the EAG's recommendation that multistate transitions should, where possible, be derived directly from the MAESTRO-NASH trial. However, it disputes the suggestion that two-stage improvements in fibrosis within one year are clinically implausible, citing empirical evidence from MAESTRO-NASH demonstrating that some patients achieved a two-stage regression in fibrosis. The company further notes that equivalent data on multistage fibrosis progression are not currently available from MAESTRO-NASH, as disclosure would risk unblinding the trial. It states that this limitation necessitated the use of Singh *et al.* to inform the proportion of patients progressing by more than one fibrosis stage within a single model cycle.

In response to the EAG's concerns, the company presents three scenario analyses to explore alternative parameterisation of the modelled transitions. The first scenario restricts both fibrosis progression and regression to a maximum of one stage per year. The second restricts transitions to a maximum of two stages and uses individual patient data (IPD) from MAESTRO-NASH to inform the proportion of patients experiencing two-stage regression, while continuing to rely on Singh *et al.* to model multistage progression. The third scenario mirrors the second but restricts progression to a maximum of one stage per year; consequently, Singh *et al.* is no longer used to inform progression in this scenario.

The EAG's response

The EAG is concerned that the company's response does not directly address the core critique set out in the EAR, namely the suitability of the Singh *et al.* data to inform annual transition probabilities. As described in the EAR (pp 75 to 77), the Singh review collated evidence on changes in fibrosis stage from studies with heterogeneous follow-up durations (with a minimum of one year). This is not consistent with the way these data are used in the model, where they are used to parameterise transitions within a fixed annual cycle length.

Both the clinical advice received and the focus of the critique in the EAR relate to the clinical plausibility of patients progressing by more than one fibrosis stage within a single year. The company's cited evidence refers to regression events and therefore does not directly refute the concern about multistage progression. In this context, the additional clinical submissions provided as part of the technical engagement response appear to further support the view that multiple-stage transitions would be uncommon. The EAG therefore considers it reasonable to limit fibrosis progression to at most one stage per model cycle.

With respect to regression, the EAG considers the incorporation of IPD from the MAESTRO-NASH trial to be appropriate and methodologically preferable. This represents the most relevant and robust source of evidence to inform the proportion of patients experiencing multistage fibrosis regression. Consequently, the EAG incorporates company scenario 3 into its base case.

2.9 Issue 9: Natural history

2.9.1 Interpretation of current literature

The EAG raised concerns about the company's approach to modelling natural history, which relies on repeating transitions from the standard of care arm of the MAESTRO-NASH trial; the explicit rejection of natural history evidence, such as Le *et al.*;⁵ and the repeated emphasis in the company's original submission on a phenotype of fast-progressors.

The company's response highlights the limited evidence on the natural history of patients with MASH and outlines several counter-arguments rebutting the EAG interpretation of the evidence. The key points from the company's response are as follows:

- The company notes that Singh *et al.*⁶ reported a limited ability to estimate fibrosis progression rates in patients with intermediate or advanced fibrosis at baseline. The company also highlights that patients with advanced disease may be less likely to undergo repeat histologic examination, potentially leading to underestimation of progression rates in these patients.
- The company expresses concerns regarding the reliability and applicability of Le *et al.*⁵ They clarify that their rejection of this study as a natural history source was not based solely on the apparent clinical implausibility of its findings (that progression slows with advancing fibrosis) but also reflects observations of rapid fibrosis progression in the MAESTRO-NASH advanced fibrosis population. The company further states that clinical advice from 10 UK experts across hepatology, gastroenterology, and endocrinology does not support the EAG's interpretation of Le *et al.*'s⁵ findings.
- Finally, the company cites evidence from several published sources indicating that the incidence of cirrhosis, liver transplantation, and other clinical outcomes increases with fibrosis stage. In particular, they highlight Luthra *et al.*, which they interpret as showing that both the frequency and rate of cirrhosis increase with advancing fibrosis.

The EAG's response

The EAG acknowledges the limitations of the evidence reported by Singh *et al.* and recognises the potential for bias within these data. However, the EAG considers that the analysis presented by Singh *et al.*⁶ broadly supports the findings reported in Le *et al.*,⁵ indicating that progression to advanced liver disease typically occurs over a prolonged period. Importantly, the limitations identified by the company reflect uncertainty within the available evidence base rather than providing support for the assumption that fibrosis progression accelerates at higher fibrosis stages.

The EAG also notes the company's concerns regarding the reliability of the natural history estimates reported by Le *et al.* While some anomalies in the calculations are apparent, it is difficult to fully assess the appropriateness of individual methodological choices or the rationale underlying the authors' approach without additional information. Moreover, these discrepancies do not necessarily invalidate the broad conclusions of the study. Even allowing for these issues, the findings reported by Le *et al.* suggest that fibrosis progression generally occurs over many years, which contrasts with the company's characterisation of this population as requiring urgent intervention.

The EAG further acknowledges that the studies included in Le *et al.* represent a heterogeneous population. However, heterogeneity does not invalidate estimates derived from the included studies, nor is it clear that these populations are less representative of the target population than the patients recruited to MAESTRO-NASH. Moreover, the observation that some higher-risk patients may progress more rapidly does not, in itself, demonstrate that fibrosis progression accelerates systematically with increasing fibrosis stage, as suggested by the company.

Finally, the EAG maintains that the evidence cited by the company from studies such as Luthra *et al.*⁷ and Roden *et al.*⁸ does not directly address the rate of fibrosis progression between disease stages. As previously outlined in the EAR, these studies estimate the risk of clinical outcomes conditional on fibrosis stage at index, rather than the rate of transition between fibrosis stages. The EAG does not dispute that fibrosis stage is a strong prognostic indicator and that clinical event rates are higher among patients with more advanced fibrosis. However, these studies do not provide evidence regarding the relative speed of progression between fibrosis stages and therefore do not directly contradict the possibility that progression may slow at later fibrosis stages.

2.9.2 Company scenario analysis

The company presents four additional scenarios that incorporate natural history evidence into the economic model. These analyses adapt the transition probabilities used in the model based on evidence from two natural history cohorts Le *et al.*⁵ and Ng *et al.*⁹ A summary of each scenario is outlined below:

- Scenario 1, Le *et al.* (unadjusted): Stage-to-stage fibrosis transition probabilities were derived directly from Le *et al.* and converted into annual probabilities for SoC, allowing movements of up to two fibrosis stages in a single year as observed in the source data.
- Scenario 2, Ng *et al.* (unadjusted): Annual probabilities of fibrosis progression and regression were derived from the 12-month outcomes reported in Ng *et al.* 2022; because stage-specific magnitudes were not reported, transitions were restricted to a maximum change of one fibrosis stage per year/cycle in either direction.
- Scenario 3, combined Le *et al.* and Ng *et al.* (1 stage maximum): Stage-specific transitions from Le *et al.* were used for all fibrosis stages except F3, which was replaced with estimates from Ng *et al.*; transitions were limited to a maximum change of one stage per year.
- Scenario 4, combined Le *et al.* and Ng *et al.* (2 stages maximum): As in the previous scenario, F3 transitions were taken from Ng *et al.* and other stages from Le *et al.*; however, patients in stages other than F3 were allowed to transition by up to two fibrosis stages per year in line with the movements observed in the Le *et al.* data.

The EAG's response

An important feature of the company's scenario analyses is how treatment effects are incorporated into the model. In the base case, fibrosis progression is explicitly conditional on whether a patient achieves MASH resolution, reflecting the biological relationship between resolution and subsequent fibrosis changes. By contrast, the scenario analyses model fibrosis progression by applying a relative risk to standard-of-care transition probabilities derived from natural history data. This represents a fundamental structural difference. The scenario approach effectively distributes treatment benefit across the entire cohort, rather than linking it mechanistically to patients who achieve MASH resolution. As a result, fibrosis benefits are more broadly allocated rather than accruing specifically to responders, so outcomes from these scenarios are not directly comparable to those of the base case.

Although these scenarios have limited interpretability as alternative estimates of treatment effect, they remain informative for assessing the face validity of model predictions under standard care.

Comparison of health state occupancy across the four natural history scenarios and the base case reveals clear and consistent differences. As shown in Table 2, patients in the standard-of-care arm of the 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. The EAG considers this discrepancy to be driven by the repeated application of transition probabilities for MASH resolution and indicates that the current implementation of treatment effects generates clinically implausible predictions.

Table 2 Comparison of health state occupancy in the standard of care arm

	F0/NAFL	F1/F1R	F2/F2R	F3/F3R	F4 CC	DCC	HCC	Post liver transplant	Total
Base case	████	████	████	████	████	████	████	████	████
Scenario 1	████	████	████	████	████	████	████	████	████
Scenario 2	████	████	████	████	████	████	████	████	████
Scenario 3	████	████	████	████	████	████	████	████	████
Scenario 4	████	████	████	████	████	████	████	████	████

2.9.3 Fast progressors

In its response, the company cites literature showing ~18–25% of patients progress quickly (Singh *et al.*; Sanyal *et al.* 2019; Jambulingam *et al.* 2023; Schattenberg *et al.* 2024)^{6, 10-12} and highlights emerging research using biomarkers, polygenic scores, and clustering to explore factors associated with rapid progression. The company also highlights analyses of TARGET-NASH data, which suggest patients with higher baseline fibrosis experience a faster onset of adverse liver outcomes. The company presents these findings to support the concept of fast progression while recognising that validated tools for identifying such patients in clinical practice are not yet available.

The EAG's response

The EAG's position remains unchanged. The EAG acknowledges that MASH is a heterogeneous condition and that some patients may progress faster than others. It also recognises that the cited literature suggests that some patients may represent a clinical phenotype of "fast progressors". However, as previously noted, this evidence remains emergent, and there is no established clinical consensus on a clearly defined phenotype. Importantly, as highlighted in the company's response, 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.

2.10 Issue 10: Limited justification for selected input parameters, poor referencing, and lack of clarity regarding how some input values are generated

This issue relates to the limited justification provided by the company for certain model input parameters, the extensive reliance on secondary citations, and the lack of clarity regarding how these values were derived. The EAG was particularly concerned with the provenance and rationale of several transition probabilities used in the model, including those for advanced liver complications (F4/CC, DCC, HCC, liver transplantation) and mortality.

In response, the company has comprehensively updated 28 input parameters for advanced liver complications and mortality. A new targeted supplementary literature search was conducted to address the concerns raised by the EAG. Applying an evidence hierarchy, the company incorporated newly published studies available since the original submission. Additionally, the company provided a table of four updated UK baseline probabilities for key diabetes-related complications.

The EAG's response

The company has provided a rationale and detailed description of the methods used to select input parameters populated by evidence from the published literature sources. This includes extensive documentation provided in Appendix BC, which outlines transition probabilities for advanced liver complications and mortality, including any calculations or assumptions applied when transforming reported data into model values.

The EAG is satisfied with some of these changes and updates to model parameters, including new input values for diabetes-related complications, but has some new concerns relating to some of the transition sources used to inform transition probabilities for advanced liver complications and mortality presented in Table 6 of the technical engagement response.

The EAG notes the new evidence provided by the company from Davidson *et al.*,¹³ which was used to inform the transitions from F3 to DCC and F4 to DCC. This evidence, however, relies on unpublished data not reported in the manuscript, limiting the EAG's ability to independently verify the

calculated values. Further, while the F4 to DCC transition probability (0.076) appears reasonable, the F3 to DCC value (0.029) is substantially higher than reported elsewhere in the literature. Evidence from Vilar-Gomez *et al.*,¹⁴ a study also used by the company to inform several other parameters, indicates a transition probability of 0.006, while two studies included in the Barrett *et al.*¹⁵ systematic review suggest rates of 0.0021 and 0.0025.

Given this discrepancy, the EAG prefers to use Vilar-Gomez *et al.* 2018¹⁴ for the F3 to DCC transition, as this source is already used in the model for other parameters and is also consistent with the company's original parametrisation of the model. To maintain consistency in sources used in the model, the EAG also prefers this source for the F4 to DCC transition, as it improves internal consistency by minimising the number of sources used to inform parameter values.

The company also uses Shang *et al.*,¹⁶ a Swedish registry-based cohort of 3,657 patients with compensated cirrhosis (CC/F4) and decompensated cirrhosis (DCC) diagnosed between 2001 and 2020. While this population is broadly relevant to the decision problem, the EAG notes that these patients are older (median age 71 years), newly diagnosed (unlike the MAESTRO-NASH trial population), and have a higher prevalence of type 2 diabetes (88%). Median follow-up is also relatively short for liver-related complications, such as HCC and mortality, at 1.1 years for CC/F4 patients. Nevertheless, this data informs a large number of parameters, allowing for greater internal consistency, and represents a substantial cohort.

The EAG, however, is concerned that the specific data used by Shang *et al.* may be inappropriate. The company's calculations rely on events reported in Table 4, which presents the proportion of patients experiencing an event in year 1 and year 2 or later. Using the year 2+ event proportions to represent annual risk may be inappropriate because the at-risk period for these events is undefined, as they are reported only as one year or more. For this reason, Table 3 of Shang *et al.*,⁶ which reports cumulative incidence over five years, is preferred for calculating annual probabilities. Values derived from Table 3 are broadly consistent with Barrett *et al.*,⁵ although definitions of F3 and F4 may differ across studies.

The EAG also notes a concern raised by the authors regarding the interpretation of the reported evidence, which highlights that the incidence of DCC and HCC events is much higher in the first year than in subsequent years. The authors speculate that this may reflect a delayed diagnosis of such outcomes and state that the estimates should therefore be interpreted as the event rate one can expect in a clinically diagnosed patient with cirrhosis rather than the true rate of progression. The EAG considers this further justification for using Table 3 instead because the 5-year cumulative incidence rates mitigate this issue.

For HCC progression to liver transplant and liver-related mortality probabilities, the company cites Faulkes *et al.*,¹⁷ a UK single-centre (Birmingham) study of HCC referrals for liver transplant. This source is considered reasonable, and no alternative was explored.

Overall, the EAG notes that changing individual input values has minimal impact on the ICER. Modifying groups of interrelated parameters, such as transition probabilities to advanced liver complications and liver-related mortality, however, has a substantial effect. This underscores the importance of parameter interconnections within the model.

2.11 Issue 11: Appropriateness of modelled utility values and MASH resolution increment

This issue concerns the appropriateness of modelled utility values and the application of a MASH resolution increment in the economic model. The company has accepted the EAG's recommendation for alternative utility values for the F1–F4 health states. The updated company base-case now uses MAESTRO-NASH trial-derived values for F1–F3 (with and without MASH resolution) and Papatheodoridi *et al.*¹⁸ for F4 (compensated cirrhosis).

In its response, the company reiterates that Papatheodoridi *et al.*⁸ reports EQ-5D-5L data. The company aligns with the current NICE methods guidance⁹ by mapping the published utility value (0.725) to the EQ-5D-3L value set, resulting in a utility value of 0.640.

Regarding the inclusion of the MASH resolution utility increment, the company cites regression analyses previously presented in response to EAG clarification question B16, which they state provide empirical support for its incorporation into the model

The EAG's response

The EAG considers that the updated utility values address the principal concerns raised in the EAR. However, some issues remain.

The mean utility values applied to F1–F3 health states are not fully consistent with disease progression, as they do not always decrease with increasing severity. The EAG considers this clinically implausible and likely reflects the limited sample size. As noted in the EAR, the preferred approach is to assume utilities are independent of fibrosis stage, since evidence for a significant gradient is limited and clinical advice indicates that most patients up to (but excluding) F4 CC are largely asymptomatic. The EAG base-case therefore uses the regression analysis presented in response to the original clarification question to inform utility values. These values are also applied to F0 and NAFL health states. Although these patients were not included in the MAESTRO population, the EAG considers extrapolation reasonable given the lack of evidence that fibrosis stage impacts

health-related quality of life. Moreover, the utility values applied by the company exceed population norms, which is implausible for a population with extensive comorbidities.

The EAG remains uncertain about the appropriateness of including a MASH resolution increment. At clarification, the company provided three regression analyses of MAESTRO-NASH data suggesting a borderline statistically significant association between MASH resolution and EQ-5D utility; however, these findings are sensitive to the choice of regression specification. The company and EAG differ in their preferred modelling approach (with the EAG favouring a Gaussian distribution with identity link, and the company a beta distribution with identity link), and the EAG considers the evidence supporting an independent utility benefit to be weak. Nonetheless, the MASH resolution increment is retained in the base-case analysis.

While the EAG considers the Papatheodoridi *et al.*¹⁸ an appropriate source for the F4 CC utility, it has concerns about the mapping exercise undertaken. The study collected EQ-5D-5L data, but these values were already crosswalked to EQ-5D-3L using the van Hout algorithm to align with the EQ-5D-3L value set and NICE methods guidance.^{20, 21} This was confirmed with the study authors. The company's additional mapping, therefore, constitutes double mapping and is incorrect. The EAG base case uses the original Papatheodoridi value of 0.725, noting that the preferred mapping algorithm in the latest NICE methods guidance has recently been updated.²²

Lastly, a minor error in the implementation of age- and sex-specific utility decrements in the company model was identified (see Section 3 for further details).

2.12 Issue 12: Health state costs and the interpretation of the Davidson study

The EAG raised concerns regarding the use of cost estimates from Davidson *et al.*,¹³ specifically the assignment of total study follow-up costs as annualised values for the F0–F4/CC health states. Costs for HCC and DCC were derived from unpublished data from the same study, creating issues around transparency and the appropriateness of the inputs. The model also annualised one-off procedural costs, notably liver transplantation, by doubling single-event costs derived from NG49.²³

In the company's revised base-case, the company updated the health state costs for F0 to F4/CC using data from the published Davidson *et al.*,³ study by dividing total costs by the follow-up period to obtain annualised values. As this study did not report stage-specific costs for F1–F3, the company apportioned these using a gradient based on supplementary evidence from Younossi *et al.*,²⁴ to reflect increasing costs with disease severity. Unpublished DCC and HCC costs were replaced with values from Younossi *et al.*²⁴ Additionally, liver-related death costs were introduced based on Younossi *et al.*,²⁴ although this was not documented in the company's TE response. Liver transplantation and post-transplant follow-up costs were updated to reflect NHS reference costs²⁵ and NG49²³, respectively.

All costs were inflated to current prices using the Hospital & Community Health Services pay-and-prices index and the NHS Cost Inflation Index (Unit Costs of Health and Social Care, PSSRU) or, where unavailable, the NHS cost uplift factor.²⁵

The company also updated CVD event costs to reflect more recent UKPDS84-based estimates. This involved averaging hospital inpatient costs for a representative 60-year-old male and female in the year of complication and subsequent years, using the cost calculator published alongside UKPDS 84 by Alva *et al.*, 2015.^{26, 27}

Although the company's TE response stated that "costs associated with diabetes-related complications were unchanged," these values were updated in the revised base-case, alongside diagnostic and monitoring costs, and a one-off outpatient consultation cost was introduced.

The EAG's response

The EAG considers the updated costing approach appropriate, particularly the apportioning of health state costs using the gradient from Younossi *et al.*²⁴ The approach is reasonably compatible with Davidson *et al.*,¹³ given the homogeneity in setting, consistent stratification of health states, and alignment with UK-specific cost profiles. The proximity of study years (2021 vs 2020) further supports comparability in treatment pathways and resource use. The EAG also notes that scenario analysis using cost values from Younossi *et al.*,²⁴ had only a limited impact on the ICER, and the EAG considers both value sets reasonable.

Several cost input changes in the revised base case were not documented. Notably, liver-related death costs from Younossi *et al.* were introduced, despite being absent from the previous base case and the TE response. These costs were erroneously applied not only as a one-off cost in the cycle a patient died, but also in all subsequent cycles after death. This error was subsequently corrected by the company and is reflected in the revised company base-case results. The EAG is satisfied that the liver-related death costs are otherwise appropriate and align with NHS reference costs and NG49.

Updates to costs for diabetes-related complications, diagnostics, and monitoring were implemented in the revised model. The EAG notes that these changes arise from revised inflation assumptions rather than substantive new evidence. While reasonable, they should have been clearly documented. Several minor issues were identified regarding how the inflation indices were applied: i) the NHS England 2024/25 cost uplift factor was updated from 1.7% to 5% in September 2024, yet the outdated 1.7% is used; ii) the 2025/26 uplift should be 4.83%, but 1.7% is applied; iii) the model double counts the 2024/25 rate by applying both the NHS cost inflation index (4.31%) and the 1.7% uplift. Additionally, a one-off outpatient consultation cost was introduced. The EAG notes that, collectively, these changes result in only a minor impact on the revised ICER. A summary of notable and undocumented cost changes compared to those in the previous base case is presented in Table 3 below.

Table 3 Summary of undocumented cost changes

Cost*	Previous company base-case	Revised company base-case
Liver related death	£0.00	£3,871
Nephropathy	£12,981	£13,770
Retinopathy	£2,171	£2,303
Outpatient consultation	£0.00	£197
MRE	£218	£132
*Diagnostic and monitoring costs (liver enzyme test, ultrasound/FibroScan and ELF) were increased negligibly. Abbreviations: ELF; Enhanced Liver Fibrosis, MRE; Magnetic resonance elastography		

2.13 Issue 13: Differences in dosing of resmetirom between trial and clinical practice

The EAG's initial concern was about the mismatch between the design of the MAESTRO-NASH trial and the SmPC. Participants in the trial were randomised to receive fixed doses (80 mg or 100 mg resmetirom once daily, or placebo), whereas the SmPC recommends weight-based dosing. The EAG highlighted potential for this to bias outcomes, as some participants received a lower dose, while others received a higher dose than they would in clinical practice. The EAG believed that the company's method of deriving transition probabilities- using the 100 mg arm for patients weighing ≥ 100 kg and the 80 mg arm for those weighing < 100 kg- did not solve the mismatch between trial dosing and the SmPC. Instead, the EAG suggested pooling data from the 80 mg and 100 mg arms to inform transition probabilities for all patients, as this simplified the model.

In their response to TE, the company updated the economic model with a scenario in which transition probabilities, discontinuation rates, and treatment effects are derived from pooled data from the 80 mg and 100 mg trial arms. While the company agree that a pooled approach represents a pragmatic alternative, the original approach to dosing was retained in the company's updated base-case.

The EAG's response

The company's response does not address the underlying mismatch between the trial evidence and the SmPC dosing regimen. As noted in the EAR, it is unclear whether this introduces systematic bias, as some trial participants received lower or higher doses than would occur in clinical practice.

The scenario analysis presented by the company does not resolve this uncertainty. The EAG was also unable to replicate the company's scenario results using the model as provided. This discrepancy may be due to a minor error in the Excel Master Inputs file (sheet 'M-NASH Pop&efficacy', cells D49–D50). However, because this scenario analysis has only a limited impact on the ICER, the EAG is satisfied that the company's parameterisation approach does not materially affect the cost-

effectiveness results. The EAG notes, nonetheless, that the uncertainty arising from the mismatch between trial dosing and the SmPC dosing regimen should be considered in decision-making.

2.14 Issue 14: Current and anticipated use of GLP-1 antagonists in the UK

The company sought to provide context for comments made by the EAGs' clinical advisers that they may be reluctant to prescribe resmetirom for patients with MASH successfully losing weight with a GLP-1 receptor agonists. The company appears concerned that the EAG's clinical advisers were led to believe the "inaccurate assumption inherent in the EAR that many patients eligible for resmetirom have mild, slow-progression disease for which there is no urgency to treat", and that this would explain their hesitancy with the potential concomitant prescribing of semaglutide and resmetirom.

The EAG's response

As noted previously, the EAG considers GLP-1 RAs to be currently not relevant comparators. The technology appraisal of semaglutide for patients with moderate to advanced liver fibrosis due to MASH is ongoing.

The EAG's assessment of disease progression and treatment need was informed by two clinical advisers. Clinical advice indicated that progression through fibrosis stages F1 to F3 may take between five and ten years, and that not all patients will develop decompensated cirrhosis or experience a substantial reduction in quality of life (EAR Section 2.1, p. 25). The EAG's assumptions regarding disease progression are consistent with this clinical input and the literature describing natural history.

The EAG invited both clinical advisers to provide further clarification regarding concomitant use of resmetirom and GLP-1 RAs. Both advisers indicated that resmetirom is not generally considered necessary for patients who are losing weight on a GLP-1 RA and demonstrating improvements in liver blood tests or liver stiffness. Resmetirom may be considered in addition to a GLP-1 RA if fibrosis does not regress.

The EAG notes that many patients eligible for resmetirom could also be eligible for, or already receiving, semaglutide. Semaglutide may have beneficial effects on fibrosis (subject to ongoing evaluation), and it remains uncertain whether both therapies would be prescribed concomitantly. Clinical experts suggested that concomitant use could be considered in patients with a stabilised GLP-1 RA dose for at least 24 weeks (Dr Aspinall) and may theoretically benefit some patients (Prof Anstee).

2.15 Issue 15: Deviations from HTA Lab recommendations

This issue relates to the NICE Health Technology Assessment Innovation Laboratory (HTA Lab) report on developing an economic model concept for evaluating MASH therapies. The EAG noted

deviations between the company's model and the recommendations set out in this report and considered that these deviations should have been more clearly justified. The EAG also highlighted that failure to adopt, or adequately justify deviations from, the HTA Lab recommendations risks undermining the broader aim of promoting consistency in decision-making for the evaluation of MASH treatments.

In its response, the company states that this issue does not have a material impact on the Committee's ability to make an informed decision regarding resmetirom. The company provided an Appendix BD responding to Table 10 of the EAG report (Comparison of HTA Lab recommendations and company model). In this appendix, the company refers to several technical engagement issues (2, 5, 6, 13, and 16) and notes that scenario analyses addressing points raised in the HTA Lab report have been provided as part of the technical engagement response.

The EAG's response

As stated in the NICE scope²⁸, the HTA Lab report²⁹ sets out NICE's expectations and specifications for the economic model concept. These specifications are intended to be referenced in the scoping documentation for future MASH treatments evaluated by NICE in order to support consistency and more streamlined decision-making by committees. The EAG therefore considers that the HTA Lab report should be adhered to where possible. Deviations should be clearly justified, as they may affect the Committee's ability to make an informed decision regarding resmetirom and subsequent therapies in this area.

Given the substantive updates to the economic analysis and the extensive scenario analyses provided, the EAG considers that the company has addressed the majority of the recommendations outlined in the NICE HTA Lab report. The EAG further acknowledges that stratification of the model population and subgroup analyses specified in the HTA Lab report were not included in the NICE final scope and therefore considers their exclusion from the presented analyses to be reasonable.

2.16 Issue 16: Extrahepatic treatment effects

2.16.1 Metabolic risk factor and BMI

The company outlines how the mechanism of action of resmetirom is expected to impact extrahepatic outcomes. Specifically, it highlights that THR- β stimulation improves metabolic outcomes, leading to increased insulin sensitivity and reductions in serum lipids. The company outlines that these benefits are modelled by assuming a one-off treatment effect applied to low-density lipoprotein-cholesterol (LDL-C), high-density lipoprotein-cholesterol (HDL-C), and triglycerides based on observed differences in the MAESTRO-NASH trial. Thereafter, these parameters evolve according to long-term background trends informed by relevant epidemiological data. The company emphasises that it

considers this approach conservative and that it does not imply a permanent treatment effect as implied by the EAR.

The company further outlines that body mass index (BMI) is similarly modelled using age- and sex-specific population trends from NHS Digital data, in addition to a treatment-specific effect applied while patients are on treatment, informed by the MAESTRO-NASH trial.

The EAG's response

The EAG reiterates the concerns described in the EAR. Despite the company's claims, the economic model imposes a persistent treatment effect on LDL-C and HDL-C. While the company is correct that the treatment effect is not repeatedly applied (i.e., it does not increase over time), the model assumes a permanent treatment-related difference in both LDL-C and HDL-C that continues throughout the time horizon, including after treatment discontinuation. This assumption is problematic given that there was no statistically significant difference in HDL-C observed in the MAESTRO-NASH trial. Furthermore, as outlined in the EAR, it is unclear why a persistent treatment effect is applied to LDL-C and HDL-C but not to triglycerides.

With respect to BMI, the EAG similarly rejects the company's arguments. As discussed in the EAR, the model imposes a persistent and increasing treatment effect on BMI, resulting in all patients experiencing a continuous decline in weight (and BMI) over the entire time horizon in both the resmetirom and standard of care arms, with a more rapid decline modelled in the resmetirom arm. This is not clinically plausible and is not supported by the available evidence. Repeatedly applying the one-year treatment effect over time is inconsistent with evidence on the natural history of weight change in MASH/MASLD populations, where sustained clinically meaningful weight loss under supervised management is uncommon. Moreover, there is no long-term evidence or statistically significant evidence supporting a persistent or differential weight-loss effect for resmetirom, particularly after treatment discontinuation, making it unclear whether any treatment effect on weight should be modelled.

The EAG position remains unchanged and prefers to assume LDL-C, HDL-C and BMI return to baseline after year 2, applying only natural history changes thereafter.

2.16.2 Cardiovascular disease (CVD) event risks

The risk of CVD events in the economic model is calculated using risk equations: QRISK3 for first events in non-diabetics; UKPDS for diabetes; and Framingham for recurrent events. These risks are also linked to fibrosis stage, with higher risks modelled in patients with more severe fibrosis (F3), CC, and DCC. The company responds to the EAG's critique that these impacts lack supporting evidence from literature or the MAESTRO-NASH trial, stating their approach is deliberately conservative and

citing a recently published study by Shen et al (2026), which reports higher risks of cardiovascular events and mortality in patients with increased fibrosis severity.

The EAG's response

The EAG previously outlined concerns that the provenance of the applied relative risk was unclear. While informed by the US ICER model, no clear empirical evidence was provided to justify the magnitude of the relative risks applied. The EAG further noted that although observational studies have reported associations between increasing fibrosis stage and higher rates of CVD events and CVD mortality, these associations are likely to reflect shared underlying cardiometabolic risk factors. There remains limited evidence to support the existence of an independent effect of fibrosis stage on CVD outcomes.

The company's response does not substantively address these concerns. While the study by Shen et al³⁰ provides additional prospective evidence of an association between increasing fibrosis severity and cardiometabolic disease and mortality risk, it does not support an independent effect of fibrosis stage. The multivariable models reported in Shen *et al.* adjust primarily for lifestyle and demographic factors but do not adjust for established cardiometabolic risk factors, including BMI, glycaemic status, blood pressure, triglycerides, HDL-C, or diabetes diagnosis. The analyses, therefore, do not establish whether fibrosis stage confers risk independently of conventional cardiometabolic risk factors. Furthermore, as acknowledged by the study authors, the observational design limits causal interpretation, and it remains unclear whether interventions targeting MASLD would reduce the risk of cardiometabolic multimorbidity.

The EAG therefore remains uncertain as to whether fibrosis is an independent causal factor of CVD outcomes. Consequently, the EAG does not believe there is enough evidence to support the modelled relative risk and does not find it appropriate to model fibrosis stage as directly affecting CVD event risks.

3 UPDATED MODELLING ASSUMPTIONS

In response to the issues noted in the EAR, and following the additional analyses undertaken by the company, an updated base-case cost-effectiveness model was presented.

The company's updated base incorporated the following changes to the economic model:

- Advance liver disease transition probabilities updated based on targeted literature review.
- Baseline prevalence of IHD, CHF, retinopathy, and diabetic foot ulcer updated using UK real-world data sources specific to T2DM populations.
- Transition probabilities updated using IPD to inform regression of fibrosis stage. Fibrosis progression capped at 1 stage.
- Utility values for F0-F3 fibrosis updated based on MAESTRO NASH data. F4 CC updated to use data from Papatheodoridi *et al.*
- Health state costs updated to use published Davidson *et al.* values supplemented by data from Younossi *et al.*
- Liver-related death cost added.
- CVD event costs to reflect more recent UKPDS84-based estimates.
- Costs for diabetes-related complications, diagnostics, and monitoring were updated for inflation.

3.1 Company revised base case

The results of the company's updated base case are summarised in Table 4.

Table 4 Revised company base case for Technical Engagement

	Treatment	Total costs (£)	Total QALYs	Incremental costs (£)	Incremental QALYs	Cumulative ICER £/QALY
Company's updated base case	SoC			NA	NA	NA
	Resmetirom					35,943

3.2 EAG's exploratory analyses using company's EAG corrected base case

3.2.1 Model validation and face validity check

The EAG identified several errors in the company's economic analyses. The most significant relates to the application of liver-related death costs, which were incorrectly applied not only in the cycle in which a patient dies but also in subsequent cycles. This error had a substantial impact on the ICER but was corrected by the company following correspondence with the EAG and is reflected in the revised base case.

In addition, the EAG identified two minor errors. The first concerns the calculation of age adjustments to utility values, which incorrectly assumed a mean age of 50 rather than 56, the mean age of the cohort used to derive the utilities. The second relates to the inflation indices applied to some cost values (see issue 12). Both errors were corrected by the EAG, resulting in a small reduction in the ICER.

3.2.2 EAG's exploratory analyses using company's base case

Table 5 provides a summary of the EAG's explanatory analyses using the company's corrected base case, while Table 6 present the results of the EAG's explanatory analyses.

Table 5 Summary of EAG's exploratory analyses using company's EAG corrected base case

Exploratory analysis number	Company's base-case assumption	EAG scenario	Justification for EAG assumption	Issue
1	No eligibility assessment costs.	Include additional costs: one extra visit and one FibroScan for the Resmetirom arm only.	NITs have limited accuracy; repeat testing may reduce errors.	5/6
2a	Modelled population based on the MAESTRO-NASH PLB-W52 population.	Modelled population based on subgroup analysis of patients in PLB-W52 with LSM $\geq$ 8 kPa	An exploratory scenario examining the impact of restricting the modelled population to patients who meet the NIT-based eligibility criteria.	1
2b		Modelled population based on subgroup analysis of patients in mITT-W52 with LSM $\geq$ 8 kPa		
3a	Patients stop treatment on regression to F0 or F1.	Patients continue to be treated in F0 and F1.	It is unclear whether the stopping rule can be implemented in practice, and clinical support is equivocal.	5/6
3b	All patients discontinue on progression to F4 CC.	50% of patients continue on treatment on progression to F4 CC.	Exploratory scenario assessing the impact of continued treatment. While clinical support for continuing treatment appears limited, this is contingent on the outcomes of the ongoing MAESTRO-NASH-OUTCOMES trial.	5/6
4a	No additional costs on stopping treatment.	Adds 3 months Resmetirom costs for F0/F1 regression or F4 progression, plus 1 visit and 1 FibroScan.	NITs have a limited ability to distinguish between fibrosis stages. These scenarios assume repeat testing to mitigate errors.	5/6
4b		Adds 6 months Resmetirom costs for F0/F1 regression or F4 progression, plus 1 visit and 1 FibroScan.		

Exploratory analysis number	Company's base-case assumption	EAG scenario	Justification for EAG assumption	Issue
5	MASH resolution transition probabilities derived from MAESTRO-NASH PLB-W52 data.	MASH resolution transition probabilities derived from MAESTRO-NASH mITT-W52 data.	mITT analysis is the primary analysis.	3
6	Cycle 1 transitions for MASH resolution repeated.	MASH resolution is only possible in the first cycle/year of the model.	Current evidence extends only to 1 year, making it impossible to determine the proportion of patients who might achieve MASH resolution beyond this period.	7
7	Treatment effects modelled separately for 80 mg and 100 mg doses.	Treatment effect pool data from 80 mg and 100 mg doses.	Simplified parameterisation	13
8a	Utility values for F0 to F3 sourced from the MAESTRO-NASH trial and include MASH resolution increment. F4 CC utility value set to 0.64.	Utility value derived from Gaussian regression analysis of MAESTRO-NASH data. F4 CC utility value set to 0.64. F4 CC utility value set to 0.725.	NAFL/F0 values exceed general population norms. Resolves inconsistencies in utility values applied to F1–F3. F4 CC value updated to reflect prior mapping to EQ-5D-3L.	11
8b		Utility values drawn from Papatheodoridi <i>et al.</i> MASH resolution decrement removed	Exploratory scenario examining literature-based utility values.	11
9	Health state costs based on Davidson <i>et al.</i> supplemented with data from Younossi <i>et al.</i>	Health state costs based on Younossi <i>et al.</i> only.	Exploratory scenario examining an alternative source of health state costs.	12
10a	Standard of care transitions based on MAESTRO-NASH data.	Standard of care transitions based on Le <i>et al.</i>	Exploratory scenarios considering alternative sources of natural history data.	9
10b		Standard of care transitions based on Ng <i>et al.</i>		
10c		Standard of care transitions based on Le <i>et al.</i> and Ng <i>et al.</i> , combined (limited to one stage change per cycle)		
10d		Standard of care transitions based on Le <i>et al.</i> and Ng <i>et al.</i> , combined (limited to two stage change per cycle)		

Exploratory analysis number	Company's base-case assumption	EAG scenario	Justification for EAG assumption	Issue
11	Transition probabilities for F3 to DCC and F4 to DCC are 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 are based on Vilar-Gomez 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 3).	Davidson <i>et al.</i> values are based on unpublished data, and the value for F3 to DCC does not align with other sources. Shang et al. (Table 4) values are based on the assumption that year 2+ data represent an annual risk.	10
12	Repeats cycle 1 weight changes throughout the time horizon, with an additional natural history effect.	Cycle 1 weight changes are applied during the first cycle only. Thereafter, a natural history effect is applied, consistent with the company's base case.	Repeated application results in clinically implausible changes in weight and BMI.	16

Table 6 Results of EAG's exploratory analyses using EAG corrected company's base case

#	Treatment	Total costs (£)	Total QALYs	Incremental costs (£)	Incremental QALYs	Cumulative ICER £/QALY
Company's base case [corrected]	SoC					
	Resmetirom					35,034
1	SoC					
	Resmetirom					35,102
2a	SoC					
	Resmetirom					42,203
2b	SoC					
	Resmetirom					33,120
3a	SoC					
	Resmetirom					123,296
3b	SoC					
	Resmetirom					42,974
4a	SoC					
	Resmetirom					38,400
4b	SoC					
	Resmetirom					41,652
5	SoC					
	Resmetirom					39,301
6	SoC					
	Resmetirom					112,623
7	SoC					
	Resmetirom					35,552
8a	SoC					
	Resmetirom					39,158
8b	SoC					
	Resmetirom					44,736
9	SoC					
	Resmetirom					35,579
10a	SoC					
	Resmetirom					162,238

#	Treatment	Total costs (£)	Total QALYs	Incremental costs (£)	Incremental QALYs	Cumulative ICER £/QALY
10b	SoC					
	Resmetirom					117,464
10c	SoC					
	Resmetirom					106,446
10d	SoC					
	Resmetirom					93,630
11	SoC					
	Resmetirom					40,336
12	SoC					
	Resmetirom					34,826

3.3 EAG's preferred assumptions

The EAG's preferred assumptions include scenarios 4a, 5, 6, 7, 8a, 11 and 12. Table 7 shows the cumulative impact of the EAG's preferred assumptions on the company's base case ICER. Table 8 presents the results of the probabilistic analysis using the EAG's preferred assumptions.

Table 7 Results using EAG's preferred model assumptions (deterministic)

Preferred assumption	Strategies	Total costs	Total QALYs	Incremental costs (£)	Incremental QALYs	ICER £/QALY
Company's base case	SoC					
	Resmetirom					35,943
EAG's corrected company base case	SoC					
	Resmetirom					35,034
EAG's base case	SoC					
	Resmetirom					170,103

Table 8 Results using EAG's preferred model assumptions (probabilistic)

Preferred assumption	Strategies	Total costs	Total QALYs	Incremental costs (£)	Incremental QALYs	ICER £/QALY
EAG's base case	SoC					
	Resmetirom					160,591

Results run for 1000 iterations

3.4 Scenario analyses using EAG's preferred assumptions

To further explore uncertainty around key assumptions, the EAG conducted additional analyses based on the EAG base case. These included: removing the gated stopping rule (scenario 3a) and excluding scenario 6. The results of these analyses are presented in Table 9.

Table 9 Deterministic results of EAG's scenario analyses using EAG's preferred assumptions

Scenario analysis number	Scenario applied to EAG's base case	Strategies	Total costs	Total QALYs	Incremental costs (£)	Incremental QALYs	ICER £/QALY
	EAG base case	SoC					
		Resmetirom					170,103
1	EAG's base case + gated stopping rule	SoC					
		Resmetirom					330,571
2	EAG's base case + repeat transitions (remove)	SoC					
		Resmetirom					58,174

3.5 Conclusions and interpretation of EAG analyses

The EAG analysis demonstrates that the results of the company's economic model are highly sensitive to key assumptions and parameter choices. In particular, assumptions regarding the effect of continued resmetirom treatment on MASH resolution serve as a critical driver of QALY gains. When MASH resolution is restricted to the first cycle by assuming a plateau after 12 months, QALY gains are substantially reduced and the ICER increases. This highlights the significant uncertainty stemming from the limited follow-up data available in the MAESTRO-NASH trial.

The model's stopping rules also have a marked impact on the results. Removing these rules increases the ICER because continued treatment outside F2 and F3 fibrosis stages provides minimal additional QALYs while incurring substantially higher costs. This underscores the need to establish the plausibility of using NITs to implement the company's preferred stopping rules.

Several further uncertainties remain unaddressed by the presented scenario analysis that are important to the interpretation of the results. While the model structure is based on histologically defined fibrosis stages, treatment decisions in practice will rely on NITs. Additionally, the modelled benefits are primarily driven by the avoidance of advanced liver disease and its complications, yet there is no direct evidence of such outcomes from the MAESTRO-NASH trial. Instead, the model depends on a complex network of surrogate relationships with limited empirical support. Collectively, these factors indicate that the reported ICERs are subject to substantial additional uncertainty and should be interpreted accordingly.

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EAG ADDENDUM

Review of the company's response to Technical Engagement: Resmetirom for treating moderate to advanced liver fibrosis (without cirrhosis) caused by metabolic dysfunction-associated steatohepatitis MIDD001

Produced by

York Technology Assessment Group, University of York, Heslington, York, YO10 5DD

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None

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Richard Parker, Leeds Teaching Hospitals NHS Trust.

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1 OVERVIEW

Following submission of the Evidence Assessment Group (EAG) response to technical engagement, the company notified the EAG that the functionality used to implement EAG scenario 6, relating to the repeat application of the transition probabilities, had been implemented incorrectly. This addendum therefore presents revised results for scenario 6, together with updated results for the EAG base case and associated scenarios.

Table 1 presents updated results for Scenario 6.

Table 1 Results of EAG's exploratory analyses using EAG corrected company's base case

#	Treatment	Total costs (£)	Total QALYs	Incremental costs (£)	Incremental QALYs	Cumulative ICER £/QALY
EAG's corrected company base case	SoC					
	Resmetirom					35,034
6	SoC					
	Resmetirom					

1.1 EAG's preferred assumptions

Table 2 presents the results of the deterministic analysis using the EAG's preferred assumptions and inclusive of the revisions to scenario 6. Table 3 presents the results of the probabilistic analysis using the EAG's preferred assumptions.

Table 2 Results using EAG's preferred model assumptions (deterministic)

Preferred assumption	Strategies	Total costs	Total QALYs	Incremental costs (£)	Incremental QALYs	ICER £/QALY
Company's base case	SoC					
	Resmetirom					35,943
EAG's corrected company base case	SoC					
	Resmetirom					35,034
EAG's base case	SoC					
	Resmetirom					55,280

Table 3 Results using EAG's preferred model assumptions (probabilistic)

Preferred assumption	Strategies	Total costs	Total QALYs	Incremental costs (£)	Incremental QALYs	ICER £/QALY
EAG's base case	SoC					
	Resmetirom					

Results run for 1000 iterations

1.2 Scenario analyses using EAG's preferred assumptions

The EAG explores two scenarios on the EAG base case: i) removing the gated stopping rule, and ii) repeat first year transition probabilities (remove scenario 6). The results of these analyses are presented in Table 4.

Table 4 Deterministic results of EAG's scenario analyses using EAG's preferred assumptions

Scenario analysis number	Scenario applied to EAG's base case	Strategies	Total costs	Total QALYs	Incremental costs (£)	Incremental QALYs	ICER £/QALY
	EAG base case	SoC					
		Resmetirom					55,280
1	EAG's base case + gated stopping rule	SoC					
		Resmetirom					140,633
2	EAG's base case + repeat transitions (remove)	SoC					
		Resmetirom					58,174

EAG ADDENDUM

Review of the company's response to Technical Engagement: Resmetirom for treating moderate to advanced liver fibrosis (without cirrhosis) caused by metabolic dysfunction-associated steatohepatitis MIDD001

Produced by

York Technology Assessment Group, University of York, Heslington, York, YO10 5DD

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Date completed 24/04/2026

Declared competing interests of the authors

None

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Richard Parker, Leeds Teaching Hospitals NHS Trust.

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1 OVERVIEW

Following submission of the Evidence Assessment Group (EAG) addendum to the response to the technical engagement, transcription errors were identified in the transition probabilities for liver complications (F3 to DCC, F3 to HCC, and F4 to DCC). This addendum therefore presents revised results for scenario 11, along with updated results for the EAG base case and associated scenarios.

Table 1 presents updated results for Scenario 11.

Table 1 Results of EAG's exploratory analyses using EAG corrected company's base case

#	Treatment	Total costs (£)	Total QALYs	Incremental costs (£)	Incremental QALYs	Cumulative ICER £/QALY
EAG's corrected company base case	SoC					
	Resmetirom					35,034
11	SoC					
	Resmetirom					43,560

1.1 EAG's preferred assumptions

Table 2 presents the results of the deterministic analysis using the EAG's preferred assumptions and inclusive of the revisions to scenario 11. Table 3 presents the results of the probabilistic analysis using the EAG's preferred assumptions.

Table 2 Results using EAG's preferred model assumptions (deterministic)

Preferred assumption	Strategies	Total costs	Total QALYs	Incremental costs (£)	Incremental QALYs	ICER £/QALY
Company's base case	SoC					
	Resmetirom					35,943
EAG's corrected company base case	SoC					
	Resmetirom					35,034
EAG's base case	SoC					
	Resmetirom					66,081

Table 3 Results using EAG's preferred model assumptions (probabilistic)

Preferred assumption	Strategies	Total costs	Total QALYs	Incremental costs (£)	Incremental QALYs	ICER £/QALY
EAG's base case	SoC					
	Resmetirom					

Results run for 1000 iterations

1.2 Scenario analyses using EAG's preferred assumptions

The EAG explores two scenarios on the EAG base case: i) removing the gated stopping rule, and ii) repeating the first year transition probabilities (remove scenario 6). The results of these analyses are presented in Table 4.

Table 4 Deterministic results of EAG's scenario analyses using EAG's preferred assumptions

Scenario analysis number	Scenario applied to EAG's base case	Strategies	Total costs	Total QALYs	Incremental costs (£)	Incremental QALYs	ICER £/QALY
	EAG base case	SoC	██████	██████			
		Resmetirom	██████	██████	██████	██████	66,081
1	EAG's base case + gated stopping rule	SoC	██████	██████			
		Resmetirom	██████	██████	██████	██████	159,621
2	EAG's base case + repeat transitions (remove)	SoC	██████	██████			
		Resmetirom	██████	██████	██████	██████	63,808

EAG ADDENDUM

Review of the company's response to Technical Engagement: Resmetirom for treating moderate to advanced liver fibrosis (without cirrhosis) caused by metabolic dysfunction-associated steatohepatitis MIDD001

Produced by

York Technology Assessment Group, University of York, Heslington, York, YO10 5DD

Authors

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None

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1 OVERVIEW

Following the Evidence Assessment Group (EAG) addendum to correct transcription errors in liver complication transition probabilities (F3 to DCC, F3 to HCC, and F4 to DCC), a further error was identified in the 'F4 (CC) to DCC' transition probability. This has now been changed to 0.06263, in line with Table 3 from Vilar-Gomez et al.¹ We note that it was approximately correct (0.065) in the original EAG base case, but was changed to 0.019 in later EAG addenda models. Furthermore, the values for F3 to DCC (0.6%) and F3 to HCC (0.2%) have also been converted to probabilities to correspond to those reported in Table 3 of Vilar-Gomez et al.¹ While the original intention was to use values from Vilar-Gomez et al.,¹ this addendum now presents revised results for scenario 11, along with updated results for the EAG base case and associated scenarios.

Table 1 presents updated results for Scenario 11.

Table 1 Results of EAG's exploratory analyses using EAG corrected company's base case

#	Treatment	Total costs (£)	Total QALYs	Incremental costs (£)	Incremental QALYs	Cumulative ICER £/QALY
EAG's corrected company base case	SoC					
	Resmetirom					35,034
11	SoC					
	Resmetirom					39,367

1.1 EAG's preferred assumptions

Table 2 presents the results of the deterministic analysis using the EAG's preferred assumptions and inclusive of the revisions to scenario 11. Table 3 presents the results of the probabilistic analysis using the EAG's preferred assumptions.

Table 2 Results using EAG's preferred model assumptions (deterministic)

Preferred assumption	Strategies	Total costs	Total QALYs	Incremental costs (£)	Incremental QALYs	ICER £/QALY
Company's base case	SoC					
	Resmetirom					35,943
EAG's corrected company base case	SoC					
	Resmetirom					35,034
EAG's base case	SoC					
	Resmetirom					57,755

Table 3 Results using EAG's preferred model assumptions (probabilistic)

Preferred assumption	Strategies	Total costs	Total QALYs	Incremental costs (£)	Incremental QALYs	ICER £/QALY
EAG's base case	SoC	██████	██████			
	Resmetirom	██████	██████	██████	██████	██████

Results run for 1000 iterations

1.2 Scenario analyses using EAG's preferred assumptions

The EAG explores two scenarios on the EAG base case: i) removing the gated stopping rule, and ii) repeating the first year transition probabilities (remove scenario 6). The results of these analyses are presented in Table 4.

Table 4 Deterministic results of EAG's scenario analyses using EAG's preferred assumptions

Scenario analysis number	Scenario applied to EAG's base case	Strategies	Total costs	Total QALYs	Incremental costs (£)	Incremental QALYs	ICER £/QALY
	EAG base case	SoC	██████	██████			
		Resmetirom	██████	██████	██████	██████	57,755
1	EAG's base case + gated stopping rule	SoC	██████	██████			
		Resmetirom	██████	██████	██████	██████	145,990
2	EAG's base case + repeat transitions (remove)	SoC	██████	██████			
		Resmetirom	██████	██████	██████	██████	62,290

1. Vilar-Gomez E, Calzadilla-Bertot L, Wai-Sun Wong V, Castellanos M, Aller-de la Fuente R, Metwally M, et al. Fibrosis severity as a determinant of cause-specific mortality in patients with advanced nonalcoholic fatty liver disease: a multi-national cohort study. *Gastroenterology* 2018;**155**:443–57.

Additional Input from Clinical Experts – May 2026

Resmetirom for treating non-alcoholic steatohepatitis and liver fibrosis [ID6529]

This document contains questions to Clinical Experts from the Chair and NICE Technical Team with the Clinical Expert's response in boxes.

Professor Quentin Anstee (QA) – Nominated by Madriral Pharmaceuticals UK Ltd

1. Pathway

Considering people with MASH F2-3 the company have indicated as outlined in P42 CS that resmetirom would be started in parallel with interventions to manage the metabolic syndrome. Is that likely to be the approach if resmetirom were to be approved or would clinicians start by optimising the management of the metabolic syndrome and then add resmetirom if there was not improvement in MASH inflammation or fibrosis, ie sequential treatment?

Response from QA:

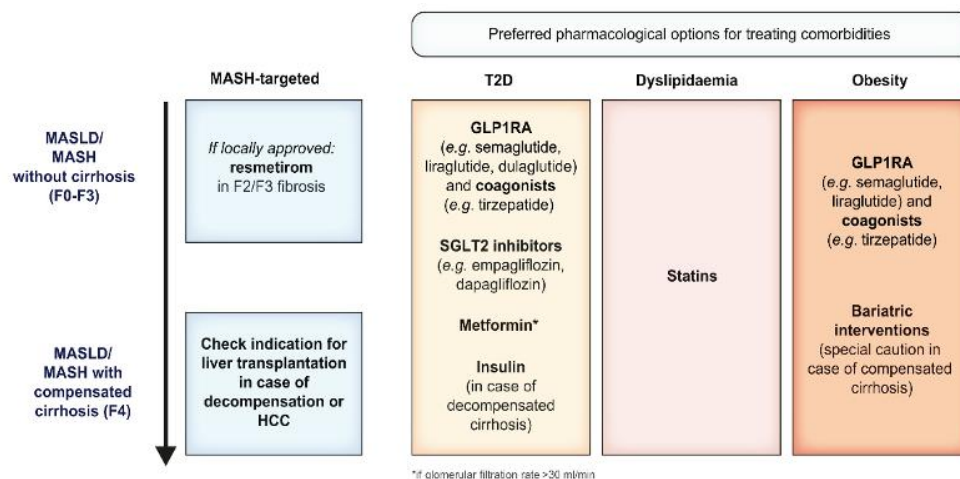
This assumes that all diagnoses are new. In my experience, it is most likely that patients are referred having already been diagnosed with specific features of the metabolic syndrome (particularly T2DM, hypertension, dyslipidaemia) for some time and already on treatment for these prior to the time of MASLD diagnosis, even if management is sub optimum. For example, statin therapy is often indicated due to cardiovascular risk but has been withheld/suspended by the primary care physician due to concerns regarding abnormal LFTs so that may need to be restarted. The most likely scenario is that patients would therefore start Resmetirom after

management of metabolic syndrome is in place although some optimisation of therapy for metabolic risk continues as with any chronic condition.

If treatment is sequential then what would be the time period to assess response to metabolic interventions?

Response from QA:

Assuming simultaneous new diagnosis, it would depend on the specific feature of the metabolic syndrome being treated and the agents used (eg statins, ACEi and some anti diabetic agents would not be expected to improve MASLD) and so should not delay starting MASLD specific therapy. However if an agent with established benefit for MASLD were to be used (eg GLP1), I would recommend a period of 3-6 months after commencing before reassessing.



Additional Input from Clinical Experts – May 2026

Resmetirom for treating non-alcoholic steatohepatitis and liver fibrosis
[ID6529]

If the answer is a mix of both approaches what would be the criteria for parallel vs sequential treatment?

Response from QA:

As above.

2. Trial generalisability and requirement for cardiometabolic risk factors

The MAESTRO-NASH study recruited patients with ≥ 3 cardiometabolic risk factors. Would that be the population you see resmetirom being used in or would it be wanted in a broader population without this requirement? Is there evidence to support the generalisability of the trial data to a broader population, i.e. would resmetirom work as well in a lower risk population or would the relative or absolute benefit be reduced?

Response from QA:

Happy to discuss further in the meeting. Many cases with F2-3 diagnosis do have multiple features of the metabolic syndrome so this is not unrepresentative. It is the degree of fibrosis that drives outcome so, if patients have the requisite amount of liver fibrosis caused by MASLD, I would not advocate withholding treatment simply because they had fewer MetS features.

Additional Input from Clinical Experts – May 2026

Resmetirom for treating non-alcoholic steatohepatitis and liver fibrosis
[ID6529]

How are the technology appraisals related to semaglutide and tirzepatide interpreted by the clinical community and specifically is MASH considered a weight related comorbidity in relation to accessing these drugs?

Response from QA:

Semaglutide and Tirzepatide are currently being assessed for the treatment of MASH. Semaglutide has positive Phase 3 data and is itself licensed in USA and EU for this indication but not in UK. It should be noted that 72 weeks of therapy was required to demonstrate histological fibrosis improvement.

In the UK, MASH is not considered an indication for incretin therapy at present.

- [TA1026 - Tirzepatide](#)
- [TA875 - Semaglutide](#)

3. Non- Invasive testing strategy

In terms of non-invasive diagnostics, our understanding is:

- FIB-4 - screening tool

Response from QA:

Correct. A simple score based on routine blood tests (age, AST, ALT, Platelets) that is cheap with high NPV to rule out cases, could be repeated annually.

Additional Input from Clinical Experts – May 2026

Resmetirom for treating non-alcoholic steatohepatitis and liver fibrosis
[ID6529]

- ELF - confirmatory with different cutoffs depending on whether an additional confirmatory test is required
- Fibroscan/VCTE, (I believe these are the same investigation), to confirm

Response from QA:

Fibroscan and VCTE refer to the same test.

Both Fibroscan/VCTE and ELF are second line tests based on complementary technologies (ELF = ECM turnover; VCTE = liver stiffness) and can be used as alternatives to each other. For both tests a range of thresholds have been proposed and can be used to select cases with greater/lesser likelihood of advanced disease (ie balancing Sens/Spec).

- Liver biopsy if there is a concern about progression to cirrhosis or diagnostic uncertainty

Response from QA:

Correct. In hepatology practice this is done less and less as NITs are widely available.

We suspect we may have simplified, but is this correct?

Response from QA:

Yes, with the caveats above.

Additional Input from Clinical Experts – May 2026

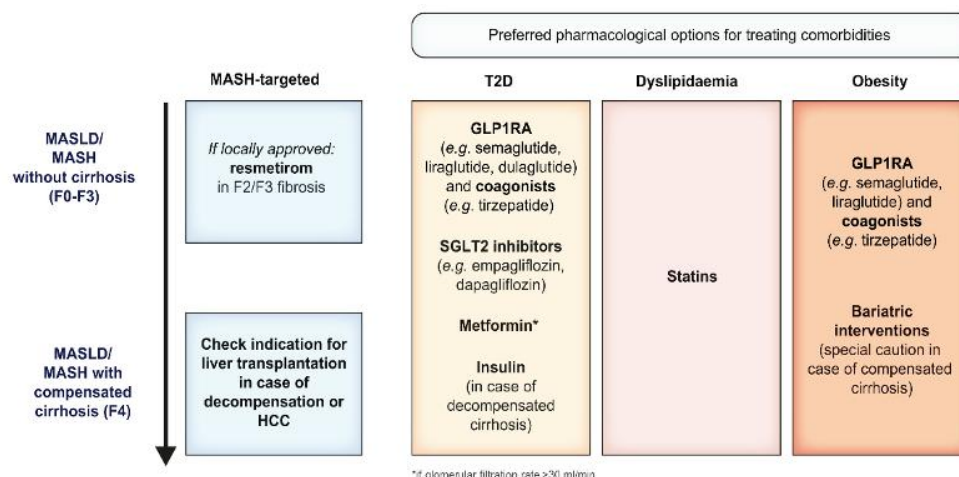
Resmetirom for treating non-alcoholic steatohepatitis and liver fibrosis
[ID6529]

Dr Richard Aspinall (RA) – Nominated by NHS England

1. Pathway

Considering people with MASH F2-3 the company have indicated as outlined in P42 CS that resmetirom would be started in parallel with interventions to manage the metabolic syndrome. Is that likely to be the approach if resmetirom were to be approved or would clinicians start by optimising the management of the metabolic syndrome and then add resmetirom if there was not improvement in MASH inflammation or fibrosis, ie sequential treatment?

If treatment is sequential then what would be the time period to assess response to metabolic interventions?



If the answer is a mix of both approaches what would be the criteria for parallel vs sequential treatment?

Additional Input from Clinical Experts – May 2026

Resmetirom for treating non-alcoholic steatohepatitis and liver fibrosis [ID6529]

Response from RA:

I would expect the wider metabolic interventions would be carried out in parallel with resmetirom therapy rather than sequentially. This would be in line with the protocols from clinical trials and would reflect the wider concerns such as cardiometabolic risk factors.

2. Trial generalisability and requirement for cardiometabolic risk factors

The MAESTRO-NASH study recruited patients with ≥ 3 cardiometabolic risk factors. Would that be the population you see resmetirom being used in or would it be wanted in a broader population without this requirement? Is there evidence to support the generalisability of the trial data to a broader population, i.e. would resmetirom work as well in a lower risk population or would the relative or absolute benefit be reduced?

How are the technology appraisals related to semaglutide and tirzepatide interpreted by the clinical community and specifically is MASH considered a weight related comorbidity in relation to accessing these drugs?

- [TA1026 - Tirzepatide](#)
- [TA875 - Semaglutide](#)

Response from RA:

It is difficult to answer questions on efficacy in populations not included in the trials without further evidence. If by a “lower risk population” you mean people with little or no fibrosis or MASH, then it would be difficult to

Additional Input from Clinical Experts – May 2026

Resmetirom for treating non-alcoholic steatohepatitis and liver fibrosis
[ID6529]

demonstrate an anti-fibrotic effect or a MASH-resolving effect in the absence of these conditions.

Regarding your follow-up question of whether MASH is regarded as a comorbidity to enable access to tirzepatide or semaglutide (for obesity), the current NHS England guidance is that it is not a qualifying comorbidity.

3. Non- Invasive testing strategy

In terms of non-invasive diagnostics, our understanding is:

- FIB-4 - screening tool
- ELF - confirmatory with different cutoffs depending on whether an additional confirmatory test is required
- Fibroscan/VCTE, (I believe these are the same investigation), to confirm
- Liver biopsy if there is a concern about progression to cirrhosis or diagnostic uncertainty

We suspect we may have simplified, but is this correct?

Response from RA:

I would say that FIB-4 is a fibrosis risk score. It has a high negative predictive value for ruling out advanced fibrosis (F3-F4).

FibroScan is a registered trademark of Echosens for VCTE but perhaps should not be used synonymously as there may be other potential providers

Additional Input from Clinical Experts – May 2026

Resmetirom for treating non-alcoholic steatohepatitis and liver fibrosis
[ID6529]

of VCTE more widely available soon (eg Hisky Medical), so perhaps VCTE would be the preferred term.

Regarding liver biopsy, rather than saying it would be reserved for “a concern about progression to cirrhosis or diagnostic uncertainty”, I would probably avoid the first part of the statement and maybe just simplify it to say biopsy could be used if non-invasive staging tests are equivocal/inconsistent or if there is diagnostic uncertainty. This would be in only a very small minority.

Additional Input from Clinical Experts – May 2026

Resmetirom for treating non-alcoholic steatohepatitis and liver fibrosis
[ID6529]

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