



EUROPEAN MEDICINES AGENCY
SCIENCE MEDICINES HEALTH

19 June 2025
EMA/194017/2025
Committee for Medicinal Products for Human Use (CHMP)

Assessment report

Rezdiffra

International non-proprietary name: resmetirom

Procedure No. EMEA/H/C/006220/0000

Note

Assessment report as adopted by the CHMP with all information of a commercially confidential nature deleted.



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List of abbreviations

AASLD	American Association for the Study of Liver Diseases
AE	Adverse event
AESI	Adverse event of special interest
ALP	Alkaline phosphatase
ALT	Alanine aminotransferase
API	Active pharmaceutical ingredient
ApoB	Apolipoprotein B
ApoCIII	Apolipoprotein CIII
AS	Active substance
AST	Aspartate aminotransferase
AUC	Area under the plasma concentration-time curve
AUC ₀₋₂₄	Area under the plasma concentration versus time curve from time zero until 24 hours post-dose
AUC _{0-inf}	Area under the plasma concentration-time curve from the time of dosing extrapolated to infinity
AUC _{0-T}	Area under the plasma concentration-time curve from the time of dosing through time t
BCRP	Breast cancer resistance protein
BMD	Bone mineral density
BMI	Body mass index
BSV	Between subject variability
BW	Body weight
CAP	Controlled attenuation parameter
CDT	Carbohydrate-deficient transferrin
CFB	Change from baseline
CI	Confidence interval
CK-18	Cytokeratin-18
CL/F	Central clearance
C _{max}	Maximum observed concentration
CMH	Cochran-Mantel-Haenszel
COVID-19	Coronavirus-19
CP	Child-Pugh

CQAs	Critical Quality Attributes
CRN	Clinical Research Network
CTC	Common Terminology Criteria
CV	Cardiovascular
CYP	Cytochrome
DDI	Drug-drug interaction
DIO1	Deiodinase 1
DHN	Division of Hepatology and Nutrition
DILI	Drug-induced liver injury
DXA	Dual x-ray absorptiometry
EAIR	Exposure-adjusted incidence rate
EASL	European Association for the Study of the Liver
ECG	Electrocardiogram
ELF	Enhanced liver fibrosis
E _{max}	Maximum effect
EOP2	End of Phase 2
F	Fibrosis stage
FAST	FibroScan AST
FP	Finished product
FSH	Follicle-stimulating hormone
FT IR	Fourier transform infrared spectroscopy
FT3	Free triiodothyronine
FT4	Free thyroxine
GC(FID)	Gas chromatography (flame ionisation detector)
GEE	General Estimating Equation
GGT	Gamma-glutamyl transpeptidase
GI	Gastrointestinal
GLP-1	Glucagon-like peptide-1
GMR	Geometric mean ratios
HAC	Hepatic Adjudication Committee
HCC	Hepatocellular carcinoma
HDL-C	High-density lipoprotein cholesterol

HDPE	High-density polyethylene
HI	Hepatic impairment
HPLC (DAD)	High-performance liquid chromatography (diode array detector)
KF	Karl Fischer titration
KM	Kaplan-Meier
ICH	International Council for Harmonisation of Technical Requirements for Pharmaceuticals for Human Use
IC ₅₀	Half-maximal inhibitory concentration
ICP-MS	Inductively couple plasma mass spectrometry
ITT	Intent-to-Treat
LC-MS/MS	Liquid chromatography with tandem mass spectrometry
LDL-C	Low-density lipoprotein cholesterol
LLN	Lower limit of normal
LLOQ	Lower limit of quantification
Lp(a)	Lipoprotein(a)
LS	Least squares
LSM	liver stiffness measurements
MACE	Major adverse cardiovascular events
MAA	Marketing authorisation application
MASH	Metabolic dysfunction-associated steatohepatitis
MASLD	Metabolic dysfunction-associated steatotic liver disease
MELD	Model for End-Stage Liver Disease
mITT	Modified Intent-to-Treat
MO	Major objection
MRE	Magnetic resonance elastography
MRI-PDFF	Magnetic resonance imaging protein density fat fraction
MS	Metabolic syndrome
NAFLD	Nonalcoholic fatty liver disease
NAS	Nonalcoholic fatty liver disease activity score
NASH	Nonalcoholic steatohepatitis
NDA	New drug application
NMR	Nuclear magnetic resonance spectroscopy

OATP	Organic anion-transporting polyproteins
PBC	Primary biliary cirrhosis
PD	Pharmacodynamic
PeTH	Phosphatidyl ethanol
Ph. Eur.	European Pharmacopoeia
PIIINP	Amino-terminal propeptide of type III procollagen
PK	Pharmacokinetic
PT	Preferred term
QC	Quality control
QP	Qualified person
QTPP	Quality Target Product Profile
Rac	Accumulation ratio
RH	Relative humidity
RSE	Root square error
RT3	Reverse triiodothyronine
SAE	Serious adverse event
SAP	Statistical analysis plan
SE	Standard error
SHBG	Sex hormone binding globulin
$t_{1/2\alpha}$	Elimination half-life during the absorption phase
$t_{1/2\beta}$	Elimination half-life during the elimination phase
T3	Triiodothyronine
T4	Thyroxine
TBG	Thyroxine binding globulin
TEAE	Treatment-emergent adverse event
TG	Triglycerides
THR	Thyroid hormone receptor
THR- β	Thyroid hormone receptor-beta
TIMP-1	Tissue inhibitor of matrix metalloproteinases-1
T_{max}	Time to maximum concentration
TSH	Thyroid-stimulating hormone
ULN	Upper limit of normal

UPLC	Ultra high performance liquid chromatography
USP	United States Pharmacopoeia
UV	Ultraviolet
V _c /F	Apparent volume of distribution of the central compartment
VCTE	Vibration-controlled Transient Elastography
VLDL-C	Very-low-density lipoprotein cholesterol
XRPD	X-Ray powder diffraction

1. Background information on the procedure

1.1. Submission of the dossier

The applicant Madrigal Pharmaceuticals EU Limited submitted on 12 February 2024 an application for marketing authorisation to the European Medicines Agency (EMA) for Rezdiffra, through the centralised procedure under Article 3 (2) (a) of Regulation (EC) No 726/2004. The eligibility to the centralised procedure was agreed upon by the EMA/CHMP on 13 October 2022.

The applicant applied for the following indication: resmetirom is indicated for the treatment of adults with non-alcoholic steatohepatitis (NASH)/metabolic dysfunction-associated steatohepatitis (MASH) with liver fibrosis.

1.2. Legal basis, dossier content

The legal basis for this application refers to:

Article 8.3 of Directive 2001/83/EC - complete and independent application.

The application submitted is composed of administrative information, complete quality data, non-clinical and clinical data based on applicant's own tests and studies and/or bibliographic literature substituting/supporting certain tests or studies.

1.3. Information on paediatric requirements

Pursuant to Article 7 of Regulation (EC) No 1901/2006, the application included an EMA Decision(s) P/0462/2022 on the agreement of a paediatric investigation plan (PIP).

At the time of submission of the application, the PIP P/0462/2022 was not yet completed as some measures were deferred.

1.4. Information relating to orphan market exclusivity

1.4.1. Similarity

Pursuant to Article 8 of Regulation (EC) No. 141/2000 and Article 3 of Commission Regulation (EC) No 847/2000, the applicant did not submit a critical report addressing the possible similarity with authorised orphan medicinal products because there is no authorised orphan medicinal product for a condition related to the proposed indication.

1.5. Applicant's requests for consideration

1.5.1. Conditional marketing authorisation

The applicant requested consideration of its application for a conditional marketing authorisation (CMA) in accordance with Article 14-a of the above-mentioned Regulation.

1.5.2. New active substance status

The applicant requested the active substance resmetirom contained in the above medicinal product to be considered as a new active substance, as the applicant claims that it is not a constituent of a

medicinal product previously authorised within the European Union.

1.6. Scientific advice

The applicant received the following scientific advice on the development relevant for the indication subject to the present application:

Date	Reference	SAWP co-ordinators
27 June 2019	EMA/H/SA/4140/1/2019/I	<i>Elmer Schabel, Stephan Lehr</i>

The Scientific advice pertained to the following quality aspects:

- Regulatory starting materials and reagents

1.7. Steps taken for the assessment of the product

The Rapporteur and Co-Rapporteur appointed by the CHMP were:

Rapporteur: Janet Koenig Co-Rapporteur: Elita Poplavska

The application was received by the EMA on	12 February 2024
The procedure started on	29 February 2024
The CHMP Rapporteur's first Assessment Report was circulated to all CHMP and PRAC members on	3 June 2024
The CHMP Co-Rapporteur's first Assessment Report was circulated to all CHMP and PRAC members on	4 June 2024
The PRAC Rapporteur's first Assessment Report was circulated to all PRAC and CHMP members on	7 June 2024
The CHMP agreed on the consolidated List of Questions to be sent to the applicant during the meeting on	27 June 2024
The applicant submitted the responses to the CHMP consolidated List of Questions on	24 January 2025
The CHMP Rapporteurs circulated the CHMP and PRAC Rapporteurs Joint Assessment Report on the responses to the List of Questions to all CHMP and PRAC members on	07 March 2025
The PRAC agreed on the PRAC Assessment Overview and Advice to CHMP during the meeting on	13 March 2025
The CHMP agreed on a list of outstanding issues in writing to be sent to the applicant on	27 March 2025
The applicant submitted the responses to the CHMP List of Outstanding Issues on	20 May 2025
The CHMP Rapporteurs circulated the CHMP and PRAC Rapporteurs Joint Assessment Report on the responses to the List of Outstanding Issues	06 June 2025

to all CHMP and PRAC members on	
The CHMP, in the light of the overall data submitted and the scientific discussion within the Committee, issued a positive opinion for granting a conditional marketing authorisation to Rezdiffra on	19 June 2025
Furthermore, the CHMP adopted a report on New Active Substance (NAS) status of the active substance contained in the medicinal product (see Appendix on NAS)	19 June 2025

2. Scientific discussion

2.1. Problem statement

2.1.1. Disease or condition

The applicant initially claimed the following indication:

“Resmetirom is indicated for the treatment of adults with non-alcoholic steatohepatitis (NASH)/metabolic dysfunction-associated steatohepatitis (MASH) with liver fibrosis”.

At the request of the CHMP, the applicant has substantiated their application for a CMA, by explaining that patients with more advanced MASH fibrosis also have increased morbidity and mortality from progression of their liver disease, including progression to MASH cirrhosis, liver failure, and hepatocellular carcinoma (HCC) (*Angulo et al, 2015; Dulai et al, 2017*).

Non-alcoholic fatty liver disease (NAFLD) was proposed to be re-labelled as “Metabolic Associated Fatty Liver Disease” (MAFLD) in 2020 which was related to the close relationship to over-alimentation and metabolic dysfunction. A multi-society Delphi consensus has finally concluded in 2023, that NAFLD should indeed be renamed as “metabolic dysfunction-associated steatotic liver disease” (MASLD), as well as to relabel NASH as “metabolic dysfunction-associated steatohepatitis” (MASH). The reasons for the relabelling were related to avoiding terms referring to exclusion of conditions, but also of potentially stigmatising nomenclature (such as “alcoholic” and “fatty”). The main aspect of this relabelling refers to MASLD, which was redefined and will compulsorily require the presence of 1 out of 5 cardiometabolic risk factors. The term MASH, contrary to MASLD does not include a revision of the definition and still includes the term steatohepatitis and is intended to ensure retention and validity of prior data from clinical studies.

In this assessment report, the new nomenclature will be used as far as possible and adequate. Partly the two terms are used in parallel (using NASH/MASH).

2.1.2. Epidemiology and risk factors, screening tools/prevention

Over the past four decades, MASLD has become the most common chronic liver disorder and is recognised to have a close association with components of metabolic syndrome, such as type-2 diabetes mellitus (T2DM), hyperlipidaemia, hypertension, and others.

MASLD prevalence has been estimated to be 30% on a global level, and 25-27% in Europe.

MASLD incidence and prevalence is also the most rapidly increasing cause of liver-related mortality worldwide and is emerging as an important cause of end-stage liver disease, primary liver cancer, and

liver transplantation with a substantial health economic burden. Despite the growing concern, MASLD is underappreciated as an important chronic disease.

The indication assessed, Metabolic Dysfunction Associated Steatohepatitis (MASH), is considered the progressive, necro-inflammatory phenotype of MASLD. It is estimated that about 20-50% of patients with MASLD suffer from MASH.

2.1.3. Biologic features, aetiology and pathogenesis

The primary driver of MASLD/MASH is considered to be overnutrition, which causes expansion of adipose depots as well as accumulation of ectopic fat. In this setting, macrophage infiltration of the visceral adipose tissue compartment creates a proinflammatory state that promotes insulin resistance. Inappropriate lipolysis in the setting of insulin resistance results in unabated delivery of fatty acids to the liver, which, along with increased de-novo lipogenesis, overwhelms its metabolic capacity. The imbalance in lipid metabolism leads to the formation of lipotoxic lipids that contribute to cellular stress (i.e. oxidative stress and endoplasmic reticulum stress), inflammasome activation and apoptotic cell death, and subsequent stimulation of inflammation, tissue regeneration, and fibrogenesis.

The progression of MASLD to MASH, and the progression of MASH itself to ultimately end-stage liver disease is associated with the presence of co-morbidities such as obesity, T2DM, dyslipidaemia, and hypertension. Genetic “modifiers” (such as PNPLA3 variant) are also involved. The risk of developing end-stage liver disease is associated with the presence of higher stages of fibrosis.

2.1.4. Clinical presentation, diagnosis and stage/prognosis

There is no specific symptomatology for the presence of MASH in patients. Usually, patients are already under treatment for their co-morbidities (e.g. such as T2DM) or are detected with routine diagnostics in primary care with elevated liver enzymes, and/or ultrasound diagnosing a fatty liver.

Despite the presence of unspecific symptoms only, the quality of life in patients with MASH has been detected to be relevantly impaired especially in more advanced stages.

The further diagnostic algorithm will usually consist of the exclusion of relevant alcohol intake, and the conduct of non-invasive tests searching for the presence of relevant fibrosis.

Ultimately, for the final distinction of MASLD and its progressive form, MASH, the conduct of a liver biopsy is necessary. Liver biopsy is evaluated using HE and trichrome staining, and evaluation of histological sample focusses on features of MASH, such as the presence of steatosis, hepatocyte ballooning, lobular inflammation and fibrosis (of which none is specific). Several systems of evaluation (grading and staging) of MASH histology samples have been developed of which the “NASH-CRN” is the most widely used.

The presence of MASH is associated with a reduced life expectancy from cardiovascular events, malignancy (HCC), or liver-related events. The mainstay of mortality is associated with cardiovascular events. MASH is a slowly progressive disease, but with more advanced fibrosis (fibrosis stage F3 or F4), liver disease progresses rapidly. End-stage liver disease is associated with the presence of liver cirrhosis and portal hypertension, and the occurrence of decompensation events, such as variceal bleeding, hepatic encephalopathy, or ascites.

Epidemiological data have shown that at early stages of MASH (fibrosis stage 1), the disease is not associated with a significant risk for progression to end-stage liver disease, contrary to the later

fibrosis stages. The current guidance document (the Reflection paper on regulatory requirements for the development of medicinal products for non-alcoholic steatohepatitis (NASH) EMA/CHMP/111529/2024) therefore recommends including patients with fibrosis stages 2-4 only into clinical trials in MASH.

2.1.5. Management

There is currently no approved pharmacological treatment available for MASH. Current available treatment used in clinical practice ranges from changes in diet and exercise (aiming at weight reduction), to bariatric surgery (of different kinds/techniques) for the non-pharmacological treatments, to pharmacological treatments used off-label. In the past, substances such as vitamin E and pioglitazone have been recommended (and partially tested in randomised clinical trials with demonstration of histological effects). More recently, GLP-1 agonists (especially in patients with co-existing T2DM and/or obesity) are studied with phase 2 trial results in MASH being publicly available. The European clinical practice guidelines for NAFLD/NASH do recommend treatment with diet and exercise to achieve weight reduction, and also discuss treatment recommendations such as vitamin E or bariatric surgery.

It is therefore concluded that – since there is no approved pharmacological treatment available - there is clearly an unmet medical need. Pharmacological treatment would aim to reduce inflammation, liver cell stress, and steatotic load in the hepatocytes, and halt or even reverse fibrosis.

2.2. About the product

Resmetirom is an orally active, partial agonist for the thyroid hormone receptor beta (THR- β). Resmetirom has approximately a 28-fold selectivity for the beta receptor relative to the THR alpha receptor as compared to the active thyroid hormone, triiodothyronine (T3). THR- β stimulation improves mitochondrial function and lipid metabolism in the liver.

Resmetirom is available for oral use as:

- 60 mg resmetirom tablet: white oval-shaped film-coated tablets debossed "P60" on one side and plain on the other side.
- 80 mg resmetirom tablet: yellow oval-shaped film-coated tablets debossed "P80" on one side and plain on the other side.
- 100 mg resmetirom tablet: beige to pinkish-coloured oval-shaped film-coated tablets debossed "P100" on one side and plain on the other side.

2.3. Type of application and aspects on development

The CHMP did not agree to the applicant's request for an accelerated assessment as the product was not considered to be of major public health interest. This was based on the fact that the CHMP did not consider that an accelerated assessment would be relevant for the disease, which has a slow progression to a real clinical concern. The CHMP also agreed that the applicant has failed to describe the available treatment modalities that are likely to prevent disease progression, in comparison to the product to be assessed. In addition, there were concerns related to the clinical relevance of the effects

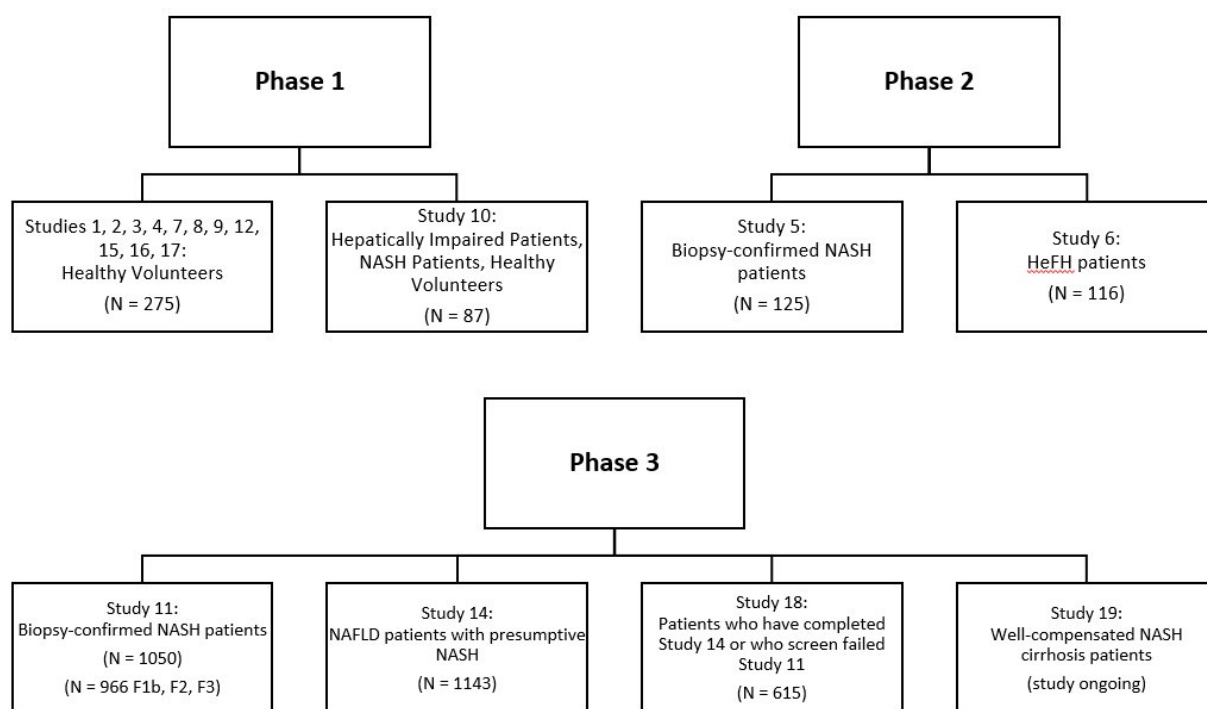
achieved, as well as uncertainties associated with the use of these non-validated surrogate endpoints and the generation of the long-term outcome data.

The applicant requested consideration of its application for a CMA in accordance with Article 14-a of the above-mentioned Regulation, based on the following criteria:

- The benefit-risk balance is positive.
- It is likely that the applicant will be able to provide comprehensive data. The pivotal study is currently on-going and proposes to evaluate the liver-related outcomes (including manifestation of cirrhosis). Additionally, a trial in the cirrhotic population evaluating liver outcomes (Study 19, MAESTRO NASH OUTCOMES) and supportive study (Study 18 MAESTRO-NAFLD-OLE) evaluating safety and biomarkers has been initiated. This will be supplemented by an integrated documentation of cardiovascular safety, reflecting the requirements of the EMA reflection paper on cardiovascular safety (EMA/CHMP/505049/2015).
- Unmet medical needs will be addressed, as there is no treatment available for the indication proposed. The applicant has stressed the need for an approved therapy for the treatment of MASH or MASH cirrhosis, which has seen increased prevalence with the increasing global prevalence of obesity (Konerman et al, 2018; Younossi et al, 2018) and which is associated with a reduced life expectancy from malignancy or from cardiovascular or liver-related events in its advanced stages.
- The benefits to public health of the immediate availability outweigh the risks inherent in the fact that additional data is still required. As mentioned above, MASH may impose a relevant burden on the society, and the immediate availability of a specific treatment is considered to alleviate this burden.

Based on the provided data the CMA is considered justified.

The clinical development program for resmetirom for the treatment of MASH comprises 18 clinical studies: twelve Phase 1 studies, two Phase 2 studies, and four Phase 3 studies (see the following figure). The safety and tolerability of resmetirom have been assessed in doses ranging from 5 mg to 200 mg per day across the Phase 1, 2, and 3 clinical studies. As of the time of this marketing authorisation application (MAA) submission, data are available for patients who have been assigned to treatment with resmetirom 80 mg (n = 776) or 100 mg (n = 1356) in Applicant-sponsored clinical studies.



Of the 776 and 1356 patients having been treated with resmetirom 80 and 100 mg respectively, 702 were treated for ≥ 3 months, 657 and 1127 for ≥ 6 months, 229 and 733 for ≥ 12 months, and 20 and 127 for ≥ 24 months.

Although no clinical Scientific Advice has been received, the applicant has mainly followed the relevant guidance available ("Reflection paper on regulatory requirements for the development of medicinal products for non-alcoholic steatohepatitis (NASH)"; EMA/CHMP/111529/2024).

2.4. Quality aspects

2.4.1. Introduction

The finished product (FP) is presented as immediate release film-coated tablets containing 60 mg or 80 mg or 100 mg of resmetirom as active substance.

Other ingredients are:

- *tablet core*: microcrystalline cellulose, mannitol, croscarmellose sodium, colloidal anhydrous silica, magnesium stearate
- *tablet coating for 60 mg film-coated tablets*: poly(vinyl alcohol), titanium dioxide (E171), macrogol, talc;
- *tablet coating for 80 mg film-coated tablets*: poly(vinyl alcohol), titanium dioxide (E171), macrogol, talc, yellow iron oxide (E172);
- *tablet coating for 100 mg film-coated tablets*: poly(vinyl alcohol), titanium dioxide (E171), macrogol, talc, yellow iron oxide (E172), red iron oxide (E172).

The product is available in PVC/PCTFE blisters with aluminium foil lidding. Resmetirom tablets are provided as 28 blistered tablets in a carton.

2.4.2. Active substance

2.4.2.1. General information

The chemical name of resmetirom is 2-[3,5-Dichloro-4-[(5-isopropyl-6-oxo-1,6-dihydropyridazin-3-yl)oxy]phenyl]-3,5-dioxo-2,3,4,5-tetrahydro-[1,2,4]triazine-6-carbonitrile, corresponding to the molecular formula $C_{17}H_{12}Cl_2N_6O_4$. It has a relative molecular mass of 435.22 and the structure in Figure 1.

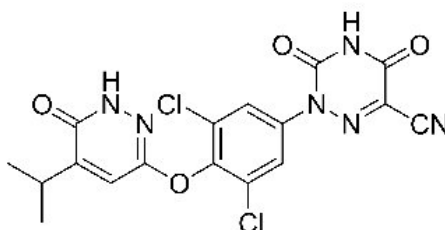


Figure 1. Resmetirom active substance structure

The chemical structure of resmetirom was elucidated by a combination of 1H and ^{13}C NMR spectroscopy, mass spectrometry, IR spectroscopy, UV spectrometry, elemental analysis, differential scanning calorimetry (DSC), and powder X-ray diffraction (PXRD).

Resmetirom is a brownish-orange solid non hygroscopic powder. It has a low aqueous solubility, which is pH-dependent.

It is an achiral molecule. Polymorphism has been observed and the thermodynamically stable form is manufactured. Polymorphism is controlled in the active substance (AS) specification.

2.4.2.1. Manufacture, characterisation and process controls

Two manufacturers of the final AS are identified. Satisfactory evidence of GMP compliance of all sites involved in the AS manufacture was provided.

The manufacturing process of resmetirom consists of four manufacturing stages and there are three well defined starting materials (SMs). Both manufacturers use essentially the same manufacturing process and identical flowcharts were provided. Some minor differences concern reaction temperatures, pressure, work-up, yields and some in-process controls. During the procedure, one of the initially proposed SMs was not found acceptable, and a Major Objection (MO) was raised by the CHMP in this regard. The applicant redefined the concerned SM as requested to earlier synthetic steps in the process, presenting acceptable specifications for the new SM and updating the relevant documentation, thus resolving the MO.

The manufacturing process is described in sufficient detail. Amounts of materials, reagents and solvents have been provided in terms of equivalents along with details on relevant process parameters. Specifications for isolated intermediates have been established and are acceptable. Critical steps and in-process controls have been indicated.

The characterisation of the AS and its impurities are in accordance with the EU guideline on chemistry of new active substances. Potential and actual impurities were well discussed with regards to their origin and characterised.

The AS container closure system complies with Commission Regulation (EU) 10/2011, as amended.

2.4.2.2. Specification

The AS specification, shown in Table 1, includes tests for: description (visual), identification (FT-IR, UPLC), assay (UPLC), impurities (UPLC, LC-MS), residual solvents (GC), acetic acid (GC-FID), elemental impurities (ICP-MS), residue on ignition (Ph. Eur.), particle size (laser diffraction), polymorphism (XRPD), water content (KF) and microbial limits (Ph. Eur.).

The AS specification used by the finished product (FP) manufacturer was set based on relevant guidelines, manufacturing experience, batch release and stability data. The proposed tests and limits have been justified and are considered acceptable.

A discussion concerning possible N-nitrosamines impurities has been presented. The N-nitrosamine risk assessment regarding the AS is acceptable.

The analytical methods used have been adequately described and non-compendial methods appropriately validated in accordance with the ICH guidelines. The information regarding the reference standards used for assay and impurities testing has been provided and is acceptable.

Batch results have been submitted for current batches manufactured by both manufacturers as well as for batches produced and used in the pre-clinical tests and clinical studies. All analysis results conform to the specifications being operative at that time. Batch sizes have been stated.

2.4.2.3. Stability

Stability data from five commercial scale batches of AS from both proposed manufacturers stored in the intended commercial package for up to 60 months under long term conditions (25 °C / 60% RH) and for up to six months under accelerated conditions (40 °C / 75% RH) according to the ICH guidelines were provided.

The following parameters were tested: description, assay, impurities, particle size, polymorphism, water content and microbial limits. The analytical methods used were the same as for release and were stability indicating.

All tested parameters were within the specifications and no significant changes are observed for any of the batches, at accelerated or long-term conditions.

Photostability testing according to ICH Q1B for one batch of AS has been carried out. Resmetirom has been exposed to visible and ultraviolet light as a dry powder and has been found stable under irradiation conditions.

Forced degradation studies results under acidic, basic, oxidative, thermal, and photolytic conditions have been presented demonstrating the analytical methods for assay and impurities are stability indicating. The AS was found sensitive to alkaline conditions.

The stability results indicate that the AS manufactured by the proposed suppliers is sufficiently stable. The stability results justify the proposed retest period of 60 months for the AS manufactured by one of the suppliers and of 36 months for the AS manufactured by the other. No special storage conditions are required.

2.4.3. Finished Medicinal Product

2.4.3.1. Description of the product and pharmaceutical development

The FP is presented as film-coated tablets in three strengths containing 60 mg, 80 mg or 100 mg resmetirom AS and differing in size, colour (white, yellow, beige) and embossing. Specifically:

- the 60-mg tablet is a white, oval-shaped film-coated tablet debossed with "P60" for 60 mg on one side and plain on the other side;
- the 80-mg tablet is a yellow, oval-shaped film-coated tablet debossed with "P80" for 80 mg on one side and plain on the other side;
- the 100-mg tablet is a beige to pinkish, oval-shaped film-coated tablet debossed with "P100" for 100 mg on one side and plain on the other side;

The complete description and composition of all strengths and coating materials of FP can be found in Table 2 and Table 3. No overage or overfill are used.

The aim of the pharmaceutical development as per the QTPP, was to develop an immediate release tablet in 60 mg, 80 mg and 100 mg tablets strengths, sufficiently differentiated, that would be film-coated to ensure ease of swallowing and product handling and be of a reasonable size for patient administration.

Resmetirom AS is claimed to be a BCS class IV compound based on the solubility profile and low permeability.

All excipients are well known pharmaceutical ingredients, and their quality is compliant with Ph. Eur. standards except the coating materials which are controlled versus in-house monographs. There are no novel excipients used in the FP formulation. The list of excipients is included in section 6.1 of the SmPC. Function, rationale for selection and level of each excipient has been discussed. Compatibility with excipients has been discussed. The function and amount of each excipient has been sufficiently described.

The development of the FP has been described in sufficient detail from capsules to film-coated tablets. Different capsule formulations were used for Phase 1 and Phase 2 clinical trials. A prototype tablet formulation was developed and this tablet formulation was compared to the latest capsule formulation *in vivo* in a relative bioavailability (BA) study (mgl-3196-08) to support bridging of early capsule formulations to the final commercial formulation. The prototype tablet formulation was optimised to a formulation which has been used for all Phase 3 clinical trials and is the proposed commercial formulation for the 100 mg tablets. The 60 mg and 80 mg tablets are the same as the 100 mg formulation but with slightly modified tablet coating colours to improve tablet strength differentiation.

Comparative dissolution profiles show similarity of commercial formulation and formulation used in the clinical phase 3 study.

The development of the dissolution method has been described. The information provided in the initial submission on dissolution method development, discriminatory power and specification limit was not satisfactory, and the CHMP raised a Major Objection (MO). In their response the applicant provided further data and justifications to support the proposed method. Based on the method development and investigation of discriminatory properties, the dissolution method was selected and validated for release and stability testing of resmetirom tablets. In addition, discrimination studies were performed with different dissolution media and the applicant has concluded that the dissolution medium demonstrated discriminatory ability for tablet formulation and manufacturing variations. The proposed time point for the dissolution specification was also further justified and supported by experimental data. Based on provided data the established conditions for dissolution method are considered justified and the proposed dissolution specification is based on results of clinical batches; the MO was thus resolved.

The FP is manufactured by direct compression (dry granulation). The development was based on a QTPP and CQAs. The development of the manufacturing process and the commercial scale-up of resmetirom 60 mg, 80 mg and 100 mg tablets has been sufficiently performed. As mentioned, the commercial formulation is the same as used in the pivotal Phase 3 clinical study. The manufacturing process has been developed in a different site, where the primary stability batches (three of each strength) and the Phase 3 batches have been produced at commercial scale with the same equipment as proposed for the commercial batches. The process was later successfully transferred to the proposed manufacturer in Europe, where three batches of each tablet strength were successfully prepared for use as registration stability batches and clinical trial material.

A Design of Experiments (DOE) was conducted at a pilot scale. The DOE was designed to identify potential critical process parameters, determine suitable target values and operating ranges for each process parameter. The applicant states that no design space is claimed for the manufacturing process.

The FP container closure system is PVC/PCTFE blisters with aluminium foil lidding. The description of materials and their specification is satisfactory. A statement of compliance with Commission Regulation (EU) No 10/2011 and EC 1935/2004 and its amendments was presented.

2.4.3.1. Manufacture of the product and process controls

Manufacturing of resmetirom tablets takes place at Corden Pharma GmbH in Germany. Valid QP declaration and GMP certificate were provided.

The FP is manufactured using a standard direct compression process, which involves blending, compression, and film-coating. The manufacturing process is sufficiently described.

The batch formula for the proposed batch size was provided and is in accordance with the composition.

The Critical Quality Attributes (CQAs) include appearance, compressibility, assay, unit dose (content) uniformity, dissolution, and product stability. Critical process steps and the related critical process parameters impacting the CQAs have been presented. The proposed in-process controls are adequate for this type of manufacturing process and pharmaceutical form.

No intermediates are isolated in the manufacturing process and the manufacturing time between the individual processes is not expected to exceed 30 days. The proposed holding times and conditions for blend and bulk (uncoated) tablets and transport arrangements has been specified. Acceptable specifications and food grade compliance statements for the packaging materials for bulk coated tablets, uncoated tablets and the blend have been provided.

The manufacturing process has been validated and the full process validation data of the first three commercial batches of the FP, manufactured at the EU site (using AS from both AS suppliers) have been presented. It has been demonstrated that the manufacturing process is capable of producing the FP of intended quality in a reproducible manner.

2.4.3.2. Product specification

The FP release and shelf-life specifications, shown in Table 4, include appropriate tests for this kind of dosage form including appearance (visual), dimensions (callipers), identification (UPLC, HPLC-DAD), assay (UPLC), related substances (UPLC), content uniformity (HPLC), dissolution (HPLC), water content (KF) and microbial limits (Ph. Eur.).

The proposed specification parameters and limits have been set based on ICH guidelines and batch data and stability data; they are typical for the type of dosage form and have been adequately justified.

No degradation products have been identified in the FP. The limits of related substances were set in accordance with ICH Q3B considering the maximum daily dose of >10 mg – 2 g. This is considered acceptable.

The dissolution testing specification is justified as discussed above.

The potential presence of elemental impurities in the FP has been assessed following a risk-based approach in line with the ICH Q3D Guideline for Elemental Impurities. Based on the risk assessment and the presented batch data it can be concluded that it is not necessary to include any elemental impurity controls in the finished product specification. The information on the control of elemental impurities is satisfactory.

A risk assessment concerning the potential presence of nitrosamine impurities in the FP has been performed and presented. The risk assessment that was initially submitted was not detailed enough and a MO was raised. The applicant in their responses revised and updated the risk assessment as requested, considering all suspected and actual root causes in line with the “Questions and answers for marketing authorisation holders/applicants on the CHMP Opinion for the Article 5(3) of Regulation (EC) No 726/2004 referral on nitrosamine impurities in human medicinal products” (EMA/409815/2020) and the “Assessment report - Procedure under Article 5(3) of Regulation EC (No) 726/2004 - Nitrosamine impurities in human medicinal products” (EMA/369136/2020). Based on the information provided, it is accepted that there is no risk of nitrosamine impurities in the AS or the related FP. Therefore, no specific control measures are deemed necessary.

Analytical methods for the test parameters have been described in detail. There are no differences between the release and shelf-life specification. Non compendial analytical methods have been sufficiently validated in accordance with ICH Q2 (R1). Satisfactory information was provided for reference standards and materials, used for routine quality control of the FP.

Batch analyses results have been presented for numerous batches of pilot up to commercial scale used in clinical trials, process validation and stability, which were manufactured at the development and the proposed manufacturing site. All batches complied with specifications confirming the consistency of the manufacturing process and its ability to manufacture to the intended product specification.

2.4.3.3. Stability of the product

Stability data from three pilot scale batches of each strength stored for up to 36 months under long term conditions (25 °C / 60% RH), for up to 12 months under intermediate stability data (30 °C/65% RH) and for up to 6 months under accelerated conditions (40 °C / 75% RH) according to the ICH

guidelines were provided. The stability batches were packed in the primary packaging proposed for marketing and were manufactured at the development site using the same process and equipment as that of the commercial site but there were some minor differences in the film coating colouring compared to the commercial process. These changes were evaluated as non-significant for the product performance. Thus, the stability batches are considered representative of those proposed for marketing.

Furthermore, stability data from another nine batches (including commercial scale batches) of each strength stored for up to 12 months under long term conditions (25 °C / 60% RH), and for up to 6 months under accelerated conditions (40 °C / 75% RH) according to the ICH guidelines were provided. These batches were packed in the primary packaging proposed for marketing and were manufactured at the proposed site.

AS from both suppliers was used for the stability batches.

Stability samples were tested for appearance, assay, related substances, dissolution, water content and microbial limits. The analytical methods used were the same as for release. Results complied with the specification for all batches under long term and accelerated conditions. However, due to some observed OOS results after 6 months at accelerated storage conditions, testing at the intermediate condition (30 °C / 65% RH) was triggered. The stability results obtained at the intermediate condition for resmetirom tablets meet the acceptance criteria through 12 months.

Photostability studies have been conducted with conditions in line with ICHQ1B. No significant change in appearance, assay, or related substances was observed for any condition evaluated, indicating that resmetirom tablets are stable to exposure to light.

Based on available stability data, the proposed shelf-life of 3 years and storage conditions "Store below 30 °C" as stated in the SmPC (section 6.3 and 6.4) are acceptable.

2.4.3.4. Adventitious agents

No excipients derived from animal or human origin have been used.

2.4.4. Discussion on chemical, pharmaceutical and biological aspects

Information on development, manufacture and control of the AS and FP has been presented in a satisfactory manner.

During the evaluation three major objections were raised concerning the definition of a starting material in the synthesis of the AS, the dissolution method development (including its discriminatory power and specification limit) and the risk assessment for the potential presence of nitrosamines. All three issues were satisfactorily resolved by provision of additional data and justifications by the applicant.

The results of tests carried out indicate consistency and uniformity of important product quality characteristics, and these in turn lead to the conclusion that the product should have a satisfactory and uniform performance in clinical use.

2.4.5. Conclusions on the chemical, pharmaceutical and biological aspects

The quality of this product is considered to be acceptable when used in accordance with the conditions defined in the SmPC. Physicochemical and biological aspects relevant to the uniform clinical performance of the product have been investigated and are controlled in a satisfactory way.

2.4.6. Recommendations for future quality development

None.

2.5. Non-clinical aspects

2.5.1. Introduction

Resmetirom is a THR agonist with preferential selectivity for the THR β over THR α . Due to this preferential selectivity, resmetirom mediates preferentially the metabolic hepatic effects known for thyroid hormone.

2.5.2. Pharmacology

2.5.2.1. Primary pharmacodynamic studies

Resmetirom is a partial agonist at the THR, a nuclear receptor, with preferential selectivity for THR β versus THR α . The IC₅₀ value of resmetirom for the inhibition of specific binding of T3 at THR- β was determined as 0.18 μ M. Resmetirom was 28-fold more selective at THR- β versus THR- α as compared with T3. The THR receptors used in functional *in vitro* coactivator recruitment assays were of human origin.

The results of an *in vitro* study demonstrate for metabolite M1 a certain degree of binding to THR- β . In an *in vitro* coactivator recruitment assay metabolite M1 showed much lower potency than resmetirom at both THR receptors, with an EC₅₀ of 75.9 μ M at THR α and EC₅₀ of 19.3 μ M at THR β .

The primary pharmacology of resmetirom was evaluated in diet-induced obesity (DIO) mice for up to 25 weeks, hyperlipidemic rats for up to 8 days, and hypercholesterolemic rabbits for up to 15 days.

Oral resmetirom doses used in the studies in DIO mice were 0.3 to 10 mg/kg/day (23-day study obviously with oral gavage), 0.3 to 3 mg/kg/day (24-day study with oral gavage) and 0.1 to 3 mg/kg/day (25-week study with diet admix administration). In the latter two studies rosiglitazone was administered to an additional group of animals.

Resmetirom associated effects observed in these studies included, compared to vehicle control, decreases in body weight (-7% to -26%), decreases in liver weight (-24% to -43%), reduction in hepatic triglyceride content (if investigated), decreases in total plasma cholesterol (-51% to -73%), decreases in plasma HDL (-53% to -68%), decreases in plasma triglycerides and decreases in plasma T4 (-44% to -60%). In one of the studies, plasma T3 levels were investigated and were shown to be decreased by up to -16%, a change which was according to the applicant remained within range of normal values. When investigated, a resmetirom treatment associated increase in energy expenditure was found (+6% to +27%).

In two of these studies, liver histology had been investigated and reduction of hepatocyte vacuolation (due to lipid) was demonstrated. In the 25-week study the degree of hepatocyte vacuolation was reduced due to resmetirom treatment even below the level seen in an additional group of control animals which had not been fed a high fat diet (in order to induce obesity) but which had been fed a standard chow instead.

In two of the studies, an intraperitoneal insulin tolerance test (IP-ITT) was performed and demonstrated improved insulin sensitivity. These *in vivo* studies in DIO mice are considered proof of principle as many pathophysiological characteristics in patients with non-alcoholic steatohepatitis

(NASH) in patients with liver fibrosis are beneficially changed in this model, as there are e.g. improved insulin sensitivity, clear reduction in liver lipid content, body and liver weight reduction.

In the same two studies, resmetirom treatment-associated gene expression changes in the liver were investigated. Among the gene expression changes investigated, both the genes for gene products involved in cholesterol metabolism, as well as the one involved in cholesterol biosynthesis were upregulated. This study showed as well that both genes related to cholesterol metabolism and biosynthesis were down-regulated in DIO mice as compared to lean mice. Therefore, the resmetirom associated gene expression changes regarding cholesterol metabolism and synthesis are somewhat contrary to the changes during development of the DIO state of this mouse model. Transcription of genes considered being involved in insulin sensitivity were increased and known thyroid responsive genes were regulated as well (e.g. the gene for deiodinase 1 was up-regulated and the gene for thyroid binding globulin was down-regulated).

The applicant remarks that doses of resmetirom from 0.3 to 3 mg/kg normalized NASH-related inflammatory and fibrosis gene transcripts that were significantly elevated in the livers of DIO mice as compared with normal chow fed, lean control mice.

In an 8-day study in female Zucker rats (which have a leptin receptor mutation) oral treatment with resmetirom doses of up to 30 mg/kg/day resulted in a dose-dependent reduction of non-HDL cholesterol (up to -65%), dose-dependent reduction in triglycerides (up to -73%), increased HDL at ≥ 10 mg/kg/day up to +96%, and significantly decreased liver weight at all dose levels (13% to 16% decrease). In addition, there was significantly decreased T4 levels in all groups up to -59%.

In a 30-day study in hypercholesterolemic rabbits a synergistic effect between resmetirom and atorvastatin was shown regarding the reduction of non-HDL cholesterol and the reduction of plasma triglycerides.

2.5.2.2. Secondary pharmacodynamic studies

In *in vitro* secondary pharmacology studies IC_{50} values for resmetirom at the peripheral benzodiazepine receptor and the vitamin D3 receptor were identified as 10 and 7 μM (4 and 3 $\mu g/mL$), respectively, which are approximately 48-fold and 33-fold higher than the EC_{50} value at THR- β , respectively.

The applicant submitted a study in male hypothyroidic rats which had been administered intraperitoneally single doses of either resmetirom (5, 20, or 37.5 mg/kg) or T3 (10 $\mu g/kg$) and in which gene expression changes in left cardiac tissue were investigated. Whereas T3 showed a significant elevation of transcription of the cardiac-specific gene, there was no induction of α -MHC hnRNA at any dose levels of resmetirom. The conclusion of the applicant that these data suggest that resmetirom, when compared to T3, has little off-target cardiac activity in the rat is considered plausible.

2.5.2.3. Safety pharmacology programme

Based on an *in vitro* hERG study submitted, the applicant concludes that IC_{50} for inhibition of this channel by resmetirom is $>30 \mu M$, respectively, which is approximately 150-fold higher than the EC_{50} value of resmetirom at THR- β . Neither a positive nor a negative control had been included in the measurements, the concentration of the resmetirom solutions used has not been verified and a possible effect of DMSO cannot be excluded. In an automated parallel patch clamp system, no indication of a relevant inhibition of the hERG potassium channel by the resmetirom metabolite MGL-3623 was found. As there was no indication of a proarrhythmic potential for resmetirom based on a

clinical tQT study, non-clinical *in vivo* data, and a hERG assay with the main metabolite of resmetirom, the conduct of a state-of-the-art hERG study with resmetirom was not requested.

In a cardiovascular safety study in conscious radiotelemetry-implanted Beagle dogs with single oral resmetirom doses of up to 120 mg/kg, no apparent resmetirom-related effects on QT or QTcV were identified. A transient reduction of the arterial blood pressure of about 30 mm Hg at the peak drug plasma concentrations was seen in mid-dose (50 mg/kg) and high-dose animals and concurrent slight to mild decrease in QRS, RR, and PR intervals are considered to be compensatory to the blood pressure decrease.

Neither a CNS-safety study nor a respiratory safety study in rats revealed safety signals and the highest dose of 300 mg/kg administered in these studies corresponds to an exposure level approximately 21-fold higher than the C_{max} achieved at the MRHD of 100 mg/day in humans.

2.5.2.4. Pharmacodynamic drug interactions

A 30-day study in hypercholesterolemic rabbits demonstrated a synergistic effect of resmetirom and atorvastatin in reduction of non-HDL cholesterol and plasma triglycerides.

2.5.3. Pharmacokinetics

GLP compliant validation for detection of resmetirom and M1 metabolite in mouse, rat, dog and rabbit plasma by LC/MS/MS has been performed. The detection limit for resmetirom is 1.00 – 1000 ng/mL and for M1 - 0.500 - 500 ng/mL. Interday precision and accuracy, analyte % recovery, analyte specificity, matrix effect, dilution precision and accuracy and analyte carry over were specified together with stability testing.

PK of resmetirom has been analysed also in a non-GLP single-dose study in monkeys, however since the bioavailability in monkey was determined to be approximately 3%, it was not selected as a suitable non-clinical species, thus the validation report was not considered needed.

Absorption

In vitro permeability was studied in Caco-2 cells, MDCK-II cells and membrane vesicles. The results indicate that resmetirom is a substrate of BCRP and it is unlikely to be a substrate for P-gp.

The applicant has submitted the results of single-dose kinetic studies in mice, rats, rabbit, dog and cynomolgus monkey. Orally, resmetirom was absorbed at a moderate rate in mice and rats [time to maximum concentration (T_{max}) values of 4 to 6 hours], but was more rapidly absorbed in rabbits, dogs, and monkeys (T_{max} =1 to 4 hours). At higher doses (up to 2000 mg/kg in rats and 180 mg/kg in dogs), T_{max} values increased (16.7 and 8 hours, respectively), suggesting slower absorption.

Maximal plasma concentration (C_{max}) and area under the plasma concentration versus time curve (AUC) values were approximately 1.5- to 3-fold higher in dogs (administered 180 mg/kg resmetirom) in the fasted state compared to the fed state.

Elimination kinetics were similar across mice, rats, dogs, and monkeys at 10 mg/kg (elimination half-life [$t_{1/2}$] range of 3.2 to 4.5 hours), whereas $t_{1/2}$ was lower in rabbits (2.2 hours). The $t_{1/2}$ tended to increase with increasing doses. The volume of distribution was low in both dogs and monkeys (0.407 and 0.235 L/kg, respectively).

Bioavailability was generally low at doses up to 10 mg/kg across species (up to 31%, 53%, 13%, and 7% in mice, rats, dogs, and monkeys, respectively), and tended to increase with increasing doses, suggesting possible saturation of hepatic uptake of resmetirom and saturation of BCRP/P-gp in the GI tract.

Resmetirom repeated dose pharmacokinetics were investigated during pharmacokinetic studies in DIO mice, hypercholesterolemic Sprague Dawley rats and hypercholesterolemic NZW rabbits.

The applicant concludes from these studies that, in repeat-dose oral PK studies in mice, systemic exposure to resmetirom increased in an approximately dose-proportional manner, while in rabbits, resmetirom exposure was variable when administered via oral admixture. T_{max} was generally consistent across dose groups in mice and rabbits. In an intraperitoneal (IP) repeat-dose PK study in rats, systemic exposure to resmetirom was approximately dose proportional and C_{max} was achieved by 2 to 4 hours post-dose.

Resmetirom's kinetics were further investigated as part of the toxicity studies.

In repeat-dose toxicity and TK studies, there were generally no sex differences in systemic exposure to resmetirom (<2-fold difference) in mice, rats, and dogs. Exposure, as assessed by C_{max} and AUC_{0-24} increased with increasing dose, generally in a dose-proportional manner in mice and rabbits (pregnant), and a more than dose proportional manner in rats at ≥ 30 mg/kg/day (except in juvenile rats) and dogs at ≥ 45 mg/kg/day. Slight accumulation was observed inconsistently across various dose levels and durations of administration up to 6 months in adult rats, 7 weeks in juvenile rats, and 9 months in dogs. High-dose acute PK data in rats (Study no. 09944) indicated that saturation at 1000 mg/kg dose is reached as the exposure did not increase at doses above 1000 mg/kg. In dogs up to doses 180 mg/kg saturation was not reached.

The overall absorption data was considered sufficient by the CHMP to conclude on exposure margins in the risk assessment.

Distribution

The distribution of resmetirom was investigated *in vitro* and *in vivo* in several models.

In vitro

Protein binding and distribution into blood cells were investigated in CD-1 mouse, Wistar Han rat, beagle dog, cynomolgus monkey, and human plasma with radiolabelled resmetirom. Protein binding in all species investigated was high (>99) over the investigated concentration range (250 – 10 000 ng/ml) and concentration independent. The binding to the plasmatic proteins HSA and AGP in independent sets of experiments showed a binding of 62.1% and 99.6% to AGP and HSA, respectively. The applicant concludes from these experiments, that resmetirom is mostly bound to HSA in humans. The blood to plasma ratio for [^{14}C]-resmetirom in mouse, rat, dog, monkey, and human blood was 0.62, 0.66, 0.55, 0.60, and 0.55, respectively, leading to the conclusion that resmetirom does not extensively partition into red blood cells. Covalent protein binding was investigated in rat, dog, monkey and liver microsomes showing a low potential for covalent protein binding.

It was agreed with the applicant that resmetirom is a substrate of OATP1B1 and OATP1B3 and that the uptake into the liver may be active. The uptake of resmetirom was not only shown in an immortalised animal cell line but in human hepatocytes. The two sets of experiments show slightly different results as anticipated, since individual differences may be apparent. However, it becomes clear that resmetirom is likely to be taken up by OATP1B1 and OATP1B3 in humans. Since the uptake is approximately 2-fold higher compared to estrone 3-sulfate, a known substrate as well as inhibitor of the OATP1B1/3 proteins, other transport process may be involved. Furthermore, although with a very small donor group, uptake into hepatocytes was shown for relevant animal species (rat and dog). It should be noted that uptake into rat hepatocytes was much higher compared to dog and human. The conclusions on drug interactions will be discussed later in this document.

Resmetirom is a substrate of the human heterotrimeric organic solute transporter OST α/β , in MDCK-II cell monolayers. OST α/β is localized in ileus, liver and kidney and is involved with the absorption and

distribution of bile acids. The applicant concludes that OSTα/β is involved in the cellular uptake of resmetirom. OSTα/β expression has been found to be elevated in liver tissues of patients with NASH (Malinen *et al* 2018) in the past. Therefore, a potential relevance in NASH, bile acid-related metabolic disorders and drug induced liver injury (DILI) has been suspected in the past. However, the role of the transporter has not been completely established. OSTα/β may enable resmetirom's entry as well as the extrusion out of the cell, dependent on resmetirom concentration gradient over the cell membrane. Inhibition of transport processes by competitive effects are also conceivable.

Biliary efflux of resmetirom and metabolite, MGL-3623, were observed in both sandwich-cultured human hepatocytes (SCHH) and sandwich-cultured dog hepatocytes (SCDH), with higher efflux observed in the dog assay compared to the human assay.

In Vivo

In vivo distribution studies following single or/and repeated oral doses have been conducted in mice, rats, rabbits and dogs.

In mice single and 21 days, repeated dose distribution has been investigated in two studies in male DIO C57Bl/6J mice by a non-radioactive method. The use of a disease model to investigate this aspect appears to be questionable. In both studies uptake of resmetirom into the liver could be shown. However, the liver to plasma ratio does not show comparable results. After 21 days, the liver to plasma ratio 2 hours after administration of 1 mg/kg resmetirom was 2.45 [study THR-28], whereas on Day 1 the ratio was with 8.2 [study THR-76] much higher. It remains unclear if intra study variability or an adaptive response may be responsible.

In a similar study with the repeated administration for 8 days of 5 or 40 mg/kg/day of radiolabelled [¹⁴C]resmetirom by intraperitoneal injection to hypercholesteremic Sprague Dawley rats, resmetirom could be detected in heart and liver. In one of two rats of the high dose group, small amounts of resmetirom were detected in the brain. The applicant concludes from this study no or a very low exposure of the brain.

The tissue distribution of radiolabeled [¹⁴C]-resmetirom, was further evaluated in pigmented male Long-Evans rats, which received a single oral dose of 5 mg/kg (39.8 mCi/mmol) [¹⁴C]-resmetirom (in 4% DMSO, 96% of 2% Klucel and 0.1% Tween 80, 0.09% methylparaben, and 0.01% propylparaben in purified MilliQ water). Tissue concentration distribution and plasma concentrations were analyzed by QWBA and LSC, respectively. At the last time-point evaluated [58 days post-dose, radioactivity was only quantifiable in blood, liver, Harderian gland, pancreas, pigmented skin, lung, and eye lens. The AUC values of [¹⁴C]-resmetirom in the liver and kidney were approximately 10-fold and 3-fold higher than in plasma, respectively, whereas skeletal and heart muscle, as well as most other tissues were lower or similar to the AUC value in plasma and blood (blood AUC was 2-fold higher than plasma AUC). The applicant concluded that these data suggest the selective uptake of resmetirom into liver and kidney cortex, while distribution in other tissues was likely due to the remaining low levels of resmetirom in the vasculature.

From the assessor's point of view the applicant's conclusions are partly questionable. Uptake of resmetirom into liver and kidney could be clearly shown and is in agreement with the pharmacodynamics activity and the investigations concerning hepatic cellular uptake in several models including cellular transport systems. Other aspects are less clear. Resmetirom can be found in the blood over the period investigated and the explanation that highly perfused tissues such as lung, liver and kidney would show consequently some remaining activity appears comprehensible, even though the applicant does not distinguish between cellular uptake and persistence within the vasculature. However, no such explanation can be claimed for less perfused organs such as Harderian gland, pancreas and eye lens and it would clearly not explain the differences between pigmented and non-

pigmented skin. Furthermore, the choice of species for this type of investigations appears to be questionable since further investigations showed that resmetirom is secreted into the bile. In opposition to rats, humans do have a gall bladder, and the bile is stored and concentrated in this organ until release into the intestine. From the toxicological point of view, exposure of the gall bladder to resmetirom is of specific interest.

In rabbits, the distribution was studied in hypercholesteremic NZW rabbits by repeated administration as dietary admix by a non-radioactive method. Plasmatic and liver homogenate concentration was determined and the liver to plasma ratio determined. In this study liver to plasma ratios decreased with increasing dose (12.6 at 0.95 mg/kg, 8.8 at 2.8 mg/kg, and 2.7 at 7.11 mg/kg). The applicant suggests that this finding may reflect saturation of hepatic uptake transporters.

In dogs, distribution of resmetirom was investigated after repeated administration by radioactive [3196-17-001] and non-radioactive [09925] methods. In study 3196-17-001, the distribution of the metabolite MG-3623 was also investigated. These investigations are limited to distribution into liver, bile, bile duct and plasma. Both studies showed higher plasmatic concentrations of resmetirom in the bile compared to plasma indicating biliary excretion. Resmetirom as the parent compound was the main component excreted in the bile (96%). For study 09925 mean liver to plasma ratios are provided. The ratios are 680, 124, and 328 for males and 368, 124, and 258 for females at 20, 50, and 100 mg/kg, respectively, on Day 15.

The applicant does not present the liver to plasma ratio for the second study [3196-17-001]. In this study (at Day 4, 4 hours post administration), the liver to plasma ratio for resmetirom for a dose of 100 mg/kg/day was much lower (liver to plasma ratio ≈ 3). In this study, the metabolite was investigated in addition, showing a much higher liver to plasma ratio (≈ 13). The concentrations of resmetirom and MGL-3623 are much higher in the bile ducts tissue than in the "whole" liver tissue. The bile duct to liver tissue ratios were ≈ 2.7 and ≈ 2.5 for resmetirom and MGL-3623, respectively. The applicant concludes from this set of experiments, that resmetirom and its metabolite are excreted into the bile. The applicant does not comment this finding further, but the CHMP agrees that enterohepatic circulation of resmetirom and its metabolites appears to be likely.

Metabolism

Metabolism of resmetirom was investigated *in vitro* and *in vivo* in different systems.

In vitro stability of resmetirom was investigated in human microsomes and in hepatocytes of mice, rats, dogs, monkeys and humans. Metabolites were further investigated by the use of radiolabelled resmetirom in microsomes and hepatocytes of mice, rats, dogs, monkeys and humans. The type of metabolite forming reactions was investigated by the use of human liver microsomes expressing different CYP450 enzymes and by an *in vitro* system, investigating metabolism by cytosolic aldehyde oxidase of mice and humans and by a chemical oxidant.

The studies show that resmetirom metabolism was low in human intestinal microsomes (intrinsic clearance [CL_{int}]=2.73 μ L/min/mg protein) and in mouse, rat, dog, monkey, and human hepatocytes (CL_{int}=0.6, 0.67, 1.18, 3.13, and 1.04 μ L/min/10⁶ cell, respectively).

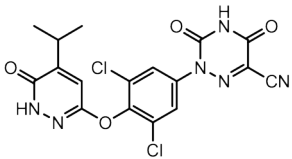
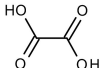
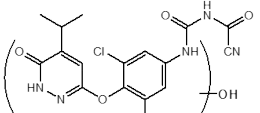
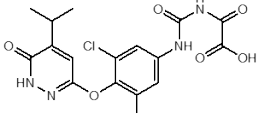
Metabolite profiling in liver microsomes revealed the formation of a hydroxy-metabolite (M1 or MGL-3623) in dog, monkey, and human microsomes but not mouse or rat microsomes. In hepatocytes, MGL-3623 was only observed in monkey and human samples, while a second metabolite (M2 or MGL-3842) was identified across rat, dog, monkey, and human samples. In an *in vitro* hepatocyte assay, MGL-3842 was found to produce identical tandem mass spectrometry (MS/MS) data to MGL-3623; thus, MGL-3842 is most likely also a hydroxy-metabolite.

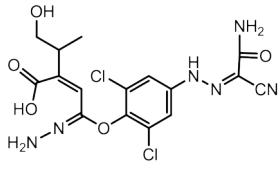
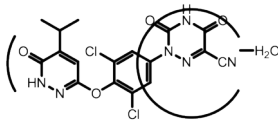
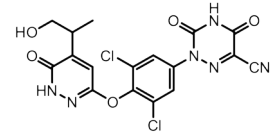
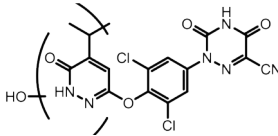
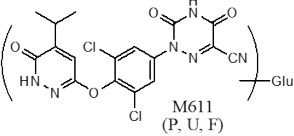
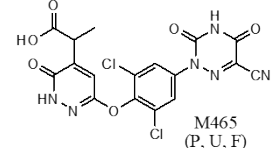
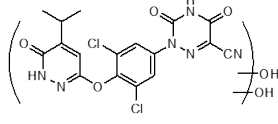
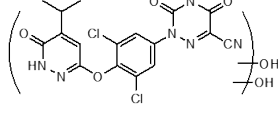
CYP450 reaction phenotyping in human liver microsomes identified CYP2C8 as the primary metabolizing enzyme responsible for the metabolism of resmetirom to MGL-3623. The formation of MGL-3842 was only slightly inhibited in the presence of CYP2C8 and CYP2C9 inhibitors, suggesting minimal involvement of CYP2C8 and 2C9 in the formation of MGL-3842.

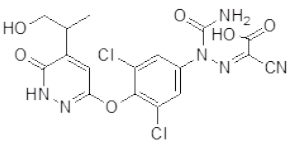
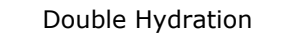
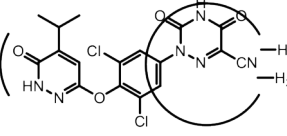
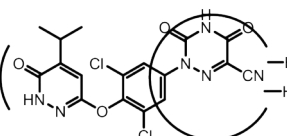
In vivo study data on metabolites is presented for rats, dogs and monkeys. In rats and dogs, metabolites were investigated in plasma, urine and faeces.

A summary of definitive ¹⁴C-resmetirom metabolite profiling and identification studies conducted in rat, dog, and humans, is provided in the table below.

Table 5. Definitive ¹⁴C-Resmetirom Cross-species Metabolite Summary

Labels	Proposed Structures	Rat	Dog	Human
MGL-3196 Parent		In Plasma (AUC = 22084 h-ng/mL), Urine (11.66% of radioactive dose), Feces (14.25% of radioactive dose)	In Plasma (AUC = 400,000 h-ng/mL), Urine (2.23% of radioactive dose), Feces (67.54% of radioactive dose)	In Plasma ("Cold" AUC = 10634 ng·hr/mL; ¹⁴ C-MGL-3196 AUC = 11637.38 ng·hr/mL or 55.22% of total radiolabeled AUC), Urine (1.02 % of radioactive dose; 5.12% of urine); Feces (detected only)
Oxalic Acid		ND	ND	In Plasma (AUC = 3047.04 ng·hr/mL; 14.46% of total radioactivity AUC)
Unk 1	NA (rat at 0.4 min; Human at 5.6 min)	In Urine (3.25% of radioactive dose), Feces (0.80% of radioactive dose)	In Feces (0.85% of radioactive dose)	Feces (1.7% of radioactive dose)
Unk 2	NA (Rat at 12.4 min; Human at 7.2 min)	In Feces (0.87% of radioactive dose)	ND	Feces (3.8% of radioactive dose)
Unk 3	NA (Rat at 12.6 min; Human at 11.9 min)	In Feces (0.84% of radioactive dose)	ND	Feces (3.7% of radioactive dose)
Unk 4	NA (Retention Time 14.7 min)	In Feces (1.22% of radioactive dose)	ND	ND
M426	 Hydrolysis	ND	ND	Feces (5.62% of radioactive dose)
M429_1-4	 Hydrolysis leading to 4 structurally related	ND	ND	In Feces (each isomer <8.5% of radioactive dose)

Labels	Proposed Structures	Rat	Dog	Human
	isomers of unknown structure			
M443	 Hydration+ Hydrolysis + Oxidation	In Feces (0.77% of radioactive dose)	ND	ND
M453	 Hydration	In Feces (4.94% of radioactive dose)	In Feces (0.63% of radioactive dose)	In Feces (5.05 % of radioactive dose)
MGL-3623 M1 (M451-1)	 Oxidation	In Plasma (detected), Urine (0.71% of radioactive dose), Feces (8.65% of radioactive dose)	In Plasma (detected), Urine (0.25% of radioactive dose), Feces (3.05% of radioactive dose)	In Plasma (15.1% of Total Radioactivity AUC), Urine (15.71% of radioactive dose; 78.43% of urine radioactivity), Feces (3.3% of radioactive dose)
MGL-3842 M2 (M451)	 Oxidation	In Plasma (detected), Urine (detected), Feces (detected)	In Plasma (detected), Urine (0.03% of radioactive dose), Feces (1.93% of radioactive dose)	In Plasma (7.46% of Total Radioactivity AUC), Urine (0.71% of radioactive dose; 3.56% of urine radioactivity), Feces (ND)
M611	 Glucuronidation	ND	ND	In Plasma (2.4% of Total Radioactivity AUC), Urine (ND), Feces (5.4% of radioactive dose)
M465	 Carboxylation	ND	ND	In Plasma (detected), Urine (detected), Feces (detected)
M467-1	 Double Oxidation	ND	ND	In Plasma (detected), Urine (detected), Feces (8.8% of radioactive dose)
M467-2	 Double Oxidation	ND	ND	In Plasma (4.6% of Total Radioactivity AUC), Urine (2.6% of radioactive dose; 12.9% of urine radioactivity), Feces (detected)

Labels	Proposed Structures	Rat	Dog	Human
M469	 Oxidation & Hydration	ND	In Feces (1.04% of radioactive dose)	ND
M471-1	 Double Hydration	In Urine (0.38% of radioactive dose), Feces (2.74% of radioactive dose)	ND	ND
M471-2	 Double Hydration	In Feces (0.97% of radioactive dose)	ND	ND
M471-3	 Double Hydration	In Feces (7.57% of radioactive dose)	ND	ND
M481	 Acetylation + reduction	In Feces (23.06% of radioactive dose)	ND	ND

NA = not available; ND = not determined

Mean Total % of ¹⁴C-MGL-3196-Derived Radioactivity Recovered per Matrix

N = 3, 8, 8 in rat, dog and human studies, respectively

Source: Study Nos. 3196-16-009, 3196-17-001, MGL-3196-07

Studies investigating specifically the conversion of resmetirom in mice and rabbits (which were used for toxicity testing) or monkeys (which were excluded from toxicity testing because of low bioavailability of resmetirom) are not provided. The applicant concluded from the experiments presented above that the M1 metabolite (MGL-3623) is a human main metabolite, and that significant exposure could not be achieved in experimental animals by oral resmetirom administration. Therefore, the M1 metabolite (MGL-3623) was characterized independently. For the M2 metabolite the human plasmatic exposure was below 10%. An independent evaluation was therefore not considered necessary. This is agreed by the CHMP.

Oxalic acid was found to be another human plasmatic metabolite with a share of approximately 15% of total exposure (AUC). Oxalic acid was not detected in toxicity studies in rats and dogs.

Excretion

Excretion mass balance was investigated in Sprague Dawley rats and beagle dogs by oral administration of radiolabelled resmetirom. In rats and dogs, most of radioactivity could be recovered from the faeces, 68.8 and 76.3% respectively. Urinary excretion of radioactivity was with 16.2% (rat) and 2.57% (dog) much lower. The recovery from cage residues (1.3 and 4.55%; rats and dogs, respectively) and total recovery (87.2 and 83.7%, rats and dogs, respectively) was in the range of similar studies. *In vitro* and *in vivo* distribution studies with resmetirom indicate hepato-biliary

excretion in rats and dogs and with regard to human hepatocyte sandwich cultures in humans. However, the share of resmetirom via hepatobiliary excretion in comparison to not absorbed resmetirom is unclear.

The finding in this study, that low degrees of resmetirom could be detected in the carcass of rats, is a rather unexpected result since the results of the whole-body distribution studies in rats do not indicate distribution into bone. Three days after administration approximately 1% of the dose could be detected in the bones. This finding was attributed to residual resmetirom within the bone vasculature.

The applicant does not present studies on excretion into the milk of lactating animals. This was accepted by the CHMP.

Overall, faecal elimination was the dominant and urinary elimination the minor route in rats, dogs and humans. Hepatobiliary elimination is considered the main elimination pathway in humans and in animals used in toxicity testing.

Pharmacokinetic drug interactions

Resmetirom's potential for drug interactions was investigated in a set of *in vitro* experiments.

The applicant concludes from this set of experiments the following:

CYP450 inhibition: Resmetirom directly inhibited CYP2C8 ($IC_{50}=0.90\ \mu M$) and was a weak inhibitor of CYP2C9 ($IC_{50}=21.8\ \mu M$). Resmetirom did not show notable direct or time-dependent inhibition (TDI) for CYP1A2, 2A6, 2B6, 2C19, 2D6, or 3A4/5 ($IC_{50}>50\ \mu M$).

UGT inhibition: Resmetirom was a weak to moderate inhibitor of all UGT isoforms tested, with IC_{50} values of 3.22, 16.7, 0.557, 44.2, 1.14, and 32.6 μM for UGT1A1, UGT1A3, UGT1A4, UGT1A6, UGT1A9, and UGT2B7, respectively.

CYP450 induction: In one assay, resmetirom demonstrated weak induction for CYP2B6 and 3A4 (EC_{50} values ranging from 37 to 50 μM across donors) and decreased CYP1A2 mRNA levels. In a separate assay (study 10182), resmetirom did not show the potential to induce the mRNA of CYP1A2, 2B6, 2C9, or 3A4/5. However, the applicant considers this study (10182) to be a pilot study with no or low relevance. This is agreed.

UGT induction: Resmetirom demonstrated the potential to induce the mRNA expression of UGT1A1 and 1A3 with EC_{50} values of 14.3 to 97.4 μM for UGT1A1 and 1.67 μM for UGT1A3. Resmetirom did not have any effects on the mRNA expression of UGT2B7. For UGT1A6 the study results are inconclusive.

Potential for Transporter-based Interactions

Transporter inhibition: Resmetirom was an inhibitor of OATP1B1 ($IC_{50}\geq 3.72\ \mu M$), OATP1B3 (64% inhibition at 10 μM), organic anion transporter (OAT)3 ($IC_{50}=4.53\ \mu M$), and was a weak inhibitor of BCRP ($IC_{50}\geq 27.4\ \mu M$) and bile salt export pump (BSEP) ($IC_{50}=34.7\ \mu M$). Resmetirom was not an inhibitor of P-gp, MRP-2, or organic cation transporter (OCT)2 and weakly inhibited OAT1, multidrug and toxin extrusion protein (MATE)1, and MATE2-K with IC_{50} values $>100\ \mu M$.

Furthermore, resmetirom inhibited BCRP-mediated transport of E3S with a mean IC_{50} value of 27.4 μM in study 3196-15-001 in Caco-2 cells. However, in Study No. 3196-23-001 in HEK239 cells IC_{50} for BCRP mediated E3S transport was 0.9683 μM . It is claimed that resmetirom is an inhibitor of BCRP.

Transporter induction: Resmetirom did not induce the mRNA expression of MRP-2 or P-gp.

The applicant concludes that resmetirom has the potential to be victim and perpetrator of drug-drug interactions involving CYP2C8. Resmetirom, being a substrate of BCRP, OAT α/β , OATP1B1 and OATP1B3, may also be a victim of drug-drug interactions involving these transporters. Conversely,

resmetirom may perpetrate drug-drug interactions involving UGT enzymes, OATP1B1, OATP1B3, OAT3, BCRP, or BSEP.

However, it should be noted that the information has to be considered limited in some details. The studies do not follow the recommendations of the guideline on drug interaction studies (CPMP/EWP/560/95/Rev.1 Corr.2*) in every detail. The deviations do not cause a concern from the non-clinical point of view, and appropriate conclusions can be drawn.

Other pharmacokinetic studies

Following the oral administration of resmetirom in non-clinical species, exposure to the primary human metabolite, MGL-3623, was substantially lower compared to the parent compound (metabolite:parent AUC₀₋₂₄ ratio <2% across repeat-dose studies in mice, rats, and dogs). However, in clinical studies, MGL-3623 was determined to be present in human plasma at >10% of the parent drug (Clinical Study No. 3196-17-016). Therefore, a comprehensive PK and TK evaluation of MGL-3623 has been conducted.

Data on absorption, distribution and drug-drug interaction potential of the metabolite MGL3623 has been submitted.

Absorption of the metabolite MGL3623

In mice and rats, a single oral dose of MGL-3623 (1 to 1000 mg/kg) was rapidly absorbed ($T_{max}=1.7$ to 6.7 hours), and systemic exposure (C_{max} and AUC_{0-24}) generally increased as dose increased in a less than a dose proportional manner. The relative bioavailability (F_{rel}) was 25% and 6.6% in mice and rats at 10 mg/kg, respectively.

The toxicity and TK of MGL-3623 was evaluated in repeat-dose studies in CD-1 mice for up to 90 days at doses from 3 to 1500 mg/kg/day. MGL-3623 plasma levels were also evaluated in repeat-dose mouse, rat, rabbit, and dog studies following resmetirom administration.

In mice, systemic exposure (C_{max} and AUC_{0-24}) to orally administered MGL-3623 increased in a less than dose-proportional manner. There were generally no sex differences in exposure (<2-fold difference), or accumulation observed.

MGL-3623 was detected in plasma samples in mice, rats, rabbits, and dogs following oral resmetirom administration in pivotal toxicity studies, with a similar plasma-time profile as resmetirom; however, the exposure to MGL-3623 was substantially lower than resmetirom (metabolite:parent ratio <2% across species).

Distribution of the metabolite MGL3623

MGL-3623 was highly protein bound in human plasma (99% bound) and nonclinical species (96% bound in mouse and dog plasma and 99% bound in rat plasma).

MGL-3623 was a substrate for the intestinal/hepatic transporter OST α / β with >2-fold difference in uptake compared to control cells at all test concentrations.

Drug-Drug interaction potential of the metabolite MGL3623

CYP450 inhibition: MGL-3623 directly inhibited CYP2C8 with an IC_{50} value of 6.10 μ M. MGL-3623 was a weak inhibitor of CYP1A2, CYP2B6, CYP2C9, CYP2C19, and CYP3A4/5 (IC_{50} values of >50, 27, 24, 33, and 35 μ M, respectively). MGL-3623 was not an inhibitor of CYP2D6 and did not demonstrate TDI of CYP3A4/5.

Transporter inhibition: MGL-3623 weakly inhibited the transport of BSEP ($IC >100 \mu$ M), OATP1B1 (22.9% inhibition at 10 μ M), OATP1B3 ($IC_{50}=44.6 \mu$ M), and BCRP (4.18% inhibition at 10 μ M).

The applicant concludes from this studies that MGL-3623 has the potential to be victim and perpetrator of drug-drug interactions involving CYP2C8. MGL-3623 was also determined to be a substrate for P-gp, BCRP, OATP1B1, OATP1B3, and OAT3 and was a weak inhibitor of BCRP, BSEP, OATP1B1, and OATP1B3.

2.5.4. Toxicology

2.5.4.1. Single dose toxicity

The applicant did not perform single dose toxicology studies with resmetirom, which is endorsed.

2.5.4.2. Repeat dose toxicity

The applicant conducted repeated dose general toxicology studies in mice (up to 3 months), rats (up to 6 months) and dogs (up to 9 months). Pivotal repeated dose toxicology studies were conducted compliant to GLP regulations. The study durations (i.e. 6 months in rodents and 9 months in non-

rodents) is from the regulatory point of view in line with the intended chronic use of the medicinal product under review. Resmetirom was orally administered in these studies, which is the same route as the clinically intended one.

In mice, apart from an exploratory 10-day repeated dose toxicity study, a 3-month GLP compliant toxicology study with a 1-month recovery phase was conducted. Resmetirom dose levels in the 10-day study were 0, 3, 10, 30, 100, and 300 mg/kg/day. The results of the 10-day study are very limited as no histopathological investigation was conducted. Therefore, changes in organ weights and clinical chemistry parameters could not be correlated to histopathology. Furthermore, TSH levels were not determined. Clinical signs were seen at the highest dose. Deaths could not be attributed to resmetirom. The dose of 100 mg/kg/day is considered representing the MTD.

In the 3-month GLP compliant toxicology study with a 1-month recovery period, oral resmetirom doses of 0, 3, 30, and 100 mg/kg/day, plus in an additional group of only male animals, 200 mg/kg/day, were administered to mice. A larger high dose in males had been chosen as in a preceding study female animals had shown a higher exposure than males dosed at the same resmetirom dose level. However, this was not the case in this 3-month GLP compliant toxicology study and the highest dose level in males (200 mg/kg/day) was considered an adverse dose level. Reversible haematological effects were seen in that 200 mg/kg male animal group with reductions of red blood cell parameters and an increase in platelets. In females starting at the lowest dose reversible increases in Alanine amino transferase (ALT) were seen. Reversible decreases in total bilirubin (TBILI) were seen in several dosed animal groups. Reversible decreases in cholesterol (CHOL) in both genders, triglycerides (TG) in males and reversible decreases in total and free thyroxine (TT4, FT4) in males (starting at 3 mg/kg) and females (starting at 30 mg/kg) are obviously based on the pharmacological effect of resmetirom. Microscopic findings were limited to the liver and included hypertrophy and multinucleated cells which were interpreted as adaptive changes. At 200 mg/kg multifocal cell necrosis were seen in several animals and starting at 100 mg/kg in few animals mixed cell infiltration was found. As NOAEL the dosage level of 30 mg resmetirom/kg/day is considered, at a combined male and female exposure of roughly 10 times (AUC) or 4.5 times (C_{max}) the intended clinical exposure. The applicant considers 100 mg/kg as NOAEL of the study.

The applicant conducted four GLP-compliant repeated dose general toxicology studies in the rat, which are considered as pivotal by the applicant: a 4-week study with a 4-week recovery period, two 3-month studies (with administration of differing dosage-levels) with recovery phases of one month, each, and a 6-month study with a recovery phase of 2 months.

In the 4-week study with a 4-week recovery period, oral resmetirom doses of 0, 3, 30 and 100 mg/kg/day were administered. Starting at 30 mg/kg changes in a variety of haematological and clinical chemistry parameters were found, among them increases in platelets, decreases in plasma proteins and increases in bone alkaline phosphatase (ALP bone). Starting at the same dosage level an increase in heart weight (not reversible during the recovery phase), intramedullary formation of woven bone, atrophy of the follicular epithelium of the thyroid, and decreases in TSH, triiodothyronine (T3) and T4 (already starting at 3 mg/kg) were found, the latter findings being in line with a central hypothalamic-pituitary-thyroid (HPT) axis suppression. As NOAEL the dosage level of 3 mg resmetirom/kg/day is considered at a combined male and female exposure of roughly 2.6 times (AUC) or 1 time (C_{max}) the intended clinical exposure.

In the first of the 3-month general toxicity studies with 4-week recovery phases, each, oral resmetirom doses of 0, 1, 3, and 30 mg/kg/day were administered. Changes seen in only few laboratory parameters were mild and reversible. No change in TSH serum levels was observed and no change in thyroid weight was found. Increases in heart and kidney weights were found (by +14% and +18%, respectively) but in general no histological changes in any organ were seen. As NOAEL of this study the

dosage level of 30 mg resmetirom/kg/day is considered at a combined male and female exposure of roughly 4.5 times (AUC) and 2.4 times (C_{max}) the intended clinical exposure.

In the second study, only one dose level of 150 mg/kg/day, increased at Day 15 to 200 mg/kg/day, was administered in comparison to a vehicle group. Among the effects reported by the applicant in treated vs. vehicle control animals are increases in platelet and leukocyte counts, increases in ALT and AST, increases in bone ALP, decreases in TSH, TT4, FT4, TT3 and FT3. Regarding organ weights, decreases in thyroid weight, and increases in kidney, liver, spleen and heart weights are reported without histopathological correlates. The conclusion of the applicant that the dose of 150/200 mg/kg/day (the only dose administered to animals in this study) is above the NOAEL is considered plausible.

In the 6-month general toxicity study in rats with an 8-week recovery phase oral doses of 0, 3, 30, and 200 mg/kg/day were administered. No mortalities or clinical signs were attributed to resmetirom. Haematological effects started to be seen already at the low dose of 3 mg/kg but were more prominent at the higher doses and included increases in platelets (PTL; up to +108%) and white blood cells (WBC; up to +41%). At 200 mg/kg slight reductions in red blood cell (RBC) parameters were documented. Increases in plasma phosphorus and of the bone isoform of alkaline phosphatase (ALP) were already found at the lowest dose and increased at the two higher dose levels (up to +45% and +681%, respectively). Increases in plasma TBILI and potassium and decreases in plasma protein started from the medium dose level and at 200 mg/kg increases of plasma aspartate amino transferase (AST, up to +129%) and alanine amino transferase (ALT, up to +31%) were among the effects found. Effects on T4 (up to 93%), T3 (up to -45%) and TSH (up to -87%) were dose-dependent with decreased plasma levels observed for T4 from 3 mg/kg, for TSH from 30 mg/kg on and for T3 at 200 mg/kg. For several organs, weight changes were observed. These started for heart, spleen, and kidneys already at the lowest dose and were most pronounced at the high dose (organ-to-body weight ratios at 200 mg/kg were up to +33%, up to +73%, and up to +46% for heart, spleen, kidneys, respectively). At the high dose organ-to-body weight ratios for the thyroid/parathyroid was decreased (up to -36%) and increased for the liver (up to +50%). Resmetirom-related histopathological changes were found in the liver and in the muscle at doses ≥ 30 mg/kg/day. In the liver mononuclear cell infiltrates (primary macrophages) and non-specific hepatocellular cytoplasmic alterations (described as granular to "ground-glass" appearance) and at 200 mg/kg subcapsular or interlobular fibrosis was found.

In skeletal muscle minimal to mild degeneration/regeneration of individual myofibers (at 200 mg/kg in nearly all male in one third of female animals) was documented, which was considered as non-adverse by the study pathologist.

The myofiber degeneration/regeneration observed, although it was clearly dose-dependently drug related, was of minimum magnitude only (with the exception of 2 male rats at 200 mg/kg/day, in which it was graded as mild). This finding per se does not qualify clearly as an adverse effect and no SmPC change would be required.

At the dosage level of 3 mg resmetirom/kg/day the combined male and female exposure equals 1 time (AUC) or 0.6 time (C_{max}) of the intended clinical exposure. At the next higher dose level of 30 mg resmetirom/kg/day, which the applicant considers as the NOAEL, the exposure was 5.7 times (AUC) or 2.7 times (C_{max}) the intended clinical exposure.

Regarding possible effects on the thyroid system in the 6 month rat study, the applicant pointed out that the (statistically non-significant) reduction in the thyroid/parathyroid weight relative to body weight by 11% seen in male rats was due rather to an increase in mean body weight in the group of animals treated with 30 mg resmetirom/kg/day than to a decrease in absolute thyroid/parathyroid weight itself and that there was no microscopic finding in the thyroid/parathyroid at this dose level.

Although mean TSH was decreased by 40% (reported to be mostly within historical control data), total and free T4 were decreased by 54% and 57%, respectively, animals were considered being in a euthyroid state with free T3, the most active thyroid hormone, being slightly increased (by 16%). It was agreed with the applicant that at the dose level of 30 mg resmetirom/kg/day for 6 months in rats the central HPT axis is considered not being suppressed and that the changes in thyroid hormones at this dose level do not warrant inclusion in section 5.3 of the SmPC.

Two non-GLP-compliant experimental and three GLP-compliant repeated-dose studies were conducted in beagle dogs. In the GLP-compliant studies, the animals were treated orally once daily (by gavage) for 28 days (0, 5, 20, or 50 mg/kg/day), 3 months (0, 2.5, 5, 15, or 45 mg/kg/day) or 9 months (0, 5, 15, 45, or 100 mg/kg/day). The vehicles used were 2% Klucel LF, 0.1% Tween 80, 0.09% methylparaben and 0.01% propylparaben in purified water.

The toxicity profile was generally similar across the studies in dogs. Most effects were attributable to the pharmacological action of resmetirom.

No mortality was reported in any study. There were also no toxicologically relevant effects on body weight, food consumption, ophthalmology evaluation, ECG findings (including QTc output), haematology, coagulation and troponin levels. Clinical signs ranged from salivation, emesis, soft and mucoid faeces to diarrhoea in all resmetirom-treated groups in males and females, mainly during the first weeks of treatment, but without a clear dose-response.

Changes in thyroid hormone levels were observed in all studies in all dose groups. Dose-dependent decreases in total and free T4 occurred in all studies. In the higher dose groups, they were accompanied by decreases in total T3, but not or only transient decreases in free T3 (FT3). Decreases in TSH levels were only observed at ≥ 20 mg/kg/day in the 28-day repeat-dose toxicity study and in the 14-day range finding study. All changes in thyroid hormone levels were reversible at the end of the recovery periods. No clear gender specificity for the effects were observed, however, in male animals the decreases in hormone levels were generally more pronounced.

As resmetirom is a partial thyroid hormone receptor agonist, effects on the thyroid hormone levels were expected. Therefore, the applicant proposed that resmetirom-associated decreases in thyroid hormones were not considered adverse unless there was a concomitant, inappropriate decrease in TSH, T4, and T3, with adverse alterations in target organs, which were collectively indicative of suppression of the central HPT axis.

Reversible decreases in triglycerides and cholesterol in males and females were reported in nearly all dose groups in the 28-day, 3-month and 9-month studies. These findings were expected due to the pharmacology of resmetirom.

Reversible, non-adverse, resmetirom-related increases in mean ALT (up to 4-fold) were observed in males and females at ≥ 45 mg/kg/day in 28-day, 3-month and 9-month studies. There were no corresponding changes in AST, GGT or bilirubin and no definite histopathological correlates therefore the ALT elevations were not considered a function of hepatic parenchymal injury.

In the 9-month study reversing or reversible increases in total ALP (1.5- to 3.4-fold) were observed in males at 100 mg/kg/day and females at 5, 45, or 100 mg/kg/day. A mild increase in bone ALP relative to control was observed in males at 100 mg/kg/day and in females at ≥ 5 mg/kg/day, which had reversed or was reversing. With no microscopic correlates, these mild increases in bone ALP for all dose groups were not considered adverse. Increases in liver ALP isoenzymes were reported for males at 100 mg/kg/day (3.5-fold) and in females at ≥ 15 mg/kg/day (up to 2.8-fold) which were reversed in all recovery animals except one high dose male and female. Observed reversible or reversing elevations in liver ALP at 100 mg/kg/day in males and females appeared to be related to the magnitude of bile duct hyperplasia in individual animals.

No treatment-related absolute organ weight changes were observed in dogs. In the 9-month study in female dogs at 45 and 100 mg/kg/day statistically significant reversible decreases in mean parathyroid/thyroid to body weights but not in absolute parathyroid/thyroid weights nor in mean organ weight to brain weight ratio were observed. These changes were considered a result of the mild, trending increase in mean body weight at these dose level and the high degree of variability in absolute organ weight between individual animals rather than a centrally mediated effect. Microscopic liver findings were observed in both sexes including minimal bile duct epithelium hyperplasia at 50 mg/kg/day in the 28-day dog toxicity study and at 100 mg/kg/day in the 9-month dog toxicity study in both the dosing and recovery periods (bile stasis was evident in one of two males in the recovery period). For the 9-month study these findings were considered adverse by the applicant while in the 28-days study this finding was not considered adverse due to the restricted distribution, the absence of other hepatic lesions, and the absence of clinical pathology (total ALP or ALP liver isoenzyme) findings. Considering that bile duct proliferation occurred in the 9-month study as well as in the 28-day study in dogs and is adverse in the 9-month study, the occurrence in the 28-day study in the 50 mg/kg/day should also be regarded as adverse. Therefore, the NOAEL for bile duct proliferation should be set at 20 mg/kg/day for this study. However, the bile duct proliferation is thought to be species-specific and secondary to the pharmacology or exaggerated pharmacology due to cholesterol lowering effects, high liver uptake and high biliary excretion of resmetirom as observed in pharmacokinetic studies in dogs. Therefore, biliary hyperplasia was considered a species-specific finding that is not relevant to humans.

In the 9-month study in dogs histopathological examination showed findings of the tongues in most females at ≥ 15 mg/kg/day at the end of the dosing period with similar incidences across dosing groups (4/4, 3/4, 4/4 at 15, 45 and 100 mg/kg/day, respectively). These findings consisted of minimal to mild epithelial thickening, diffusely affecting the dorsal epithelium and/or ventral epithelium, with most of these animals also exhibiting minimal neutrophilic inflammation associated with the thickened epithelium, which not reversed in one recovery female in the 15 mg/kg/day group.

The cause and the mechanism of the histopathological tongue findings and its occurrence in female dogs only is not known, but resmetirom related effect is unlikely. There were also no clinical correlations or adverse effects on overall health, such as clinical observations, decreased food consumption or weight loss.

A NOAEL of 45 mg/kg/day was set by the applicant for the 9-month dog study. Toxicokinetic evaluations in all three pivotal repeated dose toxicity studies in dogs showed high inter-animal and inter-day variability in plasma exposure. Based on *in vivo* and *in vitro* data, the applicant suggests that this could be related to a combination of interactions with different efflux and uptake transporters and differences in solubility at different pH values in the gastrointestinal tract [Guo et al.]. Results from previous PK studies (09877, 09907, and 09942) and the two-week range-finding study [09925] suggest that emesis did not have an effect on the exposure of resmetirom.

Generally, there were no consistent sex differences in exposure observed at any dose level in the 28-day, 3-month or 9-month toxicity study (<2 -fold difference).

Exposure, as assessed by C_{max} and AUC_{0-24h} values, increased with increasing dose. At the lower dose levels in the 9-month study, there was a general trend towards dose proportionality for exposure, while exposure appeared to be generally greater than dose proportional ≥ 45 mg/kg/day. In this study, a slight accumulation of resmetirom was observed inconsistently after 272 days of repeated daily administration.

MGL-3623 is a major metabolite of resmetirom that has been shown to be present in human plasma at $>10\%$ of the parent drug (Study No. 3196-17-016). The plasma concentration-time profile for MGL-3623 was similar to resmetirom at 45 and 100 mg/kg/day; however, the exposure was substantially lower (metabolite:parent AUC_{0-24} ratio of 0.4% to 2%).

At the NOAEL of 45 mg/kg/day, the AUC-based safety margin to human exposure at the MRHD is approximately 7 fold (mean male and female dog day 272 exposure levels of 54.450 ng*h/ml and human exposure level at 100 mg of 7.740 ng*h/ml).

2.5.4.3. Genotoxicity

A standard battery of *in vitro* and *in vivo* genotoxicity tests was performed with resmetirom. Resmetirom was negative in *in vitro* Ames tests, in an *in vitro* micronucleus test in L5178Y tk+/- mouse lymphoma cells and an *in vitro* Chromosome aberration assay in human peripheral blood lymphocytes. In an *in vivo* oral micronucleus test in rats resmetirom was also negative up to exposures approximately 350-fold the human exposure at 100 mg/d based on AUC. Based on the provided studies, resmetirom is not considered to be genotoxic *in vitro* and *in vivo*.

2.5.4.4. Carcinogenicity

2-year carcinogenicity studies were conducted with resmetirom in CD-1 mice and in SD rats. Doses were selected based on the repeat-dose studies performed with those strains (see section Repeat-dose toxicity).

In the mouse study, an increased incidence of hepatocellular adenoma (10/65), carcinoma (17/65) and hepatoblastoma (3/65) at 100 mg/kg/d was observed in male mice but not in female. In female mice, there was hepatocellular hypertrophy starting at 1 mg/kg/d and non-regenerative hepatocellular hyperplasia at ≥ 6 mg/kg/d. In addition, decreased survival rate was observed in male mice, with the most common cause being resmetirom-related non-neoplastic and neoplastic liver lesions. These lesions are commonly observed in mice and are a high dose phenomenon with a threshold mode of action. The NOAEL for carcinogenicity was set at 30 mg/kg/d resulting in safety margins of 9.6 fold for males and 13 fold for females based on AUC at the 100 mg/d human dose. There was a slight increased incidence in leiomyoma (benign) or leiomyosarcoma (malignant) in the uterus and cervix at 100 mg/kg/d. Combined incidence of leiomyoma and leiomyosarcoma in the uterus was statistically significant and drug-related. No significant observations were made at the 30 mg/kg/day dose which was set as NOAEL which results in AUC-based safety margins of 9.6 fold and 13 fold to the 100 mg/day human dose. If these tumours have human relevance is currently unknown. However, based on the high safety margins at the NOAEL, no carcinogenic risk in the uterus is anticipated in female patients at the recommended doses of resmetirom. In addition, no such findings were observed in the rat study. In the rat study, a statistically significant increase in fibroadenoma in mammary gland in male (4/61) and female (47/65) rats was observed at 30 mg/kg/d. Mammary gland fibroadenoma is the most common spontaneous tumour in SD rats. Those findings are considered not relevant for patients as mammary fibroadenomas in rats are not considered a premalignant lesion in humans (Rudmann et al., 2012). Although there was an increased incidence in those tumours related to resmetirom and the NOAEL is only at 6 mg/kg/day (safety margins 1-3 fold to the patient exposure), no carcinogenic risk for patients is anticipated as mammary fibroadenomas in rats are not predictive for carcinoma in women and no similar findings were observed in the mouse study.

2.5.4.5. Reproductive and developmental toxicity

In the fertility study in rats resmetirom-related effects on mean body weights and food consumption were noted for males at ≥ 10 mg/kg/day and females at 30 mg/kg/day. In addition, potentially test article-related higher mean pituitary weights were noted for males at 30 mg/kg/day and higher mean ovary weights were noted for females at 10 and 30 mg/kg/day. Also, higher mean numbers of corpora lutea and implantation sites were noted for females at 30 mg/kg/day. However, in the absence of any

other reproductive effects, these changes were not considered adverse due to the magnitude and/or direction of the change.

There were no adverse test article-related effects on male and female survival, clinical observations, or reproductive organ weights noted at any dose level.

Based on these results, a dosage level of 30 mg/kg/day was considered to be the (NOAEL for male and female systemic toxicity when the test article was administered orally by gavage to CrI:CD(SD) rats.

Based on the absence of test article-related effects on reproductive function and embryonic survival, the NOAEL for male and female reproductive toxicity and for early embryonic toxicity was considered to be 30 mg/kg/day, the highest dosage level tested.

No effects on embryo-foetal development were observed in pregnant rats treated orally with up to 100 mg/kg/day resmetirom (19 times the maximum recommended dose based on AUC) or in pregnant rabbits treated orally with up to 30 mg/kg/day resmetirom (2 times the maximum recommended dose based on AUC) during the period of organogenesis. Oral administration of 75 mg/kg/day in pregnant rabbits (3.5 times the maximum recommended dose based on AUC) produced an increase in post-implantation loss and decreases in viable fetuses and foetal weight. These effects were likely due to maternal toxicity (i.e., marked reductions in weight gain and food consumption).

No effects on embryo-foetal development were observed in pregnant rats treated orally with up to 100 mg/kg/day of the metabolite MGL-3623. This is 3.3-fold the human therapeutic exposure (based on AUC) at the (highest) recommended dose (100 mg/day).

In the pre-postnatal study at 100 mg/kg/day (the highest dose tested), there were no adverse resmetirom-related effects on maternal clinical observations, body weights and food consumption during the gestation and lactation periods. There were also no effects observed on reproduction in the dams at 100 mg/kg/day. This is 27-fold the human exposure (based on AUC) at doses of 100 mg/day and 66-fold at the human exposure (based on AUC) at doses of 80 mg/day.

Toxicokinetic exposure of resmetirom on GDs 17 and 20 suggests the absence of accumulation of resmetirom upon repeated once-daily dosing for 15 days. The metabolite MGL-3623 in the F0 generation females was detected at markedly low levels in the systemic circulation on GDs 6, 17 and 20 in gestating F0 generation female rats.

The maternal NOAEL for resmetirom was 30 mg/kg/day (AUC₀₋₂₄ value 37800 ng·hr/mL) based on HPT suppression (reduced TSH, FT3 and FT4) at 100 mg/kg/day. This is 4.4-fold the human therapeutic exposure (based on AUC) at doses of 100 mg/day and 10.8-fold at the human exposure (based on AUC) at doses of 80 mg/day.

At the initiation of the postweaning period, there was a decrease in body weight, body weight gain and food consumption in F1 males and females at 100 mg/kg/day. There were no effects on post-weaning learning and memory or reproductive performance.

Evaluation of early landmarks of physical and neurobehavioral development (e.g. eye opening, pinna unfolding, auditory startle), sensory functions or motor activity were not evaluated in the offspring. There were no effects on post-weaning learning and memory (evaluated in passive avoidance and water maze tests) or reproductive performance.

The findings in the 100 mg/kg/day group (decrease in number and weights of viable F1 conceptuses) were associated with reductions in maternal plasma levels of T4 (88% decrease), T3 (79% decrease), and TSH (44% decrease). This maternal thyroid hormone reduction is known to affect the foetal development in rats.

The NOAEL for viability and growth in the F1 generation rats was 30 mg/kg/day based on an increase in pup mortality observed at 100 mg/kg/day, adverse clinical signs during the pre-weaning period and a decrease in pup body weights observed on the day of delivery, with recovery in pup body weights during the pre-weaning period.

There is no information regarding the presence of resmetirom in human or animal milk, the effects on the breast-fed infant, or the effects on milk production.

In the juvenile toxicity study, there were no resmetirom-related mortalities or effects on clinical signs, sexual maturation (male or female), estrous cycling, mating (male or female), fertility (male or female), ophthalmology, macroscopic findings, or ovarian/uterine parameters, and no adverse effects on food consumption, clinical pathology, litter observations, or behaviour.

Non-adverse increases in body weight were observed at ≥ 30 mg/kg/day, which were sustained in the recovery period and corresponded with increases in bone size in males (200 mg/kg/day) and females (≥ 30 mg/kg/day), as evidenced by increases in femur length, increases in femur metaphysis and diaphysis total and/or cortical areas, and increases in bone circumference. Bone mass effects were different between sexes, with minimally increased bone mineral content in females but not in males, resulting in minimally decreased bone density in males.

At recovery, males had increased femur lengths at all dose levels, but bone size/density recovered fully, while females had sustained increases in bone size and bone mineral content at 200 mg/kg/day only. Similar findings (intramedullary bone formation) were observed in the 6-month repeated toxicity rat study.

Liver weight was significantly increased in females at ≥ 100 mg/kg/day in the main necropsy group and in females at ≥ 3 mg/kg/day in the recovery necropsy group. Minimal to mild necrosis and minimal to moderate mixed cell inflammation was observed in both sexes at ≥ 3 mg/kg/day, while minimal single cell necrosis and glycogen depletion were observed at ≥ 30 mg/kg/day. Microscopic findings were reversing during the recovery period with lower incidence.

Increased organ weights were observed in the heart, kidney, liver, thymus, and spleen, with corresponding microscopic findings in the heart, kidney, liver, and spleen. Microscopic findings in the heart, kidney, lung and liver were present at the recovery necropsy.

Similar organ weight changes occurred in the repeated dose rat toxicity study.

Overall, the set the NOAEL was 30 mg/kg/day in male and female juvenile rats, (14 and 11 times the maximum recommended human dose based on AUC, respectively). This was acceptable to the CHMP.

2.5.4.6. Toxicokinetic data

In repeat-dose toxicity and TK studies, there were generally no sex differences in systemic exposure to resmetirom (<2 -fold difference) in mice, rats, and dogs. Exposure, as assessed by $C_{\max}$ and AUC_{0-24} increased with increasing dose, generally in a dose-proportional manner in mice and rabbits (pregnant), and a more than dose proportional manner in rats at ≥ 30 mg/kg/day (except in juvenile rats) and dogs at ≥ 45 mg/kg/day. Slight accumulation was observed inconsistently across various dose levels and durations of administration up to 6 months in adult rats, 7 weeks in juvenile rats, and 9 months in dogs.

Resmetirom exposure in rats, as assessed by $C_{\max}$ and AUC_{0-24} , increased in a dose proportional manner and was similar on GD 6 and 17.

Resmetirom exposure in rabbits, as assessed by C_{max} and AUC, also increased in a dose proportional manner from 10 to 30 mg/kg/day on GD 7 and 20. In both species no accumulation is suggested.

2.5.4.7. Local tolerance

No stand-alone local tolerance studies were conducted with resmetirom. Local tolerance was assessed in the repeat-dose toxicology studies, which is considered appropriate.

2.5.4.8. Other toxicity studies

Neither non-clinical studies investigating antigenicity, nor immunotoxicity, nor dependence were conducted which is, taking the results of the non-clinical safety studies as a whole into account, considered acceptable.

Resmetirom induced an increase in spleen weight of female mice at 3 and 100 mg/kg/day dose, however since correlation with other immune-related finding was not observed, the risk of immunotoxicity was considered low. Similarly, in a mice 2-year carcinogenicity study extramedullary haematopoiesis was detected in livers and spleens of female mice at 3 and 30 mg/kg/day dose and both sexes at 100 mg/kg/day dose, however it did not correlate with other changes in haematology.

In dog 9-month repeated toxicity increases in mean GLO were noted, accompanied by decreased mean ALB/GLO ratio for males dosed at 100 mg/kg/day, however these changes were reversible and were not associated with other immunotoxic findings.

Overall studies in mice, rats and dogs indicate that resmetirom is not an immunotoxic compound.

Studies on metabolites

MGL-3623 is a major metabolite of resmetirom (M1) that has been shown to be present in human plasma at >10% of the parent drug. Its potential toxicity was assessed in various studies including computational toxicity assessments, repeat-dose toxicity studies in mice for up to 90 days, *in vitro* and *in vivo* genotoxicity studies, a 6-month carcinogenicity study in transgenic rasH2 mice, and an EFD study in rats.

MGL-3623 induced micronuclei in TK6 human lymphoblasts with metabolic activation. However, the increase in micronuclei was only observed at single concentration at high cytotoxicity (>50%). In addition, MGL-3623 was negative in the Ames test and in the *in vivo* rat micronucleus assay and not carcinogenic in transgenic RasH2 mice. Therefore, no genotoxic and carcinogenic potential is anticipated from MGL-3623. Repeat-dose toxicity studies of MGL-3623 in mice did not show toxicities which were not observed with resmetirom. AUC-based safety margins to the 100 mg/d human dose at the NOAELs of the 10-, 28-, and 90-Day studies were 7-, 21- and 4-fold, respectively. No human relevant toxicities of MGL-3623 are anticipated in patients.

Based on the lack of effects on maternal condition, EFD and morphology, a dosage level of 100 mg/kg/day (the highest dosage level tested (AUC₀₋₂₄ of 10100 ng·hr/mL on GD 17) was considered to be the NOAEL for maternal toxicity and EFD when MGL-3623 was administered orally by gavage to time-mated SD rats. This is 3.3-fold the human therapeutic exposure (based on AUC) at 100 mg/day.

Minor metabolite MGL-3842 was subjected to *in silico* mutagenicity analysis and considered as non-mutagenic.

Studies on impurities

Potential mutagenic process impurities and resmetirom-related impurities were subjected to *in silico* mutagenicity predictions using complimentary QSAR analyses by means of DEREK (expert-based, DEREK 6.1.1, Nexus 2.4.0) and LMSA (statistical-based, version 2.3.7-1 or 3.0.2-4) QSAR tools in accordance with ICH M7. The assessment is considered adequate. The ICH M7 classifications assigned based on the QSAR results are endorsed.

For other impurities, an adequate literature search was performed.

Phototoxicity studies

Resmetirom was evaluated for its phototoxic potential in a GLP-conform *in vitro* Neutral Red Uptake (NRU) assay in BALB/c 3T3 mouse fibroblasts. Based on the negative result of the *in vitro* NRU assay with resmetirom and the low potential to bind to pigmented tissue, no relevant phototoxic potential is anticipated for patients.

2.5.5. Ecotoxicity/environmental risk assessment

Table 6. Summary of main study results

Substance (INN/Invented Name):		Resmetirom	
CAS-number (if available):		920509-32-6	
PBT screening		Result	Conclusion
Bioaccumulation potential- log K_{ow}	OECD 107	2.1 (pH=5) 0.57 (pH=7) 0.054 (pH=9)	Potential PBT: N
PBT-assessment			
Parameter	Result relevant for conclusion		Conclusion
Bioaccumulation	log K_{ow}	2.1 (pH=5)	not B
	BCF	Not required	B/vB/not B
Persistence	DT50 Values are derived from the OECD 308 have been recalculated to 12°C	450 d (Total System /Sediment)	vP
Toxicity	NOEC or CMR	510 µg/L	not T
PBT-statement :	The active substance is considered to be not PBT, nor vPvB		

Phase I			
Calculation	Value	Unit	Conclusion
PEC _{sw, refined} (prevalence)	0.0179	µg/L	≥ 0.01 threshold: Y/N
Other concerns (e.g. chemical class)			N

Table 7. Phase II – Physical-chemical properties and fate

Phase II - Physical-chemical properties and fate			
Study type	Test protocol	Results	Remarks
Adsorption-Desorption Soil 1 = sandy loam Soil 2 = sandy loam Soil 3 = clay Sludge 1 = Tilburg Sludge 2 = Aa & Maas	OECD 106	$K_{oc, \text{soil } 1} = 548 \text{ L/kg}_{oc}$ $K_{oc, \text{soil } 2} = 829 \text{ L/kg}_{oc}$ $K_{oc, \text{soil } 3} = 592 \text{ L/kg}_{oc}$ $K_{oc, \text{sludge } 1} = 1744 \text{ L/kg}_{oc}$ $K_{oc, \text{sludge } 2} = 1566 \text{ L/kg}_{oc}$	List all values
Ready Biodegradability Test	OECD 301 B	2% in 28 d, Not readily biodegradable	
Aerobic and Anaerobic Transformation in Aquatic Sediment systems Sediment 1 = clay loam Sediment 2 = sand	OECD 308	$DT_{50, \text{water}} = 19 / 41 \text{ d}$ $DT_{50, \text{sediment}} = \text{n a d}$ $DT_{50, \text{whole system}} = 123 / 210 \text{ d}$ $CO_2 = 9 / 2 \%$ $NER = 23 \%$ (both) $NER_{TYPE I} = 8 / 12 \%$ Transformation products >10% = No	DT50s at 20°C 1 / 2 at test end at test end EDTA-Extraction

Table 8. Phase II effect studies

Phase II effect studies surface water					
Study type	Test protocol	Result	Value	Unit	Remarks

Phase II effect studies surface water					
Algae, Growth Inhibition Test/ <i>Raphidocelis subcapitata</i>	OECD 201	EC ₁₀	47,000	µg/L	growth rate
<i>Daphnia magna</i> , Reproduction Test	OECD 211	EC ₁₀	5,100	µg/L	applicable endpoint(s)
Fish, Early Life Stage Toxicity Test/ <i>Pimephelas promelas</i>	OECD 210	EC ₁₀	9,600	µg/L	Applicable endpoint(s)
Activated Sludge, Respiration Inhibition Test	OECD 209	NOEC	2500	µg/L	respiration
Phase II sediment assessment					
Sediment dwelling organism/ <i>Chironomus riparius</i>	OECD 218/219	NOEC / EC ₁₀	30.4	mg/kg _{dw}	applicable endpoint(s)
Risk characterisation					
Compartment	PEC	PNEC	RQ	Conclusion	
STP	1.79 µg/L	250 µg/L	0.07	No risk	
Surface water	0.179 µg/L	510	0.00035	No risk	
Groundwater	0.045 µg/L	51 µg/L	0.0009	No risk	
Sediment	0.0155 mg/kg _{dw}	0.304 mg/kg _{dw}	0.05	No risk	

The provided PEC calculation is acceptable. The rationale for not submitting a tailored ERA is also considered acceptable.

Considering the above data from Phase I and Phase II, resmetirom is not expected to pose a risk to the environment.

Considering the above data of the definitive hazard assessment, resmetirom is not a PBT or vPvB substance.

2.5.6. Discussion on non-clinical aspects

Resmetirom is a partial agonist at the THR, a nuclear receptor, with preferential selectivity for THR β versus THR α . A selectivity factor for THR- β versus THR- α of 28-fold as compared with T3 was calculated by the applicant for resmetirom.

The results of an *in vitro* study demonstrate for metabolite M1 a certain degree of binding to THR- β . In an *in vitro* coactivator recruitment assay metabolite M1 showed much lower potency than resmetirom at both THR receptors, with an EC₅₀ of 75.9 μ M at THR α and EC₅₀ of 19.3 μ M at THR β .

Non-GLP primary pharmacodynamic studies have been performed in male DIO mice up to 25 weeks, hyperlipidaemic SD male rats up to 8 days and hypercholesterolemic rabbits up to 7 days (gender not mentioned). These animal models represent features attributed to NASH and MASH – hepatic steatosis, insulin resistance, dyslipidaemia and obesity. Microscopic examination did not confirm inflammation or fibrosis. The applicant refers to external publications in which resmetirom has been shown to reduce liver fibrosis in non-clinical models of NASH. Although the non-clinical data submitted by the applicant does not clearly confirm liver fibrosis formation in DIO mice, clinical findings from the Phase 3 trial (MGL-3196-11) demonstrate that resmetirom reduces liver fibrosis. Therefore, no additional non-clinical information is required.

In some *in vivo* primary pharmacology studies, resmetirom treatment associated gene expression changes in the liver were investigated. The applicant remarks that doses of resmetirom from 0.3 to 3 mg/kg normalized NASH-related inflammatory and fibrosis gene transcripts that were significantly elevated in the livers of DIO mice as compared with normal chow fed, lean control mice. The applicant refers to a 30-day study in New Zealand White rabbits in which resmetirom doses up to 14.1 mg/kg/day and a combination with atorvastatin were assessed – THR-79. This study was conducted to evaluate the effects of resmetirom, atorvastatin, or a combination of resmetirom and atorvastatin on the lipoprotein profile of hypercholesterolemic rabbits. The THR-79 study report demonstrated the synergistic effect of resmetirom with atorvastatin in hypercholesterolemic rabbits, as evidenced by a reduction of non-HDL cholesterol and plasma triglycerides. Resmetirom is a substrate of the human heterotrimeric organic solute transporter OST α/β , in MDCK-II cell monolayers. OST α/β is localized in ileus, liver and kidney and is involved in the absorption and distribution of bile acids.

The expected average C_{max} of resmetirom at 100 mg dose in patients is 2.23 μ M which is sufficiently lower than the K_m value for OST α/β transporter (313 μ M). Consequently, it can be agreed that OST α/β transporter is not expected to significantly affect the pharmacokinetics of resmetirom.

The *in vitro* studies in microsomes and hepatocytes showed similar patterns across the species investigated, characterised by a consistent high stability (between 100 and 98%) of the parent compound resmetirom. The potential of resmetirom to be oxidised to metabolite M1 and M2 (MGL-3623/ 3842) was investigated by chemical oxidation and in cytosolic preparations of mice and human hepatocytes. The results show an only marginal potential. Results on *in vivo* studies are only presented for rats and dogs. Comparison with human data lead to the conclusion that the M1 metabolite (MGL-3623) is a human main metabolite, and that significant exposure could not be achieved in experimental animals by oral resmetirom administration. Therefore, the M1 metabolite (MGL-3623), but not the M2 metabolite was characterized independently.

Oxalic acid was found to be another human plasmatic metabolite with a share of approximately 15% of total exposure (based on AUC). Oxalic acid was not detected in toxicity studies in rats and dogs and was not investigated further in clinical studies. However, resmetirom associated oxalic acid intake and exposure is expected to be in the physiological range, hence it was agreed that further studies were not necessary.

Overall, marked differences in the metabolic patterns between humans and the species used in toxicity testing have been shown (rats and dogs) or can be anticipated (mice and rabbits). Concerning the M1 metabolite (MGL-3623), the applicant refers to the Guideline ICH M3 and the respective Question and Answer Document. In accordance with the guideline the applicant has investigated the M1 metabolite (MGL-3623) in one species used in the general toxicity evaluation, one species used in a carcinogenicity study, and one species used in an embryo-foetal development study. Adequate exposure to the metabolite was reached in these studies. The approach is agreed to and further studies investigating the M1 metabolite are not considered necessary.

The finding that low degrees of resmetirom could be detected in the carcass of rats is a rather unexpected result of the distribution studies. However, this finding could be attributed to residual resmetirom within the bone vasculature. Female rats were excluded from distribution studies based on data from a 6-month GLP toxicity study, which showed no significant differences in C_{max} and AUC_{0-24} values between sexes at doses of 3, 30, and 300 mg/kg/day. Additionally, according to the toxicology data resmetirom did not adversely affect female reproductive organs, suggesting that the absence of data on its distribution to these organs is not clinically significant and thus the exclusion of female rats from distribution studies is in line with 3R principles.

Faecal elimination was the dominant and urinary elimination the minor route in rats, dogs and humans. Hepatobiliary elimination is considered the main elimination pathway in humans and in animals used in toxicity testing.

In the 6-month general toxicity study in rats with an 8-week recovery phase in skeletal muscle minimal to mild degeneration/regeneration of individual myofibers (at 200 mg/kg in nearly all male in one third of female animals) was documented. In dogs at similar exposures no such finding had been found. Due to the low degree with absence of necrosis or inflammatory infiltration, lack of clinical signs in the animals and reversibility, no SmPC mention was required. Hepatocellular cytoplasmic alterations reported in rats were considered attributable to an increase in endoplasmatic reticulum as an adaptive response to microsomal drug metabolising enzyme induction. Despite decreases in TSH, total and free T4, at the dose level of 30 mg resmetirom/kg/day for 6 months in rats, the central HPT axis was considered not being suppressed as the animals were in a euthyroid state (slight increase in free T3, the most active thyroid hormone), the absolute organ weight of the thyroid/parathyroid remained unchanged and no histologic correlates were seen.

Two non-GLP-compliant experimental and three GLP-compliant repeated-dose studies were conducted in beagle dogs.

The toxicity profile in dogs was generally similar across the studies. Most effects were attributable to the pharmacological action of resmetirom.

Dose-dependent decreases in total and free T4 occurred in all studies in dogs, which were accompanied by decreases in total T3 at higher dose levels. Decrease in TSH levels were only observed at ≥ 20 mg/kg/day in the 28-day repeat-dose toxicity study and in the 14-day range finding study. It was agreed that resmetirom-associated decreases in thyroid hormones were not considered adverse since no study showed a concomitant, inappropriate decrease in TSH, T4, and T3, with adverse alterations in target organs, which were collectively indicative of suppression of the central HPT axis. Although in the 45 mg/kg/day and 100 mg/kg/day dose groups of the 9-month study there were statistically significant reversible decreases in mean parathyroid/thyroid to body weight ratio in females and transient significant decrease in free T3 hormone levels in male and female animals these changes are rather viewed as a result of other contributing factors (e.g. small number of animals used and biological variability of organ weights and thyroid hormone levels) and not as an indication for a centrally mediated TSH suppression.

In the 9-month study in dogs histopathological examination showed findings of the tongues (minimal to mild epithelial thickening, diffusely affecting the dorsal epithelium and/or ventral epithelium, associated with minimal neutrophilic inflammation) in most females at doses ≥ 15 mg/kg/day with similar incidences across all affected dosing groups. The cause or the mechanism of these findings is not known. Tongue findings have neither been seen in male dogs in this study nor in the other dog studies and were also not observed in the repeated dose toxicity studies in rats or the carcinogenicity studies in mice and rats. In addition, a review of MedDRA terms conducted by the applicant identified only a single individual on resmetirom (swollen tongue, EIAIR= 0.02%) but no other tongue related AEs which supported the lack of clinical correlates. It is likely that the tongue findings in female dogs may not be resmetirom related. This is also supported by the lack of a dose dependent increase in severity.

Therefore, the NOAEL of 45 mg/kg/day proposed by the applicant for the 9-month dog study is acceptable. At the NOAEL of 45 mg/kg/day the AUC-based safety margin to human exposure at the MRHD is approximately 7-fold (mean male and female dog day 272 exposure levels of 54.450 ng*h/ml and human exposure level at 100 mg of 7.740 ng*h/ml).

Genotoxicity and carcinogenicity

Resmetirom is not considered to be genotoxic *in vitro* and *in vivo*.

2-year carcinogenicity studies were conducted with resmetirom in CD-1 mice and in SD rats. Increased incidences of liver tumours (hepatocellular adenomas and carcinomas, and hepatoblastomas) were reported in the mouse carcinogenicity study in males only at the highest dose of 100 mg/kg/day (safety margins >10-fold at the NOAEL). These lesions are commonly observed in mice and are a high dose phenomenon with a threshold mode of action. Human relevance for leiomyoma (benign) and leiomyosarcoma (malignant) in the uterus observed at the 100 mg/kg/d dose mouse study is unknown. Due to safety margins > 10-fold at the NOAEL no patient risk is anticipated. Benign mammary gland fibroadenoma observed in the rat study at 30 mg/kg/day are not considered a concern despite low safety margins as mammary fibroadenomas in rats are not considered a premalignant lesion in humans. All tumour findings are adequately labelled in the SmPC.

Reproductive and developmental toxicity

Results from the conducted studies on male and female fertility and early embryonic development, embryo-foetal development and pre- and post-natal development study do not indicate a risk of adverse effects. Information regarding developmental and reproductive toxicology nonclinical data in the proposed SmPC (sections 4.6 and 5.3) is considered adequate.

Juvenile toxicity

The applicant has performed a juvenile toxicity study in rats although use in the paediatric population is currently not intended. Increase in bone size and geometry was observed in juvenile rats after resmetirom administration. Although mostly effects on bones were reversible, higher femur length remained in males at doses ≥ 3 mg/kg/day, while in females an increase related to bone size/geometry and mass remained at 200 mg/kg/day after the recovery period. Although bone effects have not been observed in adult patients in clinical trials, bone should be considered as a possible target organ in the paediatric population based on non-clinical findings in juvenile rats. Effects on bones will be considered as part of the safety assessment in planned clinical trials. This is agreed by the CHMP.

Studies on metabolites

The major metabolite MGL3632 was evaluated in several toxicity studies. No human relevant toxicities are anticipated in patients.

Studies on impurities

Genotoxic and non-genotoxic process impurities and resmetirom-related impurities were qualified in line with ICH M7 and Q3A7B guidance.

Phototoxicity studies

Based on the negative result of the *in vitro* NRU assay with resmetirom and the low potential to bind to pigmented tissue, no relevant phototoxic potential is anticipated for patients.

Environmental risk assessment

The applicant provided a Phase I and Phase II ERA. The provided studies were acceptable.

Assessment of paediatric data on non-clinical aspects

The PDCO agreed on a waiver in a subset of children from birth to less than 8 years of age on the grounds that the specific medicinal product does not represent a significant therapeutic benefit over existing treatments.

2.5.7. Conclusion on the non-clinical aspects

The pharmacological characteristics of resmetirom are in line with the intended clinical indication. The non-clinical development is considered adequate with no outstanding issues.

2.6. Clinical aspects

2.6.1. Introduction

GCP aspects

The clinical trials were overall performed in accordance with GCP as claimed by the applicant.

The applicant has provided a statement to the effect that clinical trials conducted outside the Community were carried out in accordance with the ethical standards of Directive 2001/20/EC.

Table 9. Resmetirom Clinical Studies – Tabular overview

Type of Study	Study code	Objective(s) of the Study	Study Design and Type of Control	Test Product(s); Dosage Regimen; Route of Administration	Number of Subjects	Healthy Subjects or Diagnosis of Patients	Duration of Treatment	Study Status; Type of Report
BA	MGL-3196-08	Compare BA of 100 mg resmetirom tablet to capsule	Open-label single dose sequential crossover	Resmetirom tablet or capsule, 40 mg and 60 mg, single dose, oral	16	Healthy subjects	5 days	Complete; Full
PK	VIA-3196-01	PK, PD, food effects	Randomized, double-blind, placebo-controlled	Resmetirom or placebo capsule, SAD, 0.25, 1, 2.5, 5, 10, 20, 50, 100 and 200 mg, oral	72 (54 resmetirom, 18 placebo)	Healthy subjects	Single dose (10 mg cohort only: 2 days [Day 1 and Day 7])	Complete; Full
PK	VIA-3196-02	PK, PD, safety, lipid changes and biomarkers	Randomized, double-blind, placebo-controlled	Resmetirom or placebo capsule, MAD, 5, 20, 50, 80, 100 and 200 mg, oral	48 (36 resmetirom, 12 placebo)	Healthy subjects	14 days	Complete; Full
PK	MGL-3196-07	PK and mass balance of ¹⁴ C-MGL-3196	Open-label	Resmetirom capsule and oral solution, resmetirom 40 and 60 mg capsules and 100 mg oral solution containing 100 µCi ¹⁴ C-MGL-3196	8	Healthy subjects	7 days	Complete; Full
PK	MGL-3196-10	PK of resmetirom and MGL-3623 in patients with HI and with NASH compared to healthy matched control patients with normal hepatic function	Open-label, matched control	Resmetirom tablets, 40 mg, 60 mg, 80 mg, or 100 mg, oral	87	Patients with hepatic impairment/ healthy subject matched controls	6 days	Complete; Full
PK	MGL-3196-21	PK of resmetirom in subjects with severe renal impairment	Open-label, matched control	Resmetirom 100mg, tablets once daily, oral, for 6 Days	14 (severe renal impairment) +14	Subjects with severe renal impairment /healthy	6 days	Draft PK report with responses

Type of Study	Study code	Objective(s) of the Study	Study Design and Type of Control	Test Product(s); Dosage Regimen; Route of Administration	Number of Subjects	Healthy Subjects or Diagnosis of Patients	Duration of Treatment	Study Status; Type of Report
		compared to healthy control subjects with normal renal function following repeated dosing Day 6			matched controls normal renal function	subject matched controls		, Seq 0004
PK	MGL-3196-20	PK of resmetirom in healthy Japanese and Caucasian subjects	Randomized, double-blind, placebo-controlled	Resmetirom tablet 40, 60, 80, 100 or 200 mg, single dose, oral	81	Healthy subjects	20 days	Complete; Full
PK/DDI	MGL-3196-03	Effect of resmetirom 200 mg/day on single-dose PK of 10 mg rosuvastatin or 20 mg simvastatin (AUC _[0 inf])	Open-label sequential crossover DDI	Resmetirom 200 mg capsules daily (4 × 50 mg), simvastatin 20 mg tablet, single dose and rosuvastatin 10 mg tablet, single dose, oral	25	Healthy subjects	11 days	Complete; Full
PK/DDI	MGL-3196-24	Effect of resmetirom 100 mg/day on single-dose PK of 10 mg rosuvastatin and N-desmethyl rosuvastatin (AUC _[0 inf])	Open-label DDI	Resmetirom 100mg tablet daily, rosuvastatin 10mg, single dose, oral		Healthy subjects		Draft PK report as part of responses , Seq 0004
PK/DDI	MGL-3196-04	Effect of resmetirom 100 mg/day on single-dose PK of 20 mg atorvastatin (AUC _[0 inf])	Open-label DDI	Resmetirom 100 mg capsule daily, atorvastatin 20 mg tablet single dose, oral	14	Healthy subjects	14 days	Complete; Full

Type of Study	Study code	Objective(s) of the Study	Study Design and Type of Control	Test Product(s); Dosage Regimen; Route of Administration	Number of Subjects	Healthy Subjects or Diagnosis of Patients	Duration of Treatment	Study Status; Type of Report
PK/DDI	MGL-3196-09	Effect of resmetirom 100 mg/day on single dose pioglitazone 15 mg PK	Open-label, DDI	Resmetirom 100 mg (40 mg + 60 mg tablets) daily, pioglitazone 15 mg tablet single dose, oral	16	Healthy subjects	13 days	Complete; Full
PK/DDI	MGL-3196-12	Effect of co-administration of clopidogrel on single and multiple-dose PK of resmetirom	Open-label, DDI	Resmetirom 100 mg tablet, single dose; resmetirom 75 mg tablet, daily; clopidogrel 300 mg tablet (4 x 75 mg), single dose; clopidogrel 75 mg tablet daily, oral	20	Healthy subjects	11 Days	Complete; Full
PK/DDI	MGL-3196-15	To determine effect of chronic resmetirom dosing on the PK of pravastatin, simvastatin and their metabolites	Open-label, DDI	Resmetirom 100 mg tablets daily, pravastatin 40 mg tablets, simvastatin 20 mg tablets, oral	25	Healthy subjects	6 Days	Complete; Full
PK/PD/DDI	MGL-3196-16	To assess effect of resmetirom on PK of warfarin (R- and S-warfarin) and on the PD of warfarin INR	Open-label, DDI	Resmetirom 100 mg tablets daily, warfarin 1 mg, 2.5 mg or 5 mg tablets daily (titrated), oral	27	Healthy Subjects	8 Days	Complete Full
PK/DDI	MGL-3196-22	To assess effect of cyclosporine on resmetirom PK	Open-label, DDI	Resmetirom 100 mg tablets daily, cyclosporine 175 mg BID	22	Healthy subjects	16 days	Complete; Full
Safety	MGL-3196-17	To assess effects of resmetirom after single and multiple supratherapeutic dose	Randomized, double-blind, placebo and positive-controlled, cross-over	Resmetirom or placebo 200 mg (2 x 100 mg tablets) daily, moxifloxacin 400 mg tablet single dose, oral	36	Healthy subjects	6 Days	Complete Full

Type of Study	Study code	Objective(s) of the Study	Study Design and Type of Control	Test Product(s); Dosage Regimen; Route of Administration	Number of Subjects	Healthy Subjects or Diagnosis of Patients	Duration of Treatment	Study Status; Type of Report
		administration on cardiac repolarization (Q-T interval of ECG)						
Efficacy	MGL-3196-05	Effect of daily resmetirom 80 mg versus placebo on percent change in hepatic fat fraction by MRI-PDFF from baseline in patients with biopsy-proven NASH	Randomized, double-blind, placebo-controlled	Resmetirom or placebo 80 mg daily (2 x 40 mg capsules) for 4 weeks; 40, 60, 80, or 120 mg (40 mg or 60 mg capsules) resmetirom or placebo (dose adjustments Week 4 on), oral	125	Patients with NASH	12 weeks Extension: 36 weeks	Complete Full
Efficacy	MGL-3196-06	Effect of QD oral dosing of 60 mg or 100 mg resmetirom versus placebo on percent change from baseline in LDL-C in patients with HeFH	Randomized, double-blind, placebo-controlled	Resmetirom or placebo 100 mg capsules daily for 2 weeks, then resmetirom or placebo 60 mg daily capsules Weeks 2-4, then dose adjustments to 60 mg or 100 mg resmetirom or placebo, oral	116	Patients with HeFH	12 Weeks	Complete Full
Efficacy	MGL-3196-11	Dual Primary: To determine the effect of once-daily resmetirom versus matching placebo on NASH To determine the effect of once-daily resmetirom versus matching placebo on	Randomized, double-blind, placebo-controlled Open-label Active Arm: Patients who experience a Composite Clinical Outcome event at Week 52 or later have the option to enter an	Resmetirom or placebo 80 mg or 100 mg tablets (or 60 mg in patients with dose reductions) Open-label active arm: patients entering the open label active arm who have either normal liver function or mild/moderate HI, will receive 80 mg resmetirom.	1563	NASH	54 Months	Complete (primary analysis report); Full

Type of Study	Study code	Objective(s) of the Study	Study Design and Type of Control	Test Product(s); Dosage Regimen; Route of Administration	Number of Subjects	Healthy Subjects or Diagnosis of Patients	Duration of Treatment	Study Status; Type of Report
		histologic improvement from baseline	open-label active treatment arm of the study	Dose may be adjusted up to 100 mg or down to 60 mg based on the drug exposure at Week 2				
Safety/ Efficacy	MGL-3196-14	Safety and tolerability of 80 or 100 mg resmetirom versus placebo	Randomized, double-blind, placebo-controlled study	Resmetirom or placebo 80 mg or 100 mg tablets (or 60 mg in patients with dose reductions)	1143 (823 resmetirom, 320 placebo)	NAFLD patients with presumptive NASH	12 months	Complete Full
Safety/ Efficacy	MGL-3196-14 (addendum)	Safety and tolerability of 80 or 100 mg resmetirom versus placebo	Randomized, double-blind, placebo-controlled study	Resmetirom 80 mg or 100 mg tablets (or 60 mg in patients with dose reductions)	183	NAFLD patients with presumptive NASH	24 Weeks	Complete Full
Safety	MGL-3196-18	To evaluate the safety and tolerability of once-daily, oral administration of resmetirom for 52 weeks	Multicenter, active-treatment, rollover study for patients who completed Study MGL-3196-14, as well as screen fail patients from Study MGL 3196-11, MGL-3196-19, and de novo meeting eligibility criteria	Tablets, resmetirom or placebo 80 mg or 100 mg (or 60 mg in patients with dose reductions)	1080 (anticipated) ; 615 included in interim CSR	NAFLD/ NASH	52 Weeks	Ongoing

AUC = area under the curve; AUC_[0-inf] = area under the plasma concentration-time curve from time zero to infinity; BA = bioavailability; DDI = drug-drug interaction; HeFH = heterozygous familial hypercholesterolemia; HI = hepatic impairment; INR = international normalized ratio; LDL-C = low-density lipoprotein cholesterol; MAD = multiple ascending dose; MRI-PDFF = magnetic resonance imaging-proton density fat fraction; NAFLD = Non-Alcoholic Fatty Liver Disease; NAS = Non-Alcoholic Fatty Liver Disease activity score; NASH = non-alcoholic steatohepatitis; PD = pharmacodynamics; PK = pharmacokinetics; QD = once daily; SAD = single ascending dose

2.6.2. Clinical pharmacology

2.6.2.1. Pharmacokinetics

The pharmacokinetics of resmetirom and its main metabolite MGL-3623 were evaluated in 36 *in vitro* studies, in 17 Phase 1 clinical pharmacology studies applying rich sampling, and with sparse sampling in Phase 2 and Phase 3 studies. Furthermore, modelling and simulation were conducted to fully characterise the PK-PD profile.

Eight bioanalytical methods (4 for plasma, 1 for plasma:plasma ultrafiltrate, 3 for urine) were developed for determination of resmetirom and MGL-3623, with further method revisions. Determination of analytes other than resmetirom and MGL-3623 in DDI studies involved further bioanalytical methods specific for these compounds.

PK analysis involved standard non-compartmental methods and standard PK parameters in the phase 1 studies, as well as population PK modelling.

Absorption

Based on low solubility and estimated medium-low *in vitro* permeability, it was concluded that resmetirom may be classified as a BCS class IV molecule.

91% oral absorption was estimated based on mass balance in study MGL-3196-07. Resmetirom appeared in the systemic circulation with a median T_{max} of 4 hours. A formal absolute bioavailability study was not conducted.

Relative bioavailability was evaluated in non-randomised sequential cross-over study MGL-3196-08 following administration of single dose of 100 mg resmetirom as tablets (1x40 mg plus 1x60 mg, formulation 7) vs. earlier capsules (1x40 mg plus 1x60 mg, formulation 5 and 6, respectively).

Following a single dose 100 mg resmetirom (1 x 40 mg tablet and 1 x 60 mg tablet, Formulation 7), mean (%CV) C_{max} was 1,080 ng/mL (58.1), mean AUC_{0-inf} was 4.080 ng h/mL (53.3). Median (range) T_{max} was 4 (2-6) h and mean (CV%) $t_{1/2}$ was 2.05 h (35.7).

Resmetirom C_{max} met bioequivalence criteria, however AUC was about 12% greater for tablets (formulation 7) as compared to capsules (formulations 5 and 6). Exposures of main metabolite MGL-3623 (C_{max} and AUC) were about 22 to 23% higher for tablets relative to the earlier capsule formulations.

No bioequivalence studies were conducted and considered necessary by the applicant given that formulation 8 intended for marketing was used in the phase 3 trials. Bridging of the PK data obtained with the various earlier formulations to tablet formulation 8 (100 mg) and 8a (80 mg, 60 mg) intended for marketing is proposed to rely on *in vitro* dissolution data in release media. In addition, PK of formulation 8 intended for marketing has been substantiated in late comprehensive SAD and MAD PK study MGL-3196-20.

The effect of food was evaluated in 2 studies (VIA-3196-01 and MGL-3196-09) with similar conclusions.

Following repeated dosing with 100 mg resmetirom (1x40 mg and 1x60 mg, formulation 7) in study MGL-3196-09, intake of a high fat meal within 30 minutes prior to dosing resulted in a 33% decrease in C_{max} , an 11% decrease in AUC, and a delay in median T_{max} by about 2 hours compared to intake

under fasting condition. Differences in resmetirom PK observed following administration with a high-fat meal were not considered clinically meaningful and resmetirom was administered with or without food in phase 3 studies. Accordingly, the method of administration mentioned in the product information is "Resmetirom may be taken with or without food (see section 5.2).".

Distribution

Resmetirom and main metabolite MGL-3623 were highly plasma protein bound *in vitro* (>99% and 98.8%, respectively) independent of concentration, and for resmetirom, human serum albumin appeared the major contributor. Blood to plasma partitioning in human mass balance study in the range of 0.5 to 0.6 suggests low association of resmetirom with cellular components of blood.

No significant covalent protein binding of resmetirom was observed during *in vitro* microsomal incubation, suggesting that the potential for reactive metabolite formation caused covalent protein binding liability is low.

Resmetirom and MGL-3623 were demonstrated to be substrates of BCRP, OATP1B1 and OATP1B3, and of OSTα/β transporters *in vitro*, but not of MRP-2 and BSEP. A later *in vitro* vesicular transport substrate assay challenged the results for resmetirom to be a substrate for BCRP (study 3196-24-001). Results for P-gp were inconclusive, or accuracy of results was rated questionable, hence resmetirom and MGL-3623 may have to be additionally regarded weak substrates of P-gp. Substrate potential for OSTα/β was postulated to facilitate uptake of resmetirom. MGL-3623 was additionally determined to be a substrate for renal uptake transporter OAT3, but not of OAT1 and OCT2.

Results from an *in vitro* hepatic uptake, biliary excretion, and biliary clearance assay using sandwich-cultured human hepatocytes suggested that both parent and metabolite have potential for elimination in the bile.

Being highly correlated with body weight, the volumes of distribution (central and peripheral) were quantified using population PK analysis. The estimated volume of distribution was fixed as 20 L in peripheral compartment based on rich sampling in healthy subjects and was 42.1 L in central compartment for a typical 98 kg patient with NASH/MASH after a single oral dose of 80 mg, with variability in Vc/F of 121%.

Elimination

CL/F from population PK modelling:

Single dose: The estimated central clearance (CL/F) of resmetirom was 30.6 L/h for a typical 98 kg patient with NASH/MASH after single dose of 80 mg. Based on the PK parameters, (CL/F, Vc/F, Q/F and Vp/F) the model-predicted elimination ($t_{1/2\beta}$) half-life of resmetirom after a single dose in a typical NASH/MASH patient was 3.60 hours.

Steady-State: The CL/F of resmetirom was reduced by approximately 48.5% following repeated dosing as per the I_{max} function (i.e., to 15.8 L/h). The model-predicted $t_{1/2\beta}$ of resmetirom under steady state conditions for a typical 98 kg NASH/MASH patient was 4.50 hours.

The clearance and volume of distribution of resmetirom were found highly dependent on body weight. The results from the popPK model suggest a faster CL/F of resmetirom in patients with higher body weight (see population PK/PD modelling below).

Excretion

Following a single radiolabelled dose of 100 mg resmetirom in steady-state human mass balance study MGL-3196-07, total recovery of radiolabelled resmetirom-derived radioactivity from urine and faeces as determined by LSC ranged from 84.95 to 93.29% (mean $\pm$ SD: 91.01 $\pm$ 2.15%) in the 8 healthy subjects in mass balance study MGL-3196-07. Faecal excretion of radioactivity was the predominant route of elimination and accounted for a mean $\pm$ SD of 67.37 $\pm$ 3.98% of the administered dose. Renal excretion was a minor, but significant route of elimination, with a mean $\pm$ SD of 23.64 $\pm$ 4.01% of the radioactive dose recovered in urine.

Resmetirom was eliminated mainly as metabolites. Time restricted pooling approaches were applied for metabolite profiling, identification and quantitation in study MGL-3196-07.

20.03% and 63.51% of the administered dose was found excreted in 0-24h urine and 0-72h faecal pooled samples, respectively, and was attributed by the applicant in urine to radiolabelled resmetirom (1.02% of dose) and 3 metabolites MGL-3623 (15.71%), M467_2 (12.89%) and M2 (3.56%) and in faeces to 13 metabolites (10 of these identified), each accounting for less than 9% of the dose.

Metabolism

In plasma, resmetirom was determined the major radioactive component (55.22% based on AUC), followed by MGL-3623 as the most abundant metabolite (16%), and oxalic acid metabolite (14.5%) that was observed in plasma but not in urine. MGL-3842 (M2) was considered a minor metabolite (7.46%), as were M467_2 (4.56%) and M611 (2.38%).

The resmetirom mono-oxygenate (hydroxy-) metabolite MGL-3623 was formed *in vitro* in human intestinal microsomes, cryopreserved hepatocytes, and human liver microsomes. Resmetirom had low clearance/high stability in human cryopreserved hepatocytes. CYP2C8 was identified as the primary CYP450 enzyme responsible for the metabolism of resmetirom to MGL-3623.

Overall, concentration-time profiles of MGL-3623 paralleled those observed for resmetirom and declined in a multi-exponential manner with a slightly longer $t_{1/2}$.

Statistical evaluation of the impact of genetic polymorphisms on the pharmacokinetics of resmetirom and its metabolite MGL-3623 included data on SLCO1B1 and CYP2C8 (based on Phase I studies), ABCG2 (based on Phase I, II, and III studies), and UGT1A1 (based on Phase III studies). The applicant concluded that body weight is the most important factor explaining the variability in exposure to resmetirom and its metabolite MGL-3623.

Dose proportionality and time dependencies

While the applicant concluded from the data in the SAD and MAD studies VIA-3196-01 and-02 that resmetirom C_{max} and AUC_{0inf} increase in a less-than-dose proportional manner between doses of 0.25 mg and 200 mg following single dosing, and that resmetirom C_{max} and AUC_{0-24} increase in a dose-proportional manner between 5 mg and 200 mg following repeated dosing, data from HI study MGL-3196-10 indicated more than dose proportional increase of AUC_{0-24} with increasing dose from 40 mg to 80 mg following repeated dosing in subjects with normal hepatic function. However, limitations were noted with regard to bioanalysis in all three studies. Based on population PK analysis, exposure parameters for 100 mg doses in patients with fibrosis stage F0, F1-F2 and F3, increased by approximately 25-30% relative to the 80 mg dose, as expected for dose-proportionality at steady-state. Claims on dose proportionality included in the SmPC were substantiated with the D180 responses for tablet formulation 8 in late comprehensive PK study MGL-3196-20: resmetirom steady state exposure increases in a dose proportional manner between doses of 40 mg (0.5 times the lowest approved recommended dose) and 100 mg. Resmetirom exposure increases in a greater than dose

proportional manner between doses of 100 mg and 200 mg (2 times the highest approved recommended dose) by about 5.6-fold.

Following repeated dosing at 100 mg resmetirom QD, resmetirom C_{max} and AUC accumulated with ratios up to 2.4 and 2.9, respectively, across different studies. Drug accumulation observed for doses ≥ 50 mg was greater than predicted by the plasma terminal half-life. Higher accumulation was observed following dosing at 200 mg resmetirom QD, with accumulation ratios of 2.71 and 3.94 for C_{max} and AUC, respectively, in thorough QT study MGL-3196-17, suggesting saturation of metabolism of resmetirom to MGL-3623 at higher doses. Even higher accumulation ratios of 3.98 and 5.46 for C_{max} and AUC were observed following repeated dosing at 200 mg QD in the presence of single dose rosuvastatin in study MGL-3196-03. In all studies, MGL-3623 exhibited little to no accumulation as compared to parent drug.

Overall, in all studies, following repeated dosing, resmetirom exposure increased, while no or negligible accumulation was detected for MGL-3623.

Based on pre-dose concentrations, time to steady state was reached following 3 to 7 days across the various studies.

Variability

PK of resmetirom was revealed to be highly variable both in non-compartmental PK analyses as evidenced based on large %CV values, as well as based on population PK modelling. In the population PK model, the variability was partly explained by bodyweight, fibrosis stage and concomitant administration of clopidogrel (see Population PK/PD Modelling below).

PK in the target population

Based on non-compartmental analysis of non-cirrhotic NASH/MASH patients with normal hepatic function in HI study MGL-3196-10, following repeated dosing at 100 mg QD for 6 consecutive days, mean C_{max} was 2,490 ng/mL (geometric mean 1,760 ng/mL) and mean AUC_{0-24} was 16,000 ng h/mL (geometric mean 8270 ng h/mL). Day 6/Day 1 accumulation ratio was 2 for C_{max} and 1.8 for AUC_{0-24} . Metabolic ratio on Day 6 was 34.7% based on C_{max} and 45.5% based on AUC_{0-24} . In the product information, the applicant proposes to present slightly lower exposure values estimated from predicted concentrations in MASH patients (F2, F3) based on popPK modelling.

The therapeutic window has been defined to lie within C_{avg} of 120 to 1750 ng/mL (corresponding to AUC_{τ} range of 2800 to 42000 ng*h/mL) based on clinical experience in Phase 2 and 3 studies (see Population PK modelling below).

Special populations

Renal impairment

The popPK analysis revealed an effect of renal impairment in addition to the body weight effect. For fibrosis stage F0-3 moderate renal impairment resulted in a 28% lower CL/F (30% for F4). This was considered not clinically relevant by the applicant due to the minor impact on the $t_{1/2\beta}$ and R_{ac} . The applicant provided no information on the -fold increases in C_{max} and AUC that result from a 28% reduction in clearance.

The population PK model was updated with new data from MGL-3196-21 to assess the impact of severe renal impairment on resmetirom clearance. Previous models demonstrated that mild and moderate renal impairment had no significant effect. When severe renal impairment was analyzed as a covariate on clearance, the estimated effect was -0.241 (95% CI: -0.764 to 0.282), indicating no statistically significant impact. Furthermore, the comparison of weight-normalized clearance (CL/F) indicated that

patients with moderate renal impairment had about a 22% reduction compared to normal renal function, while severely impaired subjects showed roughly a 15% reduction relative to healthy individuals.

Based on the results of MGL-3196-21—including the limited role of renal clearance in resmetirom elimination, the favourable safety profile in renally impaired individuals, and the expected exposure variability at 100 mg in healthy subjects—resmetirom can be safely administered to patients with severe renal impairment.

A dose adjustment for mild, moderate and severe renal impairment is not needed. The proposed language for the SmPC has been acceptable.

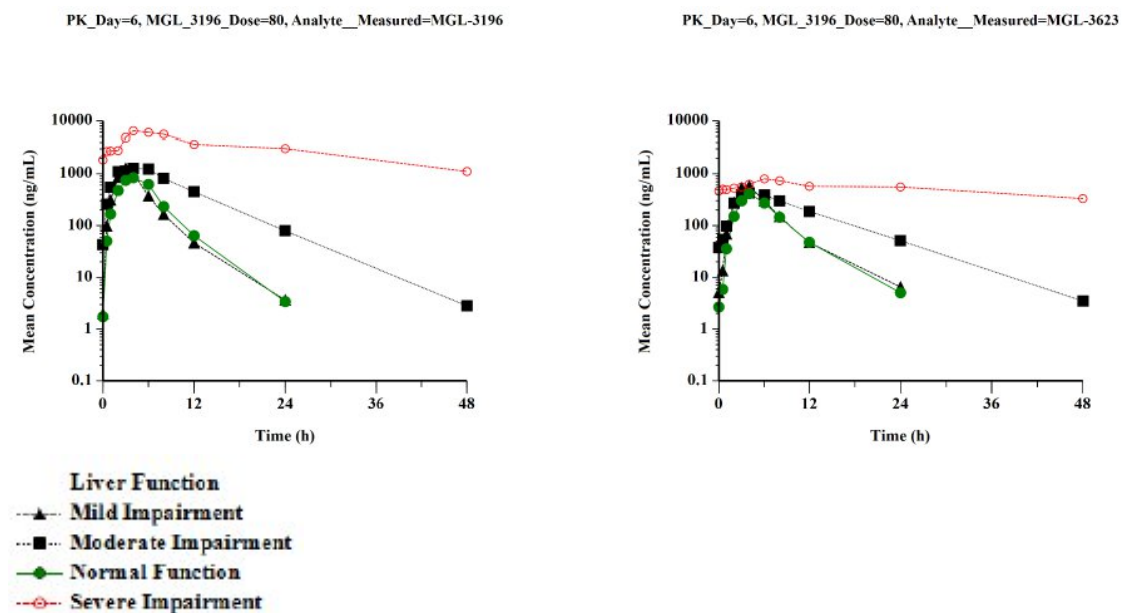
Hepatic impairment

A dedicated PK study in subjects with HI and patients with NASH with or without cirrhosis was conducted (MGL-3196-10).

Repeated dosing 80 mg resmetirom QD for 6 Days in HI as compared to normal hepatic function

Mean concentration time profiles of resmetirom and MGL-3623 following repeated dosing of 80 mg resmetirom QD for 6 Days in subjects with hepatic impairment as compared to matches subjects with normal hepatic function are shown in the Figure below.

Figure 4. Mean Plasma Concentration-Time Profiles of resmetirom and MGL-3623 on Day 6 after Repeated Once-Daily Dosing of 80 mg resmetirom to Subjects with Normal Liver Function or Hepatic Impairment Patients in study MGL-3196-10 (semi-logarithmic scale)



Resmetirom: Based on %Ratio of geometric mean (%GMR; Test/Reference), following repeated dosing of 80 mg resmetirom QD for 6 days, compared to subjects with normal hepatic function, AUC_{0-24} of resmetirom in subjects with mild, moderate, or severe HI was 1.03-, 2.71-, and 21-fold higher, and C_{max} was 1.17-, 1.73-, and 8.12-fold higher, respectively. The corresponding 90% CI for AUC_{0-24} %GMR were 52.77% to 200.01%, 134.38% to 544.60%, and 947.53% to 4648.41% for mild, moderate and severe HI.

T_{1/2} was 2.24h in subjects with normal hepatic function and 2.64, 3.71 and 10.8h in subjects with mild, moderate and severe HI, respectively. Accumulation based on Day 6/Day1 C_{max} ratio and Day 6/Day1 AUC ratio was 1.5 and 2.03 in subjects with normal hepatic function, and 1.56 and 1.61, 1.14 and 1.24, and 2.32 and 2.76 in subjects with mild, moderate and severe HI, respectively.

Metabolite MGL-3623: Based on %Ratio of geometric mean (%GMR; Test/Reference), following repeated dosing of 80 mg resmetirom QD for 6 days, compared to subjects with normal hepatic function, AUC₀₋₂₄ of MGL-3623 in subjects with mild, moderate, or severe HI was 1.28-, 1.87-, and 5.9-fold higher and C_{max} was 1.45-, 1.43-, and 2.07-fold, respectively.

The metabolite, MGL-3623, was detected in systemic circulation of subjects with normal hepatic function with median (range) MGL-3623 T_{max} value of 4.14 (3-6) h, and of 4.00 (3-6), 5.11 (3-8), and 8.0 (6-24) h, in subjects with mild, moderate and severe HI, respectively. Metabolic ratio %MGL-3196 C_{max} and %MGL-3196 AUC₀₋₂₄ were 44.8 and 56.7 in subjects with normal hepatic function, and 56.2 and 73.6, 40.7 and 46.7 and 11.0 and 15.6 in subjects with mild, moderate and severe HI, respectively, indicating that metabolism of resmetirom to MGL-3623 was progressively reduced in moderate to severe HI.

Accumulation based on Day 6/Day1 C_{max} ratio and Day 6/Day1 AUC ratio was 0.888 and 1.15 in subjects with normal hepatic function, and 1.07 and 1.10, 0.927 and 1.02, and 1.23 and 1.31 in subjects with mild, moderate and severe HI, respectively, indicating negligible accumulation of MGL-3623 following repeated dosing.

Renal clearance for resmetirom progressively decreased with increasing severity of HI. Following 6 days of dosing at 80 mg resmetirom, renal clearance in subjects with mild, moderate and severe HI was 74.4%, 14.5% and 5.5% of that in subjects with normal liver function, based on not body weight normalised data and without consideration of furosemide administration in some subjects and patients.

Plasma PK in Non-cirrhotic NASH Patients and Cirrhotic NASH Patients with mild HI

Main PK parameters of resmetirom in cirrhotic NASH/MASH and non-cirrhotic NASH/MASH patients following doses of 80 and 100 mg are presented in *Table 10*.

Table 10. PK Parameters of Resmetirom after Single and Multiple Doses of Resmetirom in Non-cirrhotic or Cirrhotic NASH/MASH Patients

	Cirrhotic NASH/MASH (n = 10)	Cirrhotic NASH/MASH (n = 1)	Cirrhotic NASH/MAS H (n = 20)	Non- cirrhotic NASH/MAS H (n = 8)
HI Classification From Child-Pugh Scoring system	Mild HI	Moderate HI	Mild HI	Normal Liver Function
Dose Level	80 mg	80 mg	100 mg	100 mg
Day 1				
C _{max} (ng/mL)	1,850 (55.9)	6,810	1,550 (64.8)	1,200 (45.6)
T _{max} (h)	3.70 (2,6)	4.00	4.20 (E A2,6)	4.75 (2,8)
AUC ₀₋₂₄	7,330 (52.4)	73,100	7,820 (78.2)	6,820 (50.2)
T _{1/2} (h)	2.91 (10.1)	6.76	2.88 (25.3)	2.78 (20.3)
Day 6				
C _{max} (ng/mL)	1,890 (54.4)	9,040	2,020 (77.8)	2,490 (94.7)
T _{max} (h)	3.70 (3,6)	6.00	3.90 (2,6)	4.00 (3,6)
AUC ₀₋₂₄	9,780 (59.9)	114,000	13,200 (99.6)	16,000 (162)
T _{1/2} (h)	3.27 (32.7)	11.3	3.39 (32.1)	3.25 (40.6)

Note: Data are presented as mean (%CV), except T_{max}, presented as median (min, max).
HI=hepatic impairment; MASH = metabolic dysfunction-associated steatohepatitis; NASH=non-alcoholic steatohepatitis

100 mg: The exposure of resmetirom and MGL-3623 appeared to be similar in NASH/MASH subjects without cirrhosis and NASH/MASH subjects with cirrhosis and categorised with mild HI using the Child-Pugh scoring system, following a single and multiple oral doses of 100 mg resmetirom.

Following a single dose of 100 mg, mean C_{max} of resmetirom was 1.29-fold and mean AUC_{0-24} was 1.15-fold higher in subjects with cirrhotic NASH (mild HI) than in subjects with noncirrhotic NASH. Following repeated 100 mg dosing on Day 6, mean C_{max} and mean AUC_{0-24} in subjects with cirrhotic NASH (mild HI) were reduced to 0.8-fold and 0.825-fold the values in subjects with noncirrhotic NASH, respectively. The modest effect of mild HI on PK of resmetirom in NASH patients is in agreement with the results observed with a dose of 80 mg in non-NASH patients.

Following a 100 mg dose in NASH/MASH subjects with cirrhosis (mild HI) renal clearance was similar to that in NASH/MASH subjects without cirrhosis (normal liver function).

80 mg: In subjects with NASH/MASH cirrhosis and mild HI, C_{max} and AUC_{0-24} values following a single dose of 80 mg were 1.19-fold and 0.94-fold of those following a dose of 100 mg, respectively.

Following repeated dosing on Day 6, C_{max} and AUC_{0-24} values with 80 mg were 0.93-fold and 0.74-fold those with 100 mg, respectively.

A separate study in well-compensated (Child-Pugh A) NASH/MASH cirrhosis patients to evaluate the efficacy and safety of resmetirom in this population is currently ongoing (MGL-3196-19).

Although differences in body weight were not taken into account, the impact of mild HI on PK appears to be not clinically relevant and the dose recommendation given in the proposed product information that no dose adjustment is required in patients with mild hepatic impairment (Child Pugh A) was endorsed. However, up to ~1.6-fold higher exposure based on mean $AUC_{tau,ss}$, $C_{ave,ss}$ and $C_{max,ss}$ was estimated in NASH patients with fibrosis stage F4 (with HI) as compared to patients with fibrosis stage F0, F1-F2 and F3 with normal hepatic function. F4 patients were categorized together as mild moderate although most of the patients from trial MGL-3196-14 are expected to have actually suffered from mild HI and higher increase in exposures would be expected in a true patient group F4 all having moderate HI.

Consistent with this notion is the finding that exposure based on C_{max} and AUC_{0-24} were 4.8- and 11.7-fold higher in one patient with NASH cirrhosis and moderate HI as compared to respective mean values in cirrhotic NASH subjects with mild HI in the non-compartmental analysis in study MGL-3196-10.

Although NCA data is available for only one patient with NASH cirrhosis and moderate HI, given that no data on efficacy and safety are available for NASH/MASH patients with moderate HI, use of resmetirom cannot be recommended from a PK perspective at present. This is reflected in the product information by the dosing restriction to avoid use of resmetirom in patients with decompensated cirrhosis and/or moderate or severe hepatic impairment (Child-Pugh B or C).

Race, ethnicity

Based on population PK analysis, no effect of race on the PK of resmetirom was found in addition to the included weight effect (see Population PK/PD Modelling below). Potential differences in ethnicity were not evaluated.

In late comprehensive SAD and MAD PK study MGL-3196-20 submitted with the D180 responses, the PK of resmetirom and its metabolite MGL-3623 were evaluated by NCA in healthy male and female Japanese (N=40) and BMI ($\pm 15\%$) matched Caucasian (N=41) following resmetirom oral dosing at 40, 60, 80, 100, and 200 mg/day for 6 consecutive days. Both Caucasian and Japanese subjects showed similar PK for resmetirom and MGL-3623 in plasma and urine.

Gender, age and weight

Impact of sex, age and weight on PK of resmetirom and MGL-3623 were not evaluated in dedicated PK studies.

Based on population PK analysis, no effect of gender and age on the PK of resmetirom was found in addition to the included weight effect (see Population PK/PD Modelling below).

The applicant has specified the age ranges studied in the elderly population as follows.

Table 11. Subject Age Distribution Across Various Studies by Specific Age Group

Study	< 65 yrs	64 to 75 yrs	74 to 85 yrs
VIA-3196-01	54 / 54 (100%)	0 / 54 (0.0%)	0 / 54 (0.0%)
VIA-3196-02	36 / 36 (100%)	0 / 36 (0.0%)	0 / 36 (0.0%)
MGL-3196-03	25 / 25 (100%)	0 / 25 (0.0%)	0 / 25 (0.0%)
MGL-3196-04	14 / 14 (100%)	0 / 14 (0.0%)	0 / 14 (0.0%)
MGL-3196-09	16 / 16 (100%)	0 / 16 (0.0%)	0 / 16 (0.0%)
MGL-3196-10	69 / 86 (80.2%)	16 / 86 (18.6%)	1 / 86 (1.16%)
MGL-3196-12	20 / 20 (100%)	0 / 20 (0.0%)	0 / 20 (0.0%)
MGL-3196-15	25 / 25 (100%)	0 / 25 (0.0%)	0 / 25 (0.0%)
MGL-3196-16	26 / 26 (100%)	0 / 26 (0.0%)	0 / 26 (0.0%)
MGL-3196-17	35 / 35 (100%)	0 / 35 (0.0%)	0 / 35 (0.0%)
MGL-3196-05	71 / 80 (88.8%)	9 / 80 (11.2%)	0 / 80 (0.0%)
MGL-3196-11	503 / 669 (75.2%)	151 / 669 (22.6%)	15 / 669 (2.24%)
MGL-3196-14	690 / 948 (72.8%)	214 / 948 (22.6%)	44 / 948 (4.64%)
Overall	1584 / 2034 (77.9%)	390 / 2034 (19.2%)	60 / 2034 (2.95%)

Overall, 77.9% of the participants were under 65 years of age, 19.2% were between 64 and 75 years of age, and 2.95% were between 74 and 85 years of age.

No information is available in the paediatric population. This is reflected accordingly in the proposed product information.

Weight

See Population PK Modelling below.

Pharmacokinetic interaction studies

In vitro:

Potential of resmetirom and MGL-3623 as substrate, inhibitor and inducer of major CYP enzymes and as inhibitor and inducer of major UGT enzymes was evaluated *in vitro*. In further *in vitro* studies, the potential of resmetirom and MGL-3623 as substrate and inhibitor of transporters was investigated.

Resmetirom inhibited CYP2C8 and CYP2C9 *in vitro* with IC₅₀ values of 0.90µM and 22µM, respectively. Resmetirom inhibited UGT isoforms with IC₅₀ values of 3.22, 16.7, 0.557, 44.2, 1.14, and 32.6 µM for UGT1A1, UGT1A3, UGT1A4, UGT1A6, UGT1A9, and UGT2B7, respectively.

Resmetirom was found to have no potential for induction of CYP1A2 but significantly decreased mRNA levels with the potential to suppress CYP1A2 enzyme activity in 2 *in vitro* studies (enzyme activity in 48 h assay: ≥0.58-fold relative to vehicle control).

Resmetirom induced CYP2B6 with EC₅₀ values ranging from 37 to 45 µM and E_{max} values ranging from 6 to 8-fold-over-control (FOC). Resmetirom induced CYP3A4 with EC₅₀ values ranging between 40 and 50 µM.

Resmetirom produced a significant induction response for UGT1A1 (EC₅₀ ≥14.3 µM and E_{max} ≤5.47 FOC in 2 donors) in a dose-dependent manner and for UGT1A3 (EC₅₀ 1.67 µM and E_{max} 2.52 FOC from 1 donor), with no significant mRNA induction response for UGT1A6 or UGT2B7 at concentrations up to 100µM.

Resmetirom inhibited BCRP with IC₅₀ value of 0.968 µM, OATP1B1 with IC₅₀ 3.72µM, OATP1B3, and OAT3 (IC₅₀ 4.53µM) *in vitro*. Resmetirom inhibited BSEP-mediated transport of TCA with an IC₅₀ value of 34.7 µM, but did not inhibit MRP2 at concentrations up to 100µM. Resmetirom was determined to be a weak inhibitor of probe substrate transport mediated via OAT1 (IC₅₀ > 100 µM), MATE1 (IC₅₀ > 100 µM) and MATE2-K (IC₅₀ > 100 µM) and P-gp (IC₅₀ 99.6 µM), but not via OCT2 at concentrations up to 100µM.

MGL-3623 directly (i.e., no pre-incubation) inhibited CYP2C8 with an IC₅₀ of 6.10 µM *in vitro*. There was weak direct inhibition of CYP1A2, CYP2B6, CYP2C9, CYP2C19, and CYP3A4/5 (both midazolam and testosterone substrates) with IC₅₀ values of >50, 27, 24, 33, and 35 µM, respectively. There was no inhibition of CYP2D6 at the highest concentration tested, 50 µM.

MGL-3623 inhibited OATP1B1 and inhibited OATP1B3 with IC₅₀ value of 22.6µM. MGL-3623 did not demonstrate concentration dependent inhibition of P-gp up to 100µM. MGL-3623 inhibited BSEP with IC₅₀>100µM, but not MRP-2 at concentrations up to 100µM.

Based on *in vitro* studies, MGL-3623 was stated to inhibit the transport of probe substrates mediated by BSEP (IC₅₀>100 µM), OATP1B1 (22.9% inhibition at 10 µM), OATP1B3 (IC₅₀=22.6 µM), and BCRP (4.18% inhibition at 10 µM).

Risk for displacement interactions was considered low.

In vivo:

Eight dedicated *in vivo* DDI studies were conducted.

- DDI study MGL-3196-09 was a single centre, open-label, drug interaction study assessing the effect of repeated doses of resmetirom (100 mg QD) as perpetrator (inhibitor of CYP2C8) on the PK of single dose pioglitazone (15 mg) in healthy volunteers.

Resmetirom repeated daily administration of 100 mg for 7 days resulted in a 1.5-fold increase in the overall exposure (AUC) of moderate sensitive CYP2C8 substrate pioglitazone following single dose of 15 mg co-administered pioglitazone with little change in peak exposure observed. Resmetirom may hence be classified a mild inhibitor of CYP2C8. Therefore, the dose adjustment was not considered necessary.

- DDI study MGL-3196-16 was a single-centre, open-label, drug-drug interaction study to determine whether repeated doses of resmetirom 100 mg as perpetrator (weak inhibitor of CYP2C9) altered the PK and PD of steady state warfarin as a substrate of CYP2C9 (S-warfarin) in healthy male and female volunteers.

8 consecutive days of co-administration of 100 mg/day resmetirom and warfarin did not change the exposure (C_{max} and AUC₀₋₂₄) of R-warfarin and S-warfarin. The median (range) T_{max} 2.00 (0.5-4) was also unchanged for both metabolites and conditions.

- Study MGL-3196-04 was a single center, open-label, drug interaction study assessing the effect of repeated dosed resmetirom (100 mg QD) on the PK of single dose of 20 mg atorvastatin in healthy volunteers.

When a single dose of 20 mg atorvastatin was co-administered with 100 mg/day resmetirom following 7 consecutive days of resmetirom dosing, the AUC_{last} of atorvastatin increased by 1.4-fold with no change in C_{max} . Little change was observed for o-hydroxy-atorvastatin with 1.2-fold increase in C_{max} and no change observed in AUC. However, for metabolite atorvastatin lactone, C_{max} and AUC_{last} increased by 2.0- and 1.8-fold, respectively

In the proposed product information, limitation of atorvastatin to 40 mg daily is suggested if co-administered with resmetirom.

- Study MGL-3196-03 was a single-centre, open-label, drug interaction study assessing the effect of repeated dosed resmetirom (200 mg once daily [QD]) on the PK of single dose rosuvastatin (10 mg) and simvastatin (20 mg) in healthy volunteers.

Co-administration of a single dose of 10 mg rosuvastatin with 200 mg/day resmetirom increased C_{max} , AUC_{last} and AUC_{0-inf} of rosuvastatin by 2.9-, 1.9- and 1.8-fold, respectively, and decreased AUC_{last} and AUC_{inf} of N-desmethyl rosuvastatin by 23% and 19%, respectively, with no change in N-desmethyl rosuvastatin C_{max} .

In the proposed product information, limitation of rosuvastatin to 20 mg daily is suggested if co-administered with resmetirom.

For simvastatin, a further DDI study with resmetirom 100 mg was conducted:

- Study MGL-3196-15 was a single-center, open-label, drug interaction study to determine the effect of repeated dosed resmetirom (100 mg QD) on the PK of single dose pravastatin (40 mg) and simvastatin (20 mg) in healthy volunteers.

Following coadministration of a single 40 mg dose of pravastatin with 100 mg/day resmetirom, the C_{max} and AUC_{0-24} of pravastatin increase 1.26- and 1.39-fold, respectively, and the C_{max} and AUC_{0-24} of metabolite 3 α -hydroxy pravastatin increase by 1.18- and 1.63-fold.

When pravastatin was administered in the evening, C_{max} and AUC_{0-24} of pravastatin decreased by about 54% and 65%, respectively, as compared to morning co-administration (Day 9 vs. Day 11) and C_{max} and AUC_{0-24} of 3 α -hydroxy pravastatin were increased by 1.29- and 1.18-fold, respectively.

Coadministration of a single dose of 20 mg simvastatin with 100 mg resmetirom QD increased C_{max} and AUC_{0-24} of simvastatin by 1.39- and 1.75-fold, respectively, and increased C_{max} and AUC_{0-24} of metabolite simvastatin acid by 2.01- and 1.57-fold, respectively.

In the proposed product information, limitation of pravastatin to 40 mg daily and of simvastatin to 20 mg daily is suggested if co-administered with resmetirom.

The applicant does not currently propose staggering the administration of resmetirom and statins due to the lack of evidence of reduced interaction or improved safety. It is also stated that the interactions are mild. The applicant is of the opinion that there is no justification for a warning to monitor for safety in patients on statins and resmetirom and that guidance to limit the dose of concurrently used statins is sufficient. This was agreed by the CHMP.

- Study MGL-3196-12 was a Phase 1, single-center, open-label, multiple-dose, drug interaction study to determine whether clopidogrel, as a CYP2C8 inhibitor, alters the PK of resmetirom in 20 healthy male and female volunteers.

At steady state, co-administration of clopidogrel and resmetirom resulted in a 1.3-fold and 1.7-fold increase in resmetirom C_{max} and AUC, respectively, and C_{max} and AUC₀₋₂₄ of MGL-3623 decreased by 69% and 50%, respectively.

The proposed product information recommends a dose reduction to 80 mg of resmetirom per day (for patients weighing ≥ 100 kg) or 60 mg per day (for patients weighing < 100 kg) if concomitant use of clopidogrel, deferasirox or teriflunomide is required (see Population PK below).

- Study MGL-3196-22, "A Phase 1, Single-centre, Open-label, Drug Interaction Study of Resmetirom with Cyclosporine in Healthy Subjects"

Five consecutive days of co-administration of 100 mg/day resmetirom and 175 mg BID cyclosporine (Days 12-16) did not affect the exposure (C_{max} and AUC_T) of resmetirom or resmetirom metabolite, MGL-3623. All of the 90% CI with repeated dosing were within the 80-125% limit for the standard bioequivalence model. Based on the results from study MGL-3196-22, it is generally agreed that the dedicated cyclosporine interaction study demonstrated a lack of clinically relevant interaction with resmetirom, no restriction on the concomitant use of OATP1B1/OATP1B3 inhibitors with resmetirom is needed.

- Study MGL-3196-24 study, titled "A Phase 1, Single-centre, Open-label, Drug Interaction Study of Resmetirom with Rosuvastatin in Healthy Subjects"

The data indicate that when 100 mg/day resmetirom is administered at steady state alongside 20 mg rosuvastatin in the morning, there is an increase in both the AUC and C_{max} of rosuvastatin by less than two-fold, accompanied by an approximate 20% decrease in the AUC of N-desmethyl rosuvastatin, with no impact on its C_{max} . Although exploratory analyses remain in progress, these preliminary findings—obtained using a lower resmetirom dose compared to the previous study (MGL-3196-03, which employed 200 mg)—suggest a mild impact on rosuvastatin pharmacokinetics, consistent with earlier observations. Preliminary data further indicate that the lower resmetirom dose (100 mg versus 200 mg) results in reduced interaction. The applicant's position is that any advantage from staggered dosing appears to be marginal, and that limiting rosuvastatin to 20 mg remains an acceptable safety measure. This was agreed by the CHMP.

Population PK/PD Modelling

Population PK analyses of resmetirom and its main metabolite MGL-3623 were conducted to identify sources of variability in patients with NASH/MASH. Exposure parameters derived with the above population model were used for further exposure-response analysis to support dosing of resmetirom in patients with MASH.

A previous model based on data from Phase 1 and 2 was updated by including data from MGL-3196-11 and MGL-3196-14. Absorption parameters were fixed to the parameter estimates derived in the base model for studies with rich sampling in absorption phase. The absorption of resmetirom was described with a duration of absorption (D_1) of 3.99 h, a K_a of 0.840 h⁻¹ and an absorption lag time of 0.240 h. Rich data collected in Phase 1 and 2 studies were used to support the development of the absorption model of resmetirom. No RSE and shrinkage could be calculated for these parameters. The disposition of resmetirom was described with a 2-compartment model. The CL/F and Vc/F for a typical 98 kg patient with NASH/MASH after a single dose of 80 mg were 30.6 L/h and 42.1 L, respectively. The PK of resmetirom was highly variable with between-subjects variability of CL/F and Vc/F of 55.3% and 121%, respectively. Parameters describing the distribution into peripheral tissues (Q/F and Vp/F) were fixed to those observed in Phase 1 and 2 studies due to the sparse data collected in Phase 3 studies.

Based on the above PK parameters (CL/F, Vc/F, Q/F and Vp/F), the model predicted distribution ($t_{1/2\alpha}$) and elimination ($t_{1/2\beta}$) half-life of resmetirom after a single dose in a typical NASH/MASH patient were 0.876 and 3.60 h, respectively. Statistically significant covariates in the popPK model were body weight, fibrosis stage, and concomitant medication of statins or clopidogrel: body weight was identified as the most important influence with effects on PK on CL/F and Vc/F. The population PK model included an allometric component that accounted for differences in body weight. The exponent for the effect of body weight on CL/F was 1.39 that suggested a faster CL/F of resmetirom in patients with higher body weight. The exponent for the effect of body weight on Vc/F was 1.38 that suggested a larger Vc/F of resmetirom in patients with higher body weight.

- MASH patients with fibrosis stage F3 and F4 showed a lower CL/F, this effect was rather small for F3 patients (CL/F 5% lower) and more pronounced for F4 patients (CL/F 25% lower). PK results for the F4 population are therefore presented separately.

- For concomitant medication statins, clopidogrel and bile acid sequestrants were investigated, showing no significant effect on CL/F for bile acid sequestrants, a small but significant effect for statins (CL/F 2% lower) and a pronounced effect of clopidogrel on the PK of resmetirom resulting in a 50% lower CL/F. Parameters derived with the final population PK model of resmetirom are presented in the next table. The goodness-of-fit derived with the final population PK model of resmetirom in the overall population (all studies) is presented in the next figure.

Table 12. Final Population PK Model of Resmetirom Parameter Estimates

Parameter	Estimate	RSE%	95% CI	Shrinkage
Typical Values - Absorption				
Ka (1/h)	0.840, Fixed	NA	NA	
D1 (h)	3.99, Fixed	NA	NA	
Tlag (h)	0.240, Fixed	NA	NA	
F _{tot} (Fraction)	1.00, Fixed	NA	NA	
Typical Values - Disposition				
CL/F (L/h)	30.6	2.35	29.2, 32.0	
Q/F (L/h)	4.62, Fixed	NA	NA	
V _c /F (L)	42.1	4.41	38.5, 45.7	
V _p /F (L)	20.0 Fixed	NA	NA	
Typical Values – Time and Dose Effects				
Time Effect - I _{max} on CL/F (fraction)	0.485, Fixed	NA	NA	
Time Effect - Dose ₅₀ on CL/F (unitless)	1.76, Fixed	NA	NA	
Time Effect - Hill on CL/F (unitless)	1.42, Fixed	NA	NA	
Dose Effect on CL/F	-0.0710	43.7	-0.132, -0.0102	
Covariate Effects				
Weight on CL/Q	1.39	4.95	1.25, 1.52	
Weight on V _c /V _p	1.38	5.71	1.22, 1.53	
Study 005 on CL	0.351	36.8	0.0983, 0.605	
Fibrosis Stage 3 on CL/F	-0.0213	161	-0.0884, 0.0458	
Fibrosis Stage 4 on CL/F	-0.295	14.6	-0.380, -0.211	
Non-NASH with normal hepatic function or Mild HI on CL/F	0.452	12.9	0.337, 0.566	
Non-NASH moderate HI on CL/F	-0.174	130	-0.617, 0.269	
Non-NASH severe HI on CL/F	-1.00	15.5	-1.31, -0.698	
Statin on CL/F	-0.0207	103	-0.0625, 0.0210	
Clopidogrel on CL/F	-0.683	5.29	-0.754, -0.612	
Between-Subject Variability (%)				
On Ka	7.72, Fixed	NA	NA	93.4%
On D1	31.2, Fixed	NA	NA	63.1%
On CL/F	55.3	1.92	53.3, 57.4	17.0%
On V _c /F	121	3.98	112, 131	36.7%
Residual Error				
Log Additive Error	1.01	0.290	1.00, 1.01	NA
Log Additive Error for Study VIA-3196-01 and VIA-3196-02	0.721 Fixed	NA	NA	NA

Ka = first-order rate constant of absorption; D1 = duration of zero-order absorption; Tlag = lag time of absorption; F_{tot} = total relative bioavailability; I_{max} = maximum effect of multiple doses on CL; Dose₅₀ = number of dose associated with 50% of maximum effect on CL; CL/F = apparent clearance; Q/F = apparent intercompartmental clearance; V_c/F = apparent central volume; V_p/F = apparent peripheral volume; NA = not applicable. The correlation of parameters is presented in [Appendix 4 \(Section 14.16\)](#).

Note 1: Population PK parameters are for a typical NASH patient with a body weight of 98 kg, a Fibrosis 0, 1, or 2 who received a 80 mg dose who did not receive statin or clopidogrel.

Note 2: BSV (RSE) and shrinkage could not be estimated for absorption (Ka, D1, Tlag, F_{tot}) and peripheral parameters (Q/F and V_p/F) due to sparse data available in Phase 3 studies.

Objective function value: 20827.77

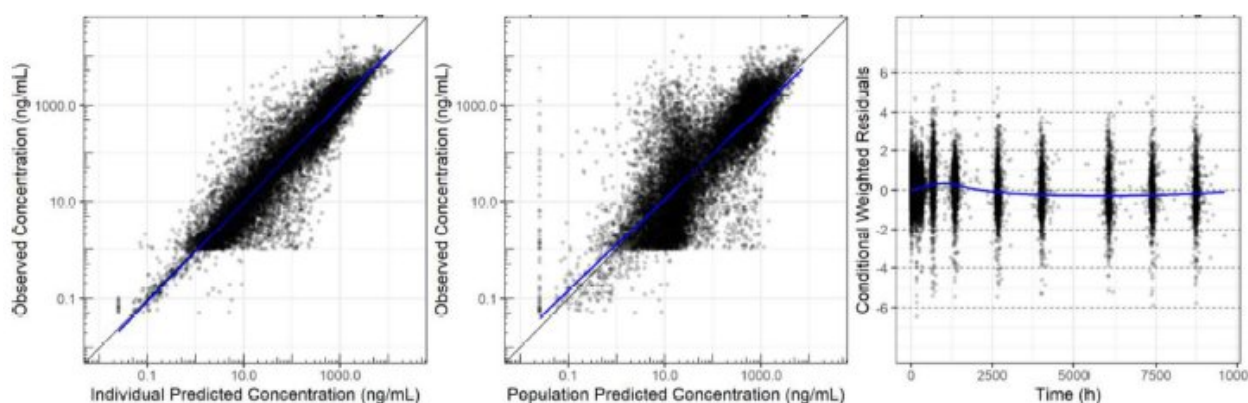


Figure 5. Goodness-of-Fit of Final Population PK Model of Resmetirom All Studies

As requested, the weight effect was described using smaller weight bands by 10 kg body weight increments. The weight cut-off at 80 kg body weight was changed to 100 kg body weight to achieve

more comparable exposures and more efficacy for patients with higher body weights. This is reflected in the SmPC ensuring comparable pharmacokinetics (PK) across body weight categories.

Therapeutic window

The therapeutic window has been defined to lie within C_{avg} of 120 to 1750 ng/ml (corresponding to AUC $_{\tau}$ range of 2800 to 42000 ng*h/ml) based on clinical experience in Phase 2 and 3 studies.

The exposure levels in each body weight interval were compared to the reference exposure for patients with a body weight of 70-80 kg by reporting the geometric mean ratio and 95% CI distribution. Summary statistics of the predicted model-based exposure metrics (C_{max} , C_{min} , AUC $_{\tau}$) at steady state, stratified by dose and revised body weight groups, were reported.

The applicant has provided stratified analyses representing lower and higher body weight groups. The predicted model-based exposure metrics (C_{max} , C_{min} , AUC $_{\tau}$) at steady state, stratified by dose and the revised body weight groups, have been reported. Exposure levels in each body weight interval were compared to the reference exposure for patients with a body weight of 70-80 kg by reporting the geometric mean ratio and the 95% CI distribution. While significant inter-individual variability was observed across studies, the proposed 100 kg cut-off is deemed to ensure more comparable exposure levels. The proposed posology is considered adequately justified, and the dosing for both higher and lower body weight tertiles is deemed adequate.

For resmetirom 80 mg, the AUC $_{\tau,ss}$ geometric mean ratio ranged from 0.4 in patients weighing >140 kg to 1.3 in those weighing >60-70 kg, with similar ranges observed for $C_{max,ss}$. For the 100 mg dose, the ratio ranged from approximately 0.3 in patients >140 kg to 1.7 in those weighing 50-60 kg, again with similar ranges for $C_{max,ss}$. In patients weighing 50 to 130 kg, the 95% confidence intervals overlapped across body weight groups, whereas in patients above 130 kg, the 95% confidence interval did not include 1.

E_{max} models were used to investigate the relationship between PK and PD, efficacy and safety endpoints. Exposure-response analyses for PD endpoints (SHBG, T4, ApoB, LDL-C9), imaging markers (MRI-PDFF reduction probability $\geq 30\%$ and $\geq 50\%$), efficacy (NASH/MASH resolution/fibrosis response, and safety (diarrhoea, any GI event, nausea grade ≥ 1) were conducted and the impact of age, sex, race, alcohol intake and body weight was investigated regarding the significance as covariates. The relationship between SHBG as PD response parameter and probability of response (MRI-PDFF reduction, NASH/MASH resolution or fibrosis response at week 52 was analysed as well, showing a correlation between SHBG concentration and efficacy endpoints. SHBG levels increased with increasing resmetirom exposure, for female and Asian patients a higher E_{max} was observed. For FT4, ApoB and LDL-C higher exposure was associated with a higher reduction of the PD markers. For ApoB, a higher decrease was found in female patients, the E_{max} for LDL-C reduction was affected by statin intake and age of the patients. The probability of response regarding MRI reduction and MASH resolution or fibrosis response increased with increasing exposure. Probabilities of diarrhoea, any GI events and nausea slightly increased across quartiles with higher resmetirom exposure.

The exposure-response relationship at Week 52 was characterized by a maximum increase of 220% (2.2-fold) and an EC $_{50}$ of 277 ng/mL. For the 80 and 100 mg dose levels, 25% and 45.0% of $C_{ave,ss}$ values at Week 52 were above the EC $_{50}$, respectively. Based on these results, median exposure associated with the 100 mg dose of resmetirom was close to the EC $_{50}$. Female patients presented a 37.7% higher (i.e., exp0.320) E_{max} relative to male patients. Asian patients presented a 63.2% higher (i.e., exp0.490) E_{max} relative to white patients.

2.6.2.2. Pharmacodynamics

Mechanism of action

Resmetirom is a partial agonist for the thyroid hormone receptor (THR). THR belongs to the nuclear hormone receptor superfamily. Stimulation of the THR results in upregulation of gene transcription and translation and are known to play critical roles in the regulation of metabolism, but also in regulation of heart rate and development of organisms.

Resmetirom is an agonist at the THR- β form, which is the most abundant THR isoform in the liver but is also expressed in other tissues.

The *in vitro* potency and selectivity of resmetirom and metabolite, MGL-3623, for THR- β were evaluated. The IC₅₀ values of resmetirom and MGL-3623 for the inhibition of specific binding at THR- β were 0.18 μ M and 6 μ M, respectively. The results confirmed that resmetirom is a partial agonist of THR- β ; resmetirom was approximately 14-fold less potent than T3 at THR- β and 374-fold less potent than T3 at THR- α . Resmetirom had EC₅₀ values of 0.21 and 3.74 μ M for THR- β and THR- α , respectively (17.8-fold more potent at THR- β relative to THR- α). Overall, resmetirom was 28-fold more selective at THR- β versus THR- α as compared with T3 (see pre-clinical dossier).

The development of a THR- β agonist is based on the known associations of progressive liver disease, including MASH with subclinical (hepatic) hypothyroidism and the commonalities of metabolic changes in hypothyroidism and steatotic liver diseases. Chronic liver disease goes along with a reduced hepatic conversion of thyroxine (T4) to the active thyroid hormone T3 (mediated by deiodinase 12 (DIO1) a liver THR- β gene). In animal models, deficiency of THR- β leads to fatty liver and impaired liver regeneration with increased apoptosis. T3 administration in THR- β knockout mice was not effective at lowering hepatic lipids, suggesting a crucial role for THR- β in the liver.

Since THR- β is highly expressed in hepatocytes, the applicant considers resmetirom a “liver directed therapy” which is supported by the fact that resmetirom has been shown to be a substrate of OATP1B1 and OATP1B3, as well as OST (organic solute transporter) α/β . Resmetirom is insensitive to the action of deiodinases, and therefore has the potential to correct the thyroid hormone deficiency in the livers of patients with NASH/MASH.

THR- β stimulation is expected to improve mitochondrial function and lipid metabolism in the liver. THR- β agonistic action leads to decreased liver fat, increased fatty acid beta oxidation and autophagy, and is expected to lead to increased insulin sensitivity, reduction of serum lipids, including LDL-C. Subsequently, it is expected that liver cell stress, lobular inflammation, and ultimately, fibrosis can be reduced and will also lead to reduced incidence of HCC and atherosclerosis in the long-term.

Primary and secondary pharmacology

Primary pharmacology

The documentation of pharmacodynamic activity was based on the documentation of the effects on thyroid haemostasis, and mainly on biomarkers documenting changes in serum lipids. Investigations also comprised glucose haemostasis, and - as a general PD marker - sex-hormone binding globulin (SHBG).

Moreover, since potentially associated changes of sex hormone homeostasis have been evaluated only in a minority of studies, a more systematic evaluation would have been desirable. However, the potential changes in sex-hormones have been evaluated within the phase 3 study and are part of the safety documentation.

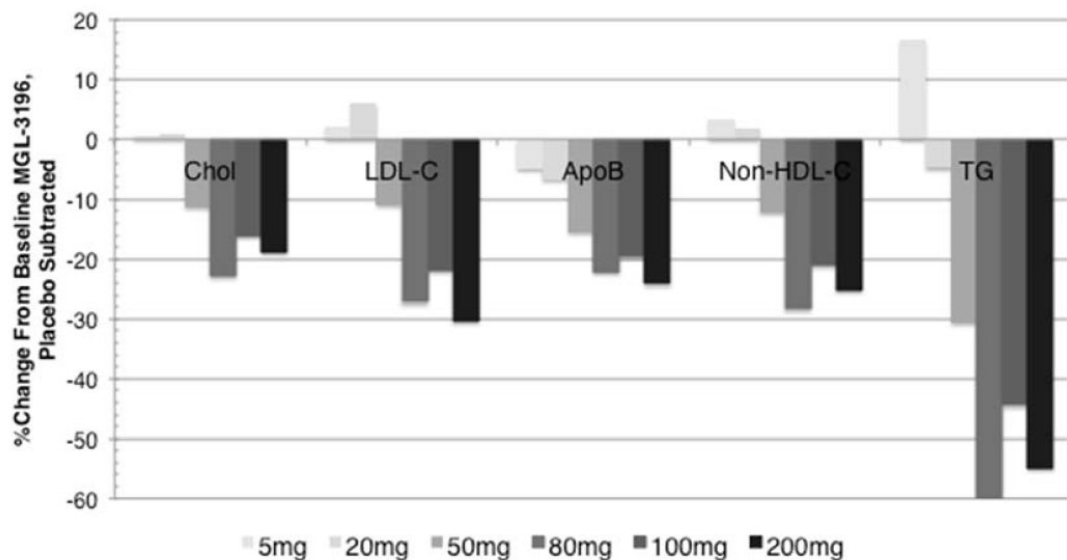
The primary pharmacology of resmetirom was evaluated in the pharmacology studies 3196-01, -02 and -03, as well as in the drug-drug interaction studies with rosuvastatin and simvastatin (3196-03), atorvastatin (3196-04), pioglitazone (3196-09), warfarin (3106-16), and clopidogrel (3196-12). In addition, the tQT study 3196-17 also assessed PD, similar to the bioavailability study 3196-08, and the study in hepatically impaired patients (Study 3196-10). Pharmacodynamic parameters were also included into the clinical efficacy studies 3196-05, 3196-11 and 3196-14.

In the early single- and multiple-dose ascending studies (studies 01 and 02), it could be shown that effects on serum lipids, TSH, T3 and T4 were not detectable after single-dose administration.

After 14-day treatment, in these healthy volunteers, at doses ranging from 50 to 200 mg daily, statistically significant and dose related reductions relative to placebo of up to 30% for LDL cholesterol, 28% for non-HDL cholesterol, and 24% for ApoB were demonstrated. A strong trend of up to 60% reduction in TGs was seen as well. Significant increases relative to placebo in SHBG of up to approximately 85% were observed at doses from 50 to 200 mg. Doses of 80, 100, and 200 mg showed no obvious difference.

The main lipid parameter changes are shown in the following figure:

Figure 6. Changes in Plasma Lipids in the MAD study 3916-02



Source: [Table 14.4.2](#).

Changes in lipids after 14 doses. The percent change from baseline (CFB) for each subject was determined, averaged by dose and corrected to placebo. The baseline determination was fasting, just prior to the first dose and the determination was made fasting 24 hours after the 14th dose. ApoB, apolipoprotein B; Chol, total cholesterol; LDL-C, LDL cholesterol directly measured; Non-HDL-C, non-HDL cholesterol, TG, triglycerides (median % CFB).

Small and reversible reductions in prohormone T4 levels were seen at the highest doses and there was no change in TSH (mild elevation within the reference range).

SHBG increased by up to 85%. There were apparent trends in increased total testosterone in males at 100 and 200 mg that would be expected given the increases in SHBG. No effects on follicle stimulating hormone (FSH) or luteinizing hormone (LH) were seen. For the further evaluation of the sex hormone changes, see safety.

The results with regard to lipid lowering (including HDL-C) and SHBG were confirmed with the different DDI studies conducted, with a variety of doses and treatment durations of 7-14 days. In these studies, depending on dose and exposure (by DDI partially increasing the exposure), partial reductions in FT4 were observed, while T4 remained stable. Other markers such as CK-MB, brain natriuretic peptide (BNP) as well as troponin I were also partially evaluated but did not show consistent or clinically relevant changes.

Study MGL-3196-10 was the study evaluating the influence of hepatic impairment which included a relevant proportion of both healthy subjects, and patients with different levels of hepatic impairment, as well as two groups of NASH/MASH patients, one group being non-cirrhotic, and one being diagnosed with NASH/MASH-cirrhosis. Doses of 80 mg resmetirom or lower (depending on the degree of hepatic impairment at baseline) were administered for 6 days.

In this study, the reductions of ApoB, LDL-C, and triglycerides was documented in all treatment groups, albeit effects not surprisingly appeared to be smaller in healthy controls. In this study, also a decrease of HDL-C was documented, however, not consistently across the different groups, with almost no changes in normal hepatic function subjects, and in patients with non-cirrhotic NASH/MASH.

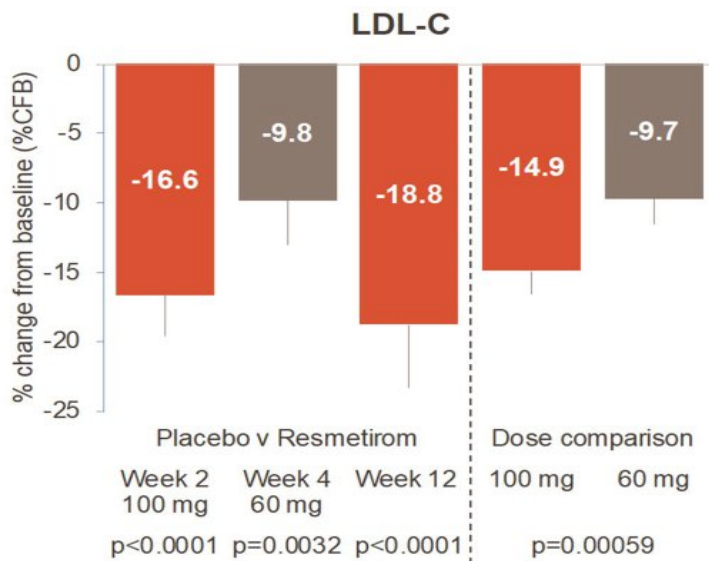
With regard to thyroid biomarkers, inconsistent changes were documented, with the exception of FT3 which showed a consistent reduction across all treatment groups.

The changes in SHBG were documented also in all treatment groups, with increases ranging from just under 30% to just above 60%.

One interaction study with warfarin also looked at the potential for pharmacodynamic interaction. It included not only an evaluation of the lipid biomarkers, the thyroid biomarkers, as well as the SHBG (determined at day 14 (baseline) and 22, but also the parameters INR, aPTT, and PT. The results of the study indicate that 8 consecutive days of co-administration of 100 mg/day resmetirom and warfarin was not associated with any important changes in INR, PT, and aPTT biomarkers.

Pharmacodynamics were also documented in the phase 2 study MGL-3196-06 with a treatment duration of 8 weeks in patients with familial heterozygous familial hypercholesterolaemia in which patients were required to have increased levels of LDL-C at baseline. The following graphical display shows the main results with regard to the primary efficacy parameter LDL-C:

Figure 7. LDL Cholesterol Percent Change from Baseline Comparison of MGL-3196 to Placebo and Comparison of MGL-3196 Doses (mITT Population)



%CFB = percent change from baseline; LDL-C = low-density lipoprotein cholesterol; mITT = modified intent-to-treat

Source: Table 14.2.1.2 and Hovingh et al. manuscript Central Illustration A

Note: Lane 1, Week 2, 100 mg (all MGL-3196 patients received 100 mg from Week 0 to Week 2); Lane 2, Week 4, 60 mg (all MGL-3196 patients received 60 mg from Week 2 to Week 4); Lane 3, Week 12 (pharmacokinetic-based adjusted dose of either 60 mg or 100 mg, Week 4 to Week 12); MGL-3196 treatment comparison of 76 patients on Lane 4, 100 mg (Week 2) or Lane 5, 60 mg (Week 4). P-values are shown comparing MGL-3196 to placebo (first three lanes) (placebo corrected values) or comparing doses 100 mg and 60 mg (lanes 4 and 5) (within dose group % change from baseline). n = 37 placebo; n = 76 MGL-3196 for all assessments.

Consistent decreases were seen in the parameters ApoB, total cholesterol, lp(a), HDL-C, ApoA1, and triglycerides.

The changes in SHBG were +3.35% for placebo, and +85.391% for active treatment with higher increases observed in females.

As part of the secondary objective to evaluate the safety profile of MGL-3196 versus placebo, free and total T4, FT3, reverse T3, TT3, and TSH were assessed at each study visit, and TBG was assessed at all study visits except the Screening Visit. The mean difference in change of thyroid hormone parameters in the MGL-3196 group versus placebo from Baseline to Week 12 was significantly decreased for FT4 (p<0.0001) and TBG (p<0.0001); a minor change in FT3 (-0.14 [p=0.0324]) and no change in TSH were observed (p=0.245). Reverse T3, an inactive hormone, was decreased (p<0.0001).

Study MGL-3196-05 was a proof-of-concept study which evaluated the effects on liver fat based on several imaging methods, as well as histology. The results of the study are reported in the efficacy part of this assessment report. With regard to OD parameters, the following could be seen after a treatment duration of 36 weeks in patients with MASH:

Table 13. Analysis of Lipids by Percent Change from Baseline – Main Study (mITT Population) – Study 05

	n	Placebo LS Mean (SE)	n	MGL-3196 LS Mean (SE)	LS-Mean Difference (95% CI)	p-value
LDL-C (mg/dL)	36	6.2% (3.1)	77	-11.2% (2.1)	-17.3% (-24.8, -9.9)	<0.0001
LDL-C (BL ≥100 mg/dL)	24	6.1% (3.8)	47	-16.2% (2.7)	-22.3% (-31.6, -12.9)	<0.0001
HDL-C (mg/dL)	36	2.2% (3.4)	77	6.0% (2.3)	3.8% (-4.4, 12.0)	0.36
Lp(a) (nmol/L)	36	30.2% (14.7)	76	7.0% (10.1)	-23.2% (-58.5, 12.1)	0.1961
Lp(a) (BL >10 nmol/L)	20	15.3% (8.9)	40	-22.7% (6.3)	-37.9% (-59.7, -16.2)	0.0009
ApoB (mg/dL)	36	5.1% (2.7)	76	-16.8% (1.8)	-21.9% (-28.2, -15.5)	<0.0001
ApoB (BL LDL-C ≥100 mg/dL)	24	7.4% (3.5)	47	-20.2% (2.5)	-27.6% (-36, -19.1)	<0.0001
TG (mg/dL)	35	20.5% (5.5)	76	-15.4% (3.8)	-36.0% (-49.2, -22.7)	<0.0001
TG (BL >150 mg/dL)	15	9.5% (7.9)	41	-21.4% (4.8)	-30.8% (-49.4, -12.2)	0.0016
ApoCIII	32	24.5% (5.4)	68	-12.0% (3.7)	-36.5% (-49.6, -23.5)	<0.0001

ApoB = apolipoprotein B; ApoCIII = apolipoprotein CIII; BL = baseline; HDL-C = high-density lipoprotein cholesterol; LDL-C = low-density lipoprotein cholesterol; Lp(a) = lipoprotein(a); LS = least squares; SE = standard error; TG = triglycerides

Note: Lipid statistics (LDL-C, HDL-C, Lp(a), ApoB) were based on Week 30, a prespecified timepoint. For triglycerides, combined results from Weeks 30 to 36 were used because of variability. Apolipoprotein CIII was measured at Week 36.

The results confirm the effects seen in the earlier studies, with the exception of the fact that in this population, an increase of HDL-C is observed, which is considered reassuring.

MGL-3196 significantly reduced the levels of FT4 from Baseline to Week 36 ($p < 0.0001$), with no changes in the other thyroid axis hormones FT3, TSH, or thyroxine-binding globulin (TBG).

MGL-3196 significantly increased SHBG at Week 12 and Week 36 as assessed by absolute change from baseline and percent change from baseline in both genders combined, as well as when separated by sex (all $p < 0.0001$). Other sex hormones were assessed for change at Week 36, separated by sex, of which only testosterone was significantly increased in females ($p = 0.0003$) and males ($p = 0.0283$).

The observed increases in SHBG could be assumed to be beneficial in the target population. The increases in SHBG and the potential consequences and the influence on sexual/reproductive hormone-related endocrine regulatory pathways were not studied. Since the pivotal trial 11 also included the evaluation of sex-hormone levels over a longer treatment period, and with considerably more patients, the issue was looked at within the evaluation of safety.

Secondary Pharmacology

As part of the secondary pharmacology documentation, potential changes in cardiac conduction were documented in three studies.

There was no indication from the pre-clinical data of any influence of resmetirom on cardiac conduction based on the *in vitro* and *in vivo* (beagle dogs).

The early SAD and MAD studies in healthy subjects included 24 hours continuous 12 lead Holter recordings to allow use of time matched ECG and PK data for concentration-QTc analysis.

There was no evidence of a clinically significant effect of resmetirom on HR, PR interval, or QRS duration in either the SAD or MAD trials. Concentration-QTc analysis and the by timepoint analyses for both the SAD and MAD trials demonstrated no evidence of a relationship between plasma concentrations of resmetirom or MGL-3623 and placebo-corrected QTcF change-from-baseline at mean resmetirom plasma concentrations up to approximately 1500 ng/mL.

The applicant presented a tQT study in accordance with the requirements of the ICH E14 guideline. Study MGL-3196-17 was a 3-period, 6-sequence crossover design study performed in a blinded manner in 36 healthy volunteers to assess the effects of resmetirom after single and multiple supratherapeutic-dose administration on cardiac repolarization (Q-T interval of the ECG).

Resmetirom was administered at a dose of 200 mg, and the positive control treatment was moxifloxacin 100 mg. Treatment duration was 6 days in each of the periods.

The primary study endpoint included evaluation of a change from baseline in QTc, QTcF, and placebo-corrected change from baseline in QTcF ($\Delta\Delta\text{QTcF}$). This analysis was based on concentration effect modelling, which evaluated the relationship between ΔQTcF and time matched plasma concentrations of resmetirom and its metabolites.

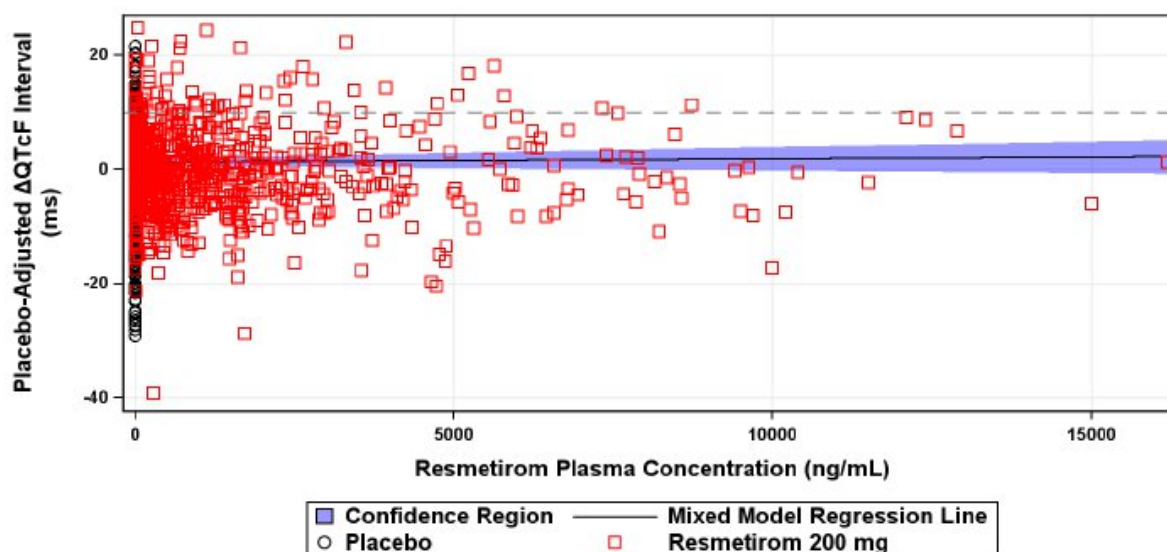
Secondary study endpoints included evaluation of:

- Change from baseline HR, QTcF, PR, and QRS intervals using by-time point analysis;
- Placebo-corrected change from baseline HR, QTcF, PR, and QRS intervals using by-time point analysis;
- Categorical outliers for QTcF, HR, PR, and QRS intervals;
- Frequency of T-wave morphology and U-wave presence changes;
- Evaluation of the relationship between the plasma concentration of moxifloxacin and the change from baseline for QTcF in order to demonstrate assay sensitivity.

The following figure presents the relationship between the observed plasma concentrations of resmetirom and MGL-3623, respectively, and $\Delta\Delta\text{QTcF}$. The plot of the standardized residuals versus the fitted values, concentrations of resmetirom, and centred baseline QTcF showed that the standardized residuals are distributed symmetrically around zero, with an approximately constant variance.

The plot does not indicate any departure from the model assumptions for the within-event errors, except for a few possible outlying observations with standard residuals located outside ± 3 . A second model (Model 2) showed similar results.

Figure 8. Scatterplot of Resmetirom Plasma Concentration (ng/mL) and Placebo adjusted Δ QTcF (msec) with Mixed Model Regression Lines for Model 1 (PK/QTc Population)



Δ QTcF = change from baseline QTcF

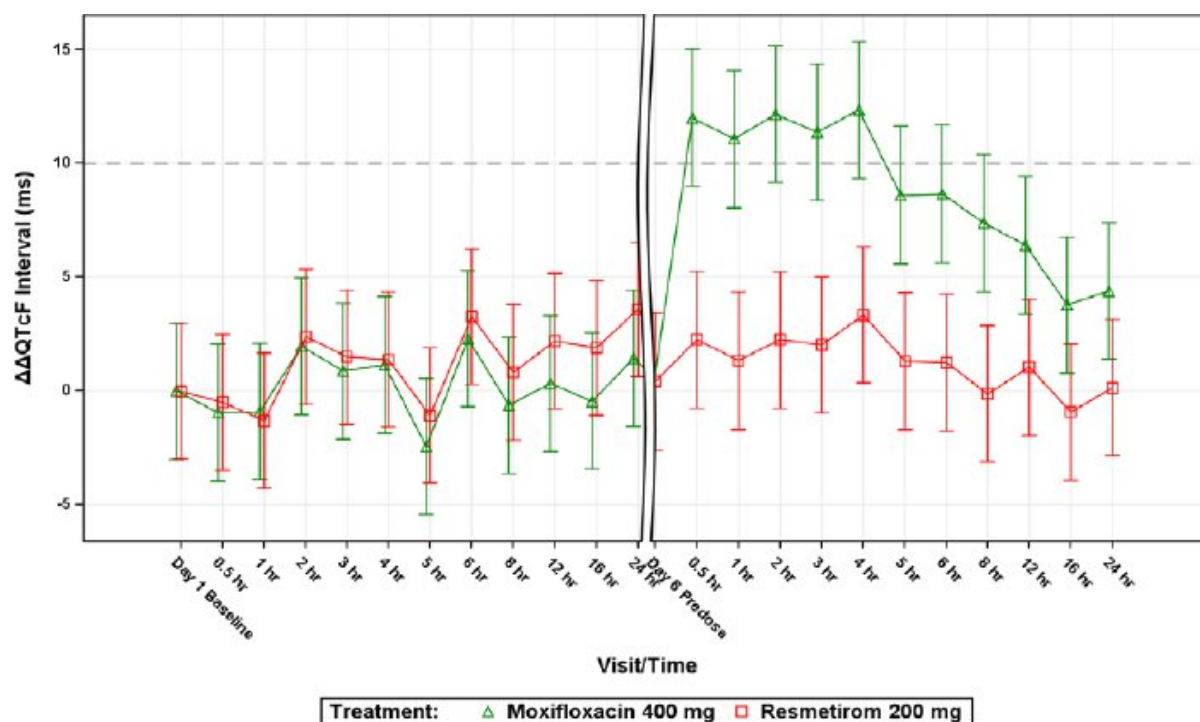
Note: The mixed effects regression line and confidence region are based on the 2-sided 90% confidence limits calculated using the Concentration-QTc model. Concentration was removed from random effects in order to achieve convergence. Note the confidence region is based on bootstrap methodology with 1000 replicates and accounts for random effects. Due to mixed effects model, confidence region is calculated by calculating the confidence interval at the minimum and maximum values connecting a linear line. It is not a true confidence interval (due to the mixed effects model).

The predicted estimates for the Δ Δ QTcF interval showed an upper 90% CI of 2.00 and 2.30 ms in the two models.

Moxifloxacin showed a positive relationship and produced an estimated $\Delta\Delta$ QTcF effect of 12.46 msec (90% CI 11.50 to 13.30 msec) at its $C_{\max}$. It was therefore concluded that assay sensitivity was demonstrated, as the slope of the moxifloxacin plasma concentration/ Δ QTcF relationship was positive (0.00432 msec/ng/mL) with $p < 0.0001$, and the lower bound of the 2-sided 90% CI for the predicted QT effect at the observed geometric mean $C_{\max}$ of 2515 ng/mL was 11.5 msec. Hence, assay sensitivity was demonstrated.

The by-time-point analysis demonstrated no clinically significant effect of resmetirom on QTcF. The largest LS mean $\Delta\Delta$ QTcF for resmetirom was 3.6 msec (90% 2-sided upper confidence interval [UCI]: 6.6 msec) at 24 hours after dosing on Day 1, and 6.3 msec (90% UCI: 3.3 msec) at 4 hours after dosing on Day 6. The 90% upper confidence bound for $\Delta\Delta$ QTcF was <10 msec at all time points. The results are shown in the following figure:

Figure 9. Placebo-corrected Change-from-baseline QTcF Interval (msec) Across Time with Statistical Modeling (QT/QTc Population); Study 3196-17.



QTcF = QT interval corrected for heart rate using Fridericia's formula; $\Delta\Delta\text{QTcF}$ = placebo-corrected change from baseline in QTcF

Categorical evaluations were unremarkable. It was concluded that resmetirom had no clinically significant effect on heart rate or on cardiac conduction, as measured by the PR and QRS intervals. No subjects had new, clinically significant ECG morphology changes.

2.6.3. Discussion on clinical pharmacology

Pharmacokinetics

The pharmacokinetics of resmetirom and its main metabolite MGL-3623 were evaluated in 36 *in vitro* studies, in 17 Phase 1 clinical pharmacology studies applying rich sampling, and with sparse sampling in Phase 2 and Phase 3 studies. Full CSR for studies MGL-3196-21 (severe renal impairment) and MGL-3196-24 (DDI study resmetirom 100 mg with rosuvastatin 10 mg), are anticipated by the end of 2025. In addition to PK evaluation by non-compartmental methods (NCA), modelling and simulation were conducted to fully characterise the PK-PD profile.

Bioanalysis

Overall, eight bioanalytical methods were developed for determination of resmetirom and MGL-3623 in plasma, plasma ultrafiltrate and urine. Method validations were not fully in line with regulatory guidance applicable at time of conduct (EMA Guideline on bioanalytical method validation), e.g. regarding evaluation of haemolysis and lipaemic effects (missing), dilution linearity (insufficient), interference evaluation by concomitant medication administered for AE (missing) and cross validation to support the comparison of data obtained by different methods and facilities (missing). However, the claims on dose proportionality and the qualitative statements advising against use of resmetirom in moderate and severe hepatic impairment included in the SmPC could still be supported, despite the bioanalytical deficiencies identified.

Population PK modelling

Population and individual predicted resmetirom concentrations were adequately fitted with the final population PK model, as far as the submitted boxplot VPCs can assure that. A bias was observed for population predicted values close to 10 ng/mL which might be due to deviations associated with the dosing and/or sampling times. Additional plots showed that C_{max} was slightly underestimated by the popPK model, whereas the predicted concentrations in the elimination phase were rather overestimated. The fit of the model was considered not optimal but still appropriate as the individual predictions were in agreement with the observed data.

Sensitivity analysis was performed by withholding the PK data collected in VIA-3196-01, VIA-3196-02, and MGL-3196-10 considered less reliable due to bioanalytical issues from the population PK model and inclusion of the PK data collected in MGL-3196-20 considered more reliable and more relevant to the tablet formulation proposed for marketing. While model parameter values appeared to be impacted by exclusion of data from the older studies, it is considered reassuring that the PK metrics over the doses of primary interest appeared not relevantly changed. Exposure predictions across the dose-proportional range of 40-100 mg were not substantially impacted across the scenarios.

Absorption

Absence of an absolute bioavailability study was not justified, but this was considered acceptable.

Exposure in the target population estimated by population PK modelling was proposed to inform the product information which was considered acceptable.

Distribution

Resmetirom was highly plasma protein bound *in vitro* (>99%) independent of concentration, and human serum albumin appeared the major contributor; however, in both of these assays, assay validity was not demonstrated by means of a control reference compound. This is not of concern as low fraction unbound was confirmed in samples from dosed subjects in renal impairment study MGL-3196-21.

The *in vitro* DDI study MGL-3196-22 with cyclosporine (an inhibitor of OATP1B1, OATP1B3, BCRP, and P-gp) showed that the PK of resmetirom was not affected by concomitant use of cyclosporine.

Being highly correlated with body weight, the volumes of distribution (central and peripheral) were quantified using population PK analysis. The information provided in the product information on V_d/F was amended to reflect the target population.

Elimination

Based on mass balance in study MGL-3196-07, more than 90% of the radioactive dose as measured by LSC was recovered in excreta over the whole collection period. Excretion of radiolabelled material in urine appears almost entirely covered in the mass balance as values were below the limit of quantitation (BLQ) in sampling intervals from 96 hours post-dose onwards in all but one subject. However, fecal samples from late sampling intervals past 168 hours post-dose were not received for analysis for half of the subjects, and in 3 of the other 4 subjects, BLQ values started only from ≥ 192 h onwards. Incomplete coverage of fecal excretion may thus account at least partially for the 15 to 7% of unrecovered dose.

Since the majority of 63.51% of the dose-related material as measured by LSC was eliminated via faeces within 72 hours, and 20.03% was excreted in 0-24h urine, time restricted pooling approaches covering these intervals were applied for metabolite profiling, identification and quantitation and considered appropriate with risk to miss the presence of significant late-occurring metabolites in excreta considered low.

It should be noted, however, that the presented calculations in the metabolite profiling, identification and quantification report were not corrected for the %extraction and %reconstitution recoveries, contrary to recommended common practice.

With the mean overall %recovery (extraction and reconstitution) amounting to only 66.5% for pooled faecal homogenate, and recovery from lyophilisation of the pooled urine sample amounting to 88.8%, only 42% rather than 63.51% of the radiolabelled material in faeces and 18% rather than 20.03% of the radiolabelled material in urine were accessible to metabolite profiling, identification and quantification and could be attributed to the 13 metabolites in faeces, and to resmetirom and 3 metabolites in urine. Overall, only ~60% rather than 83.54% of the radiolabelled material recovered in excreta could be identified, which is considerably less than the 80% required according to guideline recommendation.

It is furthermore unclear whether resmetirom and its metabolites were all affected equally by the low extraction/reconstitution recoveries, which if not could have caused bias in the reported relative frequencies. Together with the time restricted pooling approach, some risk remains that some /late metabolites may not have found (adequate) consideration.

The mass balance study was conducted at steady-state given that PK was less than dose proportional following single dose in early SAD and MAD studies, and accumulation in the latter had been found to be greater than expected from half-life, together preventing extrapolation from a single dose mass balance study for resmetirom. Conduct at steady-state may however limits the interpretability of the results as this approach only evaluates the elimination pathway of the radiolabelled resmetirom, which may be altered after repeated doses as compared to single dose. Overall, the percentages attributed to resmetirom and identified metabolites should be viewed cautiously.

Metabolism

In plasma, resmetirom was presented as the major radioactive component (55.22% based on AUC), followed by MGL-3623 as the most abundant metabolite (16%), and oxalic acid metabolite (14.5%) that was observed in plasma but not in urine. MGL-3842 (M2) was considered a minor metabolite (7.46%), as were M467_2 (4.56%) and M611 (2.38%). However, similar to urine and faeces, overall mean % recovery in plasma (79%) was not taken into account in the metabolite profiling, identification and quantitation calculations in plasma, and use of a time restricted pooling approach could similarly have biased the results. Thus, resmetirom, MGL-3623 and 4 further metabolites including oxalic acid were profiled and identified from a pooled sample consisting of 1 to 8 hours post-dose plasma samples only and were then radio-quantitated in a second set of samples pooled across subjects per sample collection time point up to 48 hours post-dose. Metabolites formed later than 8 hours post-dose did not find consideration, only early metabolites already present prior to 8 hours post-dose were quantitated, all of which were BLQ already at 24 hours post-dose. However, in human mass balance study MGL-3196-07, mean (SD) plasma $t_{1/2}$ of total radioactivity was 34.39 (27.23) hours, compared to mean (SD) $t_{1/2}$ of non-labelled resmetirom and MGL-3623 in plasma of 2.55 (0.730) and 3.61 (1.11) hours, respectively, indicating further metabolites in plasma with slower elimination rate limited clearance. Relative frequencies of resmetirom and identified metabolites have therefore to be regarded cautiously and the presence of long-lasting circulating and/or late metabolites cannot be ruled out, the identified metabolites are characterized adequately.

The resmetirom mono-oxygenate (hydroxy-) metabolite MGL-3623 was formed *in vitro* in human intestinal microsomes, cryopreserved hepatocytes, and human liver microsomes. Resmetirom had low clearance/high stability in human cryopreserved hepatocytes. CYP2C8 was identified as the primary CYP450 enzyme responsible for the metabolism of resmetirom to MGL-3623.

Dose proportionality and time-dependency

The claims on dose proportionality included in the SmPC are considered sufficiently substantiated.

Following repeated dosing at 100 mg resmetirom QD, resmetirom C_{max} and AUC accumulated with ratios up to 2.4 and 2.9, respectively. Drug accumulation observed for doses ≥ 50 mg was greater than predicted by the plasma terminal half-life. Higher accumulation was observed following dosing at 200 mg resmetirom QD. In all studies, MGL-3623 exhibited little to no accumulation as compared to parent drug. The fact that resmetirom is not only a substrate but also an inhibitor of CYP2C8 (IC_{50} 0.90 μ M) may explain the observation that the metabolic ratio decreased with repeated dosing and increasing dose. Based on the superposition principle, the temporal change parameter (TCP) (also called Predictive Ratio (PR)), calculated as $AUC_{0-\tau}$ (steady-state) / AUC_{0-inf} (single dose), may be used to assess deviation from linear PK with respect to time-dependency (non-stationary PK). TCP (PR) was not presented. In an approximation, using $D9 AUC_{0-24}$ / $D4 AUC_{0-inf}$ from study MGL-3196-09 (dose 100 mg), TCP calculates as 3.1 for resmetirom and 1.14 for MGL-3623. Using AUC_{0-24} following repeated dosing / AUC_{0-inf} following single dose from study MGL-3196-17 (dose 200 mg), TCP calculates as 3.41 for resmetirom and 0.99 for MGL-3623. It is agreed, that at a 100 mg dose, the accumulation of resmetirom is modest, with little to no accumulation observed at doses below 60–80 mg. Notably, the AUC of MGL-3196 increased both in the absence of and in the presence of clopidogrel, a moderate CYP2C8 inhibitor.

PK in the target population

Based on non-compartmental analysis of non-cirrhotic NASH/MASH patients with normal hepatic function in HI study MGL-3196-10, following repeated dosing at 100 mg QD for 6 consecutive days, mean C_{max} was 2,490 ng/mL (geometric mean 1,760 ng/mL) and mean AUC_{0-24} was 16,000 ng h/mL (geometric mean 8270 ng h/mL). In the PI, estimated systemic exposure at steady state in patients with MASH with fibrosis (F2 and F3) derived from population PK modelling are presented with slightly lower values. On the basis of the explanations provided with the D180 responses this appears acceptable.

Population PK analyses of resmetirom and its main metabolite MGL-3623 were conducted to identify sources of variability in patients with NASH/MASH. Exposure parameters derived with the above population model were used for further exposure-response analysis to support dosing of resmetirom in patients with MASH.

A previous model based on data from Phase 1 and 2 was updated by including data from MGL-3196-11 and MGL-3196-14. Absorption parameters were fixed to the parameter estimates derived in the base model for studies with rich sampling in absorption phase. The absorption of resmetirom was described with a duration of absorption ($D1$) of 3.99 h, a K_a of 0.840 h^{-1} and an absorption lag time of 0.240 h. Rich data collected in Phase 1 and 2 studies were used to support the development of the absorption model of resmetirom. No RSE and shrinkage could be calculated for these parameters. The disposition of resmetirom was described with a 2-compartment model. The CL/F and V_c/F for a typical 98 kg patient with NASH/MASH after a single dose of 80 mg were 30.6 L/h and 42.1 L, respectively. The PK of resmetirom was highly variable with between-subjects variability of CL/F and V_c/F of 55.3% and 121%, respectively. Parameters describing the distribution into peripheral tissues (Q/F and V_p/F) were fixed to those observed in Phase 1 and 2 studies due to the sparse data collected in Phase 3 studies. Based on the above PK parameters (CL/F , V_c/F , Q/F and V_p/F), the model predicted distribution ($t_{1/2\alpha}$) and elimination ($t_{1/2\beta}$) half-life of resmetirom after a single dose in a typical NASH/MASH patient were 0.876 and 3.60 h, respectively. Statistically significant covariates in the popPK model were bodyweight, fibrosis stage, and concomitant medication of statins or clopidogrel.

Body weight was identified as the most important influence with effects on PK on CL/F and Vc/F. The population PK model included an allometric component that accounted for differences in body weight. The exponent for the effect of body weight on CL/F was 1.39 that suggested a faster CL/F of resmetirom in patients with higher body weight. The exponent for the effect of body weight on Vc/F was 1.38 that suggested a larger Vc/F of resmetirom in patients with higher body weight. MASH patients with fibrosis stage F3 and F4 showed a lower CL/F, this effect was rather small for F3 patients (CL/F 5% lower) and more pronounced for F4 patients (CL/F 25% lower). PK results for the F4 population are therefore presented separately. For concomitant medication statins, clopidogrel and bile acid sequestrants were investigated, showing no significant effect on CL/F for bile acid sequestrants, a small but significant effect for statins (CL/F 2% lower) and a pronounced effect of clopidogrel on the PK of resmetirom resulting in a 50% lower CL/F.

Therapeutic window

The therapeutic window has been defined to lie within Cavg of 120 to 1750 ng/ml (corresponding to AUC_T range of 2800 to 42000 ng*h/ml) based on clinical experience in Phase 2 and 3 studies.

Pharmacokinetics in special populations

The popPK analysis revealed an effect of renal impairment in addition to the body weight effect. For fibrosis stage F0-3 moderate renal impairment resulted in a 28% lower CL/F (30% for F4). This was considered not clinically relevant by the applicant due to the minor impact on the t_{1/2β} and Rac. The applicant provided no information on the -fold increases in C_{max} and AUC that result from a 28% reduction in clearance. Within studies MGL-3196-11 and MGL-3196-14, the geometric mean of the weight normalized clearance (CL/F) in patients with moderate renal impairment (0.135 L/hr/kg) was approximately 22% lower than in patients with normal renal function (0.174 L/hr/kg). In the matched study population for MGL-3196-21, the weight-normalized CL/F in subjects with severe renal impairment (0.184 L/hr/kg) was approximately 15% lower than in subjects with normal renal function (0.217 L/hr/kg). Considering the results of MGL-3196-21—including the limited role of renal clearance in resmetirom elimination, the favorable safety profile in renally impaired individuals, and the expected exposure variability at 100 mg in healthy subjects—it is supported that resmetirom can be safely administered to patients with severe renal impairment. Based on these observations, it is agreed that in cases of mild, moderate and severe renal impairment, no dose adjustment is needed, as resmetirom is mainly hepatically eliminated, with only 1% excreted as unchanged resmetirom in urine.

A dedicated PK study in subjects with HI and patients with NASH/MASH with or without cirrhosis was conducted (MGL-3196-10). Body weight normalised evaluation was not presented in study MGL-3196-10 and bioanalytical issues were noted pertaining to use of different bioanalytical methods and facilities without cross-validation. Impact of mild HI on PK appears to be not clinically relevant and accordingly, no dose adjustment is recommended in the product information for patients with mild hepatic impairment (Child Pugh A).

Based on population PK analysis, no dosage adjustment is recommended in older patients ≥ 65 years of age, although an increased incidence of adverse events and discontinuation rates were observed in this population. Dose adjustment recommendations for tolerability offered no evidence that dose reductions effectively manage adverse reactions. While a dose effect was observed, with a 100 mg dose being associated with a slightly higher probability of diarrhoea and other gastrointestinal events. The efficacy outcomes seen with 100 mg in higher body weight patients are equivalent to those observed with 80 mg in lower body weight patients. Consequently, implementing weight-based dosing may help mitigate the risk of treatment discontinuation due to these adverse events while ensuring maintained efficacy. Furthermore, based on the available PK/PD data for resmetirom, there was insufficient evidence to justify a fixed dose reduction for intolerance. No information is available in the paediatric population. This was reflected accordingly in the proposed product information.

Exposure parameters of resmetirom decreased with increasing body weight. Based on population PK analysis, body weight was identified as the most significant covariate influencing the variability in CL/F and Vc/F of resmetirom and the use of a weight cut-off is endorsed. While significant inter-individual variability was observed across studies, the proposed 100 kg cut-off is deemed to ensure more comparable exposure levels. The proposed posology was considered adequately justified, and the dosing for both higher and lower body weight tertiles was deemed adequate.

Pharmacokinetic interactions studies

High plasma protein binding was observed for both resmetirom and MGL-3623 *in vitro*. Nevertheless, the risk for displacement interactions was considered low.

The only enzyme identified as contributing to its metabolism was CYP2C8, which plays a key role in converting resmetirom into its main metabolite, MGL-3623. No additional enzymes involved in resmetirom metabolism were found. Resmetirom was determined to be both a substrate and an inhibitor of CYP2C8. These findings were followed up in dedicated *in vivo* DDI study MGL-3196-09 with moderate CYP2C8 substrate pioglitazone (resmetirom as perpetrator), and in DDI study MGL-3196-12 with clopidogrel, a moderate inhibitor of CYP2C8 (resmetirom as victim).

It was found that a resmetirom repeated daily administration of 100 mg for 7 days resulted in a 1.5-fold increase in the overall exposure (AUC) of moderate sensitive CYP2C8 substrate pioglitazone while little change in peak exposure was observed. Resmetirom may hence be classified a mild inhibitor of CYP2C8. As such, the co-administration of a single oral dose of pioglitazone (15 mg), a moderately sensitive CYP2C8 substrate, with resmetirom (100 mg/day) resulted in a 1.5-fold increase in the AUC of pioglitazone, with no change in C_{max} . It was concluded that no dose adjustment is required; however, clinical monitoring is recommended when resmetirom is used with certain CYP2C8 substrates for which small increases in exposure may lead to serious or dose-related adverse reactions. Based on the DDI study with moderate CYP2C8 inhibitor clopidogrel, at steady state, co-administration of clopidogrel and resmetirom resulted in a 1.3-fold and 1.7-fold increase in resmetirom C_{max} and AUC, respectively. In addition, the C_{max} and AUC of metabolite MGL-3623 decreased by 69% and 50%, respectively. Clopidogrel was identified as significant covariate in population PK analysis and a pronounced effect of clopidogrel on the PK of resmetirom in NASH/MASH patients resulting in a 50% lower CL/F was revealed. The proposed product information therefore recommends a dose reduction to 80 mg of resmetirom per day (for patients weighing ≥ 100 kg) or 60 mg per day (for patients weighing < 100 kg) to mitigate the significant increase in exposure resulting from co-administration of resmetirom with clopidogrel. The applicant has provided a statistical evaluation of the impact of genetic polymorphisms on the pharmacokinetics (PK) of resmetirom and its metabolite MGL-3623. This evaluation includes data on SLCO1B1 and CYP2C8 (based on Phase I studies), ABCG2 (based on Phase I, II, and III studies), and UGT1A1 (based on Phase III studies). The pharmacogenetic analysis concludes that polymorphisms associated with CYP2C8, BCRP, and OATP1B1—while neither the ABCG2 genotype nor the UGT1A1 genotype has a significant impact—do not introduce additional risks in the disposition of resmetirom, regardless of concomitant medication use, including those that could potentially result in drug-drug interactions with resmetirom. In summary, the analyses from Phase I, II, and III studies support the conclusion that body weight is the most important factor explaining the variability in exposure to resmetirom and its metabolite MGL-3623. Moreover, it is agreed with the applicant that MGL-3623, a CYP2C8-mediated metabolite of resmetirom, shows low potential for clinically significant drug-drug interactions at both intestinal and hepatic levels. No further studies were considered necessary.

Resmetirom as weak CYP2C9 inhibitor perpetrating DDI was evaluated in DDI study MGL-3196-16 with warfarin. Under the conditions of study MGL-3196-16, no clinically significant differences in the PK of R-warfarin or S-warfarin were observed following 8 consecutive days of co-administration of 100 mg/day resmetirom and warfarin in healthy subjects with stable INR values.

Given the potential of resmetirom to inhibit OATP1B1, OATP1B3, BCRP, CYP3A4 and/or UGT1A1/3 *in vitro* and the potential for co-administration, resmetirom as perpetrator of DDI was also evaluated in DDI study MGL-3196-04 with atorvastatin, in study MGL-3196-03 with simvastatin and rosuvastatin, in study MGL-3196-15 with simvastatin and pravastatin, in study MGL-3196-22 with cyclosporine and in study MGL-3196-24 with rosuvastatin.

The dedicated cyclosporine interaction study demonstrated a lack of clinically relevant interaction with resmetirom, warranting removal of any restriction on concomitant use with OATP1B1/OATP1B3 inhibitors. Nonetheless, an increase of AUC for the various statins by 1.4 to 1.8-fold was observed with resmetirom 100 mg QD co-administration, suggesting that resmetirom may be an inhibitor of OATP1B1/3. Additionally, the study of resmetirom with rosuvastatin, a BCRP substrate, demonstrated an increase in both the AUC and C_{max} of rosuvastatin by less than two-fold suggesting a mild impact on rosuvastatin pharmacokinetics. With chronic dosing, high plasma concentrations of statins are directly correlated with the potential for clinically relevant myopathies.

The SmPC is considered appropriate, as it encompasses findings from both *in vitro* and *in vivo* studies and adequately addresses the potential risks in a suitable manner.

Pharmacodynamics

Population based studies have shown an association between overt or subclinical hypothyroidism and MASLD (Bikeyeva, V *et al.*, 2022; He, W. *et al.*, 2017). Also, patients with higher baseline TSH levels and no evidence of liver disease were more likely to develop MASLD. In addition, the prevalence of MASLD was found to significantly increase as serum TSH level increased, even after adjusting for age, gender and smoking status. Hypothyroidism was found to be significantly associated with the presence and severity of MASLD. Moreover, animal model data have also shown liver disease in THR- β deficient animals.

Based on this rationale, the development of THR- β agonists was expected to potentially ameliorate not only subclinical hypothyroidism but also improve metabolic function within and outside the liver. Since THR- β belongs to the nuclear hormone receptor superfamily, a wide range of potential effects could be expected.

In the pre-clinical studies, resmetirom (and its metabolite MGL-2623) has been characterised as partial THR- β agonist and has shown specific binding to this receptor as compared to the THR- α receptor. Liver selectivity of the compound appears not only to be based on high expression of the receptor in the liver, but also on the transporter based, expected "accumulation" of the compound in this organ. Expected effects include de-novo lipogenesis, fatty acid oxidation, mitophagy and mitochondrial biogenesis, and cholesterol metabolism to be increased. With regard to thyroid haemostasis, THR- β stimulation is also expected to increase in levels of DIO1 (deiodinase 1) which itself leads to an increased conversion of T4 to T3. This is also expected to lower reverse T3 (the inactive form of T3). Since, however, free T3 is the relevant active form of the thyroid hormones, the impact on the hypothalamus pituitary-thyroid axis was expected to be limited especially in the MASH population.

Based on these facts and assumptions, the applicant has chosen to investigate the most immediate relevant pharmacodynamic parameters such as serum lipids (mainly LDL-C, but also Apolipoproteins, triglycerides etc.), and the thyroid hormone parameters FT4, FT3, TT4, TT3, and TSH. As a general parameter of pharmacodynamic activity, sex-hormone-binding globulin was chosen.

The "immediate" pharmacodynamic action on the changes in serum lipids were evaluated both in the SAD and MAD studies in healthy volunteers, and in several other phase 1 pharmacology studies, including drug-drug interaction studies, food interaction study, the study in hepatically impaired patients, and the early clinical studies. Moreover, the changes in serum lipids were also included as efficacy parameters in MASH phase 2 and phase 3 studies.

All these studies also included the evaluation of SHBG, and the hormones relating to the thyroid haemostasis. Partly other biomarkers were evaluated (e.g. cardiac safety, and others) and did not show relevant changes.

In the SAD study 01, no effects on relevant PD parameters could be seen since the exposure was too short.

The MAD study in healthy volunteers (albeit with mildly elevated LDL-C; treatment for 2 weeks) using 6 different dose levels clearly showed a dose-dependent activity with regard to LDL-C and other serum lipid parameters, as well as for SHBG. The dose level of 80 mg demonstrated a near maximal effect on serum lipids. With regard to thyroid hormones, no relevant changes were seen for FT3 and TT3. Slight reductions in FT4 and TT4 were seen, as well as a mild elevation of TSH.

These effects, both on serum lipid parameters as well as the SHBG were clearly confirmed in the further phase 1 studies investigating primarily healthy populations.

Diverse but potentially clinically insignificant effects have been observed with regard to TSH, T3 and T4, depending on the treatment duration and doses administered. Some of the studies in healthy subjects also showed some tendency for changes, but with all parameters remaining within the reference ranges.

Some trials indicated that there could be a mild rather untoward change in HDL-C (decrease). However, this trend, observed in healthy subjects was finally not seen in the later PD studies in diseased populations, including the phase 2 (and phase 3; see below) studies conducted.

A potential pharmacodynamic interaction was evaluated in one study testing the concomitant administration of resmetirom with warfarin, which, however, could not detect a relevant change in the haemostasis parameters INR, PT, and aPTT.

The applicant has also evaluated the potential for secondary pharmacology on the heart evaluating Holter ECGs in the early PK studies 01 and 02 which did not show effects on HR, PR interval, or QRS duration in either the SAD or MAD trials.

The applicant has also conducted a tQT study which investigated the effects of supra therapeutic doses on cardiac repolarisation. In this study, 200 mg resmetirom (twice the regular dose) were compared to placebo, and moxifloxacin 400 mg included as positive control. The design of the study, as well as the mode of evaluation of the ECG parameters have been found to be compliant with the requirements as of the ICH E14 guideline. Study dosing, timing of PK and ECG measurements were considered appropriate. Assay sensitivity was demonstrated with clear increase of QT ($\Delta\Delta\text{QTcF}$) above the threshold of 10 ms was clearly shown. Measured parameters, and model-based evaluations showed that the effects of resmetirom on cardiac conduction parameters was negligible, categorical evaluations did not show any parameter to be of concern. The placebo-corrected change in QTcF remained below the critical value of 10 ms for all time-points. Since the results of the clinical investigations was in accordance with the pre-clinical test results (*in vivo* and *in vitro*), the substance is considered to be devoid of any influence on cardiac conductance.

The evaluation of the primary pharmacodynamic effects, as the basis for clinical efficacy in the MASH population have therefore not been evaluated directly within the dedicated PD programme. Since the mechanism of action of resmetirom relates – with some simplification – to the removal of liver fat from hepatocytes, and thus removing the lipid toxicity attributed as one of the principles of MAFLD/MASH pathogenesis, the measurement of serum lipids, or the effects on SHBG and thyroid hormones must be seen to not directly measure what is happening in the liver. The on-going process of high fat deposition in the hepatocytes, the liver cell stress, and inflammation, and the resulting fibrosis development have all not been included in the early, dedicated pharmacodynamic studies. However, the observation that

the expected potential to remove fat from the liver does not increase the “steatotic burden” in the serum seems to be reassuring, and it can be assumed that the induction of the THR- β related “general” induction of metabolic processes does not only lead to a reduction of liver fat, but is also able to induce a further reduction of the serum lipid burden assumed to be present in the MASH population.

The reduction of liver fat burden, and its potential downstream effects (along with other metabolic changes) have been evaluated in the clinical studies only. This was justified and accepted on the basis that the parameters cannot be evaluated in healthy subjects, and usually require long-term observation with considerable efforts and input in terms of evaluation equipment and patient burden (based on imaging methods, and/or histology evaluations).

Based on these facts, as well as the fact that no dedicated dose-finding study is available, the applicant has justified the proposed dosing based on the clinical observations mainly in the pivotal phase 3 study 11, which has tested both the 100 mg as well as the 80 mg dose. The evaluations conducted have shown that the proposed dosing seems to be an adequate compromise based on PK properties of the compound (increased clearance with high body weight) and the evaluation of the adequacy of different cut-offs for the different doses to be given. The administration of 100 mg for patients above 100 kg body weight, and 80 mg for those below has been justified.

2.6.4. Conclusions on clinical pharmacology

The pharmacokinetics of resmetirom and MGL-3623 have been acceptably investigated.

Population PK analyses of resmetirom and its main metabolite MGL-3623 were conducted to identify sources of variability in patients with NASH/MASH. Exposure parameters derived with the above population model were used for further exposure-response analysis to support dosing of resmetirom in patients with MASH.

The pharmacodynamic properties of the compound have been elucidated adequately. The influence of the compound on fat deposition in the liver itself, and even the “downstream effects” on cell stress, inflammation and fibrosis were not evaluable in healthy subjects, and due to the long-term development of these parameters, were not suitable to be included in the pharmacodynamic evaluations.

Both efficacy-related as well as safety-related parameters have been investigated. The evaluations demonstrate that there is considerable reduction of the main part of the serum lipids, with a small increase in HDL-C, which is, however, only observed in patients.

The effects on the thyroid haemostasis appear to be limited to a reduction of FT3, with no major changes induced in any of the other relevant hormones.

The general PD marker SHBG shows a marked increase, both in healthy subjects, and even more so in patients. The associated potential changes in sex hormones are dealt with in the evaluation of safety.

The CHMP considers the following measures necessary to address the issues related to pharmacology:

In line with EMA/CHMP/83874/2014, a dedicated renal impairment study is considered necessary to inform dosage recommendation in patients with severe renal impairment and has been recently completed. The final CSR is anticipated by the end of 2025. Furthermore, a dedicated *in vivo* DDI study to evaluate effect of resmetirom on the PK of BCRP substrate rosuvastatin has been conducted and the final CSR is anticipated by end of 2025.

2.6.5. Clinical efficacy

The applicant presented a total of 5 studies in Module 5 of the submitted dossier. One of these studies (MGL-3196-06) is not regarded to be a clinical efficacy study for the proposed indication but has

investigated PD parameters in a population of patients with heterozygous familial hypercholesterolaemia.

The applicant has conducted one phase 2 study, which is a proof of concept and preliminary efficacy study which, however, investigated the 80 mg dose only (with subsequent potential adaptations of the dose).

One pivotal trial (study 11) was submitted, with an interim study report, since the trial was designed to further evaluate efficacy in the long-term, based on liver-related outcomes. This trial and the phase 2 study have included the dedicated target population of patients with MASH.

Two supportive studies were also submitted, study 14 and 18. The study 14 was a study in a non-invasively diagnosed population with presumed MASLD/MASH, and the second study, 18, was a long-term extension study of Study 14, as well as of patients rolled over from other studies. An overview on the development is given in the following table.

Table 14. *Clinical studies*

Enrolment status Start date Total enrolment/ Enrolment goal	Design Control type	Study & control drugs Dose, route of administration and duration Regimen	Population Main inclusion/ exclusion
Completed/ Jan 2019 PLV Extension ongoing) n = 125	Multicenter, double-blind, randomized, placebo-controlled study with open- label extension	Main Study: Resmetirom 80 mg tablet or matching placebo once daily Extension Study: Resmetirom 80 mg once daily; Dose adjustments for Main and Extension Phase: 40 mg, 60 mg, 100 mg, 120 mg n = 41 (placebo) n = 84 (resmetirom) Study completion at Week 36,	Biopsy-proven NASH
Completed for interim Week 52. Interim Data Cut-off Date: 31 Jul 2022. n = 1050 Study ongoing with extended duration of 54 months	Multicenter, double-blind, randomized, placebo-controlled study	Resmetirom 80 mg or 100 mg tablet PO once daily or matching placebo Dose adjustment with doses as low as 40 mg was allowed n = 349 (placebo) n = 352 (resmetirom 80 mg) n = 349 (resmetirom 100 mg)	Biopsy-proven NASH diagnosed as "high" (F1B) or F2/F3 F1 A/C exploratory
Completed n = 1143 PLV: 13 Dec 2021	Multi-center, double-blind, randomized, placebo-controlled study with open- label phase in NAFLD/MASLD	Resmetirom 80 mg or 100 mg tablet PO once daily or matching placebo Dose may have been decreased to 60 mg based on drug exposure at Week 2 Dose titration for NASH/MASH cirrhosis cohort may have been reduced to 40 mg once daily or 80 mg every other day N = (1143) n = 320 (placebo) n = 327 (resmetirom 80 mg) n = 325 (resmetirom 100 mg) n = 171 (OLNC)	NAFLD/MASLD (pre NASH/MASH, not M cohorts with comp NASH/MASH cirrho moderate renal im Study MGL-3196-1 meeting eligibility r
Ongoing; Interim CSR n = (~1080; anticipated) 20 de novo or Study patients with minimally compensated NASH/MASH cirrhosis)	Multicenter, active- treatment, rollover study	Resmetirom 40, 60, 80, or 100 mg tablet N= 615 included in interim CSR Patients who completed Study MGL-3196-14, as well as screen fail patients from Study MGL 3196-11, MGL-3196-19, and de novo meeting eligibility criteria	MASLD/MASH



2.6.5.1. Dose response studies

No dedicated dose-response study has been presented.

Study MGL-3196-05:

This was a phase 2, multi-centre, double-blind, randomized, placebo-controlled study of MGL-3196 in patients with non-alcoholic steatohepatitis, to evaluate the safety and efficacy of resmetirom in patients with NASH/MASH. It was an early, explorative study.

Patient population:

The study population to be included had to have suspected or confirmed NASH/MASH diagnosis by historical data, or with current concomitant conditions and non-invasive assessments. For inclusion, patients had to have $\geq 10\%$ liver fat content on MRI-PDFF, as well as biopsy proven NASH/MASH within 180 days of randomization with fibrosis stage 1 to 3 and a NAS of ≥ 4 with at least a score of 1 in each of the NAS components. Patients not fulfilling any of the single component conditions could also be included but only up to 10% of the total population. Alcohol use was excluded at a level of 20 g/week for women and 30 g/week in men.

The study population was therefore not compliant with the population generally considered at risk for disease progression, since a correlation to liver outcomes has only been shown for fibrosis stage 2 and above. Also, a lower threshold for the single NAS components were applied than required by the (then) draft reflection paper. This underlines the explorative nature of the study.

Study design:

In this study, patients were randomised 2:1 to a 36-week treatment of either 80 mg resmetirom or placebo. Following 12 weeks of treatment, the primary endpoint, percent change from baseline in hepatic fat fraction measured by MRI-PDFF, was evaluated. At 36 weeks, all patients underwent a liver biopsy.

After a PK assessment at Week 2 patients were assigned new doses at Week 4 according to the AUC cut-off at 5500 ng·hr/mL (for resmetirom and its metabolite MGL-3623). Patients remaining below this

threshold continued on 80 mg, and those above the threshold then received 60 mg. For those being even below a threshold of 3000 ng·hr/ml and being predicted to remain below the other threshold (of 56500 ng·hr/ml when receiving 100 mg, were then switched to 100 mg. Patients even being at an exposure of >11,000 ng·hr/mL plus an SHBG increase of more than 150% were down-titrated to 40 mg at Week 4. If SHBG increase was less than 150%, these patients were down-titrated to 60 mg.

The threshold of 5500 ng·hr/ml has been chosen on the fact that a combined MGL-3196 and MGL-3196-M1 exposure ≤ 5500 ng·hr/mL has not demonstrated a drug-related decrease in free T4 (FT4) to below the lower limit of normal (LLN) (<0.7 ng/dL) in Phase 1 studies. During the study further down-titration rules applied according to changes in TSH and FT3.

Within 60 days of completion of the main study Week 36 Visit, patients who meet Inclusion Criteria #9 (referring to the availability of efficacy evaluations) were eligible to participate in an extension phase of the study for an additional 36 weeks of treatment. The extension study was initially blinded to treatment group, but the extension study will become unblinded at the time of completion of the main study.

During the Extension Study, based on additional safety results from the Main Study, all Extension Study patients had doses adjusted to at least 80 mg per day, and several Extension Study patients took 100 or 120 mg per day.

The study design was considered rather complicated, and the switching of the doses according to criteria not related to efficacy or safety does not really allow a sensible evaluation of efficacy and safety according to different doses. Rather the study was giving input for the modelling exercises, which were concluded to support the final proposed doses used in the pivotal trial.

Study objective/endpoints

The primary objective (and endpoint) of the study was to determine the effect of resmetirom 80 mg vs placebo on percent change in hepatic fat fraction (MRI-PDFF) after 12 weeks of treatment in patients with biopsy-proven NASH/MASH.

Secondary objectives included safety and tolerability, changes in MR-PDFF after 36 weeks, responder type-evaluations of MR-PDFF (threshold 30%) reductions after 12 and 36 weeks, changes in CRP, ALT, LDL-C and other serum lipids, and the biomarkers CK-18, FIB4, and ELF also after 12 and 36 weeks. In addition, after 36 weeks, NASHG biopsy response was evaluated, according to the following criteria (among others):

- number and percentage of patients achieving a 1-point reduction in NAS
- number and percentage of patients achieving a 2-point reduction in NAS
- number and percentage of patients achieving a 2-point reduction in NAS at 36 weeks; and either ≥ 1 -point reduction in lobular inflammation or ≥ 1 -point reduction in hepatocellular ballooning
- number and percentage of patients achieving a 2-point reduction in NAS and no worsening of fibrosis
- NAS component responders (ballooning, steatosis and lobular inflammation)
- Fibrosis responders (1 stage reduction; 1 stage reduction and no worsening of NAS, 2-stage reduction)

Further objectives included the evaluation of Quality of Life, glucose homeostasis (fasting glucose, insulin, HOMA-IR, HbA1c), and effects of body weight, BMI, blood pressure and waist circumference. The exploration of the relationship between plasma resmetirom exposure and changes in safety and efficacy parameters was included as exploratory/tertiary objective.

Statistics

The protocol defined first of all the populations to be analysed with the ITT population defined as all patients who are randomized to the study and receive at least 1 dose of study drug, and the Per-Protocol population defined as all ITT patients who finish the Week 12 visit with valid PDFF-MRI measurements and do not have major protocol deviations.

The primary efficacy variable was to be analysed using an ANCOVA model. Normality was to be tested for the model residuals. For certain efficacy variables (such as hsCRP and triglycerides), logarithm transformation has been performed prior to fitting the ANCOVA model.

The sample size calculation was based on the assumption of a 30% decrease in PDFF compared to placebo with active treatment and requested a power of 90%, a significance level at 0.025 (considering 2 dosing regimens). With a 10% drop-out rate, 117 patients were to be recruited. A confirmatory approach was not included for the biopsy data evaluation.

Results:

One hundred and twenty-five (125) patients from 18 sites were randomized in a 2:1 manner to receive MGL-3196 (n=84) or placebo (n=41). All 125 patients were included in the ITT and Safety Populations, 118 patients were included in the mITT Population analysis for biomarkers, 116 patients were included in the MRI-PDFF Evaluable population.

Overall, 3 and 6 patients in the placebo and active groups discontinued treatment up to week 12, and 4 more in each of the treatment groups discontinued treatment before week 36. Finally, 34 and 74 patients had a liver biopsy at the end of the blinded treatment period (of which 1 was inadequate).

Thirty-one out of 38 eligible patients (14 of 19 placebo and 17 of 19 MGL-3196-treated) from 12 sites from the Main Study signed an ICF to participate in the Extension Study; all received active treatment in the Extension Study.

During the study, most patients were treated with the doses 60 mg and 80 mg.

The included study population was comparable with regard to their baseline characteristics and had a mean age of about 50 years, with only 8% above the age of 65. Both sexes were represented equally. The mean baseline weight of the patients was almost 100 kg with a BMI of 35.07 kg/m².

About 40% of the population had T2DM. The evaluation of baseline MASH features showed that most patients had no or mild fibrosis only, with 25% and 20% having fibrosis stage 2 and 3. The baseline MRI-PDFF was 20.05%, and about half of the population had NAS>5. The population was therefore not fully matching a target population of patients with moderate or significant fibrosis (F2/F3).

The following table shows the results of the primary evaluation, as well as the different responses according to dose groups (however, related to exposure, not to the dose administered), and according to PD response (based on SHBG), baseline fibrosis stage, and degree of weight loss:

Table 15. Percent Change in MRI Proton Density Fat Fraction from Baseline to Week 12 – Main Study (MRI-PDFF Evaluable Population)

	n	Placebo, % (SE)	n	MGL-3196, % (SE)	LS mean difference from baseline (95% CI)	p value
Week 12 relative to baseline	38	-10.4% (4.3)	78	-32.9% (3.0)	-22.5% (-32.9, -12.2)	<0.0001
High exposure group			44	-39.7% (3.9)	-29.3% (-40.6, -18.0)	<0.0001
Low exposure group			34	-24.1% (4.4)	-13.8% (-25.8, -1.7)	0.025
High SHBG Group			48	-38.7% (3.7)	-28.3% (-39.4, -17.2)	<0.0001
Low SHBG Group			30	-23.7% (4.7)	-13.3% (-25.8, -0.8)	0.037
Fibrosis Stage 0-1	19	-14.0% (6.6)	45	-34.3% (4.3)	-20.3% (-36.1, -4.5)	0.0127
Fibrosis Stage 2-3	19	-7.1% (5.3)	33	-30.9% (4.0)	-23.7% (-37.0, -10.5)	0.0007
<5% weight loss	31	-3.8% (4.5)	70	-31.5% (3.0)	-27.8% (-38.4, -17.1)	<0.0001
≥5% weight loss	7	-36.4 (10.5)	8	-47.9 (9.7)	-11.5% (-44.0, 20.9)	0.4542

AUC = area under the plasma concentration-time curve; CI = confidence interval; LS = least squares; SE = standard error; SHBG = sex hormone binding globulin.

Note: The high exposure group consisted of individuals with 2700 ng·hr/mL or more estimated AUC, and the low exposure group consisted of individuals with an estimated AUC of less than 2700 ng·hr/mL. The high SHBG group consisted of individuals with 75% or greater change from baseline at Week 12. Exposure and SHBG groups were prespecified on the basis of blinded data and compared with all placebo patients (Week 12 n=38, Week 26 n=34).

Source: CSR MGL-3196-05, Section 14, [Tables 14.2.1.2.1, 14.2.1.2.2, 14.2.1.2.3, 14.2.1.2.5, 14.2.1.2.9](#)

Similar hepatic fat reductions compared with baseline and with placebo were observed at 36 weeks as were observed for the primary efficacy endpoint at Week 12. MGL-3196-treated patients (n=78) demonstrated a relative reduction (%) of hepatic fat compared with placebo (n=38) at Week 36 (-37.3% MGL-3196 (n=74), -8.9% placebo (n=34); -28.4% (-41.3%, -15.4%), p<0.0001).

The evaluation of the “responder” evaluation regarding MRI-PDFF reductions resulted in the following:

Table 16. Proportion of Patients with at Least 30% Fat Reduction at Weeks 12 and 36 – Main Study

		Placebo, n (%)	n	MGL-3196, n (%)	Odds ratio (95% CI)	P value
Week 12 $\geq$30% fat reduction	38	7 (18.4)	78	47 (60.3)	6.8 (2.6, 17.6)	<0.0001
High exposure group			44	33 (75.0)	13.8 (4.6, 40.9)	<0.0001
Low exposure group			34	14 (41.2)	3.08 (1.0, 9.1)	0.042
High SHBG Group			48	31 (64.6)	8.33 (3.0, 23.3)	<0.0001
Low SHBG Group			30	16 (53.3)	4.99 (1.7, 15.0)	0.0043
Fibrosis Stage 0-1	19	5 (26.3)	45	27 (60.0)	4.4 (1.2, 15.9)	0.023
Fibrosis Stage 2-3	19	2 (10.5)	33	20 (60.6)	14.61 (2.7, 78.0)	0.0017
<5% weight loss	31	2 (6.5)	70	41 (58.6)	27.9 (5.5, 142.2)	<0.0001
$\geq$ 5% weight loss	7	5 (71.4)	8	6 (75.0)	2.9 (0.2, 53.3)	0.47
Week 36 $\geq$30% fat reduction	34	10 (29.4)	74	50 (67.6)	4.9 (2.0, 11.9)	0.0006
High exposure group			43	32 (74.4)	6.9 (2.5, 19.3)	0.0002
Low exposure group			31	18 (58.1)	3.1 (1.1, 8.9)	0.032
High SHBG Group			44	34 (77.3)	8.3 (2.9, 23.5)	<0.0001
Low SHBG Group			30	16 (53.3)	2.5 (0.9, 7.2)	0.084
Fibrosis Stage 0-1	16	6 (37.5)	43	29 (67.4)	3.1 (0.9, 10.7)	0.069
Fibrosis Stage 2-3	18	4 (22.2)	31	21 (67.7)	7.3 (1.9, 28.6)	0.0040

AUC = area under the plasma concentration-time curve; CI = confidence interval; SHBG = sex hormone binding globulin.

Note: The high exposure group consisted of individuals with 2700 ng·hr/mL or more estimated AUC, and the low exposure group consisted of individuals with an estimated AUC of less than 2700 ng·hr/mL. The high SHBG group consisted of individuals with 75% or greater change from baseline at Week 12 and 88% or greater change from baseline at Week 36. Exposure and SHBG groups were prespecified on the basis of blinded data and compared with all placebo patients (Week 12 n=38, Week 26 n=34).

Populations included the MRI-PDFF Evaluable Population and mITT Population - LOCF.

Multiple atherogenic lipids and lipoproteins were statistically significantly reduced with MGL-3196 therapy compared to placebo. Transaminase reductions were seen in both treatment groups, with overall higher reductions in the actively treated groups and with nominally statistically significant changes achieved at Week 36.

Assessments of non-invasive fibrosis markers ELF and PRO-C3, which are markers of collagen formation and fibrogenic activity, showed statistically significant decreases at 12 and 36 weeks with MGL-3196 treatment compared with placebo (Week 36: PRO-C3, -21.4 ng/mL, p=0.003; ELF -0.48, p=0.017). Serum CK-18 fragments, detected using the M30 antibody, may reflect hepatocyte apoptosis, were statistically significantly reduced within group at Week 12 and 36 and relative to placebo at Week 36. Concentrations of adiponectin, an adipokine associated with hepatic health, were increased, and reverse T3, a marker of hepatic inflammation, was decreased by MGL-3196 treatment.

On liver biopsy, features of MASH were reduced with MGL-3196 therapy. NAS was reduced in MGL-3196-treated patients compared with placebo-treated patients, particularly in patients with higher MGL-3196

exposure. The results are shown in the following table again with evaluation of the relevant study group (based on patients with paired biopsies):

Table 17. Biopsy Responder Analyses – Main Study (mITT Population – Subjects with Post-Baseline Liver Biopsy) – Study 05

	n	Placebo n (%)	n	MGL-3196 n (%)	Odds Ratio (95% CI)	p value
≥1-point NAS reduction	34	22 (64.7%)	73	56 (76.7%)	1.8 (0.7, 4.4)	0.24
High exposure group			43	37 (86.0%)	3.4 (1.1, 10.2)	0.034
Low exposure group			30	19 (63.3%)	0.9 (0.3, 2.6)	>0.9999
High SHBG group			44	37 (84.1%)	2.9 (1.0, 8.4)	0.064
Low SHBG group			29	19 (65.5%)	1.0 (0.4, 2.9)	>0.9999
MRI-PDFF Responders			46	41 (89.1%)	4.5 (1.4, 14.3)	0.012
<5% weight loss	27	15 (55.6%)	61	45 (73.8%)	2.3 (0.9, 5.8)	0.14
≥2-point NAS reduction	34	11 (32.4%)	73	41 (56.2%)	2.7 (1.1, 6.3)	0.024
High exposure group			43	28 (65.1%)	3.9 (1.5, 10.1)	0.0059
Low exposure group			30	13 (43.3%)	1.6 (0.6, 4.4)	0.44
High SHBG group			44	28 (63.6%)	3.7 (1.4, 9.4)	0.012
Low SHBG group			29	13 (44.8%)	1.7 (0.6, 4.7)	0.44
MRI-PDFF Responders			46	32 (69.6%)	4.8 (1.8, 12.4)	0.0014
<5% weight loss	27	5 (18.5%)	61	30 (49.2%)	4.3 (1.4, 12.7)	0.0090
≥2-point NAS reduction with ≥1-point reduction in lobular inflammation or hepatocellular ballooning	34	11 (32.4%)	73	37 (50.7%)	2.2 (0.9, 5.0)	0.096
High exposure group			43	26 (60.5%)	3.2 (1.2, 8.2)	0.021
Low exposure group			30	11 (36.7%)	1.2 (0.4, 3.4)	0.79
High SHBG group			44	25 (56.8%)	2.8 (1.1, 7.0)	0.041
Low SHBG group			29	12 (41.4%)	1.5 (0.5, 4.1)	0.60
MRI-PDFF Responders			46	30 (65.2%)	3.9 (1.5, 10.0)	0.0063
<5% weight loss	27	5 (18.5%)	61	28 (45.9%)	3.7 (1.3, 11.2)	0.017
≥2-point NAS reduction and no worsening of fibrosis	34	11 (32.4%)	73	33 (45.2%)	1.7 (0.7, 4.1)	0.29
High exposure group			43	24 (55.8%)	2.6 (1.0, 6.7)	0.065
Low exposure group			30	9 (30.0%)	0.9 (0.3, 2.6)	>0.9999
High SHBG group			44	20 (45.5%)	1.7 (0.7, 4.4)	0.26
Low SHBG group			29	13 (44.8%)	1.7 (0.6, 4.7)	0.44
MRI-PDFF Responders			46	27 (58.7%)	3.0 (1.2, 7.5)	0.025
<5% weight loss	27	5 (18.5%)	61	23 (37.7%)	2.7 (0.9, 8.0)	0.087
NASH Resolution (without fibrosis worsening) (%)	31	2 (6.5%)	73	18 (24.7%)	4.75 (1.03, 21.9)	0.032
MRI-PDFF Responder	31		46	17 (37.0%)	8.50 (1.80, 40.2)	0.0026
Including weight loss >9.5%	34	5 (14.7%)	73	18 (24.7%)	1.9 (0.64, 5.6)	0.32
MRI-PDFF Responder (including weight loss >9.5%)	31			17 (37.0%)	3.4 (1.1, 10.4)	0.042
Fibrosis Responder (%)	34	8 (23.5%)	73	21 (28.8%)	1.3 (0.51, 3.36)	0.65
MRI-PDFF Responder			46	15 (32.6%)	1.6 (0.58, 4.29)	0.46
NASH Resolution Responder			18	11 (61.1%)	5.1 (1.5, 17.6)	0.014

CI = confidence interval; MRI-PDFF = proton density fat fraction magnetic resonance imaging; NAS = non-alcoholic fatty liver disease activity score; NASH = non-alcoholic steatohepatitis; SHBG = sex hormone binding globulin.

Note: Unless otherwise specified, MRI-PDFF responders are patients treated with MGL-3196 with ≥30% decrease in hepatic fat at Week 12, fibrosis responders are patients with one stage or more reduction in fibrosis and no worsening of NAS, NASH resolution is ballooning score of 0 and inflammation score of 0 or 1, with at least a 2-point reduction in NAS and no worsening of fibrosis (assessed in patients with <9.5% weight loss), and NASH resolution responders were patients with NASH resolution with at least a 2-point reduction in NAS and no worsening of fibrosis (MGL-3196 treatment group only).

The evaluations of quality of life showed that a response could be achieved in the domains bodily pain, physical functioning, vitality, and mental health for those that were responders in the MRI-PDFF evaluation.

The 36-week exploratory Extension Study was conducted in patients with NASH/MASH predicted to have an incomplete response to either placebo or resmetirom treatment in the main 36-Week study based on residual minimally to markedly elevated liver enzymes (ALT and/or AST) at the end of the Main Study.

The Extension Study provided an opportunity to determine whether increasing the dose of resmetirom from 60 mg to at least 80 mg in patients who received resmetirom since the study start (Res/Res) patients and/or switching to resmetirom treatment in patients who were on placebo in the Main Study (Pbo/Res) would improve the biomarker and MRI-PDFF responses. As reported above, only a minority of the patients was included. The main results are shown in the following table:

Table 18. Change in MRI-PDFF – Extension Study (All Patients Enrolled in the Extension Study) – Study 05

	n	Pbo/Res Mean (SE)	P-Value	n	Res/Res Mean (SE)	P-Value	n	All Mean (SE)	P-value
Week 12 %CFB	13	-39.9 (4.2)	<0.0001	15	-33.5 (5.6)	<0.0001	28	-36.4 (3.6)	<0.0001
Week 36 %CFB	11	-52.0 (7.1)	<0.0001	15	-45.8 (5.1)	<0.0001	26	-48.4 (4.2)	<0.0001
Primary	11	-52.0 (7.1)	<0.0001	10	-52.6 (5.2)	<0.0001	21	-52.3 (4.4)	<0.0001
80 mg							19	-44.6 (4.9)	<0.0001
100 mg							7	-58.8 (6.8)	<0.0001
Week 12 CFB	13	-7.4 (1.4)	0.0002	15	-7.8 (1.8)	0.0006	28	-7.6 (1.1)	<0.0001
Week 36 CFB	11	-10.1 (2.0)	0.0005	15	-10.3 (1.7)	<0.0001	26	-10.2 (1.3)	<0.0001
Primary	11	-10.1 (2.0)	0.0005	10	-12.2 (2.2)	0.0003	21	-11.1 (1.5)	<0.0001
80 mg							19	-8.7 (1.5)	<0.0001
100 mg							7	-14.3 (1.9)	0.0003

CFB = change from baseline; MRI-PDFF = proton density fat fraction-magnetic resonance imaging; OLE = open label extension; Pbo = placebo; Res = MGL-3196/resmetirom; SE = standard error

Note: Baseline is defined as the value at the main study screening visit for Res/Res patients and main study Week 36 for former Pbo/Res patients. Week 12 and 36 are OLE Week 12 and 36, respectively. Patients with >9.5% weight loss or gain from baseline to OLE Weeks 12 and 36 and patients who are not compliant were excluded from the respective analyses. The means, standard errors, and P values come from a paired t test.

2.6.5.2. Main study

Study MGL-3196-11

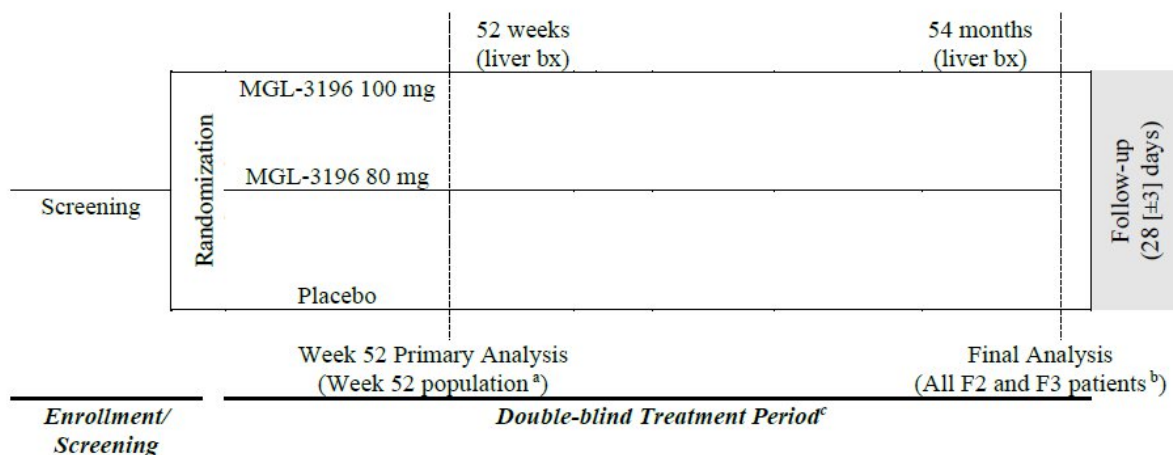
A Phase 3, Multinational, Double-Blind, Randomized, Placebo-Controlled Study of MGL-3196 (Resmetirom) in Patients With Non-Alcoholic Steatohepatitis (NASH) and Fibrosis to Resolve NASH and Reduce Progression to Cirrhosis and/or Hepatic Decompensation

Methods

The study is a three-arm, randomised, double-blind, placebo controlled, multi-centre study. The study was conducted in 245 sites across 15 countries between 20 Jun 2019 (first patient enrolled) and (last patient completed for interim evaluation) 31 Jul 2022. The randomisation was to be stratified by type-2 diabetes status (presence/absence) and fibrosis stage (1, 2, or 3) based on eligibility biopsy read of fibrosis stage score. The trial is presented with the first interim evaluation after 52 weeks of treatment. The study was planned to be continued and experience a further interim analysis when 110 composite clinical outcomes

have occurred, and a final analysis thereafter. The overall design and study plan is shown in the following figure:

Figure 10. Study schema – Study 11



• Study participants

Study patients were to be included based on at least 3 out of 5 metabolic risk factors (waist circumference, body mass index, dyslipidaemia, arterial hypertension, and T2DM). Alcohol consumption was excluded with not more than 2 alcoholic drinks per day for males, and 1.5 drinks per day for females. Furthermore, patients had to have either elevated transaminases, or a FibroScan based VCTE ≥ 8.5 kPa and CAP ≥ 280 as well as a historic liver biopsy less than 2 years old demonstrating fibrosis stage 1B, 2 or 3 with MASH. These criteria were rather applied as screening tools. The inclusion criteria in the strict sense included the following:

Suspected or confirmed diagnosis of MASH fibrosis suggested by the historical data. Meet one of the following criteria that is consistent with MASH liver fibrosis:

- Historical biochemical test for fibrosis: PRO based on a historic value and is not obtained at screening; PRO-C3 >14 ng/ml; or ELF ≥ 9 (ELF is based on a historic value and is not obtained at screening; PRO-C3 is based on historic PRO-CE and not the screening PRO-C3).
- FibroScan with transient elastography of ≥ 8.5 kPa; and controlled attenuation parameter ≥ 280 db $\times$ m⁻¹. (FibroScan does not need to be repeated if done at pre-screening and/or a historical FibroScan was done in the prior 3 months).

Historical liver biopsy obtained <2 years before expected randomization showing Stage 1B, 2 or 3 fibrosis with MASH based on existing pathology review, with no significant change in body weight $>5\%$ or medication that might affect NAS or fibrosis stage

MRI-PDFF fat fraction $\geq 8\%$ obtained during the screening period (baseline MRI-PDFF)

Biopsy proven MASH (baseline liver biopsy) based on a liver biopsy obtained ≤ 6 months before anticipated date of randomisation (if the biopsy is deemed acceptable for interpretation by the central reader) with fibrosis stage 1A/1C, 1B, 2, or 3 on liver biopsy and MASH of ≥ 4 with a score of 1 in each of the individual components (steatosis, ballooning, and lobular inflammation). Fibrosis stage 1A/1C patients

must also have elevated PRO-C3 (>14 ng/mL) obtained at screening to be eligible to participate. Additional numbers for restrictions to stage 1 patients apply (see above).

Biopsies were read on glass slides for eligibility at the time of screening (Baseline biopsies) by one of two central histopathologists. These slides were re-read for the primary analysis beginning around 6 months prior to the 31 Jul 2022 database lock by each of the two central pathologists in large groups of baseline glass slides (50-100 slides per group including a few which were from biopsy screen failures). Approximately 10-12 groups of baseline and Week 52 slides were prepared by an unblinded CRO Excilone, which also digitized all of the slides. In a secondary read, pairs of digitized slides containing a baseline and Week 52 from the same patient were read by the two central pathologists.

Exclusion criteria comprised a history of significant alcohol consumption, use of drugs associated with MASLD, active hyperthyroidism, history of bariatric surgery, recent weight gain or loss, uncontrolled T2DM, GKP-1 or vitamin E therapy unless stable for the last 6 months, presence of cirrhosis, MELD score >12, and presence of other relevant liver disease, or active autoimmune disease.

The applicant initially included the F1B population into the primary analysis population, arguing that the F1B population appeared to be similarly advanced to F2, with moderate fibrosis.

Moreover, the F1B population was shown to have at least as high if not higher rate of progression to F3 than F2 patients in the placebo arm by each pathologist, possibly because the F1B population had a higher rate of diabetes that would lead to higher rates of progression (*Rinella, Neuschwander-Tetri, et al. 2023*).

However, multiple epidemiological data available demonstrate that the correlation of liver outcomes with fibrosis stage 1 is not significant (while this is the case for F2-F4), which was the reason that the reflection paper also clearly recommends the inclusion of patients with moderate or more severe fibrosis only. The F1B population was thus excluded from the primary analysis and the approved indication only refers to F2/F3 population.

- **Treatments**

Patients who qualified for study inclusion were randomized in a 1:1:1 manner to receive 80 or 100 mg resmetirom tablets or matching placebo to be administered orally once daily in the morning for up to 54 months.

Study patients and site personnel who administered the study drug and performed the clinical assessments on patients were blinded to individual patient treatment assignments (resmetirom or placebo). Select individuals were not blinded to patient treatment assignments to facilitate operations (e.g., to prepare Data Monitoring Committee [DMC] materials); these individuals were not otherwise involved in the study. Results of several laboratory tests (e.g., SHBG, lipids, FT4), were blinded to study personnel and Investigators during the study to preserve the blind.

A Blinding/Unblinding Plan document detailed how the blind was to be maintained throughout the study. The Week 52 Primary Analysis was conducted by an unblinded team. The team comprised representatives of the applicant and the CRO not otherwise involved in study management at the time of the 52-week analysis.

Study medication was provided at the (active treatment) doses of 60 mg, 80 mg, or 100 mg. In patients assigned to 80 mg or 100 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 2 consecutive regularly scheduled visits 4 weeks apart, specifically, at Weeks 4 and 8. In patients assigned to the 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 was further decreased to 60 mg at Week 24. No dose reductions were made later than Week 24 and the dose was not reduced to <60 mg. No rescue therapy was given to the patients, since no approved treatment for MASH is available.

- **Objectives**

The primary objective of the trial was

1. to determine the effect of once-daily, oral administration of 80 or 100 mg resmetirom versus matching placebo on NASH, as measured by:

The resolution of NASH associated with an at least 2-point reduction in NAFLD activity score (NAS) and without worsening of fibrosis by liver biopsy after 52 weeks of treatment (Week 52 Primary Endpoint) in the Week 52 Livery Biopsy Modified Intent-to-Treat (mITT) Population.

Resolution included:

- The total absence of ballooning (score = 0) and absent or mild lobular 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 was not considered 1-stage worsening.

And

2. to determine the effect of once-daily, oral administration of 80 or 100 mg resmetirom versus placebo on the histological improvement from Baseline demonstrated by at least a 1-point improvement in fibrosis (NASH Clinical Research Network [CRN] system) by liver biopsy with no worsening of NAS (total of 3 NAS components: ballooning, lobular inflammation, and steatosis) at Week 52. For F1B patients, a 1-point improvement in fibrosis was a change to F0. For F2 patients, a 1-point improvement in fibrosis was a change to F1A or F1C (a change of F2 to F1B was not considered a 1-point improvement).

- **Outcomes/endpoints**

The primary endpoints were defined accordingly with the following specifications:

A "NASH Resolution Responder" was defined as ballooning = 0, lobular 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.

A "Fibrosis Responder" in this study was defined as at least a 1-point reduction in fibrosis stage with no worsening of (total) NAS as compared with the baseline liver biopsy.

While the study report is reporting the week 52 evaluations only, the protocol for the study does of course also include the objectives and endpoints for the final evaluation (planned to be at month 54). This objective was defined as adjudicated Composite Clinical Outcome with the following:

Clinical Outcome is composed of all-cause mortality, liver transplant, and significant hepatic events (including hepatic decompensation events [ascites, encephalopathy, or gastroesophageal variceal haemorrhage], histological progression to cirrhosis, and a confirmed increase of MELD score from <12 to ≥ 15).

The definition of the primary objectives as well as the corresponding primary endpoints mostly comply with the requirements of the reflection paper on NASH and even includes a somewhat increased

requirement for the definition of a “NASH resolution responder” since the requirement also includes a 2-point reduction of NAS.

The use of the NAS-CRN system for the evaluation of histology is considered “standard” and therefore acceptable.

Estimands

For Week 52 primary endpoints, the clinical question/estimand addressed concerns the difference between resmetirom and placebo for the treatment of biopsy-proven NASH (fibrosis stage F1B, F2, or F3) in the proportion of patients who achieved NASH resolution response (fibrosis response) at Week 52 without dying or experiencing a liver related clinical outcome event regardless of treatment discontinuation or other changes in medication, diet, exercise or alcohol consumption. This was overall agreed and in line with respective guidance. The primary analysis excluded the F1B population, as requested by CHMP.

The clinical question/estimand addressed for the key secondary endpoint concerns the difference between resmetirom and placebo for the treatment of biopsy-proven NASH (fibrosis stage F1B, F2, or F3) in the mean percent change in LDL-C at Week 24 had supply of medication not been hampered by COVID-19 pandemic and regardless of experiencing a composite clinical outcome event, treatment discontinuation or other changes in medication, diet, exercise or alcohol consumption.

Secondary Outcomes/endpoints

The secondary objectives/endpoints included a couple of histology-based evaluations such as:

- 2-point improvement in NAS with at least 1-point improvement in ballooning or lobular inflammation without worsening of fibrosis At least a 2-point improvement in NAS with at least 1-point improvement in ballooning or lobular inflammation and at least a 1-point improvement in fibrosis.
- An improvement in each histologic NAS component (ballooning, lobular inflammation, steatosis) by at least one point; or improvement by at least one point in both ballooning and lobular inflammation with a magnetic resonance imaging (MRI)- proton density fat fraction (PDFF) response ($\geq 30\%$ relative fat reduction) at Week 16 or at Week 52 if no data were available at Week 16.
- The above with no worsening of fibrosis.
- The resolution of fibrosis (reduction to F0).
- 2-stage Fibrosis Responders (a ≥ 2 -point reduction in fibrosis patients with no worsening of NAS) in patients with baseline fibrosis $\geq F2$.
- A composite of NASH/MASH Resolution Responder and Fibrosis Responder.
- No worsening of fibrosis, defined as any progression ≥ 1 stage (for F1B patients, a change to F2 was not considered worsening).

Furthermore, these included the changes in each component of the NAS score.

There were a couple of endpoints referring to the presence of certain conditions, which were not to be evaluated in the total population. These comprised the following:

MR-PDFF based evaluations:

- Relative and absolute changes in MRI-PDFF and evaluation of $\geq 30\%$ or $\geq 50\%$ relative reduction of hepatic fat fraction by MR-PDFF with post-baseline MR-PDFF available
 - The effect on "conventional" liver biomarkers such as ALT, AST, and GGT in those with baseline ALT ≥ 30 IU/L

The following serum lipid evaluations were defined as secondary endpoints also:

- Changes from baseline in LDL-C (the 24-weeks changes was defined as "key secondary"), apolipoprotein B (ApoB), triglycerides (in patients with baseline triglycerides > 150 mg/dL), apolipoprotein C-III (ApoCIII), non-HDL-C, and lipoprotein(a) (Lp[a]; in patients with baseline Lp[a] > 10 nmol/L. Additional evaluations were to be conducted on those with elevations of baseline thresholds.

The following general MASH-related biomarkers were also defined as secondary endpoints:

Reverse T3, cytokeratin-18 (CK-18), adiponectin, N terminal type III collagen propeptide (PRO-C3; baseline ≥ 36 ng/mL), and enhanced liver function (ELF) test with 3 direct components (ELF baseline ≥ 9.8 ; amino-terminal propeptide of type III procollagen (PIIINP) ≥ 9 μ g/L; tissue inhibitor of matrix metalloproteinases-1 (TIMP-1) ≥ 240 μ g/L; hyaluronic acid (HA) ≥ 50 μ g/L.

Further objectives comprised effects on quality of life (QOL), as assessed by the NAFLD/MASLD//NASH/MASH Chronic Liver Disease Questionnaire (CLDQ), the Short Form Liver Disease Quality of Life (SF-LDQOL), and the Work Productivity and Activity Index (WPAI)-NASH.

Effects on fibrosis based on MRE with evaluation of the number and percentage of patients with $\geq 19\%$ reduction from baseline and on the number and percentage of patients with $\geq 19\%$ increase from baseline in patients with baseline MRE as ≥ 2.9 kPa. F3, F1B, and F2 were assessed separately.

Effects on fibrosis based on the number and percentage of patients with a $\geq 25\%$ and $\geq 30\%$ reduction and a $\geq 25\%$ and $\geq 30\%$ worsening from baseline in FibroScan vibration controlled transient elastography (VCTE) over time. F3, F1B, and F2 were assessed separately.

In addition, the change from baseline in FibroScan determined CAP, percent change in liver and spleen volume (determined with "conventional" ultrasound) were also evaluated.

There was a multitude of "explorative" endpoints referring to the following:

Histological evaluations according to the SAF score, AI based pathology evaluations using the Path AI tool "AIM-NASH" as well as the "Second Harmonic Generation Microscopy (Histoindex)", changes in MR based evaluation of CT1, markers of insulin resistance, body weight and BMI, blood pressure and heart rate, bone mineral density, evaluation of MACE events, and DILI events and others.

The secondary endpoints were mostly considered acceptable and relevant. Some of these were regarded to more clearly relate to the evaluation of safety, rather than efficacy, which was most obvious in the definition of the key secondary endpoint for the LDL-C.

No estimands were explicitly defined for other secondary/exploratory endpoints which was regrettable, since some of them would be considered clinically more relevant than the "key" secondary endpoint.

- **Sample size**

This study was planned to enrol 2000 patients. The sample size calculations were performed based on the original study design. Several changes in study design affecting e.g. population, type 1 error and primary endpoint (dual instead of single primary endpoint at Week 52) could have impact the power of the study.

For the purposes of this Week 52 interim analysis, the sample size was estimated using a 2-sided, $\alpha=0.01$ CMH test to provide 95% power for testing each resmetirom dose vs placebo. A placebo response rate of 8% and resmetirom response rates of 22% were assumed for both dose levels. Assuming up to 10% of dropouts to be counted as non-responders, a minimum of 780 total patients was needed (260 in each arm) to reach the desired power of 95% per dose comparison.

- **Randomisation and Blinding (masking)**

Eligible patients were randomized in a 1:1:1 manner to receive 80 or 100 mg resmetirom tablets or matching placebo to be administered orally once daily in the morning for up to 54 months. The randomization was stratified by Baseline type-2 diabetes status (presence/absence) and fibrosis stage (1, 2 or 3).

Study patients and site personnel who administered the study drug and performed the clinical assessments on patients were blinded to individual patient treatment assignments (resmetirom or placebo). Select individuals were not blinded to patient treatment assignments to facilitate operations (e.g., to prepare Data Monitoring Committee [DMC] materials); these individuals were not otherwise involved in the study. Results of several laboratory tests (e.g., SHBG, lipids, FT4), were blinded to study personnel and Investigators during the study to preserve the blind.

A Blinding/Unblinding Plan document detailed how the blind was to be maintained throughout the study. The Week 52 Primary Analysis was conducted by an unblinded team. The team comprised representatives of the applicant and the CRO not otherwise involved in study management at the time of the 52-week analysis.

- **Statistical methods**

Specification of the statistical analysis was not straightforward and has changed during the course of the trial - also close to and after unblinding.

There were a number of amendments in the protocol and the SAP. According to the applicant the change in FDA's position in later interaction phases led to the late amendments (v 1.0 after data cut off on 31 Jul 2022 and v 2.0 after database lock on 18 Nov 2022) of the SAP and protocol.

SAP 3.0 which was used for the Week 52 analysis was approved on 05 Dec 2022 after unblinding of patient treatment assignment at the CRO on 02 Dec 2022. This is generally considered of serious concern and questions proper pre-specification, given the substantial changes in the analysis as compared to the original study protocol. It is noted that changes to SAP 3.0 compared to prior versions which were finalized prior to unblinding any data, appear to be related to clarifying language about patients that were reevaluated as having fibrosis stage 4 at baseline. The analysis of confirmatory endpoints was not impacted aside from changes in the population to be evaluated with respect to fibrosis stage. This is however not considered of concern, as the F2/F3 population is considered the relevant one. The overall planning and conduct (late amendments and handling of SAP) raises some concern and is highly unusual and in part lacks GCP compliance. Still, the risk associated with the reliability of the study data and results

in particular for multiplicity-controlled Week 52 endpoints is considered low. Analyses of these endpoints can still be considered sufficiently pre-specified. However, this issue contributed to the need for requesting additional data as a condition for the CMA.

In addition, the current protocol version refers to the SAP only, which is not in line with standard GCP guidance (see ICH E6), and concerning given that the analyses described in the SAP should follow those in the study protocol.

The following description of the analysis pertains to SAP 3.0 version.

Analysis sets

The following analysis sets were defined, which were overall agreed. The analysis was presented on the population of F2/F3, in line with the approved indication. Exclusion of patients with missing biopsy due to COVID-19 pandemic from the analysis set is questionable, however not considered of further concern given the low number of exclusions (11 in total).

- ~ The Intent-to-Treat (ITT) Population included all patients who were randomized in the study according to their randomized treatment assignment.
- ~ The Modified Intent-to-Treat (mITT) Population included all patients who were randomized in the study according to their randomized treatment assignment.
- ~ The Week 52 mITT Population included all patients in the mITT population that were randomized on or before 31 Jul 2021.
- ~ The Week 52 Liver Biopsy mITT Population was the subset of the Week 52 mITT Population that did not include patients who were missing a Week 52 biopsy due to the COVID-19 pandemic that resulted in study discontinuation and/or inability or delay (outside biopsy window) in obtaining the Week 52 biopsy.
- ~ The Week 52 Paired Liver Biopsy mITT Population included all patients in the Week 52 mITT Population who took at least one dose of study medication, had a Baseline liver biopsy, and finished the Week 52 visit with an acceptable liver biopsy.
- ~ The Week 52 Per-protocol (PP) Population included all patients in the Week 52 Paired Liver Biopsy mITT Population who did not have any protocol deviations that significantly impacted the interpretability of their data.
- ~ The Safety Population subset included all F1B, F2, and F3 patients in the ITT population who received at least 1 dose of study drug according to treatment actually received.

The Week 52 mITT Population was used for all Week 52 efficacy analyses that were not based on liver biopsies and the Week 52 Liver Biopsy mITT for all Week 52 efficacy analyses that were based on liver biopsies, including the dual primary endpoints. The Safety Population subset was used for all safety analyses.

Dual primary endpoints

Biopsies were read on glass slides for eligibility at the time of screening (Baseline biopsies) by one pathologist and were re-read for the primary analysis beginning around 6 months prior to the 31 Jul 2022 data cut-off by each of the two central pathologists in large groups of baseline glass slides (50-100 slides

per group including a few which were from biopsy screen failures). Definition of the analysis sets as well as the primary analysis was based on these biopsy re-reads and the eligibility read of the biopsy at screening was not used.

Two NASH Resolution Responder endpoints for each patient were derived from two independent pathologist readings – one from each pathologist's scores. While there is no way to determine whether the patient truly is a NASH Resolution Responder (or Non-Responder), it is reasonable to conclude that cases where both pathologists agree are more suggestive of a true Responder or Non-Responder. Cases where both pathologists disagree, outcomes land somewhere between Responder and Non-Responder. Based on these paired biopsy data (Pathologist A, Pathologist B), an ordinary score was calculated as 1 (both pathologists agree on response), 0.5 (pathologists disagree on response) and 0 (pathologists agree on non-response) and analysed with the Cochran-Mantel-Haenszel test accounting for the baseline diabetes and baseline fibrosis stage stratification factors. An estimate of the average of the two pathologist's difference of proportions was obtained by averaging the CMH estimates of the difference of proportions for each pathologist. Patients with missing biopsy or out of window biopsy were accounted for with non-response imputation. In line with the targeted estimand, patients who experienced a composite clinical endpoint prior to their Week 52 biopsy (e.g., liver transplant, death) were also considered non-responders. To assess the impact of variability of the histological evaluation on the study results, a sensitivity analysis assigning cases of differing evaluations of the two pathologists as non-response were also provided.

Primarily non-response imputation was used for analysis, which likely provides conservative estimates for the targeted estimand. To evaluate the uncertainty associated with imputed values, the applicant presented placebo-based multiple imputation analysis aligned to the targeted estimand (treatment policy strategy).

As sensitivity/supportive analysis, an evaluation based on a modified Consensus Model, a GEE model treating scores from the two pathologists as repeated measurements, an evaluation using missing-at-random-based multiple imputation, an evaluation treating a change from F1B to F2 as a 1-stage worsening of fibrosis stage, a *post-hoc* tipping point analysis, an observed case analysis, and an analysis based on secondary reads of digital biopsy images were also conducted. These analyses were overall supported, but the analysis based on the consensus read should be considered with caution, as the consensus read was in part done after unblinding.

Fibrosis response was evaluated using the same methodology used for the NASH Resolution Response.

Key secondary endpoint

For the key secondary endpoint (change from baseline to Week 24 in LDL-C), in line with the targeted estimand, missing values caused by shortages in medication due to COVID-19 were imputed by the valid measurement just before (or after) the missing visits. A similar single imputation approach was applied for several intermittent missing data in a row. Remaining missing data (e.g. following discontinuation) were handled with missing-at-random (MAR) based multiple imputation. While the latest SAP version 3.0 states that imputed data sets were analysed with a mixed model, results reported in the CSR are in fact based on an ANCOVA per visit accounting for treatment, baseline and stratification factors. This change was only mentioned in the table headings in the CSR. This clearly violates standard principles of trial reporting and supports issues of improper pre-specification, but is not considered of further concern, as MMRM (using an unstructured covariance matrix) and an ANCOVA will generally provide similar results. In addition, the applicant provided further analysis using J2R and CR approach discussed in *Carpenter et al (2013)* to ensure alignment with the targeted estimand.

Secondary endpoints

No estimand was defined for secondary endpoints, although it would have been useful given the clinical relevance of some of these endpoints. In most cases, evaluation of secondary endpoints was restricted to observed cases only or at least to those patients for which a baseline observation was available for the respective parameter. This was not supported as bias may be introduced and depending on the endpoint the amount of missing data is non-negligible. Furthermore, if an estimand similar to the ones defined for primary and key secondary objectives is applied, OC analysis is clearly not aligned to this.

For secondary endpoints of special clinical relevance (MR-PDFF, MRE, transaminases and GGT, CK-18, ELF-test and its components, and FibroScan VCTE and CAP), re-evaluations were requested that are based on the Week 52 mITT set (restricted to the F2/F3 population). Patients with missing data were requested not to be excluded from the analysis but rather handled with a proper approach: e.g. non-response imputation for binary data or placebo-based multiple imputation for continuous endpoints. However, although the different imputation methods have shown robust results overall, part of these parameters still suffer from the fact that only those patients with baseline data, or those with a baseline pathological value were included.

Multiplicity control

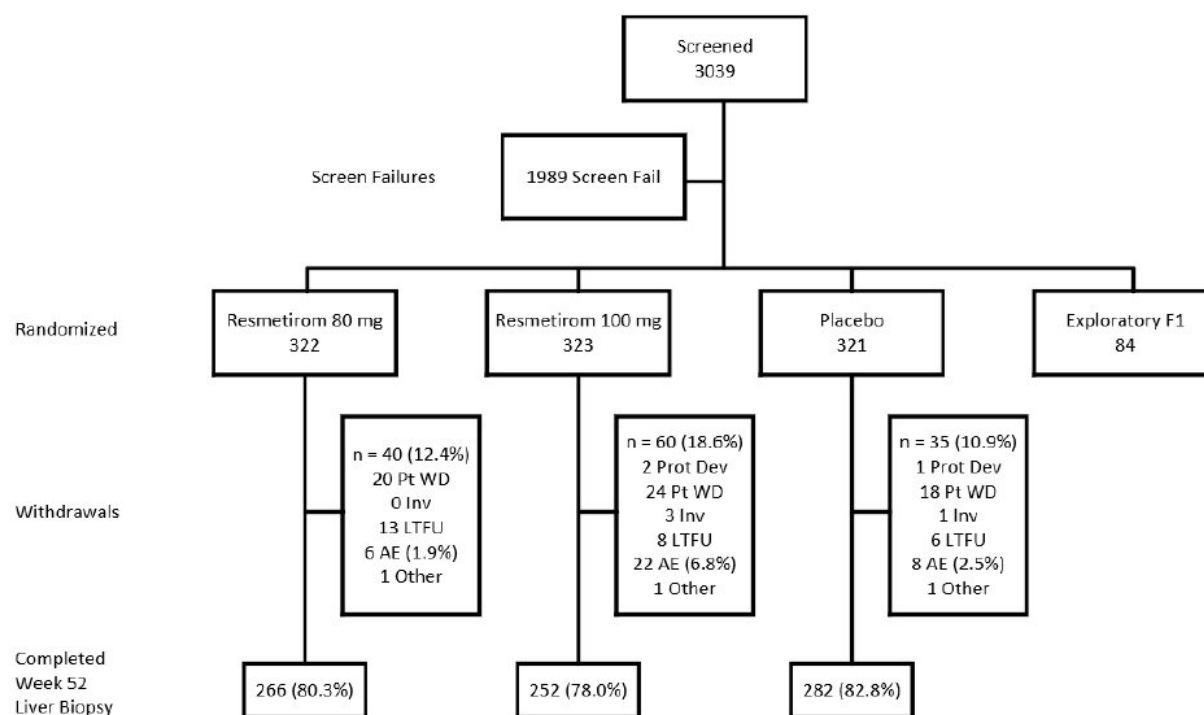
The study was designed to maintain an overall study-wise type I error rate of $\alpha=0.05$. The error rate was controlled by first splitting the overall $\alpha=0.05$ into 2 partitions via the weighted Bonferroni method: 80% ($\alpha=0.04$) was allocated to the Week 52 analysis (dual primary endpoints of NASH Resolution Responder and Fibrosis Responder) and 20% ($\alpha=0.01$) was allocated to the month 54 analysis (primary Composite Clinical Outcome). A two-stage parallel gatekeeping procedure (*Dmitrienko et al. 2011*) was used at Week 52 to control the type I error rate at 0.04. The first family of four hypothesis at Week 52 (two primary endpoints and two doses) is tested via truncated Hochberg procedure. Depending on the number of significant hypotheses in family 1, hypotheses in the second family (key secondary endpoint and two doses) are tested using Hochberg procedure using the corresponding alpha propagated from the first family. An α of 0.01 + any alpha propagated from the Week 52 Analysis level will be used for the primary analysis of the Composite Clinical Outcome. This approach properly controls the type 1 error in the strong sense.

Based on this approach, dual primary Week 52 endpoints and the key secondary LDL-C endpoints were considered statistically significant and the full alpha of 5% was used for evaluation of the composite clinical outcome (see results).

Results

- **Participant flow**

Figure 11. Patient Disposition – study 11



AE = adverse event; F1 = fibrosis stage 1; Inv = investigator; LTFU = lost to follow-up; Prot Dev = protocol deviation; Pt WD = patient withdrawal

The number of patients with a Week 52 biopsy was about 80%. Patient withdrawal was slightly higher in the active treatment groups, similar to the number of patients lost-to-follow-up. Withdrawal due to AEs was only increased in the high dose group, but not in the 80 mg-dose group.

- **Recruitment**

The first patients were enrolled on 20th June 2019. The last patient that completed the 52-week treatment for this interim analysis was dated 30th July 2022. At the time of submission of the interim study report, the study was on-going.

- **Conduct of the study**

The initial protocol was dated 03 March 2019. There is a relevant history of protocol amendments with differential regional amendments implemented at different time points. For the European region (which included "UK and RoW"), 3 substantial amendments occurred.

While the early substantial amendments appear to be amendments required for clarifications (e.g. doses of concomitant medication, clarification of inclusion criteria, change of language with regard to contraceptives) and could be seen rather not too critical, it is noted that the later ones were undertaken after the data cut-off for the interim evaluation of the study (31 Jul 2022) and / or after unblinding of the interim data. However, what is of concern, is the fact that the amendments are referring to alignments with the SAP, which is rather peculiar, because normally it would be expected that the SAP follows the protocol in the first place.

Similarly, for the protocol version V5.0 (UK) and V4.0 (ROW without UK; which is the “relevant” protocol for the EU), the table only includes reference to updates of endpoints, alignment with SAP etc, as well as the (fully acceptable) re-organisation of endpoints section according to the two time-points. However, when looking into these versions, it appears that the whole sections on statistical analysis, sample size planning, and definition of analysis populations etc, now only refer to the SAP, which is not acceptable. This is all the more important because the SAP itself has been found to have undergone revisions after data lock and unblinding.

It has to be noted that the latest revision of the EU applicable protocol version v4.0 (27th June 2023) is dated about 12 months after the data cut-off (31st July 2022) and about 7 months after Database lock (18 Nov 2022) and the last revision of the SAP is dated 05th December 2022, which is about 2 weeks after data lock.

The applicant has described reasons for protocol amendments after the data cut-off and database lock of study 11.

The amendments V5.0-UK and V4.0-ROW only aligned the objectives and endpoints with the SAP and did not introduce any new analyses.

The overall planning and conduct (late amendments and handling of SAP) was considered highly unusual and raised GCP compliance concerns. But CHMP agreed that the risk associated with the reliability of the study data and results in particular for multiplicity-controlled Week 52 endpoints is considered low. Analyses of these endpoints could still be considered sufficiently pre-specified. However, the GCP compliance concerns and missing/unclear pre-specification prevented this study being the only condition for CMA.

Information on GCP compliance of the pivotal study included in this dossier were gathered from EU and non-EU regulatory authorities. A GCP inspection was not considered necessary as it was unlikely that additional information could be obtained during the inspection.

- **Baseline data**

The baseline data according to disease stage and concomitant diseases is given in the following tables:

Table 19. Patient Disposition (F1B, F2, F3)

Characteristic, n (%)	Resmetirom 80 mg	Resmetirom 100 mg	Placebo	Overall
All Treated Patients, n (%)	352 (100)	349 (100)	349 (100)	1050 (100)
Patients receiving at least one dose of study drug	352 (100)	349 (100)	349 (100)	1050 (100)
Randomized by Stratification Levels:				
Type-2 diabetes status				
Present	225 (63.9)	223 (63.9)	224 (64.2)	672 (64.0)
Absent	127 (36.1)	126 (36.1)	125 (35.8)	378 (36.0)
Fibrosis stage on eligibility read				
1A	8 (2.3)	4 (1.1)	9 (2.6)	21 (2.0)
1B	34 (9.7)	35 (10.0)	39 (11.2)	108 (10.3)
1C	12 (3.4)	13 (3.7)	6 (1.7)	31 (3.0)
2	111 (31.5)	109 (31.2)	112 (32.1)	332 (31.6)
3	187 (53.1)	188 (53.9)	183 (52.4)	558 (53.1)
Week 52 mITT Population, n (%)	322 (91.5)	323 (92.6)	321 (92.0)	966 (92.0)
Patients with no Week 52 liver biopsy	56 (17.4)	71 (22.0)	39 (12.1)	166 (17.2)
Patients with a Week 52 liver biopsy	266 (82.6)	252 (78.0)	282 (87.9)	800 (82.8)
Patients who discontinued study drug prior to Week 52	50 (15.5)	66 (20.4)	38 (11.8)	154 (15.9)
Reason for discontinuation of study drug				
Adverse event	16 (5.0)	30 (9.3)	12 (3.7)	58 (6.0)
Protocol deviation	0	1 (0.3)	1 (0.3)	2 (0.2)
Study terminated by sponsor	0	0	0	0
Withdrawal by patient (other than AE)	19 (5.9)	23 (7.1)	16 (5.0)	58 (6.0)
Investigators discretion (other than AE)	1 (0.3)	3 (0.9)	3 (0.9)	7 (0.7)
Lost to follow-up	13 (4.0)	7 (2.2)	6 (1.9)	26 (2.7)
Other	1 (0.3)	2 (0.6)	0	3 (0.3)
Patients who discontinued study prior to Week 52	40 (12.4)	58 (18.0)	34 (10.6)	132 (13.7)
Reason for discontinuation of study				
Adverse event	6 (1.9)	22 (6.8)	7 (2.2)	35 (3.6)
Protocol deviation	0	2 (0.6)	1 (0.3)	3 (0.3)
Study terminated by sponsor	0	0	0	0
Withdrawal by patient (other than AE)	20 (6.2)	23 (7.1)	18 (5.6)	61 (6.3)
Investigators discretion (other than AE)	0	2 (0.6)	1 (0.3)	3 (0.3)
Lost to follow-up	13 (4.0)	8 (2.5)	6 (1.9)	27 (2.8)
Other	1 (0.3)	1 (0.3)	1 (0.3)	3 (0.3)

AE = adverse event; EAC = Endpoint Adjudication Committee; mITT = Modified Intent-to-Treat

Note: Percentages are based on the number of patients in the Intent-to-Treat population. The Intent-to-Treat population includes all patients who are randomized in the study.

Note: For the Week 52 analysis, only discontinuations prior to Week 52 are summarized.

The overall mean treatment compliance up to Week 52 was 96.6%, with the 100 and 80 mg resmetirom and placebo treatment groups demonstrating similar levels of compliance (96.6%, 96.5%, and 96.7%, respectively).

The demographic baseline characteristics are given in the following table:

Table 20. Baseline Characteristics in Study 11 (Conventional Units) (Week 52 mITT Population F2/F3)

	Resmetirom 80 mg (N=306)	Resmetirom 100 mg (N=308)	Placebo (N=303)	Overall (N=917)
Age at Informed Consent (years)				
Mean (SD)	55.9 (11.2)	57.0 (10.8)	57.2 (10.4)	56.7 (10.8)
Sex, n (%)				
Male	133 (43.5)	134 (43.5)	132 (43.6)	399 (43.5)
Female	173 (56.5)	174 (56.5)	171 (56.4)	518 (56.5)
Race, n (%)				
White	277 (90.5)	276 (89.6)	265 (87.5)	818 (89.2)
Black or African American	4 (1.3)	5 (1.6)	7 (2.3)	16 (1.7)
Asian	10 (3.3)	9 (2.9)	9 (3.0)	28 (3.1)
American Indian or Alaska Native	4 (1.3)	0	3 (1.0)	7 (0.8)
Native Hawaiian or other Pacific Islander	0	1 (0.3)	1 (0.3)	2 (0.2)
Other	8 (2.6)	10 (3.2)	14 (4.6)	32 (3.5)
Not able to collect	3 (1.0)	7 (2.3)	4 (1.3)	14 (1.5)
Ethnicity, n (%)				
Hispanic or Latino	68 (22.2)	79 (25.6)	49 (16.2)	196 (21.4)
Not Hispanic or Latino	234 (76.5)	224 (72.7)	249 (82.2)	707 (77.1)
Not able to collect	2 (0.7)	2 (0.6)	3 (1.0)	7 (0.8)
Unknown or not reported*	2 (0.7)	3 (1.0)	2 (0.7)	7 (0.8)
Weight (kg)				
Mean (SD)	100.2 (22.3)	101.8 (22.8)	99.5 (22.7)	100.5 (22.6)
BMI (kg/m²)				
Mean (SD)	35.6 (6.4)	36.1 (7.2)	35.2 (6.4)	35.6 (6.7)
Fibrosis stage, n (%)				
2	107 (35.0)	100 (32.5)	112 (37.0)	319 (34.8)
3	194 (63.4)	203 (65.9)	186 (61.4)	583 (63.6)
4	5 (1.6)	5 (1.6)	5 (1.7)	15 (1.6)
NAS at Screening, n (%)				
<5	51 (16.7)	32 (10.4)	64 (21.1)	147 (16.0)
≥5	255 (83.3)	276 (89.6)	239 (78.9)	770 (84.0)
Type 2 diabetes, n (%)				
Present	213 (69.6)	201 (65.3)	200 (66.0)	614 (67.0)
Hypertension, n (%)				

	Resmetirom 80 mg (N=306)	Resmetirom 100 mg (N=308)	Placebo (N=303)	Overall (N=917)
Present	230 (75.2)	242 (78.6)	243 (80.2)	715 (78.0)
Dyslipidaemia, n (%)				
Present	216 (70.6)	224 (72.7)	212 (70.0)	652 (71.1)
On thyroxine replacement therapy at Screening, n (%)				
Yes	38 (12.4)	43 (14.0)	43 (14.2)	124 (13.5)
On statin therapy, n (%)				
Yes	140 (45.8)	154 (50.0)	147 (48.5)	441 (48.1)
On GLP-1 therapy, n (%)				
Yes	52 (17.0)	40 (13.0)	39 (12.9)	131 (14.3)
FibroScan VCTE (kPa) at Screening				
Median (Min, Max)	11.5 (4.6, 75.0)	12.0 (4.3, 75.0)	11.8 (4.0, 53.6)	11.8 (4.0, 75.0)
FibroScan CAP (dB/m) at Screening				
Median (Min, Max)	349.0 (203, 400)	350.0 (154, 400)	350.0 (220, 400)	350.0 (154, 400)
Hepatic fat fraction (%) by MRI-PDFF at Screening				
Median (Min, Max)	17.0 (2.5, 35.3)	16.6 (2.8, 34.4)	16.5 (4.6, 42.1)	16.8 (2.5, 42.1)
MRE (kPa) at Screening				
Median (Min, Max)	3.3 (1.8, 7.9)	3.6 (1.9, 9.9)	3.4 (2.0, 9.2)	3.4 (1.8, 9.9)
*: only the pooled count of categories "not reported" and "unknown" is reported to avoid unblinding				

With regard to medical history, most patients had a history of hypertension (72.9%), dyslipidemia (71.3%), gastroesophageal reflux disease (42.9%), Type 2 diabetes mellitus (62.6%), and obesity (38.6%). About 24% had a history (of already known) MASH, and 17% of hepatic steatosis. 20% had a history of osteoarthritis, and 24.5% and 18.7% had a history of depression and anxiety, respectively. Almost 30% were suffering from seasonal allergy, and about 18% from drug hypersensitivity.

- **Numbers analysed**

A total of 3039 patients were screened of whom 1050 were randomized to the three double blind treatment arms (80 mg resmetirom [n=352], 100 mg resmetirom [n=349], or placebo [n=349]) and were at least 52 weeks in the study (or had early terminated) at the data cut-off date of 31 Jul 2022. A comparable proportion of patients across the three treatment groups completed the Week 52 visit with a liver biopsy for this analysis: 82.6%, 78.0%, and 87.9% in the 80 mg, 100 mg and placebo groups, respectively.

The data cut for the interim CSR of study 11 includes all data collected in this study up to 31 Jul 2022. To ensure that the duration of treatment was at least 1 year, this data cut included all patients randomized as

of 31 Jul 2021, resulting in 1050 randomized patients. Among these 1050 patients, 917 were of fibrosis stage F2, and F3 at baseline. The remaining were of fibrosis stage F1 and results are presented separately as exploratory analyses.

The analysed populations for the proposed indication population, namely F2/F3, are given in the following table:

Table 21. Study MGL-3196-11: Analysis Populations (F2/F3)

Population	Resmetiro m 80 mg	Resmetirom 100 mg	Placebo	Total
All Treated Patients (F1-F3)	352 (100)	349 (100)	349 (100)	1050 (100)
Safety Population (F2/F3)	306 (86.9)	308 (88.2)	303 (86.8)	917 (87.3)
mITT Population (F2/F3)	306 (86.9)	308 (88.2)	303 (86.8)	917 (87.3)
Week 52 mITT Population (F2/F3)	306 (86.9)	308 (88.2)	303 (86.8)	917 (87.3)
Week 52 Liver Biopsy mITT Population (F2/F3)	300 (85.2)	306 (87.7)	300 (86.0)	906 (86.3)

As given already above, the “Week 52 Liver Biopsy mITT Population” was used as the primary analysis population for efficacy (the population excluding those patients with missing biopsy due to the pandemic).

While the overall percentage of patients who permanently discontinued study drug was low (154/966, 15.9%), a numerically higher proportion of patients in the resmetirom 100 mg group discontinued study drug compared with placebo (20.7% vs 11.8% respectively), which was mainly driven by diarrhoea. The two main reasons patients discontinued study drug was due to an adverse event (AE) and due to patient withdrawal (other than an AE). Very few patients were lost to follow-up (26/966, 2.7%). The number of patients with a Week 52 biopsy is about 80% as given in the above figure, while the “Liver Biopsy mITT Population” includes more than 90% of the population. As given above, this population is considered the acceptable primary evaluation population for the biopsy-based endpoints.

- **Outcomes and estimation**

Results are presented for the target population F2/F3 reflected in the indication. Reported p-values are nominal. Results of primary and secondary endpoints for this population are consistent with the results of primary defined population (F1B, F2, F3).

Primary endpoint(s):

Both primary endpoints demonstrated statistically significant effects against placebo, which is shown in the next table.

Table 22. Summary of Dual Primary Endpoint Results (Week 52 Liver Biopsy mITT Population –F2/ F3)

Week 52 Endpoint	Rezdiffra 80 mg (N=300)	Rezdiffra 100 mg (N=306)	Placebo (N=300)
NASH Resolution (ballooning 0, inflammation 0.1) with $\geq$ 2 point reduction in NAS and no worsening of fibrosis at Week 52			
Percentage of responders	26	30	10
% difference vs placebo (95% CI)	16 (11, 22)	21 (15, 26)	
Nominal p-value	< 0.0001	< 0.0001	
$\geq$ 1 stage improvement in fibrosis with no worsening of NAS at Week 52			
Percentage of responders	27	29	17
% difference vs placebo (95% CI)	9 (4, 15)	12 (6, 18)	
Nominal p-value	0.0017	< 0.0001	

As reported above, a secondary evaluation of the primary endpoints was conducted based on “consensus” reads of the two involved central pathologists and showed similar results. The key secondary endpoint (LDL-C) also showed highly statistically significant differences to placebo, as given in the following table:

Table 23. LDL-C: Summary of Percent Change from Baseline at Week 24 (Conventional Units) – ANCOVA on Multiply Imputed Data (Week 52 mITT Population –F2/ F3)

Parameter	Rezdiffra 80 mg N = 305	Rezdiffra 100 mg N = 308	Placebo N = 303
LDL-C (% CFB)	-14	-19	0
Relative to placebo	-14 (-18, -10)	-19 (-23, -16)	
Triglycerides (% CFB)	-21	-27	2
Relative to placebo	-19 (-27, -10)	-25 (-34, -16)	

Sensitivity analysis for the secondary endpoint LDL-C for F2/F3 population were presented using J2R and CR imputation approach for missing measurements which aligns with the targeted estimand. Both analyses show favourable results for resmetirom 100 mg and 80 mg compared to placebo. Analysis using MAR assumption also indicate consistent results with other analysis. Based on the presented results it can be concluded that missing data has a limited impact on the results for the LDL-C endpoint.

Similar to the primary and secondary evaluation of the “regression of fibrosis” and “resolution of NASH” endpoints, all other secondary, histology endpoints also showed statistical significance.

Table 24. Liver Biopsy Endpoints: Summary of Responses at Week 52 (Week 52 Liver Biopsy mITT Population* –F2/ F3)

	% Response Resmetirom 80 mg (n=300)	% Response Resmetirom 100 mg (n=306)	% Response Placebo (n=300)	Diff % Response 80 mg v Pbo (95% CI)	Nominal p-value	Diff % Response 100 mg v Pbo (95% CI)	Nominal p-value
At least a 2-point improvement in NAS with at least 1-point improvement in ballooning or lobular inflammation with no worsening of fibrosis							
% Response	41.3	44.6	21.7	19.9 (13.3, 26.4)	<0.0001	23.0 (16.4, 29.5)	<0.0001
At least a 2-point improvement in NAS with at least 1-point improvement in ballooning or lobular inflammation and at least a 1-point improvement in fibrosis							
% Response	19.2	21.2	8.7	10.7 (5.8, 15.5)	<0.0001	12.7 (7.9, 17.5)	<0.0001
An improvement in each histologic NAS component with no worsening of fibrosis							
% Response	21.5	27.1	6.7	15.0 (10.0, 19.9)	<0.0001	20.6 (15.5, 25.6)	<0.0001
The resolution of fibrosis (reduction to F0)							
% Response	5.7	5.9	2.5	3.4 (0.7, 6.2)	0.0071	3.6 (0.8, 6.5)	0.0071
2-stage Fibrosis Responders (a ≥ 2-point reduction in fibrosis patients with no worsening of NAS) in patients with baseline fibrosis $\geq F2$							
% Response	8.3	10.1	2.8	5.6 (2.5, 8.7)	0.0001	7.4 (3.9, 10.8)	<0.0001
A composite of NASH Resolution Responder and Fibrosis Responder							
% Response	14.3	16.0	4.8	9.6 (5.5, 13.8)	<0.0001	11.4 (7.2, 15.6)	<0.0001

The applicant has evaluated the endpoint “No worsening of fibrosis” (defined as any progression of ≥ 1 stage) only for patients with baseline F1B and F2, since for F3 patients this would concern the evaluation of the final endpoint component “manifestation of cirrhosis” at the Month 54 evaluation, and unblinding for these patients was correctly avoided. Due to the smaller sample size, and consequent higher variability, statistical significance was only partly achieved. However, rates of non-deterioration for the F2 population were about 35% in placebo patients and about 20% in the resmetirom treatment groups.

The applicant presented various sensitivity analysis for the dual primary endpoint and most relevant secondary endpoints accounting for variability in biopsy assessments by two pathologists, classification of responders and missing biopsy results and overall efficacy was confirmed and consistent in all analyses.

Table 25. Sensitivity Analyses of the Dual Primary Endpoints (F2/F3 population)

	% Response	% Response	% Response	Diff % Response 80 mg v	Nominal p-	Diff % Response 100 mg v	Nominal p-value
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	Resmetirom 80 mg (N=300)	Resmetirom 100 mg (N=306)	Placebo (N=300)	Pbo (95% CI)	value	Pbo (95% CI)	
Placebo-based Multiple Imputation							
NASH resolution (SAP-based)*	28.1	32.7	11.3	17.0 (10.8, 23.1)	<0.001	21.8 (15.6, 28.0)	<0.0001
Consensus-based†	26.1	29.9	9.1	17.3 (11.0, 23.5)	<0.001	21.4 (15.1, 27.7)	<0.0001
Fibrosis improvement (SAP-based)*	27.9	30.1	17.3	10.9 (4.5, 17.2)	0.0017	12.8 (6.5, 19.1)	0.0002
Consensus-based†	27.3	29.5	15.0	12.5 (5.5, 19.5)	0.0011	14.6 (7.7, 21.4)	0.0001
Missing at Random Multiple Imputation							
NASH resolution (SAP-based)‡	30.6	36.0	13.5	17.3 (10.7, 23.8)	<0.001	23.0 (16.2, 29.7)	<0.0001
Consensus-based†	29.6	36.2	9.1	20.8 (14.3, 27.4)	<0.001	27.9 (20.9, 34.8)	<0.0001
Fibrosis improvement (SAP-based)‡	32.0	35.7	21.8	10.5 (3.7, 17.3)	0.0049	14.3 (7.3, 21.2)	0.0001
Consensus-based†	29.9	33.8	15.1	15.0 (7.8, 22.2)	0.0002	18.8 (11.5, 26.1)	<0.0001

The applicant also presented the worst-case analysis results for the Week 52 mITT Population and Week 52 Liver Biopsy mITT Population where (1) differing evaluations of the two pathologists were analyzed as non-response and (2) missing biopsy data in the Week 52 mITT Population imputed as non-response; (3) the fibrosis response in patients with stage 2 was defined as regression to any grade of fibrosis below 2 (1 or 0); (4) any patients with a deterioration of ballooning and/or lobular inflammation were defined as non-responder. Overall, the difference between the treatment groups and placebo was notable and similar to the primary analysis, although the number of responders was lower in both treatment and placebo groups.

Table 26. Worst Case Criteria-based NASH Resolution and Fibrosis Improvement Responses at Week 52 (Week 52 Liver Biopsy Modified Intent-to-Treat Population – F2/F3)

	% Response Resmetirom 80 mg (N=300)	% Response Resmetirom 100 mg (N=306)	% Response Placebo (N=300)	Diff %Response 80 mg v Pbo (95% CI)	Nominal p-value	Diff %Response 100 mg v Pbo (95% CI)	Nominal p-value
NASH Resolution Response*	21.0	20.9	6.7	16.5 (11.0, 22.1)	<0.0001	20.9 (15.4, 26.4)	<0.0001
Fibrosis Response†	17.3	19.0	10.3	9.1 (3.5, 14.6)	0.0128	11.6 (6.0, 17.3)	0.0026

The applicant has conducted several subgroups analyses, both according to baseline category of disease and according to demographic characteristic, as well as for categories such as MR-PDFF response, SHBG response, body weight-loss, GLP-1RA use, statin use, and thyroxine use. Overall, a high consistency of the results is demonstrated in all the analysed subgroups.

Secondary endpoints based on imaging methods

The applicant has provided analyses for the following secondary endpoints of special clinical relevance: MR-PDFF and MRE, Transaminases and GGT, CK-18, ELF-test and its components, and FibroScan VCTE and CAP. The presented analysis was based on the Week 52 mITT analysis set restricted to the F2/F3 population or in case of MR-PDFF and MRE on the Week 52 mITT patients that participated in the MRI/MRE sub study for those endpoints only collected within the sub study. Results are presented in the Table 27. Overall, all these secondary endpoints showed favourable results for resmetirom 100 mg and 80 mg compared to placebo.

Table 27. MRI-PDFF: Summary of Absolute and Percent Change from Baseline at Week 52 (Week 52 mITT Population – F1B, F2, F3)

	LSM Abs CFB (SE) Resmetirom 80 mg	LSM Abs CFB (SE) Resmetirom 100 mg	LSM Abs CFB (SE) Placebo	Diff Abs CFB Resmetirom 80 mg from Pbo (95% CI)	Nominal p-value	Diff Abs CFB Resmetirom 100 mg from Pbo (95% CI)	Nominal p-value
MRI-PDFF (MRI-PDFF Sub-study Population-only)							
n1	258	266	245				
MAR							
% change from baseline*	-33.5 (2.5)	-47.5 (2.5)	-6.8 (2.5)	-26.8 (-33.4, -20.1)	<0.0001	-40.7 (-47.4, -34.0)	<0.0001
≥30% reduction (n [%] and OR)†	136 (62.4)	153 (72.9)	53 (24.9)	4.8 (3.2, 7.2)	<0.0001	8.3 (5.4, 12.7)	<0.0001
≥50% reduction (n [%] and OR)†	89 (40.8)	113 (53.8)	19 (8.9)	6.8 (3.9, 11.7)	<0.0001	11.6 (6.7, 20.1)	<0.0001
CR (placebo-based)							
% change from baseline*	-31.2 (2.6)	-40.7 (2.6)	-7.1 (2.6)	-24.1 (-30.9, -17.2)	<0.0001	-33.6 (-40.4, -26.8)	<0.0001
MRE (kPa) (MRE Sub-study Population-only; baseline value ≥2.9 kPa)*							
n1	123	143	131				
MAR	-0.59 (0.076)	-0.45 (0.071)	-0.25 (0.067)	-0.34 (-0.52, -0.16)	0.0002	-0.21 (-0.38, -0.03)	0.0210
CR (placebo-based)	-0.54 (0.076)	-0.42 (0.070)	-0.24 (0.068)	-0.30 (-0.48, -0.11)	0.0015	-0.18 (-0.36, 0)	0.0499
FibroScan VCTE (kPa)							
n1	294	299	290				
MAR							
Absolute change from baseline*	-2.6 (0.31)	-3.4 (0.31)	-1.6 (0.31)	-0.94 (-1.8, -0.10)	0.0286	-1.8 (-2.7, -1.0)	<0.0001
≥25% reduction (n [%] and OR)†	104 (42.1)	118 (48.6)	74 (29.5)	1.7 (1.1, 2.4)	0.0144	2.2 (1.5, 3.2)	<0.0001
≥25% worsening (n [%] and OR)†	34 (13.8)	26 (10.7)	43 (17.1)	0.80 (0.50, 1.3)	0.7237	0.59 (0.35, 0.98)	0.0777

	LSM Abs CFB (SE) Resmetirom 80 mg	LSM Abs CFB (SE) Resmetirom 100 mg	LSM Abs CFB (SE) Placebo	Diff Abs CFB Resmetirom 80 mg from Pbo (95% CI)	Nominal p-value	Diff Abs CFB Resmetirom 100 mg from Pbo (95% CI)	Nominal p-value
CR (placebo-based)							
Absolute change from baseline*	-2.3 (0.32)	-3.0 (0.31)	-1.5 (0.32)	-0.82 (-1.7, 0.01)	0.0542	-1.5 (-2.4, -0.70)	0.0003
FibroScan CAP (dB/m)*							
n1	291	298	289				
MAR	-40.4 (3.6)	-42.4 (3.6)	-15.3 (3.6)	-25.2 (-34.8, -15.5)	<0.0001	-27.2 (-36.7, -17.6)	<0.0001
CR (placebo-based)	-36.0 (3.6)	-37.1 (3.5)	-15.0 (3.5)	-21.0 (-30.5, -11.6)	<0.0001	-22.2 (-31.4, -12.9)	<0.0001

Abs = absolute; CAP = controlled attenuation parameter; CFB = change from baseline; CI = confidence interval; CR = copy reference; LSM = least squares mean; MAR = missing at random; MRE = magnetic resonance elastography; MRI-PDFF = magnetic resonance imaging-protein density fat fraction; OR = odds ratio; Pbo = placebo; SE = standard error; VCTE = vibration-controlled transient elastography

* The LSMs, CIs, and p-values were obtained using an ANCOVA model with baseline value, baseline type 2 diabetes status, fibrosis stage at baseline as covariates. Missing or invalid data were multiply imputed either 1) 100 times using the non-missing values by randomised treatment group and randomisation stratification factors using MAR-based regression or 2) 250 times using the non-missing values by randomisation stratification factors using copy reference as in Carpenter et al, 2013; the results from each dataset were combined using Rubin's rule. Baseline mean and analysis visit means were computed prior to imputation.

† Calculated based on observed data prior to imputation. The OR, CIs, and p-values were obtained using a stratified CMH approach, with baseline type 2 diabetes status and fibrosis stage at baseline as the stratification factors. Missing or invalid data were multiply imputed either 1) 100 times using the non-missing values by randomised treatment group and randomisation stratification factors using MAR-based regression; the results from each dataset were combined using Rubin's rule.

Note: n1 = number of patients used to compute LSM after imputation (imputation was not done for patients with no baseline data)

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

Liver and Spleen volume reductions

An evaluation of liver and spleen volume was also undertaken restricted to those patients undergoing MR evaluations (the sample for evaluation was restricted to those with baseline and Week 52 MR-PDFF data available as per protocol). Patients in the 100 and 80 mg resmetirom dose groups achieved significantly greater percent reductions at Weeks 16 and 52 from their baseline liver volume measurements (nominal $p < 0.0001$) and their baseline spleen volume measurements (nominal p -values ranging from < 0.0001 to 0.0003) compared with placebo.

Secondary endpoints based on biomarkers

Liver enzymes

The liver enzymes ALT, AST, and GGT were evaluated, however, with the restriction that the data are shown for those with elevated ALT ≥ 30 U/L at baseline. The evaluations included 218/213/217 patients in the 80 mg, 100 mg and placebo groups, respectively and showed highly significant differences between the groups to the advantage of resmetirom ($p < 0.0001$).

Serum lipids

The percent changes at Weeks 24 and 52 in lipid and lipoprotein particle parameters were analyzed, including LDL-C only at Week 52. Patients in both resmetirom treatment groups achieved significantly greater percent reductions from baseline (nominal $p < 0.0001$) at Weeks 24 and 52 compared with placebo in all tested parameters, with patients in the 100 mg dose level showing similar or greater reductions from baseline compared with placebo than 80 mg dose patients.

Similarly, patients in both resmetirom treatment dose levels achieved greater absolute reductions at Weeks 24 and 52 in several lipoprotein parameters, including LDL particles, large LDL particles, and small LDL particles. No notable differences were seen for VLDL and HDL.

Fibrosis and inflammation biomarkers

These evaluations were looking at the parameters ELF, PIIINP, TIMP-1, Hyaluronic acid, CK-18, Adiponectin, and (rather related to safety) fT3. The evaluations of the ELF score were restricted to the population with a baseline ELF of ≥ 9.8 (which indicates advanced fibrosis).

These analyses showed that patients in both resmetirom treatment groups generally achieved significantly greater reductions from baseline at Week 52 (nominal p -values ranging from < 0.0001 to 0.0113) compared with placebo in total ELF score, including the components of PIIINP, TIMP-1, CK-18, adiponectin, and rT3. Neither of the resmetirom treatment groups showed any meaningful difference from placebo in changes in the ELF component of hyaluronic acid.

Table 28. Study MGL-3196-11: Fibrosis and Inflammation Biomarkers – Summary of Absolute and Percent Change from Baseline at Week 52 (Week 52 mITT Population –F2/F3)

	LSM Abs CFB (SE) Resmetirom 80 mg	LSM Abs CFB (SE) Resmetirom 100 mg	LSM Abs CFB (SE) Placebo	Diff Abs CFB Resmetirom 80 mg from Pbo (95% CI)	Nominal p-value	Diff Abs CFB Resmetirom 100 mg from Pbo (95% CI)	Nominal p-value
CK-18 (U/L)							
n1	303	305	295				
MAR	-280.4 (23.5)	-305.0 (24.0)	-153.6 (23.5)	-126.7 (-189.5, -64.0)	<0.0001	-151.3 (-215.2, -87.4)	<0.0001
CR (placebo-based)	-270.6 (24.5)	-292.0 (25.2)	-156.7 (24.5)	-114.0 (-178.8, -49.2)	0.0006	-135.4 (-201.2, -69.6)	<0.0001
ELF Score*							
n1	136	145	135				
MAR	-0.46 (0.070)	-0.41 (0.066)	-0.21 (0.068)	-0.25 (-0.42, -0.07)	0.0059	-0.20 (-0.37, -0.03)	0.0240
CR (placebo-based)	-0.47 (0.089)	-0.44 (0.085)	-0.25 (0.089)	-0.22 (-0.44, 0)	0.0539	-0.19 (-0.41, 0.03)	0.0943
PIIINP (ug/L)*							
n1	217	230	214				

	LSM Abs CFB (SE) Resmetirom 80 mg	LSM Abs CFB (SE) Resmetirom 100 mg	LSM Abs CFB (SE) Placebo	Diff Abs CFB Resmetirom 80 mg from Pbo (95% CI)	Nominal p-value	Diff Abs CFB Resmetirom 100 mg from Pbo (95% CI)	Nominal p-value
MAR	-2.1 (0.30)	-2.0 (0.29)	-0.68 (0.30)	-1.4 (-2.2, - 0.58)	0.0007	-1.3 (-2.1, - 0.51)	0.0012
CR (placebo- based)	-1.9 (0.31)	-1.9 (0.30)	-0.62 (0.30)	-1.3 (-2.1, - 0.48)	0.0017	-1.3 (-2.1, - 0.44)	0.0024
TIMP-1 (ug/L)*							
n1	194	201	197				
MAR	-32.4 (4.9)	-36.1 (4.9)	-14.5 (4.8)	-17.9 (-30.8, -5.1)	0.0063	-21.6 (-34.5, -8.7)	0.0010
CR (placebo- based)	-30.8 (5.0)	-34.3 (5.0)	-14.5 (4.8)	-16.4 (-29.1, -3.7)	0.0116	-19.8 (-32.7, -6.9)	0.0025
HA (ug/L) (%CFB)*,†							
n1	171	175	170				
MAR	-5.6 (5.6)	-4.8 (5.6)	7.5 (5.7)	-13.0 (-27.9, 1.8)	0.0854	-12.3 (-26.9, 2.4)	0.1003
CR (placebo- based)	-6.0 (6.1)	-4.9 (6.0)	6.5 (6.2)	-12.5 (-28.3, 3.4)	0.1237	-11.4 (-27.3, 4.4)	0.1565

Abs = absolute; CFB = change from baseline; CI = confidence interval; CK-18 = cytokeratin 18; CR = copy reference; ELF = enhanced liver fibrosis; HA = hyaluronic acid; LSM = least squares mean; MAR = missing at random; Pbo = placebo; PIIINP = procollagen 3 N-terminal propeptide; SE = standard error; TIMP-1 = tissue inhibitor of metalloproteinase 1

Note: n1 = number of patients used to compute LSM after imputation (imputation was not done for patients with no baseline data).

* For each parameter, only patients that meet the following criteria at baseline are included: ELF ≥9.8; PIIINP ≥9 ug/L; TIMP-1 ≥240 ug/L; HA ≥50 ug/L.

† For the hyaluronic acid parameter, the %change from baseline is presented as it is a clearer representation of the change.

Note: The LSMs, CIs, and p-values were obtained using an ANCOVA model with baseline value, baseline type 2 diabetes status, fibrosis stage at baseline as covariates. Missing or invalid data were either 1) multiply imputed 100 times using the non-missing values by randomised treatment group and randomisation stratification factors using MAR-based regression or 2) multiply imputed 250 times using the non-missing values by randomisation stratification factors using copy reference as in Carpenter et al, 2013; the results from each dataset were combined using Rubin's rule. Baseline mean and analysis visit means were computed prior to imputation.

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

"Metabolic biomarkers"

In support of the overall efficacy, the applicant also presents the results of the evaluation of the "biomarkers" weight, BMI, blood pressure, heart rate, glucose, insulin, HOMA-IR, and HbA1c, as well as albumin, ALP, bilirubin (direct and total), PT/INR, MELD score, Ferritin, and Fibrinogen.

Analyses of the absolute change from baseline at Week 52 in metabolic assessments showed that in general compared with placebo, the 100 mg resmetirom dose level achieved greater mean reductions from baseline than the 80 mg dose level, with significant reductions (nominal p <0.0001 to 0.0297) compared

with placebo in weight, BMI, systolic and diastolic blood pressure, heart rate measured by ECG, and glucose. While the 100 mg resmetirom treatment group achieved a significant (nominal $p = 0.0168$) reduction from baseline in glucose levels compared with placebo, there were no significant differences in the other markers of insulin resistance and glucose homeostasis, including insulin, HOMA-IR (for HOMA-IR, the CFBs were: -1.3 (0.80), -2.2 (0.81), -0.93 (0.76), in the two active and placebo groups, respectively) and HbA1c (all changes below 0.1). The evaluations were presented on an "observed cases" number of patients.

Quality of Life Analyses of the patient-reported QOL outcomes of CLDQ-NASH, SF-LDQOL Total LD QoL, and SF-LDQOL Physical Functioning. Overall, across all QOL measures, the baseline responses to these questionnaires were consistent across all 3 treatment groups. No meaningful changes were observed between baseline and Week 52 across all drug treatment groups, including placebo, and across all patient subgroups.

Overall, it is agreed that results for the secondary endpoints are consistent across MAR, J2R and CR imputation methods.

A look at the biomarkers for serum lipids and glucose homeostasis reveals that the changes induced are influencing the lipid profile as well as glucose homeostasis, and also weight and BMI in "positive" manner, which is overall reassuring with regard to (cardiovascular) safety. Obviously, no relevant effects on parameters of Quality of Life could be achieved.

Ancillary analyses

The applicant has also evaluated the variability for the evaluation of the histology preparations (inter and intra-reader), both based on the glass slides, as well as the digitized slides. As known from the literature, the variability was highest for the lobular and ballooning scores, and less so for the steatosis and fibrosis scores. The variability for the two central pathologists involved was in the order of what was reported in publications of other studies in MASH, albeit slightly higher than in the publications of the "inventors" of the NAS score, the NAS-CRN network.

Based on the known variability of manual histology reading, the applicant has also included two additional methods for evaluation of the histology, which must currently be regarded to be experimental, and in their development stage. All these methods aim at reducing variability and produce more reliable and consistent results in the determination of the different components of the NAS-score and for fibrosis.

The evaluation with the AIM-NASH tool (PathAI) resulted in the following:

Table 29. PathAI Endpoint Results – Observed Data (Week 52 Paired Liver Biopsy mITT Population – F1B, F2, F3)

	Resmetirom 80 mg (n = 257)	Resmetirom 100 mg (n = 247)	Placebo (n = 273)
NASH Resolution Responders at Week 52			
Percentage of responders	23.7%	32.4%	9.5%
Difference in percentage of responders, resmetirom vs placebo (95% CI)	14.0 (7.8, 20.3)	23.9 (17.2, 30.7)	
p-value	<0.0001	<0.0001	
Fibrosis Responders at Week 52			
Percentage of responders	23.3%	30.4%	15.8%
Difference in percentage of responders, resmetirom vs placebo (95% CI)	8.0 (1.3, 14.7)	15.3 (8.1, 22.5)	
p-value	0.0199	<0.0001	

CI = confidence interval; mITT = Modified Intent-to-Treat; NASH = non-alcoholic steatohepatitis.

Note: Only subjects with non-missing baseline and Week 52 biopsy results are included in the analysis.

The evaluation with the HistoIndex (Second Harmonic Generation Microscopy) showed the following results:

Table 30. Summary of HistoIndex Steatosis Corrected Fibrosis Stage and Change from Baseline at Week 52 Results – Observed Data (Week 52 Paired Liver Biopsy mITT Population – F1)

	Resmetirom 80 mg (n = 229)	Resmetirom 100 mg (n = 218)	Placebo (n = 244)
Change in Fibrosis Grade			
≥2 Unit Improvement, n (%)	42 (18.3%)	50 (22.9%)	17 (7.0%)
p-value	0.0002	<0.0001	
≥1 Unit Improvement, n (%)	133 (58.1%)	122 (56.0%)	83 (34.0%)
p-value	<0.0001	<0.0001	
≥1 Unit Worsening, n (%)	19 (8.3%)	21 (9.6%)	62 (25.4%)
p-value	<0.0001	<0.0001	
≥2 Unit Worsening, n (%)	1 (0.4%)	6 (2.8%)	14 (5.7%)
p-value	0.0020	0.2313	
NAFLD Activity Score – STEATOSIS 2 - Value			
Week 52 n	229	218	244
Screening mean (SD)	2.3 (0.55)	2.3 (0.59)	2.3 (0.60)
Mean Change from Baseline (SE)	-0.90 (0.061)	-1.2 (0.063)	-0.30 (0.048)
Mean Percent Change from Baseline (SE)	-36.1 (2.8)	-45.8 (5.6)	-10.3 (3.1)

mITT = Modified Intent-to-Treat; SD = standard deviation; SE = standard error.

Note: Only subjects with non-missing baseline and Week 52 biopsy results are included in the analysis.

Note: Fibrosis stage based on HistoIndex grading cut-offs dated 21 Apr 2023.

Again, different numbers were included in these evaluations, although both methods confirmed the results of the primary and secondary evaluations based on “manual” histology reads.

The table below presents the composition of the analysis populations for the exploratory PathAI and HistoIndex endpoints and the reasons samples were excluded from analysis.

Table 31. Study MGL-3196-11 – PathAI and HistoIndex Patient Disposition

	N
Patients with Week 52 paired liver biopsies	782
PathAI	
Reason excluded from PathAI analysis	
Incomplete Week 52 visit record	3
Administrative error in alignment of patient ID	2
Total Number Included in PathAI Analysis	777
HistoIndex	
Reason excluded from HistoIndex analysis	
Tissue sample insufficient or slide not received	61
Baseline slide missing or not received	12
Did not pass HistoIndex QC	15
Tissue peeled off slide	1
Discontinued study before completing Week 52 visit	2
Total Number Included in HistoIndex Analysis	691

The difference between the PathAI and HistoIndex populations from the Week 52 Paired Liver Biopsy Population are 0.6% and 11.6%. Exclusion of the samples presented in the table above was based on factors particular to the assessments that were applied across all treatment groups.

It seems that PathAI method of sample selection could not systematically influence the exploratory endpoint results, however, much more reasons for exclusion of the samples were in the HistoIndex population. The applicant has, adequately demonstrated that there are no significant differences in HistoIndex population in comparison to patients with week 52 paired liver biopsies (i.e., the primary histology evaluation).

- **Summary of main efficacy results**

The following tables summarise the efficacy results from the main studies supporting the present application. These summaries should be read in conjunction with the discussion on clinical efficacy as well as the benefit risk assessment (see later sections).

Table 32. Summary of efficacy for trial MGL-3196-11

Title: A Phase 3, Multinational, Double-Blind, Randomized, Placebo-Controlled Study of MGL-3196 (Resmetirom) in Patients With Non-Alcoholic Steatohepatitis (NASH) and Fibrosis to Resolve NASH and Reduce Progression to Cirrhosis and/or Hepatic Decompensation	
Study identifier	MGL-3196-11
Design	Three-arm, randomised, double-blind, placebo controlled, multi-centre study. The trial is presented with an interim analysis including all patients having been treated for at least 1 year until the data cut-off as of 31 st July 2022. Randomisation was stratified according to T2DM and fibrosis stage at baseline.

Title: A Phase 3, Multinational, Double-Blind, Randomized, Placebo-Controlled Study of MGL-3196 (Resmetirom) in Patients With Non-Alcoholic Steatohepatitis (NASH) and Fibrosis to Resolve NASH and Reduce Progression to Cirrhosis and/or Hepatic Decompensation			
Study identifier	MGL-3196-11		
	Duration of interim phase:	1 year	
	Duration of Run-in phase:	N/A	
	Duration of (db) Extension phase:	54 months (planned)	
Hypothesis	Superiority of resmetirom (80 and 100 mg) over placebo		
Treatments groups	Resmetirom 100 mg		N=352; mITT F2/F3=308; "biopsy mITT F2/F3"=306
	Resmetirom 80 mg		N=349; mITT F2/F3=306; "biopsy mITT F2/F3=300
	Placebo		N=349; mITT F2/F3=303; "biopsy mITT F2/F3 =300
End points and definitions	Dual Primary endpoint	Histology based	1. The resolution of NASH associated with an at least 2-point reduction in NAFLD activity score (NAS) and without worsening of fibrosis by liver biopsy after 52 weeks of treatment (Week 52 Primary Endpoint) in the Week 52 Liver Biopsy Modified Intent-to-Treat (mITT) Population. Resolution defined as ballooning score =0, and lobular inflammation 0/1. 2. The improvement of fibrosis stage by at least 1-point, with no worsening of NAS
	Secondary endpoint	Histology based	At least a 2-point improvement in NAS with at least 1-point improvement in ballooning or lobular inflammation with no worsening of fibrosis.
	Secondary endpoint	Histology based	At least a 2-point improvement in NAS with at least 1-point improvement in ballooning or lobular inflammation and at least a 1-point improvement in fibrosis.
	Secondary endpoint	Histology based	Composite of NASH resolution and fibrosis response
	Secondary endpoint	Serum biomarker	% change from baseline in LDL-C levels at week 24
	Secondary endpoint	MR-based imaging	Mean change from baseline in absolute MRI-PDFF
	Secondary endpoint	Serum biomarkers ALT/AST/GGT	Mean %change from baseline in those patients with elevated ALT >30 U/l at baseline
	Secondary endpoint	Serum biomarker ELF	Mean % change from baseline in ELF score in patients with ELF ≥9.8 kPa at baseline
	Exploratory endpoint	Histology based	Dual primary endpoints (as above) with patients having F2/F3 fibrosis at baseline (eligibility reads for baseline)
Database lock	31 st July 2022		
Results and Analysis			

Title: A Phase 3, Multinational, Double-Blind, Randomized, Placebo-Controlled Study of MGL-3196 (Resmetirom) in Patients With Non-Alcoholic Steatohepatitis (NASH) and Fibrosis to Resolve NASH and Reduce Progression to Cirrhosis and/or Hepatic Decompensation				
Study identifier	MGL-3196-11			
Analysis description	Primary Analysis			
Analysis population and time point description	Histology evaluations are based on the "52-week Liver Biopsy mITT population" Imaging endpoints based on "observed cases" or with elevations at baseline Biomarker endpoints based on "observed cases" or with elevations at baseline All evaluations based on 1-year. Evaluations based on "primary" population of patients with F2 and F3 fibrosis at baseline. LDL-C EP at 24 weeks based on mITT population			
Descriptive statistics and estimate variability	Treatment group	Resmetirom 100 mg	Resmetirom 80 mg	Placebo
	Number of subjects	306	300	300
	NASH resolution with no worsening of fibrosis (% responder)	30	26	10
	At least 1 stage improvement of fibrosis without worsening of NAS (% responder)	29	27	17
	At least a 2-point improvement in NAS with at least 1-point improvement in ballooning or lobular inflammation with no worsening of fibrosis. (% responder)	44.6	41.3	21.7
	At least a 2-point improvement in NAS with at least 1-point improvement in ballooning or lobular inflammation and at least a 1-point improvement in fibrosis.	21.2	19.2	8.7
		N=308	N=305	N=303
	% change from baseline in LDL-C levels at week 24 (LS mean of % CFB)	--19	-14	0
		N=266	N=258	N=245
	% change from baseline in absolute MRI-PDFF (SE)	-47.5 (2.5)	-33.5 (2.5)	-6.8 (2.5)

Title: A Phase 3, Multinational, Double-Blind, Randomized, Placebo-Controlled Study of MGL-3196 (Resmetirom) in Patients With Non-Alcoholic Steatohepatitis (NASH) and Fibrosis to Resolve NASH and Reduce Progression to Cirrhosis and/or Hepatic Decompensation

Study identifier	MGL-3196-11			
		N=252	N=253	N=234
	Mean % change from baseline in those patients with elevated ALT >30 U/l at baseline (ALT, AST, GGT)	-31 -26 -34	-23 -21 -27	-5 -2 1
		N=145	N=136	N=135
	Mean change from baseline in ELF score	-0.41 (0.066)	-0.46 (0.070)-	-0.21 (0.068)
Effect estimate per comparison		Difference 100 mg vs. placebo	Difference 80 mg vs placebo	
	1 st Primary endpoint (Difference in % responder (95% CI))	21 (15, 26) P<0.0001	16 (11, 22) P<0.0001	
	2 nd Primary endpoint (% responder)	12 (6, 18) P<0.0001	9 (4, 15) 0.0017	
	At least a 2-point improvement in NAS etc.; Difference in % responder (95% CI)	23.0 (16.4, 29.5)	19.9 (13.3, 26.4)	
	Combined NAS and fibrosis response (Difference in % responder; 95% CI)	12.7 (7.9, 17.5)	10.7 (5.8, 15.5)	
	LS mean of % change from baseline in LDL-C vs. placebo (95% CI)	-19 (-23, -16)	-14 (-18, -10)	
	LS Mean of % change from baseline MRI-PDFF compared to placebo (95% CI)	-40.7 (-47.4, -34.0)	-26.8 (-33.4, -20.1)	
	Mean % change of liver enzymes			
	ALT	-26 (-34, -18) -24 (-33, -16) -35 (-45, -26)	-18 (-26, -10) -19 (-27, -11) -28 (-37, -19)	
	AST			
	GGT			
	ELF Score LS mean difference; (95% CI)	-0.20 (-0.37, -0.03)	-0.25 (-0.42, -0.07)	

2.6.5.3. Clinical studies in special populations

No studies in special populations have been performed.

The number of patients overall included in the study programme in the different elderly age groups are presented. Overall, in controlled studies from involved 2147 subjects, 467 (21, 8%) were subjects in age group 75-84 years, 56 (2,6 %) subjects in age group 75-84 years, no patients in age group 85+.

Table 33. Enrolled Patients by Age Category

	N	Age 65-74 n (%)	Age 75-84 n (%)	Age 85+ n (%)
Controlled trials	2147	467 (21.8)	56 (2.6)	0
Study MGL-3196-05	125	11 (8.8)	0	0
Study MGL-3196-11	1050	244 (23.2)	24 (2.3)	0
Study MGL-3196-14 randomised non-OL subjects	972	212 (21.8)	32 (3.3)	0
Non-controlled trials	414	112 (27.1)	23 (5.6)	0
Study MGL-3196-14 OL subjects	371	94 (25.3)	21 (5.7)	0
Study MGL-3196-18 OL subjects who didn't roll-over from Study MGL-3196-14	43	18 (41.9)	2 (4.7)	0

OL = Open-label

Note: Study 18 subjects who rolled over from Study 14 are included in the counts of Study 14.

Note: Percentages are based on the number of total patients (N) in each category.

In vitro biomarker test for patient selection for efficacy

Patients eligible for the study had to have a biopsy proven diagnosis of MASH using NASH-CRN scoring system. Biopsies were read on glass slides for eligibility at the time of screening (Baseline biopsies). These slides were reread for the primary analysis beginning around 6 months prior to the 31 Jul 2022 database lock by each of the two central pathologists in large groups of baseline glass slides (50-100 slides per group including a few which were from biopsy screen failures). When defining the analysis populations, the applicant used the biopsy re-read scores, in which the baseline biopsy samples were read by both Pathologists A and B after the Week 52 biopsy samples were collected.

For Pathologist A reads, 99% of qualifying biopsies at eligibility qualified at the re-read, with change between similar baseline fibrosis stage. Pathologist B confirmed the eligibility in 95% of cases, with differences of scoring a few baseline biopsies as NAS<4.

2.6.5.4. Analysis performed across trials (pooled analyses and meta-analysis)

No pooled analysis was presented. This was acceptable to the CHMP.

2.6.5.5. Supportive studies

Two supportive studies are included in the submission, one of which is presented with an interim analysis.

Study MGL-3196-14:

The study, termed "A 52-week, phase 3 study to evaluate safety and biomarkers of resmetirom (MGL-3196) in patients with non-alcoholic fatty liver disease (NAFLD)", was a multi-center, randomized, double-blind, placebo-controlled study with an open-label arm in patients with NAFLD/MASLD (presumptive NASH/MASH, not non-alcoholic fatty liver) and a parallel-enrolling open-label arm with patients with compensated NASH/MASH cirrhosis (CP-A). The study was conducted between 16th December 2019 and 13th December 2021.

Patients were randomised into four treatment groups, one of which was placebo, and one each resmetirom 80 and 100 mg, respectively. While these treatments were double-blind treatments, the fourth randomisation arm was an open label treatment with resmetirom 100 mg.

This study enrolled male and female patients ≥ 18 years of age with suspected or confirmed diagnosis of NASH/MASH//NAFLD/MASLD and hence included a somewhat different population from the final target population. Patients could be recruited both on historical, non-invasive inclusion criteria suggesting MASH (FibroScan kPa ≥ 5.5 to < 8.5 and CAP ≥ 280 dB/m or MRE ≥ 2.0 to < 4.0 kPa with MRI-PDFF $\geq 8\%$) or with histological diagnosis, but also allowing patients with NAS < 4 , and fibrosis < 2 into the study (including screen failures from study 11). In addition, at later stages of the trial, patients taking thyroxine < 75 $\mu\text{g/day}$ (previously excluded from trials), and patients with moderate renal impairment (eGFR ≥ 30 to < 45 mL/min/1.73 m²; also previously excluded from the trials) could be included.

In consequence, the primary objective was to evaluate safety and tolerability. There were, however, 6 secondary objectives/endpoints allowing evaluation of efficacy, including the CFB in LDLC, apolipoprotein B, MRI-PDFF (week 16), triglycerides (in those with baseline triglycerides higher than 150 mg/dl; week 24), FibroScan based CAP (week 52), and FibroScan based VCTE/LSM.

Planning of the study, and sample size was based on the randomised treatment arms. The open-label arm was to be stopped after recruiting reaching 171 patients.

The analysis population for efficacy was defined as was to include all patients from the ITT Population (according to their randomized assignment) who took at least one dose of study medication and had a baseline and at least one post baseline measurement.

Finally, the trial included 1143 patients. Randomization to the open-label arm was discontinued 01 Jul 2021 and the remaining randomization (between 02 Jul 2021 and 31 Oct 2021) was 1:1:1 to the three double-blind arms. Overall, 972 patients were randomized to the three double-blind arms (100 mg resmetirom [n=325], 80 mg resmetirom [n=327], or placebo [n=320]) and 171 patients were randomized to the 100 mg OLNC arm. After irregularities had been detected at 2 sites, the 5 and 3 patients recruited at these sites were excluded from the analysis.

According to the definitions given above, the following numbers and defined populations were analysed:

Table 34. Study 14 Analysis Populations

Population	OLNC (N=171)	Resmetirom 100 mg DB (N=325)	Resmetirom 80 mg DB (N=327)	Placebo DB (N=320)
Safety Population	171 (100.0)	324 (99.7)	327 (100.0)	318 (99.4)
ITT Population	171 (100.0)	325 (100.0)	327 (100.0)	320 (100.0)
mITT Population	170 (99.4)	314 (96.6)	320 (97.9)	309 (96.6)
mITT Lipids Population	170 (99.4)	314 (96.6)	320 (97.9)	309 (96.6)
mITT MRI-PDFF Population	158 (92.4)	278 (85.5)	272 (83.2)	276 (86.3)

Population	OLNC (N=171)	Resmetirom 100 mg DB (N=325)	Resmetirom 80 mg DB (N=327)	Placebo DB (N=320)
mITT FibroScan Population	152 (88.9)	270 (83.1)	260 (79.5)	260 (81.3)

DB = double-blind; ITT = Intent-to-Treat; mITT = Modified Intent-to-Treat; MRI-PDFF = magnetic resonance imaging-proton-density fat fraction; OLNC = open-label non-cirrhotic.

Note: OLNC group include non-cirrhotic patients randomized on or before 01 Jul 2020.

Site 2020 and 2025 excluded from mITT Population.

The mean number of weeks of exposure to study drug was 45 weeks in the double-blind 100 mg resmetirom arm, 43 weeks in the double-blind 80 mg resmetirom arm, 47 weeks in the OLNC arm, and 45 weeks in the placebo arm. In the different arms, 19, 62, 77, and 63 patients discontinued the study before week 52 in the open-label (OLNC), resmetirom 100 mg, resmetirom 80 mg, and placebo arms, respectively. The most frequent reasons for study discontinuation were withdrawal by the patient (other than AE) and lost-to-follow-up.

There were special dosing instructions in place during the trial, with reductions based on evaluation of changes in thyroid hormones, SHBG (in those patients with cirrhosis at baseline), in patients with baseline cirrhosis, and also depending on exposure.

With regard to the latter population of compensated cirrhosis patients, the applicant provides an Addendum Report for study MGL-3196-14 which includes the analyses of the primary and selected key secondary, secondary, and exploratory objectives of the trial in patients with compensated MASH cirrhosis (see below).

The main baseline characteristics of the patient population are given in the following table:

Table 35. Demographic and Baseline Characteristics – Population: Safety – Study 14

Characteristic	OLNC (N=171)	Resmetirom 100 mg DB (N=324)	Resmetirom 80 mg DB (N=327)	Placebo DB (N=318)
Age at Informed Consent (years)				
n	171	324	327	318
Mean (SD)	55.6 (11.5)	55.9 (11.7)	56.2 (11.7)	55.7 (12.1)
Median	57.0	57.0	58.0	57.0
Min, Max	22, 80	20, 83	20, 82	20, 79
Age Category, n (%)				
<65	134 (78.4)	250 (77.2)	245 (74.9)	232 (73.0)
≥65	37 (21.6)	74 (22.8)	82 (25.1)	86 (27.0)
Sex, n (%)				
Male	55 (32.2)	147 (45.4)	145 (44.3)	150 (47.2)
Female	116 (67.8)	177 (54.6)	182 (55.7)	168 (52.8)
Race, n (%)				
American Indian or Alaska Native	0	1 (0.3)	3 (0.9)	1 (0.3)
Asian	6 (3.5)	6 (1.9)	6 (1.8)	7 (2.2)
Black or African American	10 (5.8)	22 (6.8)	21 (6.4)	20 (6.3)
Native Hawaiian or Other Pacific Islander	0	2 (0.6)	1 (0.3)	1 (0.3)
White	151 (88.3)	287 (88.6)	290 (88.7)	282 (88.7)
Other	3 (1.8)	4 (1.2)	4 (1.2)	5 (1.6)
Missing	1 (0.6)	2 (0.6)	2 (0.6)	2 (0.6)
Ethnicity, n (%)				
Hispanic or Latino	52 (30.4)	108 (33.3)	108 (33.0)	120 (37.7)
Not Hispanic or Latino	118 (69.0)	214 (66.0)	216 (66.1)	192 (60.4)
Missing	1 (0.6)	2 (0.6)	3 (0.9)	6 (1.9)
BMI (kg/m ²)				
n	171	324	327	316
Mean (SD)	36.1(6.3)	35.4 (6.4)	35.3 (5.9)	35.2 (5.8)
Median	35.3	34.7	34.4	34.4
Min, Max	25.4, 60.7	22.1, 70.9	24.3, 66.4	23.1, 60.3

During the study, drug dose adjustments (based on low FT4 levels, defined as a ≥30% decrease from baseline on consecutive visits to a value of <0.7 ng/dL) were infrequent; 12 (2.4%) patients had their doses reduced from 100 mg resmetirom to 80 mg and 2 (0.6%) patients had dose reduced from 80 mg resmetirom to 60 mg.

The pre-designated “key secondary” efficacy endpoints were met for both double-blind arms. The main results, including those for the OLNC arm, are displayed in the following table (“subgroup” analyses for those patients above certain thresholds (e.g. LDL-C≥100 mg/dl – except for the liver enzymes – are not displayed)).

Table 36. Key Secondary and Other Secondary Endpoints (mITT population) – Study 14

	OLNC (n=169)		Resmetirom 100 mg DB (n=314)			Resmetirom 80 mg DB (n=320)			Placebo DB (n=309)
	LSM %CFB (SE)	95% CI	LSM %CFB (SE)	LSM Difference (97.5% CI)	P value	LSM %CFB (SE)	LSM Difference (97.5% CI)	P value	LSM %CFB (SE)
LDL-C, mg/dL									
n	170		314			320			309
Baseline mean (SD)	115.2 (41.2)		109.1 (36.4)			111.3 (37.8)			105.9 (36.9)
Week 24	-19.4 (2.6)	-24.5 to -14.3	-13.9 (2.0)	-12.6 (-16.7 to -8.6)	<0.0001	-12.4 (2.0)	-11.1 (-15.0 to -7.2)	<0.0001	-1.3 (1.9)
Week 48	-20.5 (2.5)	-25.4 to -15.6	-13.4 (2.4)	-12.0 (-16.8 to -7.2)	<0.0001	-10.6 (2.1)	-9.2 (-14.2 to -4.3)	0.0004	-1.4 (2.4)
ApoB, mg/dL									
n	170		314			320			309
Baseline mean (SD)	101.0 (28.5)		95.4 (24.9)			97.7 (26.3)			94.5 (27.0)
Week 24	-21.3 (2.1)	-25.4 to -17.2	-16.5 (1.6)	-16.5 (-19.5 to -13.4)	<0.0001	-14.3 (1.6)	-14.3 (-17.4 to -11.3)	<0.0001	0.0 (1.5)
Week 48	-22.4 (2.1)	-26.4 to -18.4	-16.3 (1.8)	-15.1 (-18.7 to -11.6)	<0.0001	-13.8 (1.6)	-12.5 (-16.4 to -8.7)	<0.0001	-1.2 (1.8)
MRI-PDFF, % fat fraction									
n	158		268			255			268
Baseline mean (SD)	17.9 (7.1)		18.0 (7.3)			17.4 (6.6)			17.7 (6.8)
Week 16	-45.3 (3.1)	-51.3 to -39.2	-45.1 (2.6)	-38.6 (-44.7 to -32.5)	<0.0001	-41.4 (2.6)	-34.9 (-41.1 to -28.7)	<0.0001	-6.5 (2.6)
Week 52	-49.2 (3.5)	-56.1 to -42.4	-44.0 (3.0)	-33.9 (-40.8 to -27.0)	<0.0001	-38.9 (3.0)	-28.8 (-35.8 to -21.7)	<0.0001	-10.1 (3.0)
FibroScan CAP, dBm									
N	147		270			260			260
Baseline mean (SD)	339.6 (36.7)		340.7 (34.3)			339.3 (32.9)			344. (34.8)
Week 52 CFB	-46.0 (4.8)	-55.3 to -36.6	-42.8 (4.0)	-24.4 (-33.8 to -15.1)	<0.0001	-36.7 (3.9)	-18.3 (-27.8 to -8.9)	<0.0001	-18.4 (3.9)
FibroScan VCTE, kPa (Baseline VCTE ≥7.2 kPa)									
n	51		102			83			107
Baseline mean (SD)	9.0 (2.4)		8.4 (1.6)			8.5 (1.3)			8.5 (1.8)
Week 52 CFB	-2.0 (0.5)	-2.9 to -1.1	-1.7 (0.4)	-0.51 (-1.3 to 0.3)	0.17	-1.0 (0.4)	0.17 (-0.7 to 1.0)	0.66	-1.2 (0.4)

For the analysis of MRI-PDFF, a subgroup analysis was performed, which demonstrated consistent reductions in all subgroups, with the highest reductions occurring in patients with high SHBG and in those with weight loss.

As shown, the effects on Firoscan based CAP showed consistent and high reductions of liver fat in all treatment groups with significant results in both double-blind groups, and similar magnitude of effect in the OLNC group.

Approximately one-third of randomized patients had a baseline liver stiffness measurement via FibroScan VCTE that met prespecified criteria for analysis (≥ 7.2 kPa, which has been shown to have a $\geq 90\%$ positive predictive value for moderate fibrosis [F2]) (51 patients in the OLNC arm, 102 patients in the double-blind 100 mg resmetirom arm, 83 patients in the double-blind 80 mg resmetirom arm, and 107 patients in the placebo arm). Although directionally showing a treatment effect in the double-blind 100 mg resmetirom arm, the mean change from baseline in FibroScan VCTE was not significantly different between the resmetirom and placebo arms at Week 52. An explorative responder analysis showed a numerically greater proportion of patients in the resmetirom arms achieved either a ≥ 2 kPa reduction from baseline (31% to 57% in the resmetirom arms vs 32% in the placebo arm) or a $\geq 30\%$ reduction from baseline (23% to 39% vs 26%, respectively) in FibroScan VCTE at Week 52. This evaluation also suffers from a restricted number of patients included with a differential percentage in the treatment groups fulfilling the criteria.

Similar, rather small effects were seen in the evaluation of the ELF biomarker with a somewhat increased response in the OLNC and 100 mg groups as compared to the other groups.

A similar responder analysis was conducted for the MRE-based evaluation of fibrosis. Which more clearly demonstrated effects of active treatment compared with placebo, albeit with an even more reduced dataset (see the following table).

Table 37. Summary of Magnetic Resonance Elastography Responder Results Observed Data; Analysis Population: Modified Intent-to-Treat Patients With Baseline MRE Result ≥ 2.9 kPa – Study 14

Responder Category [n (%)]	OLNC (N=35)	Resmetirom 100 mg DB (N=53)	Resmetirom 80 mg DB (N=60)	Placebo DB (N=44)
Improved	9 (25.7)	12 (22.6)	13 (21.7)	5 (11.4)
Unchanged	26 (74.3)	36 (67.9)	44 (73.3)	34 (77.3)
Worsened	0 (0.0)	5 (9.4)	3 (5.0)	5 (11.4)

DB = double-blind; MRE = magnetic resonance elastography; OLNC = open-label non-cirrhotic

Note: Responder Categories:

Improved: Week 52 result $\geq 19\%$ decrease from baseline result

Worsened: Week 52 result $\geq 19\%$ increase from baseline result

Unchanged: Patient did not meet improved or worsening criteria

OLNC group includes open-label non-cirrhotic patients randomized on or before 01 Jul 2020.

Analysis excludes patients from sites 2020 and 2025.

The applicant also provides an Addendum Report for study MGL-3196-14 which includes the analyses of the primary and selected key secondary, secondary, and exploratory objectives of trial 14 in patients with compensated MASH cirrhosis (which were included in the open-label study arm).

The report was drawn up following protocol amendment 3 of June 2020, which allowed patients with compensated MASH cirrhosis to be enrolled into an open-label 80 mg treatment arm. The open-label arm of patients with compensated MASH cirrhosis was to enrol approximately 185 patients with either normal liver function or mild/moderate hepatic impairment determined by CP-A with score ≤ 6 as diagnosed by historic liver biopsy (NASH/MASH with stage fibrosis 4) or earlier stage NASH/MASH fibrosis with clinical progression to cirrhosis.

Overall, 180 patients were included. The baseline characteristics of this population showed that patients were older at inclusion (about 38% were older than 65), and predominantly female. The mean BMI was about 35 kg/m², and T2DM, hypertension and dyslipidaemia was present in more than 70% of the population.

In this patient population there were reductions from baseline in LDL-C at Week 24 and Week 48 in all patients as well as among patients with baseline MRI-PDFF $\leq 5\%$ and those with baseline MRI-PDFF $> 5\%$ (overall change from baseline was -20.4 mg/dl at week 24, and -24.1 mg/dl at week 48).

There were also reductions from baseline in ApoB at Week 24 and Week 48 (Table 6). At Week 24 in open-label cirrhotic patients there was a mean (SE) reduction of -17.5% (1.4%) from baseline. This effect was maintained after 48 weeks of treatment, with a mean reduction of -22.1% (1.4%) from baseline.

Similarly, there were reductions from baseline in triglycerides at Week 24 and Week 48. At Week 24 there was a mean (SE) reduction of -9.6% (2.5%) from baseline. This effect was maintained after 48 weeks of treatment, with a mean reduction of -16.0% (2.9%) from baseline.

Other serum lipid parameters also showed changes with reductions throughout the panel of investigations.

There were reductions from baseline in hepatic fat fraction as measured by MRI-PDFF at Week 16 and Week 52. At Week 16 there was a mean (SE) reduction of -20.8% (2.9%) from baseline. This effect was maintained after 52 weeks of treatment, with a mean reduction of -25.3% (3.3%) from baseline.

Reductions in hepatic fat were also observed in the subgroup of patients with baseline MR-PDFF >5%, with a reduction of -26.2% (2.7%) at Week 16 and -28.4% (3.5%) at Week 52 from baseline. In patients that already had low hepatic fat fraction at baseline of ≤5%, reductions from baseline in MRI-PDFF assessments were observed, although the changes were not as large as those seen in patients with higher baseline values. At Week 16 there was a mean reduction of -4.7% (7.9%) from baseline and at Week 52 there was a mean reduction of -15.9% (7.8%).

The following table shows the changes in Fibro-Scan VCTE response and according to baseline % MRI-PDFF:

Table 38. Summary of FibroScan VCTE Responder Results; Observed Data – Analysis Population: Open-label Cirrhotic Patients

Parameter Responder Category [n (%)]	Percent Change from Baseline
Open-label Cirrhotic (N=180)	
Improved	67 (37.2)
Unchanged	67 (37.2)
Worsened	23 (12.8)
Missing	6 (3.3)
MRI-PDFF ≤5% (N=42)	
Improved	15 (35.7)
Unchanged	13 (31.0)
Worsened	7 (16.7)
Missing	2 (4.8)
MRI-PDFF >5% (N=126)	
Improved	47 (37.3)
Unchanged	49 (38.9)
Worsened	14 (11.1)
Missing	4 (3.2)

MRI-PDFF = magnetic resonance imaging proton fat fraction; VCTE = vibration controlled transient elastography.

Note: Responder Categories:

Improved: Week 52 Percent Change From Baseline ≥25% decrease

Worsened: Week 52 Percent Change From Baseline ≥25% increase

Unchanged: Patient did not meet improved or worsening criteria for Change or Percent Change From Baseline

Missing: Patients who have assessment of Week 52 but no baseline assessment.

Changes in AST, ALT, and GGT (in those with elevated ALT ≥30 U/L; n=100 of the total of 180) showed reductions for all parameters.

The results for the serum biomarkers are shown in the following table:

Table 39. Summary of Fibrosis and Inflammation Biomarkers; Observed Data – Analysis Population: Open-label Cirrhotic Patients – Study 14 – Addendum

Parameter Analysis Visit Statistic	Baseline	Visit Result	Change from Baseline	Percent Change from Baseline
Cytokeratin 18 (M30) (U/L)				
Open-label Cirrhotic (N=180)				
Week 52				
n	157	157	157	-
Mean (SE)	747.000 (39.4882)	605.158 (30.2170)	-141.842 (36.1503)	-
Median	618.660	500.380	-90.700	-
Min, Max	12.50, 2001.00	12.50, 2001.00	-1613.97, 1582.35	-
Adiponectin (µg/mL)				
Open-label Cirrhotic (N=180)				
Week 52				
n	157	157	157	-
Mean (SE)	5.3838 (0.26532)	6.6245 (0.37527)	1.2407 (0.24352)	-
Median	4.7490	5.4140	0.4890	-
Min, Max	1.202, 19.098	1.343, 25.939	-11.564, 16.081	-
Enhanced Liver Fibrosis Test				
Open-label Cirrhotic with Baseline ≥ 9.8 (N=140)				
Week 52				
n	125	125	125	-
Mean (SE)	11.038 (0.0748)	10.766 (0.0896)	-0.272 (0.0715)	-
Median	10.920	10.710	-0.210	-
Min, Max	9.80, 13.35	8.21, 13.72	-3.63, 1.38	-

Overall, study 14 – with all the limitations associated with the unclear status of the population (whether they belong to the intended target population or not) as well as with the partly incomplete evaluation of the endpoints – can be regarded to be supportive, mainly for safety). However, the available efficacy data are grossly in accordance with what had been reported in the pivotal trial. What is even more important is the fact that the population included was a partly “presumed” population of MASH patients, resembling more clearly patients that would likely be receiving the medication in clinical practice, in a situation when most of the patients would probably not receive a biopsy. From this, it can be concluded that a restriction of the indication to a population having had a biopsy available is not considered necessary, since the safety has also adequately been documented in this more “natural” population (see below). Although the efficacy support in this population is somewhat limited, there is currently no indication that effects would be relevantly altered in case the patient does not have a histology-based diagnosis.

Study MGL-3196-18

This study is an on-going 52-week, multi center, active treatment study, which includes a 52-week treatment period and a 4-week follow-up period. It is primarily a roll-over study for patients who completed Study MGL-3196-14. Additionally, patients who screen failed from Study 11, or who had CP-A/B (score <8) NASH/MASH cirrhosis (screen failure patients from Study 19 or *de novo* patients [patients who did not previously screen for a Phase 3 resmetirom clinical trial]) were also eligible to enrol. The study is submitted with an interim report with a data cut-off date of 30 September 2022.

The trial was – similar to study 14 – having a primary objective of evaluation of safety and tolerability. Secondary objectives partially also related to safety and tolerability, but again included the evaluation of

serum lipids, SHBG, MR-PDFF, “conventional” liver enzymes, fibrosis biomarkers (CK-18, adiponectin and ELF, including its components), the evaluation of CAP and VCTE, MRE, and the evaluation of Quality of Life (using CLDQ-NASH, and WPAI-NASH QOL). Exploratory objectives referred to investigations of insulin resistance, body weight and BMI, blood pressure, and thyroid hormone homeostasis.

For the evaluation of efficacy, baseline was defined as the last time-point with available data on which patients had not received active study medication.

Patients were either assigned open-label resmetirom or randomly assigned to either double-blind 80 mg or 100 mg resmetirom (if they completed the double-blind treatment period of the MGL-3196-14 study based on the criteria below). The randomization was stratified by randomized double-blind resmetirom 100 mg, resmetirom 80 mg, or placebo from MGL-3196-14

The provided interim CSR includes analyses of primary and selected secondary and exploratory objectives for roll-over patients from Study MGL-3196-14 and patients who failed screening in Study MGL-3196-11 with the following different subpopulations:

- Double-blind patients from Study MGL-3196-14, who were randomized to either 80 mg or 100 mg resmetirom daily for the first 12 weeks of the study. Patients then received 100 mg open-label resmetirom, unless they met criteria for downward dose adjustment, to at least the Extension Week 28 visit before the data cut-off date.
- Open-label non-cirrhotic (OLNC) patients from Study MGL-3196-14, who continued to receive the same open-label resmetirom dose regimen in MGL-3196-18.
- Non-cirrhotic patients who screen failed from Study MGL-3196-11 and enrolled in MGL-3196-18 on open-label resmetirom prior to the data cutoff date of 30 Sep 2022.

In addition to these, the data on open-label patients from study 14 which were included into the cirrhotic patients’ arm, the screen-failed patients from study 11 with compensated cirrhosis, and the screen-failed patients from study 19 who were *de novo* patients and enrolled in study 18 on open label resmetirom will be included in the final CSR.

There were 86 placebo to 80 mg, 86 placebo to 100 mg, 171 active to 80 mg, 170 active to 100 mg, and 102 open-label patients in the study (n= 615). As of the data cutoff date of the interim CSR (30 Sep 2022), there were 8.1% of placebo to 80 mg, 8.1% of placebo to 100 mg, 8.8% of active to 80 mg, 10.6% of active to 100 mg, and 27.5% of open-label patients having completed Extension Week 52 of the study.

The reported study population used the following doses during the study, as given in the following table (based on screened patients):

Table 40. Patient Disposition – Screened Patients – Study 18

Disposition Category	Placebo to Resmetirom 80 mg (N=86) n (%)	Placebo to Resmetirom 100 mg (N=86) n (%)	Any Resmetirom to Resmetirom 80 mg (N=171) n (%)	Any Resmetirom to Resmetirom 100 mg (N=170) n (%)	Open-label 100 mg (N=102) n (%)
Stratification by Dose Assignment in MGL-3196-14					
100 mg resmetirom	0	0	87 (50.9)	86 (50.6)	-
80 mg resmetirom	0	0	84 (49.1)	84 (49.4)	-
Placebo	86 (100)	86 (100)	0	0	-

In these groups, 7, 10, 17, 15, and 3 patients discontinued the study prematurely, with the main reasons being “withdrawal by subject other than AE”, and “lost to follow-up”. At the time of the interim evaluation presented, 7, 7, 15, 18, and 28 of the patients had completed Extension Week 52.

Demographic and baseline characteristics of the Safety Population were generally comparable across the groups. Overall, the majority of the patients were <65 years old (61.6% to 68.6%), White (83.7% to 91.9%), and not of Hispanic or Latino ethnicity (66.3% to 77.2%). There was a slightly higher proportion of males in the placebo to 80 mg group (53.5%) compared to the other four groups (43.1% to 47.7%). The mean age of the patients was around 58 to 59 years.

Most efficacy evaluations presented are restricted to early time points, such as Week 12, and Week 28. For the serum lipid parameters, these showed consistent reductions of total cholesterol, LDL-C, and overall small increases in HDL-C.

The MR-PDFF based results are shown in the following table, with evaluation conducted at Week 16:

Table 41. Summary of MRI-PDFF by Visit – Full Analysis Population – Study 18

Visit Statistic	Placebo to Resmetirom 80 100 mg (N=86)	Placebo to Resmetirom 100 100 mg (N=86)	Any Resmetirom to Resmetirom 80 100 mg (N=171)	Any Resmetirom to Resmetirom 100 100 mg (N=170)	Any Resmetirom to Resmetirom (N=341)	Open-label 100 mg (N=102)
Baseline						
Mean (SD)	15.3 (7.9)	15.5 (6.4)	16.8 (6.3)	18.2 (6.9)	17.5 (6.6)	16.5 (6.8)
Extension Week 16						
Mean %CFB (SE)	-36.8 (4.3)	-40.3 (3.9)	-50.7 (2.9)	-47.4 (3.5)	-49.0 (2.3)	-53.5 (3.3)

%CFB = percent change from baseline; MRI-PDFF = magnetic resonance imaging proton density fat fraction; SD = standard deviation; SE = standard error

Note: In the column headers, the first component (Placebo, Any Resmetirom) is the treatment received in MGL-3196-14 Study. The second component (resmetirom 80|100 mg, resmetirom 100|100 mg) is the randomized treatment at Day 1 and dose level after Week 12 in MGL-3196-18 Study. Open-label 100 mg is for non-randomized patients in MGL-3196-18 Study.

Note: For the patients who had received resmetirom in MGL-3196-14, the baseline value is the baseline used in MGL-3196-14. For the patients who received resmetirom for the first time in this study, the baseline is defined as the last non-missing measurement prior to the first dose in this study (MGL-3196-18).

The evaluation of liver enzymes is again restricted to patients with elevations of ALT $\geq$ 30 U/L at baseline. There were decreases in ALT, AST, and GGT from baseline to Extension Week 12 that were also apparent at Extension Week 28 across all of the patient groups.

Changes from baseline in markers of inflammation and fibrosis were assessed after 12 and 28 weeks of the extension study. CK-18, adiponectin, and RT3 improved from baseline to Extension Week 12 in all treatment groups. For CK-18, the decreases from baseline were much larger for the active to 80 mg, active to 100 mg, and open-label groups (-234.9 to -277.8 U/L at Extension Week 12) in comparison to the placebo to 80 mg and placebo to 100 mg groups (-13.9 and -34.6 U/L at Extension Week 12), which is presumably attributed to the longer duration of treatment. At Extension Week 28, CK-18 continued to improve (decrease) in the placebo to 80 mg and placebo to 100 mg groups, while the CFB was maintained in the other groups.

At Extension Week 16, the MRE decreased across the groups, although the mean (SE) decrease observed in the active (any previous dose) to 100 mg group (-2.0% [3.3%]) was not as large as was observed in the other treatment groups (-10.5% to -12.8%).

The explorative efficacy endpoints included MELD score for which no relevant changes were observed, and Ferritin, and Fibrinogen, which both increased during the study. Fibrinogen, which was around a mean of 400 ng/dl at baseline increased to mean values being high normal (450-460 mg/dl). Ferritin increased consistently across groups but showed more variable mean baseline and increases (baseline around 100-130 µg/l with increases to 135-170 µg/l at Week 28). Individual variability was high for ferritin.

As an experimental method, Velacur ultrasound scanning was used in the study. This method is used to assess both liver fat and liver stiffness (attenuation and elasticity). Results were available for Week 16 only. The results showed consistent reductions of attenuation parameters. However, elasticity, as a measure of fibrosis, was showing more inconsistent results with increases in the placebo to resmetirom patients, and almost no effects in the open-label arm. However, the patients previously on active treatment were showing clear decreases.

Overall, the study somewhat confirms the results of the previous study 14 and can be considered weakly supportive of the previous studies. However, the submitted study report is still incomplete with a restricted number of patients treated for a limited timeframe. The applicant will provide the results when the study is completed.

2.6.6. Discussion on clinical efficacy

Design and conduct of clinical studies

The main clinical study submitted (study 11) is a double-blind placebo controlled long-term efficacy study which has been presented with an interim evaluation. The use of placebo in a setting of an unmet medical need is considered fully acceptable. The interim evaluation was conducted after all the patients included in the interim had passed 12 months of treatment. This is a relatively short period of treatment, considering the long-term course of the disease, and also not compliant with the recommendations of the NASH/MASH reflection paper. However, this short course of the trial is not considered to be of concern *per se*, since adequate results can be achieved also in shorter time-intervals.

The trial included patients with histologically diagnosed MASH mainly adhering to the recommendations of the reflection paper with regard to activity of the disease.

Initially, a considerable proportion of patients was included with a fibrosis stage of 1 only which – also according to the current scientific consensus – is not regarded to be the target population for pharmacological treatment. This population is rather deemed to be amenable to lifestyle and diet-based treatments. The available evidence was considered too weak to overcome the multitude of epidemiological

data not showing a detrimental effect on liver (and non-liver related) outcomes in the long-term course of the disease for the overall F1 population. As a result, the approved indication is restricted to F2/F3 fibrosis population.

It is concluded that the population for this study has been adequately selected, and the results of the interim evaluation show that the population shows to a high extent the features expected in such a population.

The applicant has based the interim evaluation of this single pivotal trial on two histology endpoints, defined as improvement of fibrosis without worsening of NASH/MASH, and as resolution of NASH/MASH without worsening of fibrosis. The definitions for these endpoints are mainly considered acceptable with only minor deviations from the regulatory requirements (Reflection paper on regulatory requirements for the development of medicinal products for non-alcoholic steatohepatitis [NASH]), (EMA/CHMP/299976/2018):

<i>Reflection paper on regulatory requirements for the development of medicinal products for non-alcoholic steatohepatitis (NASH)</i> (EMA/CHMP/299976/2018) intermediate endpoint	Study MGL-3196-11 (Week 52 primary objectives)
The resolution of NASH - with the presence of any grade of steatosis, no ballooning, and only minimal (grade 1) lobular inflammation and - at the same time - no worsening of the stage of fibrosis.	The resolution of NASH associated with an at least 2-point reduction in non-alcoholic fatty liver disease (NAFLD) activity score (NAS) and without worsening of fibrosis by liver biopsy
The improvement of fibrosis by at least 1 stage without any worsening of NASH (no worsening of ballooning and lobular inflammation, a 1 grade change in steatosis may be acceptable).	Histological improvement from Baseline demonstrated by at least a 1-point improvement in fibrosis (NASH Clinical Research Network [CRN] system) by liver biopsy with no worsening of NAS (total of 3 NAS components: ballooning, lobular inflammation, and steatosis)

According to current knowledge and the regulatory guidance, the endpoints are not considered to be fully validated surrogates in the strict sense but can be seen as adequately likely to predict outcome with regard to liver decompensation events.

The applicant has assigned a couple of secondary endpoints which were adequate as a whole. The fact that LDL-C effects were assigned as "key" secondary endpoint is noted, but effects on all serum lipids would rather be regarded to be lower in the hierarchy of secondary endpoints, as compared to the chosen non-invasive methods to assess the changes in the liver itself, which appears clearly more relevant for the indication aimed at.

The estimand defined for the primary endpoints was considered acceptable. The estimands for secondary endpoints were not defined *a priori*. Additional analyses have demonstrated the robustness of the results. The statistical methods/tests for evaluation were deemed adequate.

During the study, there were relevant changes to the protocol implemented, which at first mainly concerned more adequate definitions, but also taking account of the COVID-19 pandemic, which also influenced the conduct of this trial. SAP 3.0 which was used for Week 52 analysis was approved on 05 Dec 2022 after unblinding of patient treatment assignment at the CRO on 02 Dec 2022. This questions proper pre-specification, given the substantial changes in the analysis as compared to the original study protocol. It is noted that changes to SAP 3.0 compared to versions 1.0 (18 October 2022) and 2.0 (23 November 2022), which were finalized prior to unblinding any data, appear to be related to clarifying language about patients that were re-evaluated as having fibrosis stage 4 at baseline. The analysis of confirmatory endpoints was not impacted aside from changes in the population to be evaluated with respect to fibrosis stage. This is however not considered of concern, as the F2/F3 population is considered the relevant one. The overall planning and conduct (late amendments and handling of SAP) raises some concern and is highly unusual and in part lacks GCP compliance. The risk associated with the reliability of the study data and results in particular for multiplicity-controlled Week 52 endpoints is considered low. Analyses of these endpoints can still be considered sufficiently pre-specified. However, the GCP concerns, and missing/unclear pre-specification prevent this study being the only condition for CMA.

The pivotal study 11 is submitted including the first 1050 patients of the F1B, F2 and F3 population having been treated for 1 year. Some additional F1A/C patients were also included, but only in exploratory manner.

The primary endpoints have been evaluated by two central pathologists, and the primary mode of evaluation of the responder type endpoints has applied a way of evaluation with assigning "1" to patients with agreement between the two, and "0.5" with disagreement between the two (while non-response diagnosed by both has been assigned "0"). This was a rather unusual way of evaluation, and other recommendations have been given, e.g. by consensus panels and academia. However, the CHMP reflection paper does not directly demand a specific way of evaluation of biopsy material in MASH. The applicant has implemented, as a secondary analysis of the primary endpoints, a so-called "consensus" analysis, for which the discrepant results have been discussed by the two central pathologists until agreement was achieved.

Whether the mode of evaluation taken by the applicant can be considered appropriate is uncertain, however, distributing half of the cases with disagreement to the "success" group, and half to the "failure" group does not appear to be fully implausible. Nevertheless, the consensus evaluation and sensitivity analysis accounting for variable pathologist decisions provides reassurance with regards to the appropriateness of the primary evaluation.

The applicant has also included – as exploratory evaluation – AI-assisted histology evaluations, which can be taken as valuable contribution to further "validate" not only the experimental method itself but also give some feel on the adequacy of the manual evaluations conducted.

The overall methodology of evaluation of the primary endpoints (and the secondary evaluations also based on histology) is therefore considered acceptable.

The evaluation of secondary endpoints based on biomarkers and imaging methods have on one hand mainly concentrated on serum lipids (other than LDL-C) and on the other hand are reported on an observed case basis only, excluding those patients for which the respective baseline value was not available, or been pre-planned as subgroup evaluation only. This may partly be attributable to the non-availability of certain methods – especially imaging methods – in part of the study centres. However, the non-ITT-based evaluation also affect the simpler, biomarker-based endpoints.

The applicant has further presented two extension studies 14 and 18, of which one (18) is the extension of the first one (14), at least for the currently reported population (this study is presented also with an interim evaluation).

Both studies were mainly designed to recruit either patients not fully eligible to the pivotal study, or a population included in non-invasive criteria for MASH. The population is therefore somewhat uncertain for the diagnosis of MASH but could resemble (at least partly) a population that would realistically be treated in clinical practice in a situation when many patients would not receive a liver biopsy.

Overall, the results, although partly incompletely reported, can be regarded to be supportive of the conclusions of the pivotal study, however with a limited level of evidence only, mainly owing to their characters as safety studies.

Efficacy data and additional analyses

The results of study 11 both for the full and F2/F3 population demonstrated a statistically significant effect both on the NASH/MASH resolution endpoint, as well as on the improvement of fibrosis endpoint. Both doses (80 and 100 mg) of the compound were successful with p-values below 0.0001 for each of the analyses (and thus complying with the increased statistical rigour required for the presentation of only one pivotal trial).

The effect size was slightly higher with the higher dose, which achieved tripling of the response rate compared to placebo with the NASH/MASH resolution endpoint, and an almost doubling of the response rate for fibrosis reduction. Nevertheless, success of the treatment remains at about 30% for NASH/MASH resolution, and for the fibrosis improvement, leaving 70% of the patients not relevantly improved after one year of treatment. Nevertheless, considering the course of development of the disease, and the relatively short treatment period of the trial, the improvements achieved can be considered clinically relevant. It can be reasonably assumed that longer term treatment can bring about a further increase in response rates for both endpoints, and hence the compound must be regarded to be a long-term treatment, potentially not to be administered life-long, but at least for some years.

The applicant has further analysed the primary evaluations and in general the histological features with further evaluations, which all were supportive of the conclusions of the primary evaluation, in general expressing highly statistically significant results.

The applicant has furthermore presented a couple of additional and sensitivity analyses, as well as subgroup analyses of the primary endpoints which were all demonstrating a high level of robustness and consistency of the results, also supporting the acceptability of presenting one pivotal study only.

The results on the primary endpoints are supported by those on several secondary endpoints, which included imaging methods based on MR based evaluation of liver fat and fibrosis, Fibroscan based evaluations of liver stiffness and CAP, conventional serum biomarkers such as transaminases, specific fibrosis related biomarkers such as ELF, and general liver-damage biomarkers such as CK-18. The trial also evaluated a full panel of serum lipids which all have shown a certain level of improvement, with most of them demonstrating statistically significant changes compared to placebo.

However, most of the secondary evaluations are based on a restricted number of patients and are presented on an observed case basis only or excluding those patients without baseline observation. In case of some of the biomarkers for which a certain threshold for inclusion into the analyses was applied, it remains unclear how representative and balanced the subgroups were.

In accordance with the Statistical Analysis Plan for study MGL-3196-11 primary and key secondary endpoints were examined also in subgroups: weight (> 200 lbs, ≤ 200 lbs); BMI (<35, ≥35); genetic NASH single nucleotide polymorphism (SNPs), including genetic variations at PNPLA3. Results of the Study 11 dual primary and key secondary endpoints analysed by weight and BMI category subgroups for the F2/F3 population are provided. The results are consistent with the primary analysis results reported in the Study 11. The data suggest that the presence of NASH risk alleles did not influence the response to resmetirom.

The applicant has also evaluated the influence of the treatment on Quality of Life. No significant or clinically relevant changes have been detected which is expected as NAFLD, including NASH, is usually a silent disease, with few or no symptoms and most people don't experience symptoms until NASH cirrhosis has developed.

The trial has overall shown that there is only a minor, potentially clinically not relevant difference between the two doses. Nevertheless, the analyses presented (as well as the exposure data and the modelling approach for the PK-PD relationship) for the justification of the doses have shown that the high dose seems not to be the most appropriate for all patients, since high(er) rates of adverse events/reactions are expected in the high dose group, especially in the elderly population leading to a potentially early discontinuation of the medication. Besides the recommendation to take the lower dose in the elderly (which is acceptable), a cut-off has been justified to recommend the intake of 100 mg for those patients with higher body weight.

The applicant has additionally presented one initial, phase 2 proof of concept study, which also evaluated histological changes in an adequately diagnosed MASH population, which, however, included more than half of the patients with a fibrosis stage below 2. 148 patients were included into the trial. MR-PDFF was used as the primary endpoint after 36 weeks, which showed a highly significant difference to placebo. The evaluation of histology also clearly favoured the active treatment group above placebo with the exception of the fibrosis related endpoints which had a high rate of placebo response. Since a response with regard to fibrosis is not expected after such a short period, this is not of concern as such. Overall, the results are supportive of the overall conclusions. The trial also explored different dose levels (not in randomised ways) but gave relevant input into the exposure-response model which was also used to determine the doses in the phase 3 trial 11.

The applicant has also presented two supportive studies in a MASLD population of which an unknown number of the patients would be expected not to suffer from MASH, especially not in the relevant target population with F2/F3. The studies were mainly presented as safety studies. Nevertheless, the effects achieved with regard to imaging, biomarkers, and the reduction of serum lipids can overall be seen also to support the results of the pivotal study. The value of these studies may also be derived from the fact that some efficacy as well as safety is documented in a population without a liver biopsy available. A discussion on the need to restrict the indication to a biopsy-based diagnosis of MASH patients is therefore not considered necessary.

While there is strong support for a preliminary conclusion of efficacy from the data presented, the pivotal trial is still on-going and the final results will be needed to confirm efficacy in the sense of preventing the manifestation of cirrhosis, and its complications in the long-term. Also, a trial in the MASH-cirrhosis population has meanwhile been initiated, which also aims at detecting effects on liver outcomes, and is expected – with the final results – to contribute to the overall final evaluation of efficacy once the results are available.

Additional efficacy data needed in the context of a conditional MA

The applicant initially applied for a “full” MA, however, a CMA is considered more appropriate. This is based on the fact that only an interim evaluation of the pivotal study 11 has been presented. This interim evaluation was based on histology results demonstrating improvement of parameters which are considered unvalidated

surrogates for the clinical, long-term fate of the patients. The final CSR will provide further proof on the long-term benefit of the product. In addition, it is expected that study 19, although designed for a different target patient population, will support the clinical benefit of the product in the MASH indication. Please refer to section 3.7.3. for further details.

2.6.7. Conclusions on the clinical efficacy

The pivotal trial 11 has shown clear beneficial effects on the two primary efficacy endpoints in the interim evaluation conducted. Both an effect on the reduction of the fibrosis grade, as well as on the resolution and improvement of the inflammatory, steatotic, and degenerative changes in liver cells have been demonstrated. The results on these histology endpoints were considered robust and statistically compelling. The effects were consistent in sensitivity analyses as well as in relevant subgroups of patients. The beneficial changes in histology are supported by a number of evaluations based on different imaging methods, and of relevant biomarker observations. Cardiometabolic risk factors (such as the serum lipids) are positively influenced by the treatment.

The conclusion on the beneficial effects was supported by the submission of two studies conducted in a slightly different population, but which partly shows similar features as the primary target population. However, while the patients can all be diagnosed with MASLD, the final diagnosis of MASH is either uncertain, or has been excluded. Effects on serum lipids, liver fat content, non-invasive measurement of fibrosis and on biomarkers is concordant with the results achieved in the histologically diagnosed population.

The overall documentation of efficacy was limited to beneficial effects demonstrated for surrogate endpoints currently not considered acceptable to obtain a full approval in the proposed indication. Since the pivotal trial, as well as two other trials are ongoing at the time of this assessment report, it is expected that data confirming efficacy could be generated in the future and the completion of these trials is necessary to address the missing efficacy data in the context of a conditional MA.

The CHMP considers the following measures necessary to address the missing efficacy data in the context of a conditional MA:

- to fulfil the information gap on long-term efficacy and safety, data will be provided from the on-going study 11. This will be a category 2 post-authorisation measure (SOB).
- the results of study 19 MAESTRO-NASH-OUTCOMES to evaluate the effect of the medicinal product on liver-related outcomes in patients with well-compensated (Child-Pugh A) NASH Cirrhosis will be necessary provide necessary additional information on effects also in the non-cirrhotic MASH population. This will be a category 2 post-authorisation measure (SOB).

2.6.8. Clinical safety

For the assessment of clinical safety of resmetirom, safety data from three Phase 3 studies in NASH/MASH patients and two phase 2 studies are relevant:

Phase 3 studies, randomized, double-blind, placebo controlled and open label:

- MGL-3196-11 (MAESTRO-NASH) is an ongoing placebo-controlled, double-blind, randomized trial in subjects with NASH/MASH and fibrosis. Interim results are presented at Week 52. At the data cut-off date (31 July 2022), 701 subjects were on resmetirom and 349 subjects on placebo. Safety update analyses were performed using interim data snapshots including 966 patients with data cut-off 13-Jan-2023.
- MGL-3196-14 (MAESTRO-NAFLD-1), a 52-week, multicentre, double-blind, randomized, placebo-controlled study in patients with NAFLD/MASLD, 652 patients were on resmetirom, 320 on placebo. The trial had an additional open label arm with 171 patients. The study is completed.
- MGL-3196-18 is an ongoing extension study (MAESTRO-NAFLD-OLE) in approximately 1080 patients with NAFLD/MASLD who primarily completed MGL-3196-14. Additionally included were screen fail patients from Study MGL 3196-11, MGL-3196-19, and *de novo* meeting eligibility criteria. A 12-week double-blind lead-in was followed by open-label (OL) treatment. Data-cut for the first SCS was 31 July 2022. Safety update analyses were performed on 30 July 2023 in the remaining 414 subjects and 6 *de novo* subjects.

Randomized, double-blind, placebo-controlled Phase 2 studies:

- MGL-3196-05, a study in patients with NASH/MASH (84 patients on resmetirom), which included an extension study in patients with NASH/MASH with elevated liver enzymes (31 NASH/MASH patients who received resmetirom for up to 36 weeks, including 14 of whom were previously assigned to placebo).
- MGL 3196-06, a study in a different population, i.e. patients with Heterozygous Familial Hypercholesterolemia (HeFH) with a total of 116 patients, 78 patients on resmetirom and 38 on placebo.

In addition, data from 11 phase 1 studies were submitted, with a total of 275 healthy volunteers exposed to at least one dose of resmetirom and 30 subjects exposed to placebo.

2.6.8.1. Patient exposure

Table 42. Patient exposure during the clinical trials

Study ID	Patients enrolled	Patients exposed DB/OL	Study dose	Patients with long term safety data		
				36 weeks	52 weeks	> 52 weeks
MGL-3196-05/ phase 2	125	84 double-blind	40mg, 60mg, 80mg, 100mg, 120mg	n = 75		
		33 open label		n = 14		n = 17 (72 weeks)
MGL-3196-11 pivotal	1050	729 Double-blind	80mg, 100mg		n = 701 (interim analysis)	
MGL-3196-14	1363	652 double-blind	80mg, 100mg		n = 634	
		171 MASH cirrhosis OL	Dose titration		n = 144	
MGL-3196-18	1080	615 double blind for 12 weeks then open label	40, 60, 80, 100 for 12 weeks then 100mg		n = 172 (interim analysis)	n = 341
MGL-3196-06	116	HeFH patients (no NASH/MASH); 60mg, 100mg; 12 weeks; n = 72 no long-term safety data				

In Study MGL-3196-11, 77 patients in the resmetirom 80 mg group, 69 patients in the 100 mg group, and 75 in the placebo group were treated more than 102 weeks. In Study MGL-3196-18, 38 patients in the resmetirom 100 mg group were treated more than 24 months.

The applicant has analyzed pooled safety data from the double-blind randomized arms of Study MGL-3196-11 and Study MGL-3196-14.

The safety data of 180 patients with well-compensated cirrhotic NASH/MASH cirrhosis (Child-Pugh (CP)-A) were analysed separately. This included:

- 180 patients with well-compensated NASH/MASH cirrhosis enrolled into a 52-week OL active treatment, non-comparative cohort of Study MGL-3196-14 and further followed for 52 weeks in Study MGL-3196-18 planned for a total of up to two years. 166 patients were exposed to the study drug ≥ 48 up to <60 weeks.
- 52 patients who experienced a composite clinical outcome (CCO) event of cirrhosis at week 52 of Study MGL-3196-11 entered the subsequent Open-Label Phase.

87 patients with cirrhosis or NASH/MASH cirrhosis with hepatic impairment were included in the phase 1 study MGL-3196-10 for 6 days.

A subpopulation of trial MGL-3196-11 that had baseline biopsies scored as F0 and/or F1A/C by both pathologists or one score of F1A/C/F0 and one score of F1B was assessed separately. The sample size was small with 56 patients on resmetirom and 28 patients on placebo. The conclusion on safety remains therefore limited.

14 patients with moderately impaired renal function defined as eGFR ≥ 30 and < 45 mL/min/1.73m² included in the open label arm of Study MGL-3196-14 were analysed separately.

In order to assess the safety of resmetirom the focus is on the population from two phase 3, randomized, placebo-controlled trials, MGL-3196-11 and MGL-3196-14 (open label arm not included). The rationale is to focus on the intended target population, i.e. patients with stage F2/F3 fibrosis: In study MGL-3196-11, only subjects with biopsy proven stage F1B/F2/F3 fibrosis were included; in study MGL-3196-14, most patients were diagnosed non-invasively stage F2/F3 fibrosis based only on FibroScan staging.

It is noted that, although not included in the intended use population, data of 49 patients from study 11 who were staged as fibrosis F1B at baseline are included in this safety analysis. However, considering that most patients in Study MGL-3196-14 were diagnosed non-invasively based only on FibroScan staging, an unknown number of participants must be assumed to be included in this study, who do also not represent the intended population.

Study MGL-3196-18 was primarily a continuation study for subjects from MGL-3196-14. It was randomised and double blind for the first 12 weeks only. Apart from a missing placebo arm, possible disease progression in subjects who switched from placebo within trial MGL-3196-14 to resmetirom treatment in Trial MGL-3196-18 was not taken into account. Patients who failed screening in the pivotal study MGL-3196-11 (e.g. different diagnosis) were also included MGL-3196-18. Data from MGL-3196-18 should therefore be evaluated separately.

Demographic characteristics in the Non-Cirrhotic NASH Safety Population were well balanced between the pooled resmetirom 80 mg (n=761), 100 mg (n=1033) and placebo (n=708) groups. The mean age of participants was 56.1 years, and the proportion of participants over the age of 75 in the groups exposed to the intended dose of resmetirom was 3% (n=54).

2.6.8.2. Adverse events

EAIRs are not provided for all individual studies.

Due to up- titration after the first 12 weeks in Study MGL-3196-18, there were only 6 subjects left in the 80 mg treatment arm. They were not included in any comparison with the 100 mg dose.

The proportion of subjects with at least 1 TEAE was similar in both treatment groups and the placebo group in all phase 3 studies. The incidence of serious TEAEs was also comparable between the resmetirom 80 mg, resmetirom 100 mg and placebo treatment group. The proportions in the open label arm were not substantially different. TEAEs leading to study drug discontinuation were highest in the resmetirom 100 mg arm.

Table 43. Treatment-Emergent Adverse Events – 52 weeks - Overall Summary (Safety Population – F1B, F2, F3) - Study 11

	Resmetirom 80 mg (N=322) n (%)	Resmetirom 100 mg (N=323) n (%)	Placebo (N=321) n (%)
Patients – n (%)			
Any TEAE	296 (91.9)	296 (91.6)	298 (92.8)
Any Serious TEAE	35 (10.9)	41 (12.7)	37 (11.5)
Any TEAEs ≥ Grade 3	43 (13.4)	47 (14.6)	52 (16.2)
Any TEAEs leading to Study-Drug Discontinuation	23 (7.1)	36 (11.1)	18 (5.6)
Any TEAEs leading to Study Discontinuation	9 (2.8)	25 (7.7)	11 (3.4)
Any Fatal TEAEs	1 (0.3)	2 (0.6)	1 (0.3)
Any Treatment-related TEAE	124 (38.5)	134 (41.5)	88 (27.4)

Table 44. Overall Summary of Treatment Emergent Adverse Events – 52 weeks - Safety Analysis Population - Study 14

Category Criteria	OLNC (N=17 1)	Resmetirom 100 mg DB (N=324)	Resmetirom 80 mg DB (N=327)	Placebo DB (N=318)
Patients				
Any TEAE	148 (86.5)	279 (86.1)	289 (88.4)	260 (81.8)
Serious TEAE	7 (4.1)	24 (7.4)	19 (5.8)	20 (6.3)
≥ Grade 3 TEAE	12 (7.0)	29 (9.0)	25 (7.6)	29 (9.1)
TEAE related to study drug	63 (36.8)	119 (36.7)	114 (34.9)	77 (24.2)
TEAE leading to study drug discontinuation	8 (4.7)	17 (5.2)	24 (7.3)	11 (3.5)
TEAE leading to study discontinuation	2 (1.2)	10 (3.1)	8 (2.4)	4 (1.3)
TEAE resulting in death	0	1 (0.3)	0	0

Table 45. Most Common Treatment-Emergent Adverse Events (≥5% incidence for any Preferred Term in Any Treatment Group) by SOT and PT (Safety Population – F1B, F2, F3)- Study 11

System Organ Class Preferred Term*	Resmetirom 80 mg (N=322) n (%)	Resmetirom 100 mg (N=323) n (%)	Placebo (N=321) n (%)
Any TEAEs	296 (91.9)	296 (91.6)	298 (92.8)
Gastrointestinal disorders	184 (57.1)	199 (61.6)	172 (53.6)
Diarrhoea	87 (27.0)	108 (33.4)	51 (15.9)

Nausea	71 (22.0)	61 (18.9)	40 (12.5)
Abdominal pain upper	23 (7.1)	27 (8.4)	29 (9.0)
Vomiting	28 (8.7)	35 (10.8)	17 (5.3)
Abdominal pain	26 (8.1)	29 (9.0)	18 (5.6)
Constipation	21 (6.5)	28 (8.7)	17 (5.3)
Abdominal distension	14 (4.3)	13 (4.0)	17 (5.3)
Gastroesophageal reflux disease	16 (5.0)	7 (2.2)	8 (2.5)
Infections and infestations	171 (53.1)	149 (46.1)	171 (53.3)
COVID-19	69 (21.4)	54 (16.7)	67 (20.9)
Urinary tract infection	33 (10.2)	27 (8.4)	28 (8.7)
Nasopharyngitis	14 (4.3)	20 (6.2)	14 (4.4)
Upper respiratory tract infection	23 (7.1)	8 (2.5)	17 (5.3)
Sinusitis	10 (3.1)	13 (4.0)	17 (5.3)
Musculoskeletal and connective tissue	125 (38.8)	136 (42.1)	125 (38.9)
Arthralgia	48 (14.9)	35 (10.8)	40 (12.5)
Back pain	35 (10.9)	27 (8.4)	38 (11.8)
Muscle spasms	14 (4.3)	22 (6.8)	22 (6.9)
Pain in extremity	12 (3.7)	12 (3.7)	23 (7.2)
Nervous system disorders	81 (25.2)	77 (23.8)	81 (25.2)
Headache	30 (9.3)	25 (7.7)	28 (8.7)
Dizziness	20 (6.2)	19 (5.9)	11 (3.4)
Metabolism and nutrition disorders	70 (21.7)	86 (26.6)	75 (23.4)
Type 2 diabetes mellitus	24 (7.5)	26 (8.0)	25 (7.8)
Decreased appetite	5 (1.6)	16 (5.0)	4 (1.2)
Skin and subcutaneous tissue disorders	65 (20.2)	89 (27.6)	75 (23.4)
Pruritus	26 (8.1)	37 (11.5)	22 (6.9)
Rash	12 (3.7)	21 (6.5)	12 (3.7)
General disorders and administration site	63 (19.6)	69 (21.4)	79 (24.6)
Fatigue	33 (10.2)	26 (8.0)	28 (8.7)
Injury, poisoning and procedural	57 (17.7)	61 (18.9)	81 (25.2)
Procedural pain	16 (5.0)	9 (2.8)	19 (5.9)
Respiratory, thoracic and mediastinal disorders	43 (13.4)	52 (16.1)	41 (12.8)
Cough	14 (4.3)	18 (5.6)	12 (3.7)
Vascular disorders	32 (9.9)	22 (6.8)	41 (12.8)
Hypertension	16 (5.0)	13 (4.0)	25 (7.8)

Table 46. Treatment Emergent Adverse Events Reported with $\geq 5\%$ Frequency in At Least One Treatment Group – Analysis Population: Safety – Study 14

System Organ Class Preferred Term	OLNC (N=171)	Resmetirom 100 mg DB (N=324)	Resmetirom 80 mg DB (N=327)	Placebo DB (N=318)
Patients with TEAEs	148 (86.5)	279 (86.1)	289 (88.4)	260 (81.8)
Gastrointestinal disorders	86 (50.3)	173 (53.4)	161 (49.2)	122 (38.4)
Diarrhoea	51 (29.8)	101 (31.2)	77 (23.5)	44 (13.8)

Nausea	24 (14.0)	59 (18.2)	39 (11.9)	25 (7.9)
Abdominal pain	9 (5.3)	23 (7.1)	14 (4.3)	14 (4.4)
Constipation	12 (7.0)	14 (4.3)	16 (4.9)	14 (4.4)
Vomiting	12 (7.0)	20 (6.2)	8 (2.4)	12 (3.8)
Infections and infestations	54 (31.6)	109 (33.6)	114 (34.9)	93 (29.2)
COVID-19	21 (12.3)	27 (8.3)	27 (8.3)	27 (8.5)
Urinary tract infection	9 (5.3)	20 (6.2)	21 (6.4)	23 (7.2)
Sinusitis	1 (0.6)	11 (3.4)	19 (5.8)	6 (1.9)
Musculoskeletal and connective tissue disorders	45 (26.3)	89 (27.5)	92 (28.1)	90 (28.3)
Arthralgia	16 (9.4)	27 (8.3)	24 (7.3)	21 (6.6)
Back pain	7 (4.1)	18 (5.6)	17 (5.2)	14 (4.4)
Pain in extremity	5 (2.9)	18 (5.6)	16 (4.9)	16 (5.0)
Nervous system disorders	36 (21.1)	64 (19.8)	69 (21.1)	61 (19.2)
Headache	13 (7.6)	27 (8.3)	22 (6.7)	24 (7.5)
Dizziness	6 (3.5)	16 (4.9)	19 (5.8)	10 (3.1)
Metabolism and nutrition disorders	34 (19.9)	62 (19.1)	49 (15.0)	56 (17.6)
Type 2 diabetes mellitus	8 (4.7)	21 (6.5)	18 (5.5)	14 (4.4)
Skin and subcutaneous tissue disorders	41 (24.0)	44 (13.6)	50 (15.3)	46 (14.5)
Pruritus	22 (12.9)	16 (4.9)	16 (4.9)	8 (2.5)
General disorders and administration site conditions	26 (15.2)	46 (14.2)	46 (14.1)	45 (14.2)
Fatigue	11 (6.4)	15 (4.6)	21 (6.4)	13 (4.1)
Vascular disorders	16 (9.4)	22 (6.8)	26 (8.0)	22 (6.9)
Hypertension	9 (5.3)	11 (3.4)	14 (4.3)	13 (4.1)
Endocrine disorders	12 (7.0)	7 (2.2)	6 (1.8)	3 (0.9)
Hypothyroidism	10 (5.8)	4 (1.2)	2 (0.6)	2 (0.6)

The pattern of TEAEs observed in study MGL-3196-18 and in the phase 2 study MGL-3196-05 were not substantially different from the phase 3 studies.

The proportion of participants with at least one ADR was significantly higher in the resmetirom group than in the placebo (37.5% and 27.3%, respectively).

The most common AEs overall were diarrhoea, nausea, pruritus, and COVID-19 followed by abdominal pain, vomiting, constipation, and dizziness. Depending on the respective study, diarrhoea occurred in 23.5% – 27% of patients treated with 80 mg resmetirom and in 25.7% - 33.4 % of patients treated with 100 mg resmetirom (vs. 9.8% - 15% on placebo). The rates of reported nausea were 18.2% - 18.9 % on 100 mg resmetirom, 11.9 – 22.0 % on 80 mg, and 7.9 – 12.5% on placebo.

The incidence of pruritus was clearly higher in cirrhotic patients (12.9% vs 4.9% in non-cirrhotic patients and 2.5% on placebo, Study MGL-3196-14).

Diarrhoea, nausea and headache were the most frequent cause of treatment discontinuation. Diarrhoea and nausea typically occurred within the first 12 weeks after treatment initiation. The simplified exposure-adjusted method is assuming that the risk of an AE occurring is constant over time. This does not apply for diarrhoea and nausea with early onset time and much shorter total person-years at risk. Calculating the time-at-risk exposure-adjusted incidence rate would allow a more substantial assessment of the risk of these two AEs. Deducted from Study MGL-3196-14, the median duration of diarrhoea occurring in the first 12 weeks ranged from 15 to 26 days. There is no information on possible recurrences.

The AEs which may reflect drug hypersensitivity, rash and urticaria, were observed more often in the 100 mg resmetirom arms than in the 80 mg and placebo arms. Urticaria was observed more often in the resmetirom arms than in placebo. Rash and urticaria were causes of treatment discontinuations in a small number of subjects on resmetirom.

In the PK studies headache was the most common AE; headache, diarrhoea, and nausea were the most frequent cause of treatment discontinuation.

2.6.8.3. Serious adverse event/deaths/other significant events

TEAEs were assessed using Common Terminology Criteria for Adverse Events (CTCAE) Grades 1 through 5 to determine the severity of an event.

Most TEAEs were Grade 1 or 2 in severity in all treatment groups. TEAEs $\geq$ Grade 3 were evenly distributed across the study groups. They were reported in the resmetirom 80 mg arm in 7.6 % (Study 14) to 13.4 % (Study 11), in the resmetirom 100 mg arm in 9.0% (Study 14) to 14,6 % (Study 11), and in the placebo arm in 9.1 % (Study 14) to 16.2 % (Study 11).

Osteoarthritis, arthralgia and myalgia were SAEs observed within the SOC Musculoskeletal and Connective Tissue Disorders. They were balanced across treatment and placebo arms as were non-cardiac chest pain, Covid-19, Sepsis, and Urinary tract infection.

The incidence of serious gallbladder-related TEAEs (cholecystitis or biliary pancreatitis) and hepatotoxicity was low; however, they were more often reported in the treatment arms than in placebo arms.

The incidence of other SAEs (anaphylactic shock, blood phosphokinase increased, cerebral haemorrhage, obstructive pancreatitis, and papillary thyroid cancer) was low and similar between pooled resmetirom and placebo groups: 3 patients in the resmetirom groups and 2 patients in the placebo groups.

In Study MGL-3196-14, patients who were taking thyroxine at baseline were compared with those who were not. With regard to serious adverse events, there was no notable difference between these two subgroups.

- Deaths

There was a total of 10 fatal TEAEs with resmetirom versus 1 patient on placebo. According to the applicant, none of them was considered related to the study drug. However, there are 2 MACE events reported which were fatal.

- Adverse events of special interest

Overall, the proportion of patients with any AE of special interest was higher in the resmetirom group than placebo – 52.5% and 47.0% respectively.

Gastrointestinal AEs

Diarrhoea and nausea were the most common TEAEs reported across the trials. Even though most events were mild to moderate in severity, they were the most common cause of treatment discontinuations. Diarrhoea typically occurred within the first 12 weeks after treatment initiation. The Kaplan–Meier estimates for the duration of the first diarrhoea event showed that most individual diarrhoea episodes resolved within 2 to 4 weeks. However, the median time to full resolution of diarrhoea was longer: 3.86 weeks in study 11, 3.64 weeks in study 15, and up to 26 days in study 14. The frequency of 1 recurrence

was slightly higher in the treatment groups. More frequently recurring events (≥ 3) were rare: 1 % in the resmetirom groups vs. 0.1 % in the placebo group).

Adjudicated Major Adverse Cardiovascular Events (MACE) and adjudicated cardiovascular events - other than MACE

The incidence of adjudicated MACE and other cardiovascular events (assessed by a Cardiac Adjudication Committee) in the phase 2 and 3 studies was low and incidence in the treatment groups was not substantively different from placebo. However, there were 2 adjudicated MACE events in the treatment groups that were fatal.

According to the reflection paper on assessment of cardiovascular safety profile of medicinal products (EMA/CHMP/50549/2015), for MACE and other cardiovascular events, a reasonable basis for regulatory assessment of cardiovascular safety must be established, which requires an adequate number of cardiovascular events. This requirement is not met with the data that is available at this time. The ongoing Studies 11 and 18, and, for cirrhotic patients, the on-going Study 19 will provide further data in this regard. Additionally, the applicant will conduct a real-world longitudinal data study to address liver and CV related outcomes in resmetirom treated patients, as compared with a real-world control arm.

Gallstone related adverse events

In the non-cirrhotic safety population of both studies MGL-3196-11 and MGL-3196-14, the incidence of newly reported cholelithiasis was clearly higher (31 vs 1 subjects) and of newly reported cholecystitis was slightly higher (7 vs 1) in the resmetirom arms versus placebo. In the study report of Study MGL-3196-18, there are also cases of newly observed cholelithiasis listed in the resmetirom groups.

6 cases of (obstructive) pancreatitis were reported in the resmetirom arm, whereas in the placebo arms, 1 case was reported in the 120-day safety update).

Among the Non-Cirrhotic NASH population pool there were 15 patients who experienced acute gallbladder-related AEs (e.g., cholecystitis and obstructive pancreatitis), with the majority having had surgical intervention to resolve these SAEs. The surgical intervention did not lead to the study drug discontinuation or permanent study discontinuation. The normalizing of the lab values post-surgery and the recovery process resulted in the patient being discharged from the hospital within a few days after surgery. Thus, the potential risk of surgical intervention due to acute gallstone-related AEs can be viewed as minimal.

In addition to the event of obstructive pancreatitis, pancreatic failure is reported in 3 subjects on resmetirom 100 mg, and 4 pancreatic cysts were observed on resmetirom 80 mg, but none of both in the placebo group.

Gallstone disease is highly prevalent in NAFLD/MASLD. Accordingly, baseline incidence of cholelithiasis in Study 11 ranged from 10% to 15% across the treatment arms. In Study 11 and Study 14, 18% of the patients had had cholecystectomy at baseline. For patients who had a medical history of gallbladder-related illness or procedure, there were no meaningful differences in incidence of gallbladder-related procedures post treatment.

Liver enzyme elevations including potential Drug-Induced Hepatotoxicity

An adjudication committee classified 4 hepatotoxicity cases as possible drug induced hepatotoxicity ("possible" implies a 25-49% probability of being drug induced hepatotoxicity). There were no cases that were adjudicated as being probable or highly likely drug induced hepatotoxicity (greater than 50% likelihood of drug induced hepatotoxicity). Although they were regarded by the investigator and sponsor to

be not related to treatment, they have to be regarded as possible drug induced hepatotoxicity based on the judgement of the Hepatic Adjudication Committee (HAC):

1 case of hepatotoxicity meeting Hy's Law criteria in the resmetirom 80 mg group, adjudicated by the HAC as possible drug induced hepatotoxicity was reported in Study MGL-3196-14. An additional patient in the open label arm (resmetirom 100 mg) also had a possible drug induced hepatotoxicity event. Another possible case was reported in Study MGL-3196-11 (resmetirom 80 mg). None was reported in the placebo group of both studies. Another event occurred in a cirrhotic patient. The HAC adjudicated the event as possible drug induced hepatotoxicity.

The undesirable effect hepatotoxicity has to be considered an AESI.

Malignant cancers (including hepatocellular carcinoma, gastrointestinal and other malignancies)

1 case of HCC was diagnosed in Study MGL-3196-11 on study day 58 in a subject receiving resmetirom 100 mg.

2 more patients with hepatocellular carcinoma were reported in the 120-day safety report, both on resmetirom. It is not clear if the additional case with PT hepatic neoplasm (also on resmetirom) is included in these 3 cases.

Beyond that, the incidence of neoplasms was low and the incidence in the resmetirom arms was not substantively different from placebo.

Adverse events potentially related to hyperthyroidism or hypothyroidism.

Regarding MACE and other Adjudicated Cardiovascular events, no increased risk was detected (see above). Change from baseline in mean heart rate, systolic and diastolic blood pressure showed no abnormalities. It is noticeable, however, that the incidence of constipation is higher in the resmetirom arms than in the placebo arms. It should therefore be considered an ADR.

For changes in thyroid hormones levels please refer to the section on laboratory findings.

Fracture risk assessment

Study MGL-3196-11 and Study MGL-3196-14 included Bone mineral density measurements via dual X-ray absorptiometry (DXA) scan and bone biomarkers. AEs of fractures were collected. The shifts in BMD and T score/Z score calculations were examined according to sex and risk category (i.e., post-menopausal females) and according to weight loss and thyroxine status.

The number of subjects who shifted from lower to higher risk category based on T-score was similar between resmetirom arms and placebo. There were no shifts from normal to possible osteoporosis, as measured for femoral neck, femoral total, spine adjusted total, and spine total by T score, which compared bone density to that of a healthy person. There were no shifts in risk category in any other subgroup, including patients taking thyroxine.

In Study MGL-3196-11, bone turnover markers were also analysed in the subgroup of subjects with the highest potential fracture risk, namely postmenopausal women (without thyroxine intake at baseline). At Week 52, there was a small increase in both N-terminal pro-peptide type 1 procollagen and CT_x1/Beta crosslaps in patients treated with resmetirom compared to placebo. However, bone mineral density remained unchanged.

After 1 year of treatment with resmetirom, there was no evidence of drug-induced adverse effects on bone metabolism. The long-term impact of resmetirom on bone metabolism remains unknown.

Kidney disease

Chronic kidney disease and fatty kidney are strongly associated with MAFLD/MASH. THR- β are abundantly expressed in kidney tissue, and THR- β agonists might be beneficial in the management of CKD. Renal hypertrophy is classically associated with the treatment with THs. Kidney hypertrophy with TR- β agonist is described in the literature and increased kidney weight was described in the preclinical studies. However, an impact on renal function could not be observed in the submitted studies.

Pruritus

Pruritus was a cause of treatment discontinuation for clearly more subjects receiving resmetirom than placebo.

2.6.8.4. Laboratory findings

Haematology

Mean changes from baseline to haematology values were analysed for pooled 80 mg and 100 mg resmetirom group vs placebo and presented separately for phase 1 studies, phase 2 studies, Study 14 NASH/MASH cirrhosis patients, study 06 in patients with HeFH and Study 10-Hepatic Impairment Patients. This was agreed upon because of the different populations in each study and the possible impact of the background condition on haematology values. There were no notable changes in haematology parameters from baseline to Week 52. Shifts from baseline were observed for some parameters, such as haemoglobin increased, haemoglobin anaemia, white blood cell decreased, lymphocyte count increased/decreased and platelet count decreased however, no apparent differences were observed between resmetirom group and placebo.

ALT, AST, GGT

Mean ALT, AST, and GGT were significantly reduced from baseline to Week 52 in both treatment groups compared with placebo in patients with non-cirrhotic NASH/MASH. This also applies to patients who had elevated baseline values for ALT and AST. ALT and AST were lower in patients on statins. Only in study MGL-3196-11, there was an increase in mean ALT and AST at Week 4. These elevations occurred more commonly in the 100 mg than the 80 mg dose group. This resolved on continued treatment.

For GGT, regardless of statin use at baseline, a significant reduction vs placebo was observed. Shift analysis did not reveal an apparent difference between the different groups.

Serum amylase and lipase

Slight asymptomatic increases in serum amylase and lipase were observed in the placebo group to the same extent as in the treatment groups. However, a shift in serum amylase and lipase from normal and grade 1 at baseline to grade 3 and 4 was seen in numerically more subjects in the resmetirom arms than in placebo in both trials MGL-3196-11 and MGL-3196-14. This coincides with the increased rate of pancreatic incidences as described above.

Thyroid hormones

Liver injury in animal models, and also in human MASH is associated with liver-specific hypothyroidism which is caused by a decrease in deiodinase 1 that converts T4 to T3, leading to reduced levels of thyroid

regulated gene expression in the livers of MASH patients. Thyroid hormone acting through THR- β is important for maintaining multiple hepatic functions that are defective in MASH. Thus, hepatic hypothyroidism is assumed to be an important underlying pathophysiology in MASH. Based on the MoA, FT4 was used as biomarker, indicating pharmacodynamic activity of the compound.

Table 47. Thyroid Axis Hormones: Shifts from Baseline to Any Occurrence Post- baseline through Week 52 by Thyroxine Status at Baseline (Safety Population – F1B, F2, F3)- Study 11

Test (unit) Category	Resmetirom 80mg (N=322)	Resmetirom 100mg (N=323)	Placebo (N=321)
Thyroxine treatment at baseline: No, n	283	277	276
Thyrotropin (mIU/L)			
Patients with baseline ≥ 0.3	279	272	273
Patients with baseline ≥ 0.3 with any result <0.3 during study	10 (3.6)	6 (2.2)	2 (0.7)
p-value, active vs placebo*	0.0216	0.1533	
Patients with baseline ≤ 4.5	277	265	267
Patients with baseline ≤ 4.5 with any result >4.5 during study	17 (6.1)	22 (8.3)	30 (11.2)
p-value, active vs placebo*	0.0344	0.2554	
Thyroxine, Free (ng/dL)			
Patients with baseline ≥ 0.7	279	273	274
Patients with baseline ≥ 0.7 with any result <0.7 during study	43 (15.4)	79 (28.9)	7 (2.6)
p-value, active vs placebo*	<0.0001	<0.0001	
Patients with baseline ≤ 1.6	277	273	274
Patients with baseline ≤ 1.6 with any result >1.6 during study	3 (1.1)	0	8 (2.9)
p-value, active vs placebo*	0.1237	0.0044	
Triiodothyronine, Free (ng/L)			
Patients with baseline ≥ 1.7	279	273	275
Patients with baseline ≥ 1.7 with any result <1.7 during study	1 (0.4)	4 (1.5)	2 (0.7)
p-value, active vs placebo*	0.5550	0.4075	
Patients with baseline ≤ 5	279	274	275
Patients with baseline ≤ 5 with any result >5 during study	3 (1.1)	1 (0.4)	3 (1.1)
p-value, active vs placebo*	0.9858	0.3182	
Thyroxine treatment at Baseline: Yes, n	39	46	45
Thyrotropin (mIU/L)			
Patients with baseline ≥ 0.3	35	43	43

Patients with baseline ≥ 0.3 with any result < 0.3 during study	9 (25.7)	13 (30.2)	2 (4.7)
p-value, active vs placebo*	0.0074	0.0015	
Patients with baseline ≤ 4.5	33	43	41
Patients with baseline ≤ 4.5 with any result > 4.5 during study	6 (18.2)	12 (27.9)	8 (19.5)
p-value, active vs placebo*	0.8865	0.3726	
Thyroxine, Free (ng/dL)			
Patients with baseline ≥ 0.7	38	46	45
Patients with baseline ≥ 0.7 with any result < 0.7 during study	6 (15.8)	15 (32.6)	0
p-value, active vs placebo*	0.0052	< 0.0001	
Patients with baseline ≤ 1.6	34	42	42
Patients with baseline ≤ 1.6 with any result > 1.6 during study	2 (5.9)	1 (2.4)	3 (7.1)
p-value, active vs placebo*	0.8284	0.3113	
Triiodothyronine, Free (ng/L)			
Patients with baseline ≥ 1.7	38	45	45
Patients with baseline ≥ 1.7 with any result < 1.7 during study	4 (10.5)	2 (4.4)	0
p-value, active vs placebo*	0.0257	0.1561	
Patients with baseline ≤ 5	37	45	45
Patients with baseline ≤ 5 with any result > 5 during study	1 (2.7)	3 (6.7)	0
p-value, active vs placebo*	0.2728	0.0797	

Resmetirom reduced the levels of mean FT4 from Baseline to Week 52 for both resmetirom 80 mg and 100 mg vs placebo ($p < 0.0001$) in patients with and without thyroxine treatment at baseline which is explained by the mechanism of action of resmetirom. Looking at the shift tables, 28.9% of patients in the resmetirom 100 mg arm and 15.4% of patients in the resmetirom 80 mg arm had a decrease in FT4 level below normal compared to 2.6% on placebo (Study 11, no shift tables provided for study 14). Mean TSH and T3 levels remained unchanged.

Per protocol, the dose of resmetirom was reduced based on a decrease in FT4 level below normal (< 0.7 ng/dL) on two consecutive visits. This was done in 16 subjects in Study 11, in 14 subjects in Study 14 and in 20 subjects in Study 18 (most of them in the later phase of the study).

In non-cirrhotic NASH/MASH patients the dose of resmetirom was reduced on the basis of a decrease in FT4 level below normal (< 0.7 ng/dL) on two consecutive visits per protocol as FT4 was used as biomarker for efficacy. No recommendation has been included in the SmPC in this respect and this was acceptable to the CHMP.

Sex-hormone binding globulin (SHBG) and sex hormones

Low levels of SHBG have been associated with MASLD/MASH. SHBG was thus used as a biomarker of PD activity. The observed increase in SHBG is therefore of rather minor relevance for the safety assessment.

Consequently, increases in all sex hormones were noted in both sexes treated with resmetirom. In the non-cirrhotic NASH Safety Analysis Population, statistically significant changes were notable for estradiol, total testosterone, follicle-stimulating hormone, and luteinizing hormone in males, and for total testosterone in females. No changes in free testosterone levels were seen in either sex. It is assumed that estradiol refers to total estradiol, and levels of free estradiol were not presented. A summary of PTs regarding the SOC reproductive system and breast disorder is not provided.

2.6.8.5. Safety in special populations

No separate data have been presented for special populations.

Age

Only 1 to 3% of subjects across the trial arms were older than 75 years. A distinction was only made between subjects < 65 years and ≥ 65 years. Depending on the respective study, 22 - 27% of the subjects were ≥65 years of age. Though PK parameters of resmetirom were not affected by age after taking into account differences in body weight, in the non-cirrhotic patient population, these patients had numerically higher incidences of the TEAEs diarrhoea and pruritus, and higher incidence of serious AEs (not further specified) than patients <65 years of age. They also had an increased rate of discontinuations compared to patients <65 years of age. It is also noted that these events were observed higher not only in both resmetirom groups but also in the placebo group. Therefore, the applicant's conclusion that no meaningful imbalances were observed between below and above 65 years of age can be endorsed. No conclusions can be drawn about people 75 years of age as the sample is very small but missing information on elderly is included in Safety specifications and will be collected in the post-authorisation setting.

Table 48. Safety in Special Populations (Non-Cirrhotic NASH Safety Analysis Population)

MedDRA Terms	Age <65			Age 65-74			Age ≥ 75		
	Resmetirom 80 mg N=590	Resmetirom 100 mg N=764	Placebo N=529	Resmetirom 80 mg N=155 (N=171 when pooled with age ≥ 75)	Resmetirom 100 mg N=231 (N=269 when pooled with age ≥ 75)	Placebo N=163 (N=179 when pooled with age ≥ 75)	Resmetirom 80 mg N=16	Resmetirom 100 mg N=38	Placebo N=16
Total Number of AEs, n (%)	527 (89.3)	655 (85.7)	462 (87.3)	142 (91.6)	210 (90.9)	142 (87.1)	16 (100)	35 (95.2)	12 (75.0)
Serious AEs – Total, n (%)	48 (8.1)	52 (6.8)	46 (8.7)	19 (12.3)	30 (13.0)	22 (13.5)	3 (18.8)	9 (23.7)	4 (25.0)
- Fatal, n (%)	3 (0.5)	2 (0.3)	1 (0.2)	0	2 (0.9)	0	0	0	0
- Hospitalization/prolong existing hospitalization, n (%)	42 (7.1)	46 (6.0)	41 (7.8)	19 (12.3)	25 (10.8)	18 (11.0)	3 (18.8)	9 (23.7)	4 (25.0)
- Life-threatening, n (%)	5 (0.8)	4 (0.5)	5 (0.9)	1 (0.6)*	4 (1.5)*	2 (1.1)*	*		
- Disability/in capacity, n (%)	0	0	0	0	1 (0.4)	0	0	1 (2.6)	0
- Other (medically significant), n (%)	16 (2.7)	17 (2.2)	11 (2.1)	3 (1.8)*	13 (4.8)*	9 (5.0)*	*		
AE leading to drop-out, n (%)	20 (3.4)	31 (4.1)	13 (2.5)	5 (3.2)	16 (6.9)	5 (3.1)	1 (6.3)	2 (5.3)	1 (6.3)
Psychiatric disorders, n (%)	60 (10.2)	58 (7.6)	53 (10.0)	16 (10.3)	13 (5.6)	20 (12.3)	2 (12.5)	7 (18.4)	4 (25.0)
Nervous system disorders, n (%)	45 (7.6)	39 (5.1)	28 (5.3)	10 (6.5)	12 (5.2)	11 (6.7)	3 (18.8)	5 (13.2)	1 (6.3)



MedDRA Terms	Age <65			Age 65-74			Age ≥ 75		
	Resmetirom 80 mg N=590	Resmetirom 100 mg N=764	Placebo N=529	Resmetirom 80 mg N=155 (N=171 when pooled with age ≥ 75)	Resmetirom 100 mg N=231 (N=269 when pooled with age ≥ 75)	Placebo N=163 (N=179 when pooled with age ≥ 75)	Resmetirom 80 mg N=16	Resmetirom 100 mg N=38	Placebo N=16
Injury, poisoning and procedural complications, n (%)	20 (3.4)	27 (3.5)	23 (4.3)	11 (7.1)	12 (5.2)	12 (7.4)	0	6 (15.8)	2 (12.5)
Cardiac disorders, n (%)	29 (4.9)	40 (5.2)	29 (5.5)	14 (9.0)	17 (7.4)	13 (8.0)	6 (37.5)	4 (10.5)	2 (12.5)
Vascular disorders, n (%)	55 (9.3)	45 (5.9)	58 (11.0)	15 (9.7)	13 (5.6)	15 (9.2)	3 (18.8)	9 (23.7)	2 (12.5)
Cerebrovascular disorders, n (%)	1 (0.2)	0	0	0	0	1 (0.6)	0	0	0
Infections and infestations, n (%)	288 (48.8)	330 (43.2)	230 (43.5)	69 (44.5)	84 (36.4)	73 (44.8)	9 (56.3)	8 (21.1)	9 (56.3)
Anticholinergic syndrome, n (%)	0	0	0	0	0	0	0	0	0
Sum of postural hypotension, falls, loss of consciousness, syncope, dizziness, ataxia, fracture related PT, n (%)	63 (10.7)	62 (8.1)	48 (9.1)	19 (12.3)	22 (9.5)	21 (12.9)	3 (18.8)	11 (28.9)	2 (12.5)

*Age categories 65-74 and ≥ 75 for selected MedDRA terms were pooled to avoid unblinding.

Body weight

PK parameters of resmetirom were shown to be highly dependent on body weight.

Patients with lower body weight were more likely to trigger the few dose reductions that occurred based on FT4 monitoring. Patients with body weight <80 kg had more discontinuations at 100 mg versus 80 mg.

Sex

1008 women and 786 men of the placebo-controlled arms of Studies 05, 11, 14, and 18 received at least 1 dose of study drug. This is consistent with the overall higher incidence of NASH in women compared to men. > 80% of patients who were thyroxine treated at baseline were females. The TEAEs nausea and pruritus were clearly more frequently reported by female patients. For pruritus, only in the female population a difference in frequency compared to placebo population was shown. In the Healthy Volunteer Population, female patients had higher rates of nausea (5% vs 3%) and dizziness (6% vs 1%) than male patients. Men had more serious TEAEs than women in the Non-Cirrhotic NASH Extended Population (13% vs 7%, respectively). The most frequently reported serious TEAEs were non-cardiac chest pain (n=3) in female patients and COVID-19 pneumonia (n=3) in male patients. Several severe TE cardiovascular events were reported in male patients, including acute myocardial infarction, acute coronary disease and angina pectoris.

Race

Overall, approximately 90% of subjects across the treatment arms were white. Subgroup analyses by race were consistent with those of the main analysis populations. Consistent with the overall trend in TEAEs observed in the main analysis populations, diarrhoea, nausea and COVID-19 were the most frequently observed TEAEs across all race subgroups, with diarrhoea and nausea occurring in higher percentages in the pooled resmetirom treatment groups vs pooled placebo.

Cirrhotic patients/Patients with hepatic impairment

In Study MGL-3196-10, patients with mild, moderate, and severe hepatic impairment were treated for 6 days with oral doses of 40 mg, 60 mg, 80 mg, or 100 mg resmetirom. Additionally, the applicant provided an Addendum Report for study MGL-3196-14 which includes the analyses of the safety data of Study 14 in patients with compensated MASH cirrhosis. Included were data from 53 patients who experienced a Composite Clinical Outcome (CCO) event of cirrhosis at Week 52 of study MGL-3196-11 who participated in the following Open-Label Phase. This analysis was conducted explicitly only for patients with compensated NASH/MASH cirrhosis (Child-Pugh-A).

PK results indicate that moderate and severe HI increased the PK exposure, prolonged its half-life, and decreased total plasma clearance and renal clearance of resmetirom. 3/10 (30.0%) in the mild HI cohort, 4/10 (40.0%) in the moderate HI cohort, 7/15 (46.7%) in the severe HI cohort reported TEAEs, while no subjects in the "normal" cohort (N=13) reported TEAEs.

The safety analysis in the long-term Study MGL-3196-14 (addendum report) was conducted only for patients with compensated NASH/MASH cirrhosis (Child-Pugh-A). Safety data in 161 patients with compensated NASH/MASH cirrhosis (Child-Pugh-A) who finished 52 weeks treatment with resmetirom in Study MGL-3196-14 open label arm are presented. 67 patients completed at least another year of Study 18 treatment. With the exception of pruritus, no meaningful differences were observed between the pooled resmetirom 80 mg and 100 mg treatment groups vs placebo in other frequently reported TEAEs. One event of hepatotoxicity adjudicated as possible drug induced hepatotoxicity event and one adjudicated major adverse cardiovascular event (MACE) are reported. In 4 patients, hypothyroidism was reported. In 3 patients, the dose was adjusted due to decreased FT4 levels.

No safety data is available for the population with hepatic impairment Child Pugh-B/C. Since PK exposure is increased and half-life prolonged in patients with moderate and severe impairment, and additionally the duration of Study MGL-3196-10 was only 6 days with 87 patients enrolled, the safety of resmetirom in patients with moderate and severe hepatic impairment (Child-Pugh grade of B/C) has not been established.

Patients with renal impairment

Based on the results from a population PK analysis of patients, the effect of mild or moderate renal impairment on CL/F of resmetirom was minimal and not clinically relevant.

In order to collect additional safety data in patients with moderate renal impairment, the open-label arm allowed patients with eGFR ≥ 30 to <45 mL/min/1.73 m² to provide additional safety information in this population including 14 patients.

The most frequent TEAEs (≥ 3 events in 14 subjects) were diarrhoea (35.7%), hypoglycaemia (21.4%), and pruritus (21.4%). 3/14 subjects (21.4%) with moderate renal impairment reported hypoglycaemia. Although the number is small, the mechanism is unclear.

1 event each of acute kidney injury, cholelithiasis, obstructive pancreatitis (2 events of lipase increased), acute myocardial infarction, and unstable angina are reported.

Subjects with severe renal impairment (i.e., eGFR <30 mL/min/1.73 m²) were excluded from any study. There is no data on patients with severe renal impairment.

Diabetes

The subgroup analysis of patients with diabetes at baseline did not identify differences in safety parameters. In the 120-day safety update, patients with diabetes at baseline reported numerically higher events of vomiting compared to patients without diabetes at baseline (27 /229 [11.8%] vs 8 /191 [4.2%]).

2.6.8.6. Safety related to drug-drug interactions and other interactions

Resmetirom is a CYP2C8 substrate. Concomitant use with a strong or moderate CYP2C8 inhibitor can increase resmetirom C_{max} and AUC, which may increase the risk of adverse reactions. This is reflected in the SmPC.

According to the Summary of Clinical Pharmacology Studies, across multiple *in vitro* transporter inhibition assays, resmetirom consistently inhibited OATP1B1, OATP1B3. No clinically significant differences in the pharmacokinetics of resmetirom were observed when used concomitantly with ciclosporin (an OATP1B1/1B3 and BCRP inhibitor). Resmetirom is also a substrate of the human heterotrimeric organic solute transporter OST α / β and might be involved in the cellular uptake of resmetirom. OST α / β is highly upregulated in the liver of patients with NASH/MASH. Some drugs associated with hepatotoxicity inhibit OST α / β , suggesting a possible role for OST α / β in drug-induced liver injury (DILI).

However, the role of the transporter has not been completely established, and the clinical relevance of this finding was not pursued further. This was agreed by the CHMP.

Resmetirom was a weak inhibitor of Breast Cancer Resistance Protein (BCRP) and bile salt export pump (BSEP).

The interactions with warfarin, CYP1A2 substrates with narrow therapeutic index (e.g. theophylline and tizanidine) and with bile acid and binding resins have been described in the product information".

No safety issues are observed regarding drug-drug interactions.

2.6.8.7. Discontinuation due to adverse events

GI adverse events (diarrhoea and nausea) were the most common cause of study drug discontinuation. The rate of patients who discontinued the study drug due to diarrhoea was different through the placebo-controlled studies or study arms (EAIRs not available): 2.5 – 3.1% in the resmetirom 100 mg group, 0.6 – 2.5% in the 80 mg group, and 0 – 0.3% in the placebo group.

In the phase 2 study MGL-3196-05 (adaptive design), 2.4% discontinued study drug due to diarrhoea and none in the placebo group.

The overall percentage of patients who discontinued study drug in Study MGL-3196-11 was low (154/966, 15.9%), but a numerically higher proportion of patients in the resmetirom 100 mg group discontinued study drug compared with placebo (20.7% vs 11.8%, respectively) and the percentage of subjects who discontinued study drug due to AE or discontinued study due to AE was higher in the resmetirom 100 mg group than the 80 mg groups. This tendency could also be seen in Study MGL-3196-18. There was however no difference between the two resmetirom arms in Study MGL-3196-14.

2.6.8.8. Post marketing experience

N/A

2.6.9. Discussion on clinical safety

The safety assessment was based on approximately 1800 non-cirrhotic NASH/MASH patients treated with resmetirom, most of them treated with 80 or 100 mg for 6 to 12 months. Approximately 250 Patients with cirrhosis, most of them with NASH/MASH cirrhosis, were treated with mostly 80 mg resmetirom also for 6 to 12 months.

Safety data of studies MGL-3196-11, MGL-3196-14, MGL-3196-18, and MGL-3196-05 were combined to the “Non-Cirrhotic NASH/MASH Population” excluding cirrhotic patients from the open label arm in Study MGL-3196-14 and patients from Study MGL-3196-18 who had received resmetirom during trial MGL-3196-14. However, methodological differences between these studies limit benefits of the pooled safety analysis.

The most common AEs observed were diarrhoea, nausea, and pruritus, followed by abdominal pain, vomiting, constipation, and dizziness. Diarrhoea occurred in 23.5% – 27% of patients treated with 80 mg resmetirom and in 25.7% – 33.4% of patients treated with 100 mg resmetirom and in 9.8% – 15% of patients on placebo. Diarrhoea, nausea and headache were the most common causes of treatment discontinuation. Headache was the most common AE in the PK studies.

Most TEAEs were Grade 1 or 2 in severity in all treatment groups. While a numerical imbalance in deaths needs further clarification, TEAEs ≥Grade 3 were evenly distributed across the study groups.

Bile formation related adverse events, such as cholelithiasis, cholecystitis, or (obstructive) pancreatitis and hepatotoxicity were reported more often in the treatment arms than in placebo arms, albeit with low incidence overall.

The incidence of other SAEs was low and not increased in resmetirom-exposed groups.

No meaningful differences were observed between fibrosis stage (F1, F2, F3), presence/absence of diabetes at baseline, renal impairment at baseline and by a percent change from baseline in SHBG. However, in some subgroups, the sample size for several categories was too small to make any meaningful conclusions vs placebo

Bile formation related adverse events

Resmetirom targets hepatic THR- β . It is expected to promote bile formation and secretion, increase cholesterol metabolism and formation of bile acids, and increase secretion of cholesterol, thus plausibly increasing the risk of pruritus, gallstone formation, bile duct stones, and obstructive pancreatitis.

In line with an increased formation of bile acids, pruritus was reported more frequently in subjects who received resmetirom than in those who received placebo, and pruritus was a cause of treatment discontinuation for clearly more subjects receiving resmetirom than placebo.

The increased secretion of cholesterol was reflected in the significantly decreased serum LDL-C in patients receiving resmetirom. While lower serum LDL-C is certainly beneficial for the cardiovascular system, the increased secretion of cholesterol may affect the biliary tract. In both placebo-controlled phase 3 studies, the incidence of newly reported cholelithiasis and cholecystitis was slightly higher in the resmetirom arms versus placebo. In the study report of Study MGL-3196-18, there are also cases of newly observed cholelithiasis listed in resmetirom treated subjects.

Obstructive pancreatitis was rare in both resmetirom groups (n=8 cases), with just 1 case reported on placebo and only in the 120-day safety update. In line with this, a shift in serum amylase and lipase from normal and grade 1 at baseline to grade 3 and 4 was seen in numerically more subjects in the resmetirom arms than in placebo in both trials MGL-3196-11 and MGL-3196-14. In addition to the events of obstructive pancreatitis, pancreatic failure is reported in 3 subjects on resmetirom 100 mg, and pancreatic cysts were observed in 4 subjects on resmetirom 80 mg, but none of both in the placebo groups. Since the PT pancreatic cyst also includes pancreatic pseudocyst, which are frequently results of pancreatitis, this may also be indicative of (biliary/obstructive) pancreatitis. Therefore, formation of gallstones and pancreatitis are considered an AESI. A specific risk for patients with a history of gallbladder disease, including pancreatitis, cannot be excluded at this time.

Hepatotoxicity including potential Drug-Induced Hepatotoxicity

In patients treated with resmetirom, 1 case of hepatotoxicity adjudicated as possible drug induced hepatotoxicity that met Hy's Law criteria was reported in Study MGL-3196-14, an additional case was reported in an open-label patient in Study MGL-3196-14 and another case was reported in Study MGL-3196-11 (neither met Hy's Law criteria). None was reported in the placebo group of both studies. Another hepatotoxicity event occurred in a cirrhotic patient who received resmetirom (open label). The undesirable effect hepatotoxicity is considered an AESI.

Laboratory findings

Lipids and lipoprotein particles as well as thyroid hormone and sex hormone analyses are efficacy-related assessments and are therefore discussed in detail together with efficacy endpoints.

Patients in both resmetirom treatment groups demonstrated significantly greater percent reductions from baseline at Weeks 24 and 52 compared with placebo in all tested parameters, with slightly higher reductions in patients in the 100-mg dose level. No safety issues were identified when assessing lipid changes from baseline to Week 52.

The reductions in liver enzymes in resmetirom-treated patients relative to placebo have been demonstrated in all treatment groups. Reductions were dose-dependent and higher in patients with higher exposures to resmetirom ($AUC \geq 2700$ ng·h/mL). Resmetirom significantly lowered ALT, AST, and GGT throughout the study if compared to placebo. These findings are considered related to efficacy. Early asymptomatic Grade 1 increases in liver enzymes more common in patients on statins were unrelated to safety or efficacy.

Hepatic hypothyroidism is an important underlying pathophysiology in NASH/MASH. The observed significant decrease in FT4 in the resmetirom arms is considered a consequence of the resmetirom-induced increase in the activity of deiodinase 1 leading to higher conversion from FT4 into the active form T3. FT4 levels outside of the normal range were rarely seen. As TSH levels remain unchanged, i.e. TSH secretion is not elevated by low FT4 concentrations; the decrease in FT4 concentrations is considered regaining physiological status. Accordingly, the frequency of potentially thyroid-related symptoms was not increased, apart from the uncertainty regarding MACE described below. In subjects who were on thyroid hormone treatment at baseline, the findings were comparable.

The resmetirom-induced increase in concentration of SHBP may similarly be a “back to normal development” rather than indicative of adverse effects. SHBP is pathologically decreased in NASH/MASH. The observed increase in SHBP is mirrored in a parallel increase in total (i.e. mostly protein bound) sex hormones. Of note, concentration of free testosterone remains constant suggesting that hormone effects on organs and tissues will not be altered. This should be confirmed by a thorough evaluation of the SOC reproductive system and breast disorder (see also OCs on SHBP in efficacy section).

Hepatic impairment

In Study MGL-3196-14, safety data of 161 patients with compensated NASH/MASH cirrhosis (Child-Pugh-A) are presented who finished (open label) 52 weeks of resmetirom treatment. 67 patients completed at least another year of Study 18 treatment. With the exception of pruritus, no meaningful differences were observed between the pooled resmetirom 80 mg and 100 mg treatment groups vs placebo in other frequently reported TEAEs. One adjudicated possible drug induced hepatotoxicity event and one adjudicated major adverse cardiovascular event (MACE) are reported. In 4 patients, hypothyroidism was reported. In 3 patients, the dose was adjusted due to decreased FT4 levels.

The PK exposure of resmetirom is increased and the half-life is prolonged in patients with moderate and even more pronounced severe hepatic impairment. Safety data for patients with moderate and severe hepatic impairment are only available for a 6-day duration. The safety of resmetirom in patients with moderate and severe hepatic impairment (Child-Pugh grade B/C) has not been established.

Renal impairment

3/14 subjects (21.4%) with moderate renal impairment reported hypoglycaemia. Although the number is small, the pathomechanism is unclear. Diabetic hypoglycaemia due to overdose could be the underlying cause. Case narratives could provide further insight.

Currently, important uncertainties remain regarding cardiovascular events, hepatocellular carcinoma, and effects on bone metabolism. Final conclusions may not always be possible based on data from the submitted trials and may require post authorisation data.

Important uncertainties

Deaths

An imbalance of overall ten deaths in patients treated with resmetirom versus one death in the placebo-treated patients is notable. Although no apparent common cause of death or plausible pathomechanisms are obvious, further reassurance is needed, in particular but not limited to cardiovascular events.

MACE and other cardiovascular events

The incidence of MACE and other cardiovascular events in the double-blind phase 3 studies was low and incidence in the treatment groups (MACE 7/1353, other CV events 7/1353) was not substantively different from placebo (MACE 2/669, other CV events 3/669). However, according to the reflection paper on assessment of cardiovascular safety profile of medicinal products (EMA/CHMP/50549/2015), for MACE and other cardiovascular events, a reasonable basis for regulatory assessment of cardiovascular safety must be established, which requires an adequate number of cardiovascular events.

There were 2 adjudicated fatal MACE events in the treatment groups only. In addition, acute myocardial infarction was reported for a deceased patient in study MGL-3196-18 albeit together with various other potentially lethal events such as pneumonia, septic shock, hypoglycaemic coma, multiple organ dysfunction syndrome. While the ongoing Studies 11 and 18, and for cirrhotic patients, the ongoing Study 19 will provide further data in this regard, final conclusions will probably need to be based on post approval data given the low incidence of MACE and other cardiovascular events seen in the studies so far. It can be assumed that the observed LDL-C reduction reduces the overall cardiovascular risk and disease burden.

Neoplasms

Commonalities between hypothyroidism and MASH and MASLD include an increased incidence of HCC. Abnormal expression of THR- β has been shown to promote carcinogenesis. THR- α binding to T3 promotes GI cancer development.

Hepatocellular carcinoma was observed in 3 cases during the non-cirrhotic NASH, randomised, double-blind studies and was pre-existing and not treatment-emergent in 2 of the 3 cases.

However, it is hypothyroidism that is associated with an elevated risk association of HCC (*Hassan et al 2009*), whereas resmetirom is a thyroid hormone receptor agonist. The short time from start of treatment to the detection of the tumours makes a de novo induction of HCC by resmetirom implausible. An acceleration of the development or growth of pre-existing HCC seems unlikely in the context of experimental findings that thyroid hormone inhibits hepatocellular carcinoma progression (*Kowalik et al., 2020*). Given the low incidence of HCC only post-approval data may allow a final conclusion.

Bone mineral density and fracture risk

Based on theoretical considerations and non-clinical (non-adverse) findings, the collection of long-term safety data for bone metabolism and possible increase in fracture risk may be considered. While no evidence of drug-induced adverse effects on bone metabolism and bone mineral density was observed after 1 year of treatment, the impact of resmetirom on bone metabolism remains unknown over the proposed long-term treatment.

Age

Safety data were not specifically discussed in patients ≥ 75 years.

From the safety database all the adverse reactions reported in clinical trials have been included in the SmPC.

Additional safety data needed in the context of a conditional MA

An integrated documentation of long-term safety reflecting the requirements of the reflection paper on CV safety (EMA/CHMP/505049/2015) needs to be conducted, although the number of cardiovascular events was low during the clinical studies. This meta-analysis will use the studies 11 and 19 as database. This will be a category 3 study, as reflected in the RMP.

Long-term safety will also be reported through study MGL-3196-18 (MAESTRO-NAFLD-OLE), which has a primary objective of evaluation of safety and biomarkers of resmetirom.

Although the study is expected to generate additional safety data, it is not expected to address specific safety aspects (due to the overall uncontrolled design). This was therefore classified as a recommendation.

In addition, the applicant also intends to present a real-world longitudinal data study to address liver and CV related outcomes in resmetirom treated patients, as compared with a real-world control arm, that will supplement these meta-analyses. This will be reported in the post-authorisation setting and it is expected that the observational character of the study will limit the stringency of inferences to be derived from it, the study will not be part of the specific obligations but included as a recommendation only.

2.6.10. Conclusions on the clinical safety

Safety data from three Phase 3 studies with very different designs were retrieved. Interim results from the pivotal study MGL-3196-11 and data from the completed study MGL-3196-14 were collected from patients treated for 52 weeks; Study MGL-3196-18 is still ongoing and the duration of patient exposure varies widely. A 120-day safety update report was presented containing safety data from the ongoing studies after the respective initial data cut-off. Further safety data were obtained from the Phase 2 study MGL-3196-05, which was completed after 36 weeks. Safety assessment is based on ~ 1800 patients treated with resmetirom, most of them treated with 80 or 100 mg for 6 to 12 months. This safety database is sufficient and adequate.

The most frequent AEs occurring with the compound, relate to "functional" GI effects, such as diarrhoea, nausea and vomiting and abdominal pain and are likely to be reduced with appropriate dose selection

and/or adjustment. Although the majority of these were mild and transient, recurrent episodes and the risk in the elderly population should be further investigated.

The incidence rate of serious AEs including the AESIs bile formation related adverse events and hepatotoxicity, and adjudicated possible drug induced hepatotoxicity was low. However, some uncertainties remain regarding a slightly higher rate of fatal events in the treatment groups, the AESIs MACE and other cardiovascular events, hepatocellular carcinoma, and effects on bone metabolism. Data on MACE and other CV events as well as data on the incidence of HCC are limited at this point. The effect on CV risk factors however appears favourable. The relatively short duration of data collection regarding the effects on bone metabolism has to be considered.

Overall, resmetirom has an acceptable safety profile and treatment is generally well tolerated. Some of the studies are still ongoing. Since resmetirom is intended for long-term use, further data beyond 52 weeks will be needed to confirm clinical benefit and further characterize the long-term safety of resmetirom.

2.7. Risk Management Plan

2.7.1. Safety concerns

Summary of safety concerns

The applicant proposed the following summary of safety concerns in the RMP:

Part II: Module SVIII – Summary of the safety concerns

Table 49. Summary of safety concerns in proposed RMP version 0.8

Summary of safety concerns	
Important identified risks	• Cholelithiasis, including complications such as cholecystitis and obstructive pancreatitis • Hepatotoxicity
Important potential risks	• Hepatocellular carcinoma • Cardiovascular safety
Missing information	• Long term safety (i.e., ≥ 1 year) in elderly • Use in patients with severe renal impairment

2.7.2. Pharmacovigilance plan

Ongoing and planned additional pharmacovigilance activities

Table 50. Ongoing and planned additional pharmacovigilance activities

Study Status	Summary of objectives	Safety concerns addressed	Milestones	Due dates
Category 1 – Imposed mandatory additional pharmacovigilance activities that are conditional of the marketing authorisation				
None				
Category 2 – Imposed mandatory additional pharmacovigilance activities that are Specific Obligations in the context of a conditional marketing authorisation or a marketing authorisation under exceptional circumstances				
None				
Category 3 – Required additional pharmacovigilance activities				
Cardiovascular Meta-analysis Planned	To evaluate the cardiovascular safety of resmetirom via composite endpoint of MACE events including CV mortality, non-fatal stroke and non-fatal myocardial infarction	Safety analysis – no efficacy objectives Safety objective: To evaluate the effect of resmetirom on cardiovascular outcomes in patients with MASH	Protocol submission Statistical Analysis Plan Analysis Completion Final report	Q3 2028 Q1 2029 Q2 2029 Q4 2029

Part IV: Plans for post-authorization efficacy studies

Table 51. Planned and on-going post-authorisation efficacy studies that are conditions of the marketing authorisation or that are specific obligations

Study Status	Summary of Objectives	Efficacy uncertainties addressed	Milestones	Due Date
Efficacy studies that are conditions of the marketing authorisation				
Not applicable				
Efficacy studies which are Specific Obligations in the context of a conditional marketing authorization or a marketing authorisation under exceptional circumstances				
Study 11 Week 53 analysis	Week 52 Dual Primary: To determine the effect of once-daily resmetirom versus	To evaluate the effect of resmetirom on histologic conversion	Interim study report	30-Jun-2023 (data cut off 31-Jul-2022)

Study Status	Summary of Objectives	Efficacy uncertainties addressed	Milestones	Due Date
complete; Month 54 analysis ongoing	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 Primary Endpoint) To determine the effect of once-daily resmetirom versus matching placebo on histologic improvement from baseline demonstrated by at least 1-point improvement in fibrosis by liver biopsy with no worsening of NAS at Week 52 Month 54 Primary: Time to experiencing an adjudicated Composite Clinical Outcome Event (composed of all-cause mortality, liver transplant, and significant hepatic decompensation events [ascites, encephalopathy or gastroesophageal variceal hemorrhage] or confirmed increase of MELD score from <12 to ≥15	to NASH cirrhosis To evaluate the effect of resmetirom on clinical outcomes in patients with MASH	Study Completion Final study report	Q3 2028 Q1 2029
Study 19 Ongoing	To determine the effect of once-daily oral 80 mg resmetirom vs placebo on patients as measured by time to experiencing a first adjudicated CCO	To evaluate the effect of resmetirom on clinical outcomes in patients with MASH cirrhosis	Study Completion Final study report	Q3 2027 Q1 2028

2.7.3. Risk minimisation measures

Table 52. Summary table of risk minimisation activities by safety concern

Safety Concern	Routine risk minimisation activities
Important Identified Risks:	
Cholelithiasis, including complications such as cholecystitis and obstructive pancreatitis	<u>Routine risk communication:</u> EU SmPC Section 4.4 Special warnings and precautions for use Package leaflet Section 2 <u>Routine risk minimisation activities recommending specific clinical measures to address the risk:</u> EU SmPC Section 4.4 includes recommendations that if cholelithiasis is suspected, gallbladder diagnostic studies and appropriate clinical follow-up are indicated. <u>Other routine risk minimisation measures beyond Product Information:</u> Medicine's legal status: Prescription only medicine.
Hepatotoxicity	<u>Routine risk communication:</u> EU SmPC Section 4.4 Special warnings and precautions for use Package leaflet Section 2 <u>Routine risk minimisation activities recommending specific clinical measures to address the risk:</u> EU SmPC Section 4.4 includes recommendations that patients should be monitored during treatment with resmetirom for elevation in liver enzymes and signs or symptoms of hepatotoxicity. If taking concomitant statin therapy, dose of statins should be limited as per SmPC Resmetirom should be used with caution in MASH patients with other underlying liver diseases such as autoimmune liver diseases or active viral hepatitis and in patients with alcohol-related liver disease. This is also reflected in package leaflet Section 2. <u>Other routine risk minimisation measures beyond Product Information:</u> Medicine's legal status: Prescription only medicine.
Important Potential Risks:	
Hepatocellular carcinoma	<u>Routine risk communication:</u> Not applicable <u>Routine risk minimisation activities recommending specific</u>

	<u>clinical measures to address the risk:</u> Interventions to reduce prevalence of cirrhosis will lead to reductions in HCC. Lifestyle modifications and routine screening also mitigate risk. <u>Other routine risk minimisation measures beyond Product Information:</u> Medicine's legal status: Prescription only medicine.
Cardiovascular safety	<u>Routine risk communication:</u> Not applicable <u>Routine risk minimisation activities recommending specific clinical measures to address the risk:</u> None <u>Other routine risk minimisation measures beyond Product Information:</u> Medicine's legal status: Prescription only medicine.
<u>Missing Information:</u>	
Long term safety (i.e., ≥1 year) in very elderly	<u>Routine risk communication:</u> None <u>Routine risk minimisation activities recommending specific clinical measures to address the risk:</u> None <u>Other routine risk minimisation measures beyond Product Information:</u> Medicine's legal status: Prescription only medicine.
Use in patients with severe renal impairment	<u>Routine risk communication:</u> None <u>Routine risk minimisation activities recommending specific clinical measures to address the risk:</u> None <u>Other routine risk minimisation measures beyond Product Information:</u> Medicine's legal status: Prescription only medicine.

2.7.4. Conclusion

The CHMP considers that the risk management plan version 0.8 is acceptable.

2.8. Pharmacovigilance

2.8.1. Pharmacovigilance system

The CHMP considered that the pharmacovigilance system summary submitted by the applicant fulfils the requirements of Article 8(3) of Directive 2001/83/EC.

2.8.2. Periodic Safety Update Reports submission requirements

The requirements for submission of periodic safety update reports for this medicinal product are set out in the Annex II, Section C of the CHMP Opinion. The applicant did request alignment of the PSUR cycle with the international birth date (IBD). The IBD is 14.03.2024. The new EURD list entry will therefore use the IBD to determine the forthcoming Data Lock Points.

2.9. Product information

2.9.1. User consultation

The results of the user consultation with target patient groups on the package leaflet submitted by the applicant show that the package leaflet meets the criteria for readability as set out in the *Guideline on the readability of the label and package leaflet of medicinal products for human use*.

2.9.2. Additional monitoring

Pursuant to Article 23(1) of Regulation No (EU) 726/2004, Rezdiffra (resmetirom) is included in the additional monitoring list as:

- it contains a new active substance which, on 1 January 2011, was not contained in any medicinal product authorised in the EU.
- it has an obligation to conduct post-authorisation efficacy studies [REG Art 9(4)(cc), Art 10a(1)(b), DIR Art 21a(f), Art 22a(1)(b)]
- It is approved under a conditional marketing authorisation [REG Art 14-a]

Therefore, the summary of product characteristics and the package leaflet include a statement that this medicinal product is subject to additional monitoring and that this will allow quick identification of new safety information. The statement is preceded by an inverted equilateral black triangle.

3. Benefit-risk balance

3.1. Therapeutic context

3.1.1. Disease or condition

Metabolic Dysfunction Associated Steatohepatitis (MASH) is regarded to be the necro-inflammatory and progressive form of MASLD and thus associated with obesity, dyslipidaemia, T2DM, arterial hypertension, and other similar diseases. The stages of MASH with a higher grade of fibrosis (F2 to F4) have been associated with a high risk of progression to end-stage liver disease (ultimately leading to decompensation and liver failure, transplantation and death), as well as hepatocellular carcinoma. Due to the associated co-morbidities, the condition is also associated with a considerable risk of cardiovascular disease and associated morbidity and mortality.

Since there is no established pharmacological treatment available (see below), the aims of the treatment will have to rely on the assumptions made from the epidemiological data showing an association of outcomes with the (histological) burden of liver tissue based on cell stress, inflammation, and fat load, and even more so with liver fibrosis. However, whether the proposed endpoints with regard to reduction of the necro-inflammatory changes and fibrosis are adequate surrogates remains uncertain at this point of time. Ultimately, since MASH is expected to become the future main reason for liver transplantation, demonstration of efficacy for a treatment in MASH would need to show reductions in the occurrence of end-stage liver disease and its complications.

3.1.2. Available therapies and unmet medical need

A licensed pharmacological treatment is currently not available, irrespective of the stage and grade of the disease, and the currently available treatments in the first place rely on dietary and other life-style advice. As mentioned above, the concomitant diseases need to be treated adequately. In progressive disease, current treatment guidelines also give some recommendations outside regulatory approved indications (off-label treatment) for compounds such as vitamin E, pioglitazone, and GLP-1RAs. In cases with progressive disease, bariatric surgery may be indicated (e.g. gastric banding).

As mentioned above, the condition is potentially serious and life-threatening, and a growing major public health issue.

3.1.3. Main clinical studies

One pivotal clinical study, study MGL-3196-11, supported the efficacy claims in the dossier. This study has been planned as a long-term efficacy study in a randomized, controlled placebo design. For the current application, the applicant presented a planned interim analysis, for which a pre-designated part of the total population was included and has passed 1 year of treatment. The study is planned to finally evaluate the occurrence of the manifestation of end-stage liver disease, including the (histological) diagnosis of cirrhosis. This evaluation is currently planned to occur after 54 months.

The study has selected a population based on the histological evaluation of liver biopsies with the requirement to have a relevant activity of disease, as well as fibrosis being present at baseline. The

criteria for activity based on the NAS-CRN criteria, requesting a score of at least 4 (with 1 in each of the sub-scores) was considered adequate and in line with the published regulatory guidance document.

Other trials presented are considered to be supportive in nature, since the main part of the population were not considered to belong to the finally accepted target population. Also, for most of these other trials – despite being presented with a randomized controlled design – the primary objective was the demonstration of safety.

3.2. Favourable effects

The pivotal study has demonstrated statistically significant and highly consistent effects over placebo for both doses used in study 11 in pre-planned primary population and modified population including only F2/F3. The efficacy claim is mainly based on the effects in the following outcomes, defined as primary endpoints:

- Resolution of MASH without worsening of fibrosis: the results of the trial have demonstrated a statistically significant effect both on the NASH/MASH resolution endpoint, as well as on the improvement of fibrosis endpoint. Both doses (80 and 100 mg) of the compound were successful with p-values below 0.001 for each of the analyses (and thus complying with the increased statistical rigour required for the presentation of one pivotal trial only). The rate of placebo response (10.0% with NAS-score normal at the end of the 52 weeks treatment) was significantly lower than with resmetirom treatment (30.1 % with higher dose, 26.0 % with lower dose) in F2/F3 population.
- Improvement of fibrosis without worsening of NASH/MASH: The compound is able to reduce the fibrosis formation within the liver relevantly with about 27-29% of the patients achieving a reduction of at least one stage without worsening of the other features of NASH/MASH compared to placebo (response rate 17.0%) in F2/F3 population.

Highly statistically significant differences have also been documented for pre-planned and F2/F3 population for other histology-derived endpoints, such as the 2-point reduction of NAS, the combined fibrosis and NAS responder, and others.

An evaluation of sub-groups has shown high consistency of the effect, and several sensitivity analyses have demonstrated full robustness of the results.

Within a multitude of secondary endpoints, the study has also reported a relevant reduction of hepatic fat within the liver by means of non-invasive imaging methods, such as MR-PDFF (hepatic fat fraction). Similarly, reductions of disease activity have also been documented for fibrosis biomarkers, or measures of fibrosis with imaging methods, such as FibroScan based VCTE, and MRE (magnetic resonance elastography). A reduction of the disease activity is also documented for the “conventional” biomarker endpoints ALT, AST, and GGT.

The applicant also presents as “key secondary” endpoint the evaluation of the changes in LDL-C for which almost no changes have been observed in placebo-treated patients, and the changes compared to placebo amount to a reduction of 14.0% and 19.0% for the low and high dose groups. The parameter can be taken to be reassuring in demonstrating that there is not only a re-distribution of fat from the liver to the serum (or other parts of the body), but the reduction of the “fat burden” includes the whole organism.

Two supportive studies were presented, but they have not evaluated effects based on histology. However, the results of the non-invasive methods (imaging and biomarkers) reported for the pivotal study have been reproduced in the studies and support the overall favourable effects.

Similar, but somewhat weaker effects as in the pivotal study have also been observed in an early proof of concept study also showing a reduction of the NAS score-based activity of the disease, as well as reduction of fat burden in the liver by MR-PDFF.

3.3. Uncertainties and limitations about favourable effects

The pivotal study has evaluated a reduction of disease activity, which is currently deemed adequate to allow an early registration of a candidate medicinal product. However, for the primary endpoint (and the other histology-based endpoints), a proper correlation with liver outcome events (hepatic decompensation events, liver transplantation and death) under the conditions of pharmacological treatment has not been documented. A confirmation of the efficacy on the liver-related outcomes remains therefore uncertain, and the pivotal study has been designed to be on-going at the time of interim evaluation and submission and will document efficacy on liver outcomes in the future only. A CMA on the basis of the submitted data was therefore endorsed.

The applicant has chosen a somewhat exceptional way of histology evaluation. The two involved central histopathologists were not requested to reach agreement on diverging assessments, but the chosen method of evaluation assigned a "½ response" to the cases of divergence. Since the "validity" of this attribution is somewhat unclear, additional analyses including sensitivity analysis accounting for variable assessments were conducted.

The pivotal study 11 was burdened with a high frequency of late changes in the plans for the mode(s) of evaluations planned in the protocol, and of the statistical analysis plan (SAP) which makes it not fully GCP compliant with regard to pre-planning, pre-specification, and keeping the blind before evaluation was adequately adhered to.

Within the pivotal study, the secondary endpoints based on imaging methods and biomarkers are restricted to certain parts of the included population only (e.g. with certain levels of baseline elevation) or are reported on an "observed case" basis, which disregards the principles of intention-to-treat. Therefore, the chosen secondary endpoints provide somewhat limited information for clinical relevance of MASH treatment with resmetirom.

It furthermore needs to be considered that study 11 was the only "pivotal" study, and a replication of the results is currently missing.

The supportive studies have included a population which in part does not belong to the target population, because only part of the included population fulfilled the necessary (histological) requirements of moderate or significant fibrosis and adequate MASH activity, and the proportions of patients with or without fulfilling these requirements are unknown. The value of documenting effects on non-invasive indicators of MASH (biomarkers and imaging methods) is therefore limited. In addition, only part of the population has been evaluated, and results are mainly based on observed cases evaluations.

Although the early proof of concept study is also supportive overall, this study included also patients not being part of the final target population. Also, observation time was not long enough to allow the evaluation of the intermediate primary endpoints used in the pivotal trial.

3.4. Unfavourable effects

Safety assessment is based on approximately 1800 non-cirrhotic NASH/MASH patients treated with resmetirom mostly 80 or 100 mg, for 6 to 12 months. Approximately 250 patients with cirrhosis, most of them with NASH/MASH cirrhosis, were treated with mostly 80 mg resmetirom also for 6 to 12 months.

The most common AEs observed were diarrhoea (occurring in about 24-27% of subjects on resmetirom vs. 10-15% on placebo), nausea (12%-22% as compared to 8-13% on placebo), and pruritus (4.9% as compared to 2.5 % for placebo) with an increased incidence of diarrhoea and nausea for the higher dose. The incidence of pruritus was clearly highest in cirrhotic patients treated with resmetirom. Diarrhoea and nausea typically occurred within the first 12 weeks after treatment initiation. The severity of diarrhoea and nausea was mild to moderate in most cases, but diarrhoea and nausea together with headache were the most common reasons for treatment discontinuation. Headache was the most common AE in the PK studies. The second most common adverse effects were abdominal pain, vomiting, constipation, and dizziness.

Most TEAEs were Grade 1 or 2 in severity in all treatment groups. Serious adverse events were evenly distributed across the study groups.

Bile formation related adverse events were identified as AESI, some of them serious. They were reported more often in the treatment arms than in placebo arms. 6 cases of (obstructive) pancreatitis were reported in the resmetirom arm, in the placebo arms only 1 case. If cases of pancreatic failure and pancreatic cysts, both possible sequelae of pancreatitis, are added, the balance shifts further against treatment.

Hepatotoxicity is also considered a serious AESI. The incidence was very low with 4 patients. However, the events occurred only in resmetirom treated patients and the relation to treatment was adjudicated by a special safety committee (possibly related in 2 cases).

The number of fatal events was higher in the treatment groups.

Only 1 to 3% of subjects across the trial arms were older than 75 years. 22 - 27% of the subjects were ≥ 65 years of age. These patients had numerically higher incidences of the TEAEs diarrhoea and pruritus, and higher incidence of serious AEs than patients <65 years of age. The nature of these AEs is not further specified by the applicant.

Except for the TEAEs nausea and pruritus which were clearly more frequently reported by female patients, there were no noticeable differences to the male subjects.

Results of the study MGL-3196-10 indicate that the PK exposure of resmetirom is increased and the half-life is prolonged in patients with moderate and even more pronounced severe hepatic impairment. Although most of the patients with moderately impaired liver function included in this study had non-MASH cirrhosis, it must be assumed, not least due to the lack of data, that the same applies to patients with MASH cirrhosis. Safety data for patients with moderate and severe hepatic impairment are only available

for a 6-day duration. The safety of resmetirom in patients with moderate and severe hepatic impairment (Child-Pugh grade B/C) has not been established.

3.5. Uncertainties and limitations about unfavourable effects

Methodological differences between these studies limit benefits of the pooled safety analysis.

Currently, important uncertainties remain regarding cardiovascular events, hepatotoxicity, hepatocellular carcinoma, and effects on bone metabolism, and fatal events. Final conclusions may not always be possible based on data from the submitted trials and may require post authorisation data.

MACE and other cardiovascular events

The incidence of MACE and other cardiovascular events in the double-blind phase 3 studies was low and incidence in the treatment groups (10/1353) was not substantively different from placebo (6/669). There were 2 adjudicated fatal MACE events in the treatment groups only.

Due to the low number of events, the requirements of the reflection paper on assessment of cardiovascular safety profile of medicinal products (EMA/CHMP/50549/2015) are not met. The observed LDL-C reduction reduces the overall cardiovascular risk and disease burden.

Hepatocellular carcinoma

Hepatocellular carcinoma was observed in 3 cases during the non-cirrhotic NASH, randomised, double-blind studies and was pre-existing and not treatment-emergent in 2 of the 3 cases. The short time from start of treatment to the detection of the tumours makes a de novo induction of HCC by resmetirom implausible. An acceleration of the development or growth of pre-existing HCC seems unlikely in the context of experimental findings that thyroid hormone inhibits hepatocellular carcinoma progression. Given the low incidence of HCC only post-approval data may allow a final conclusion. The uncertainty based on the unequal numbers, will, however, remain.

Bone mineral density and fracture risk

Based on theoretical considerations and non-clinical (non-adverse) findings, the collection of long-term safety data for bone metabolism and possible increase in fracture risk should be considered. While no evidence of drug-induced adverse effects on bone metabolism and bone mineral density was observed after 1 year of treatment, the impact of resmetirom on bone metabolism remains unknown over the proposed life-long treatment.

Hepatotoxicity

A higher incidence of hepatotoxicity, and especially the event fulfilling the Hy's law criteria are of relevant concern. Although clarification will be obtained on the full incidence of both hepatotoxicity events as such, and those fulfilling Hy's law criteria, uncertainties will remain since the overall incidence is low.

Age, race

Regarding specific populations, in some subgroups (elderly, non-Caucasian), the sample size was too small to make any meaningful conclusions about the safety profile. Only 1 to 3% of subjects across the trial arms

were older than 75 years. A conclusion about the safety of resmetirom in this age group is therefore not possible.

Moderate and severe hepatic impairment

No safety data is available for the population with moderate and severe hepatic impairment Child Pugh-B/C. Since PK exposure must be assumed to be increased and half-life prolonged in patients with moderate and severe impairment, and additionally the duration of Study MGL-3196-10 was only 6 days with 87 patients enrolled, the safety of resmetirom in patients with moderate and severe hepatic impairment (Child-Pugh grade of B/C) has not been established.

SHBG

The changes in SHBG as such are not a safety concern. However, the preliminary conclusion that there are no relevant changes in sex hormone levels still needs to be confirmed by an examination of the SOC reproductive system and breast disorder in order to exclude any resulting AEs.

For the study 11, some uncertainties in relation to the GCP compliance were raised during the procedure. However, based on the additional information presented by the applicant, the risk for the reliability for the Week 52 analysis is considered low, however some uncertainty remains for the long-term analysis. Therefore, study 11 is not considered sufficient as stand-alone condition for a CMA.

3.6. Effects table

Table 53. Effects table for Rezdiffra (resmetirom)

Effect		Unit	Treatment 100 mg	80 mg	Control PBO	Uncertainties/ Strength of evidence
Favourable Effects ¹						
NASH resolution w/o worsening of fibrosis in F2/F3 population		%	30.	26	10.0	Evidence strong (95% CIs for difference: [11.0; 22.0] (80 mg), [15.0; 26.0] (100 mg)). Clinically highly relevant
≥1 stage improvement of fibrosis w/o worsening of NASH in F2/F3 population			29.0	27.0	17.0	Evidence strong (95% CIs for difference: [4.0;15.0] (80 mg); [6.0;18.0] (100 mg)). Clinically highly relevant
LDL-C levels at week 52 in F2/F3 population		Mean % CFB	-17.9	-13.5	0	Evidence strong (95% CIs for difference: [-17.9; -9.5] (80 mg), [-22; -13.8] (100 mg)). Clinically less relevant
Overall load of liver fat as measured by MRI-PDFF in F2/F3 population		Mean % CFB	-47.5	-33.5	-6.8	Evidence strong (95% CIs for difference: [-33.4, -20.1] (80 mg); [-47.4, -34.0] (100 mg). Clinical relevance high, however, investigated in subgroup of patients only
LFT in patients with elevated ALT >30 U/l at baseline in F2/F3 population	ALT	Mean % CFB	-31	-23	-5	Evidence strong
	AST		-26	-21	-2	Clinical relevance unclear (based on restricted patient numbers)
	GGT		-34	-27	-1	
Improvement of fibrosis as measured by ELF score in F2/F3 population		Absolute CFB	-0.46	-0.41	0.21	Evidence strong (95% CIs [-0.42, -0.07] (80 mg), [-0.37, -0.03] (100 mg) Clinical relevance high, however, however, investigated in subgroup of patients only

Effect	Unit	Treatment	Control	Uncertainties/ Strength of evidence
		100 mg	80 mg PBO	
Unfavourable Effects				
Diarrhoea ²	%	28.8	14.2	Evidence sufficiently strong (95%CI for difference: [1.65; 2.49]). Mostly grade 1 or 2. Clinically relevant
Nausea ²		17.7	9.7	Evidence sufficiently strong (95%CI for difference: [1.41; 2.36]). Clinically relevant
Pruritus ²		7.3	4.5	Evidence moderate (95%CI for difference: [1.10; 2.44]). Clinically relevant
All-cause mortality ³		0.5	0.1	Evidence moderate. RR 3.47 (95% CI for difference: [0,44; 27.34]). Probably unrelated
Adjudicated MACE ³		0.4	0.3	Evidence weak (95% CI for difference: [0.28; 6.48]) Not enough events overall
Hepatotoxicity ³		0.2	0.0	(1 possible drug-induced hepatotoxicity case in a cirrhotic patient) Evidence strong. Clinical relevance high
Cholecystitis (acute and chronic) ³		0.4	0.1	Evidence moderate (95% CI for difference: [0.33; 21.9]). Clinical relevance high
Cholelithiasis (newly observed) ³		1.8	0.1	Evidence strong. 95% CI for difference: [1.69; 90.12]). Clinically relevant
(obstructive) Pancreatitis ³		0.3	0.0	Evidence strong. Clinical relevance high

Notes: 1 Based on Study 11 interim data cut- off 31.07.2022; 2 Based on Study 11, 14 (placebo controlled patients); 3 Study 11, 14, 18 (study 18 not placebo-controlled); no events in Study 05 (adaptive design, only 36 weeks)
Abbreviations CFB = Change from baseline; RR relative risk

3.7. Benefit-risk assessment and discussion

3.7.1. Importance of favourable and unfavourable effects

There are no approved pharmacological treatments for MASH. The treatment of MASH is currently restricted to either off-label treatment or to the modification of lifestyle (weight loss, dietary modification and increased physical activity). More severe cases can undergo invasive, surgical treatment. There is a clear unmet medical need for this disease.

The pivotal study included only patients whose diagnosis of liver fibrosis (and stage) had been histologically confirmed. Currently there are no approved non-invasive tests to diagnose MASH with liver fibrosis stages F2 and F3 or to monitor response to treatment. However, considering recent guideline recommendations and on-going research in the development of non-invasive testing, it is considered acceptable (and very likely for clinical practice) that diagnosis and monitoring of MASH patients can be done with acceptable accuracy.

The immediate effects of treatment would be expected to tackle the overall fat-load, the fat-related toxicity with associated liver cell stress and degeneration as well as associated inflammation and the formation of fibrosis. Also, since MASH was originally defined on histological features, they are expected to be addressed in the first place. Currently, a full correlation between the improvement of these histological features and the long-term outcomes of the disease has not been established. Therefore, the current application has tackled the appropriate features of the disease, prioritizing the improvement of histology, as per the results reported on fibrosis improvement and MASH resolution.

The resolution of NASH (without worsening of fibrosis) and the improvement of fibrosis (without worsening of NASH) are reflecting the above-mentioned features and have been accepted by the regulatory guidance of the CHMP as primary endpoints in trials aiming at an early registration of compounds with the obvious conditions of difficulties in obtaining long-term data, and the unmet medical need being present.

The magnitude of the effects achieved in the pivotal study 11 for the histology endpoints were – under consideration that only 1 year of treatment has been evaluated – considered to be highly relevant, also since the responder rates (for the two primary endpoint) are tripled (for MASH resolution) or at least doubled (for fibrosis improvement) as compared to placebo in preplanned and modified F2/F3 population.

A prediction, however, whether the improvements in histology will translate into improvements in survival, manifestation of end-stage liver disease and liver transplantation is currently not possible, and the pivotal study is therefore on-going, with a planned total study duration of 54 months.

The additional evaluations of secondary endpoints (and the supportive studies presented) support the overall conclusions, and the methods, including the non-invasive measurement of liver fat, and fibrosis, with both, biomarkers, as well as imaging methods are considered valuable contributions. However, currently some uncertainties remain with regard to the completeness of the evaluations.

In addition to reducing liver fat, resmetirom also reduced LDL-C, a cardiovascular risk factor, which appears relevant in a population with increased cardiovascular morbidity and mortality.

The safety of the compound has been evaluated in a sufficiently large database with an adequate duration of observation. The most frequent adverse drug reactions are related to “functional” gastrointestinal complaints such as diarrhoea, nausea and vomiting, or to pruritus. Although the majority of these were mild and transient, the risk in the elderly population needs to be further investigated.

There are relevant safety concerns regarding the occurrence of bile-duct related events, which are considered to be related to the increased production of bile, as a direct effect of the mechanism of action of resmetirom. Whether the increase in diarrhoea also relates to this presumed increased production of bile remains unclear. Due to its mechanism, the compound is considered responsible for the causation of events of cholelithiasis, cholecystitis and obstructive pancreatitis.

The treatment of MASH also refers to a patient population with an increased risk of CV disease, and the current guidance document requests a separate evaluation of cardiac safety in this population, based on the "Reflection paper on assessment of cardiovascular safety profile of medicinal products" (EMA/CHMP/505049/2015). Currently only a very small number of such events has been observed in the trial programme, and a more comprehensive assessment needs to be presented also pointing to the missing comprehensiveness of the data.

The documentation of liver safety is also in the focus of the overall safety evaluation. In this regard, the number of adjudicated possible hepatotoxicity cases (and the potential Hy's law case) suggests a causal involvement of the substance.

Since patients with MASH are also at increased risk of Hepatocellular carcinoma (HCC), the currently observed numbers for this disease, although overall low, also raise concern and make a proper re-evaluation and reconsideration necessary.

Since the pivotal trial and one supportive study are ongoing, and the applicant has also started an additional study in the cirrhotic-MASH population, further efficacy and safety data are expected from these studies.

Overall, it can be considered that resmetirom would address the unmet need in MASH F2/F3 non-cirrhotic population, provided that raised concerns are addressed by the applicant. The effect on liver outcomes needs to be demonstrated to conclude that the provided data are comprehensive.

3.7.2. Balance of benefits and risks

The efficacy of resmetirom has been demonstrated based on the accepted interim endpoints recommended in the respective EMA guidance. The proposed treatment is considered to fulfil an unmet medical need and will be the first approved pharmacological treatment for MASH, a disease which is associated with life-threatening outcomes. The compound has demonstrated beneficial effects of clinical relevance, of high statistical significance, and for both endpoints, the resolution of MASH, as well as the reduction of fibrosis. Nevertheless, evidence with regard to liver outcomes is missing and will need to be generated post-marketing.

The overall safety profile of the compound regarding the most frequent adverse drug reactions is acceptable, and is mainly referring to gastrointestinal events, such as diarrhoea and nausea, as well as pruritus. The occurrence of such events appears to be manageable, and the frequency of occurrence of the gastrointestinal events is expected to be reduced by appropriate dose-selection and potentially dose-adaptation. Hepatotoxicity was identified as adverse drug reaction, however with very low incidence. Cholelithiasis, cholecystitis, and obstructive pancreatitis were identified as adverse drug reactions, but their low incidence does not affect the positive benefit risk balance.

With regard to hepatocellular carcinoma (HCC) and cardiovascular safety, it was considered that, currently low number of events, definitive conclusions cannot yet be drawn. Based on the mechanism of action of resmetirom, it is expected that liver cell stress, lobular inflammation, and ultimately, fibrosis could be

reduced, which would lead to a lower incidence of HCC in the long-term, similar to the improvements in LDL-C potentially leading to a reduction of CV events. While no detrimental effects have been observed to date, further data are needed to support a more robust assessment, which justifies the request for additional studies under category 3.

Taken together, the benefits of resmetirom are expected to outweigh the risks for a patient population with MASH and fibrosis stage of 2 or 3. Since data can currently not be considered comprehensive, the authorisation of the product should be made “conditional” (see below).

3.7.3. Additional considerations on the benefit-risk balance

Conditional marketing authorisation

As comprehensive data on the product are not available, a conditional marketing authorisation was proposed by the CHMP during the assessment, after having consulted the applicant.

The product falls within the scope of Article 14-a of Regulation (EC) No 726/2004 concerning conditional marketing authorisations, as it aims at the treatment of a life-threatening disease.

Furthermore, the CHMP considers that the product fulfils the requirements for a conditional marketing authorisation:

- The benefit-risk balance is positive, as discussed.

The efficacy of resmetirom has been demonstrated in the pivotal study based on the accepted interim endpoints. Results from two supportive studies support the overall favourable effects of resmetirom. Coupled with comprehensive long-term data that will be provided post-authorisation, the benefit/risk balance is considered positive.

- Unmet medical need will be addressed.

Given the progressive nature of MASH and its slow clinical course, coupled with the lack of approved pharmacological treatments, the unmet medical need remains high. The absence of a reference standard or validated long-term outcome biomarkers, as outlined in the reflection paper on NASH, means that intermediate endpoints—particularly histological changes—are agreed to serve as an approach to reasonably predict long-term outcomes.

- It is likely that the applicant will be able to provide comprehensive data.

Company presented comprehensive analysis and feasibility assessment of the pivotal study 11 and study 19 MAESTRO-NASH-OUTCOMES:

1. The final results of the pivotal Study 11

The on-going pivotal study 11 (MAESTRO-NASH) will have 54-month outcomes analysis that will provide evidence of long-term benefit of resmetirom in approximately 1750 patients. Patients enrolled in the MAESTRO-NASH study continue therapy after the initial 52-week treatment period for up to 54 months to accrue and measure hepatic clinical outcome events, including progression to cirrhosis on biopsy (52 weeks and 54 months) and hepatic decompensation events, as well as all-cause mortality. The proposed target of 200 events was considered sufficient and the rate of occurrence predicted that the number of events would be achieved prior to completion of the last patient to reach month 54.

However, the pivotal study 11 cannot be a stand-alone condition for the provision comprehensive data for the CMA. The study implements an unblinded interim analysis for histological endpoints (week 52) followed by an evaluation of long-term outcomes (month 54). The unblinded interim analysis might have an impact on the study integrity and validity of the long-term outcome part. Although the risks are considered low, there remain some concern with unblinding procedures and pre-specification of long-term data analysis and its impact on GCP compliance.

The applicant has discussed concerns and possible mitigation measures with discontinuation in this study as well as handling of missing data for the final analysis. The study end date is August 2028, and the expected CSR submission date is March 2029. The study is considered feasible, and the provision of the final results of the study will provide data post-authorisation for the comprehensiveness of the dossier. Therefore, it is imposed as a specific obligation (SOB) to the CMA.

2. Study 19 MAESTRO-NASH-OUTCOMES

This is a randomized controlled study with 845 well-compensated NASH cirrhosis patients. The main outcome is the time to the first adjudicated outcome event, which include cardiovascular or liver mortality, hepatic decompensation events (new onset ascites, grade 2 hepatic encephalopathy or confirmed variceal haemorrhage), confirmed increase in MELD from <12 to ≥ 15 , or liver transplant. All-cause mortality will be included as a safety endpoint. This study was primarily designed to support a new indication of well-compensated NASH cirrhosis, however it is considered that it will also support confirming clinical benefit in non-cirrhotic NASH by corroborating preliminary data from the ongoing open-label resmetirom cirrhotic NASH arms in Studies 11 and 14, in which well-compensated NASH cirrhosis patients have demonstrated 1) a potential response to resmetirom treatment similar to non-cirrhotic NASH patients, including notable reductions in liver enzyme, hepatic fat fraction (MRI-PDFF), and lipids, and 2) a similar tolerability and safety profile compared with non-cirrhotic NASH patients. The study end date is April 2027, and the expected CSR submission date is March 2028.

The study is considered feasible and the provision of the final results of the study will provide data post-authorisation for the comprehensiveness of the dossier and is therefore imposed as a specific obligation (SOB) to the CMA.

Additional studies will be performed in the post-marketing setting, and it is expected that they will provide relevant information, especially in relation to the safety aspects:

1. Study MGL-3196-18 (MAESTRO-NAFLD-OLE). It is an on-going 52-week, multicentre, open-label study, which includes a 52-week treatment period and a 4-week follow-up period. The primary objective is evaluation of safety and biomarkers of resmetirom. The study was submitted with an interim report with a data cut-off date of 30 September 2022 as part of this MAA. The study end date is April 2027, and the expected CSR submission date is August 2027. The study will, in comparison to studies 11 and 19, provide less important data and has not included an overall population for which presence of MASH was diagnosed in similar, most certain way as in studies 11 and 18 (part of the patients were even intentionally failing the inclusion criteria of study 11). Therefore, while the study complements the safety data, it is not expected to address specific safety concerns (due to the overall uncontrolled design), nor provide efficacy data on the target population (due to the non-invasive endpoints and partially non-target population included). Designation as a recommendation was therefore sufficient.

2. As a further element to complete the data and addressing the need to comply with the "Reflection paper on assessment of cardiovascular safety profile of medicinal products" (EMA/CHMP/505049/2015), an integrated analysis of cardiovascular safety will be submitted. The applicant plans to conduct a meta-

analysis of MACE events based on all completed clinical trials, with a planned completion in 2029. Since the submission was considered obligatory, it was included in the RMP as non-imposed category 3 study.

3. A real-world longitudinal data study is planned to assess liver and CV related outcomes in resmetirom treated patients, as compared with a real-world control arm. The study is intended to complement these meta-analyses (see also evaluation of clinical safety).

- The benefits to public health of the immediate availability outweigh the risks inherent in the fact that additional data are still required. The applicant discussed that the prevalence of MASH has increased in recent years, largely due to the increasing prevalence of obesity and associated conditions. Currently, there is no approved pharmacologic therapy for the treatment of MASH. Without an approved therapy specifically to treat MASH, F2/F3 patients are at high risk of disease progression to MASH cirrhosis, which increases liver-related morbidity and mortality and reduced life expectancy from malignancy, HCC and/or CV-related mortality. Rezdiffra (resmetirom) has shown a beneficial effect on the resolution of MASH as well as improvement in fibrosis compared with placebo. In combination with a manageable safety profile, immediate availability to patients is considered to outweigh the risks although additional data regarding clinically relevant outcomes are still required to render the dataset comprehensive.

Adequate input from an HCP-organisation the European Association for the Study of the Liver (EASL) has been received. The feedback first refers to the need for the adaptation to the new nomenclature replacing NASH by MASH, and NAFLD by MASLD. Subsequently, it confirms the medical need for a specific pharmacological treatment for MASH and advocates for lifestyle changes before treatment would be considered. The report further emphasizes that management of MASH patients is a multidisciplinary task that should involve management of cardiometabolic milieu. The report further indicates that clinical benefit in the long-run remains to be demonstrated, including avoidance of liver related events. Finally, the report emphasizes that there is a need for long-term safety data, and a thorough assessment of the risk for hepatotoxicity.

3.8. Conclusions

The overall benefit/risk balance of Rezdiffra is positive, subject to the conditions stated in section 'Recommendations'.

4. Recommendations

Outcome

Based on the CHMP review of data on quality, safety and efficacy, the CHMP considers by consensus that the benefit-risk balance of Rezdiffra is favourable in the following indication:

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).

The CHMP therefore recommends the granting of the conditional marketing authorisation subject to the

following conditions:

Conditions or restrictions regarding supply and use

Medicinal product subject to medical prescription.

Other conditions and requirements of the marketing authorisation

- **Periodic Safety Update Reports**

The requirements for submission of periodic safety update reports for this medicinal product are set out in the list of Union reference dates (EURD list) provided for under Article 107c(7) of Directive 2001/83/EC and any subsequent updates published on the European medicines web-portal.

Conditions or restrictions with regard to the safe and effective use of the medicinal product

- **Risk Management Plan (RMP)**

The marketing authorisation holder (MAH) shall perform the required pharmacovigilance activities and interventions detailed in the agreed RMP presented in Module 1.8.2 of the marketing authorisation and any agreed subsequent updates of the RMP.

An updated RMP should be submitted:

- At the request of the European Medicines Agency;
- Whenever the risk management system is modified, especially as the result of new information being received that may lead to a significant change to the benefit/risk profile or as the result of an important (pharmacovigilance or risk minimisation) milestone being reached.
- **Obligation to conduct post-authorisation measures**

The MAH shall complete, within the stated timeframe, the below measures:

Specific obligation to complete post-authorisation measures for the conditional marketing authorisation

This being a conditional marketing authorisation and pursuant to Article 14-a of Regulation (EC) No 726/2004, the MAH shall complete, within the stated timeframe, the following measures:

Description	Due date
In order to confirm the efficacy and safety of resmetirom in adults with non-cirrhotic metabolic dysfunction-associated steatohepatitis (MASH) with moderate to advanced liver fibrosis (fibrosis stages F2 to F3), the MAH shall submit the final results of MGL-3196-11 (MAESTRO-NASH), a phase III, double-blind, randomized, placebo-controlled study.	31 March 2029
In order to confirm the efficacy and safety of resmetirom in adults with non-cirrhotic metabolic dysfunction-associated steatohepatitis (MASH) with moderate to advanced liver fibrosis (fibrosis stages F2 to F3), the MAH shall submit the final results of MGL-	31 March 2028

Description	Due date
3196-19 (MAESTRO-NASH OUTCOMES), a phase III, double-blind, randomized, placebo-controlled study.	

Conditions or restrictions with regard to the safe and effective use of the medicinal product to be implemented by the Member States

Not applicable.

New active substance status

Based on the CHMP review of the available data, the CHMP considers that resmetirom is to be qualified as a new active substance in itself as it is not a constituent of a medicinal product previously authorised within the European Union.