European Union Risk Management Plan (EU-RMP)
REZDIFFRA (Resmetirom)

EU Risk Management Plan for REZDIFFRA (Resmetirom)

RMP version to be assessed as part of this application:

RMP Version number: 0.8

Data lock point for this RMP: 31 Jul 2022

Date of final sign-off: 23 June 2025

QPPV oversight declaration: The content of this RMP has been reviewed and approved by the marketing authorization holder´s QPPV. The electronic signature is available on file.

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Table of contents

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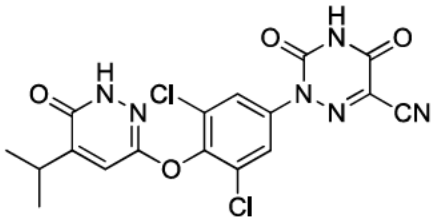
Part I: Product(s) overview

Table Part I.1 – Product(s) overview

Active substance(s) **(INN or common name)**	Resmetirom (alternate name: MGL-3196) (Resmetirom)
Pharmacotherapeutic group(s) (ATC Code)	A05Ba
Marketing Authorization Holder or Applicant	Madrigal Pharmaceuticals EU Limited
Medicinal products to which this RMP refers	1
Invented name(s) in the European Economic Area (EEA)	REZDIFFRA
Marketing authorization procedure	Centralized
Brief description of the product	Chemical class: Thyroid hormone receptor-beta agonist
	Summary of mode of action: Resmetirom is a liver-directed partial agonist for the thyroid hormone receptor beta (THR-β). Resmetirom produced 83.8% of the maximum response compared to triiodothyronine (T3), with an EC_{50} of 0.21 µM in an *in vitro* functional assay for THR-β activation. The same functional assay for thyroid hormone receptor alpha (THR-α) agonism showed 48.6% efficacy for resmetirom relative to T3, with an EC_{50} of 3.74 µM. THR-β is the predominant form of THR in the liver. Stimulation of THR-β in the liver improves mitochondrial function and lipid metabolism, and increases fatty acid β-oxidation, thereby reducing lipotoxic liver fat, inflammation and liver fibrosis. Resmetirom's liver directed THR-β agonism is particularly relevant in the treatment of MASH and leads to minimal off target activity on THR-α in tissues such as heart and bone.
	Important information about its composition: The compound is achiral and has the structure: 2-[3,5-Dichloro-4-((6-oxo-5-(propan-2-yl)-1,6-dihydropyridazin-3-yl)oxy)phenyl]-3,5-dioxo-2,3,4,5-tetrahydro-1,2,4-triazine-6-carbonitrile 

Hyperlink to the Product Information	1.3.1 ema-combined
Indication(s) in the EEA	Current: 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).
	Proposed (if applicable): Not applicable
Dosage in the EEA	Current: The recommended dose of resmetirom is based on the patient's body weight. For patients weighing: • <100 kg, the recommended dose is 80 mg taken orally once daily • ≥100 kg, the recommended dose is 100 mg taken orally once daily Resmetirom may be taken with or without food. Concomitant use of REZDIFFRA with strong CYP2C8 inhibitors (e.g., gemfibrozil) is not recommended. If resmetirom is used concomitantly with a moderate CYP2C8 inhibitor (e.g., clopidogrel), for patients weighing: • <100 kg, reduce the dose of resmetirom to 60 mg taken once daily • ≥100 kg, reduce the dose of resmetirom to 80 mg taken once daily
	Proposed (if applicable): Not applicable
Pharmaceutical form(s) and strengths	Current (if applicable): Resmetirom Tablets: • 60 mg: white, oval film-coated tablets with "P60" on one side and plain on the other side. • 80 mg: yellow, oval film-coated tablets with "P80" on one side and plain on the other side. • 100 mg: beige to pinkish, oval- film-coated tablets with "P100" on one side and plain on the other side.
	Proposed (if applicable): Not applicable
Is/will the product be subject to additional monitoring in the EU?	Yes

Part II: Safety specification

Part II: Module SI – Epidemiology of the indication(s) and target population(s)

Nonalcoholic steatohepatitis/Metabolic dysfunction-associated steatohepatitis (NASH/MASH)

Incidence/Prevalence:

Nonalcoholic steatohepatitis (NASH)/metabolic dysfunction-associated steatohepatitis (MASH) is the progressive form of MASLD, and the global prevalence of NASH/MASH occurs in approximately 1.5% - 6.5% of the general population (Francque et al, 2021). The prevalence of NASH/MASH have increased in recent years, largely due to the increasing prevalence of obesity and associated conditions. In patients with NASH/MASH, advanced fibrosis occurred at a rate of 67.95 per 1,000 person-years, or approximately 9% of patients with NASH/MASH have advancement of their fibrosis (Younossi et al, 2016).

Henceforth, throughout the document, NASH/MASH will be referred to as MASH. However, if the term "NASH" is being used as part of the study population, e.g., "Non-Cirrhotic NASH Population", it will remain as "NASH" because the source outputs were produced with this nomenclature.

Demographics of the population in the proposed indication:

Nonalcoholic steatohepatitis (NASH) or metabolic dysfunction-associated steatotic liver disease (MASH) most commonly affects middle-aged to older adults, with prevalence increasing significantly in individuals over the age of 40 (Younossi et al, 2023). While both men and women are affected, studies suggest that men may have a slightly higher risk overall, though postmenopausal women also show increased susceptibility, potentially due to hormonal changes (Gatzios et al, 2022). Ethnic background plays a notable role, with Hispanic individuals showing the highest rates of NASH in the United States, followed by non-Hispanic Whites, while African Americans tend to have a lower prevalence despite similar or higher rates of obesity and diabetes—suggesting possible genetic or metabolic protective factors (Gatzios et al, 2022).

In Europe, these trends are similarly reflected, though the influence of ethnicity is somewhat less pronounced due to different population structures. Obesity is a major risk factor, and its rising prevalence is closely tied to the increasing burden of NASH across Europe (O'Hara et al, 2020). Type 2 diabetes and insulin resistance are among the strongest clinical associations with MASH (Bril et al, 2017). Dyslipidaemia, especially elevated triglycerides and low HDL cholesterol, is commonly observed in these patients, often in the context of metabolic syndrome.

Main existing treatment options:

Currently, there is no approved therapy in Europe for the treatment of MASH.

Research is ongoing with several drugs in the treatment of MASH with liver fibrosis, including GLP-1 receptor agonists (Nevola et al, 2023). Off label treatments, such as vitamin E and pioglitazone, have also been explored. Current guidelines, such as those in Francque et al 2021, focus on treating comorbid conditions. Making lifestyle modifications to address obesity, such as increasing physical activity and improving diet, could be effective but are difficult to achieve and maintain. Treating diabetes and hypertension with approved medications may also benefit a patient with MASH, but these treatments will not reverse MASH or liver fibrosis.

Natural history of the indicated condition in the untreated population, including mortality and morbidity:

MASH is a slowly progressive disease, but with more advanced fibrosis (fibrosis stage F3 or F4), liver disease progresses rapidly (Loomba and Adams, 2019). Accordingly, the time to development of severe liver disease decreases per stage of fibrosis (9.3 years in F2 and ~5 or more years in F3, 2-3 years in well-compensated F4 to decompensated cirrhosis) (Hagstrom et al, 2017).

Patients with more advanced MASH fibrosis have increased morbidity and mortality from progression of their liver disease, including progression to MASH cirrhosis, liver failure, and hepatocellular carcinoma (Angulo et al, 2015; Dulai et al, 2017). Recent research has indicated that as their disease progresses and symptoms increase, particularly with advanced liver disease, patients experience marked deteriorations in health-related quality of life (Francque et al, 2021) and significantly increased healthcare resource use compared to the general population (Balp MM et al, 2019). Patients with MASH across five European countries also report increased fatigue (as measured by physical component scores of the short form [SF]-36v2) and worsened mental state (as measured by mental component scores of the SF-36v2) compared to the general population (Balp MM et al, 2019).

Important co-morbidities:

MASH is associated with a group of comorbid conditions that include metabolic syndrome, obesity, type 2 diabetes mellitus (T2DM), hypertension, dyslipidaemia, and hypothyroidism. Approximately 75% of patients with diabetes and up to 90% of severe obese individuals have fatty liver disease, and the percentage with MASH increases with the level of metabolic dysfunction (Toledo et al, 2006).

Part II: Module SII – Non-clinical part of the safety specification

Table 1: Key Safety Findings and Relevance to Human Usage

Key Safety findings from Non-clinical Studies	Relevance to Human Usage
Toxicity	
In the rat, both adverse and non-adverse test article related effects in the toxicology studies were considered a result of pharmacology or exaggerated pharmacology, with findings consistent with reversible alterations in thyroid hormone homeostasis and/or thyroid stimulating hormone (TSH) suppression at the highest dose, 200 mg/kg/day. The NOAEL in the 6-month rat toxicity study was determined to be 30 mg/kg/day (Day 178 $AUC_{(0-24)}$ [M/F combined] of 47,400 ng·hr/mL) which was based on adverse changes at the next highest dose of 200 mg/kg/day that were consistent with central thyroid axis suppression (decreased TSH, free T3 and mean absolute and relative thyroid gland weights). Additional findings that were considered nonadverse were largely reversible and consisted of changes in circulating thyroid hormone parameters at ≥3 mg/kg/day, and, at ≥30 mg/kg/day, liver (hepatocellular cytoplasmic alteration) and skeletal muscle (degeneration/regeneration). The Day 178 AUC_{0-24h} at 200 mg/kg/day was 440,000 ng·hr/mL (M/F combined), which is approximately 126- and 52-fold higher than the mean human AUCs at the clinical doses of 100 and 80 mg/day resmetirom, respectively	The non-clinical findings in rodents are not considered to be a safety concern for humans.
In the dog, non-adverse test article related findings were considered a result of pharmacology or exaggerated pharmacology, and the adverse finding, biliary hyperplasia at the highest dose, 100 mg/kg/day, was considered the result of high liver uptake and biliary excretion and pharmacology related to cholesterol reduction. The NOAEL in the 9-month dog study was determined to be 45 mg/kg/day. (Day 272 AUC_{0-24} [M/F combined] of 54,500 ng·hr/mL), which was based on adverse changes at the next highest dose of 100 mg/kg/day that consisted of bile duct hyperplasia. The bile duct hyperplasia was considered the result of high liver uptake and biliary excretion of resmetirom and pharmacology related to cholesterol reduction. Non-adverse findings of note were largely reversible and consisted of changes in thyroid hormone parameters and bone ALP at ≥5 mg/kg/day, tongue (epithelial thickening) at ≥15 mg/kg/day and increases in ALT at ≥45 mg/kg/day. The reversible decreases in total T3 and total T4 and free T4 were observed without concomitant changes in free T3 or TSH and no adverse changes in thyroid weight or	The non-clinical findings in dogs are not considered to be a safety concern for humans.

histopathology up to 100 mg/kg/day and were therefore considered a result of peripheral thyroid hormone receptor activation and subsequently not considered adverse. The Day 272 AUC_{0-24h} at 100 mg/kg/day was 263,000 ng·hr/mL (M/F combined), which is approximately 75- and 31-fold higher than the mean human AUCs at the clinical doses of 100 and 80 mg/day resmetirom, respectively.	
The no-observed-adverse-effect-levels (NOAEL) in the 6-month rat study and 9-month dog study were 30 and 45 mg/kg/day, respectively, based on results indicative of central hypothalamic-pituitary-thyroid (HPT) axis suppression in the rat and biliary hyperplasia in the dog	The non-clinical findings in rodents and dogs are not considered to be a safety concern for humans.
Exposure margins (fold area AUC) were determined for the 80 and 100 mg per day human dose and were 12- and 7.3-fold in the rat, and 14- and 8.4-fold for the dog, respectively.	The non-clinical findings in rodents and dogs are not considered to be a safety concern for humans.
Carcinogenicity	
In a 2-year study in CD-1 mice, resmetirom produced leiomyoma or leiomyosarcoma in the uterus at a dose of 100 mg/kg/day (51 times the maximum recommended dose based on AUC). No tumorigenic effects were observed in female mice at doses of up to 30 mg/kg/day (14 times the maximum recommended dose based on AUC) or in male mice at doses of up to 100 mg/kg/day (35 times the maximum recommended dose based on AUC). In a 2-year study in Sprague-Dawley rats, resmetirom produced benign fibroadenoma in the mammary gland of males at a dose of 30 mg/kg/day (6.5 times the maximum recommended dose based on AUC). No tumorigenic effects were observed in male rats at doses of up to 6 mg/kg/day (3.7 times the maximum recommended dose based on AUC) or in female rats at doses of up to 30 mg/kg/day (3.4 times the maximum recommended dose based on AUC).	No safety concern relevant to human use has arisen from these non-clinical data.
Genotoxicity	
Resmetirom was not genotoxic in a standard battery of genotoxicity studies.	No safety concern relevant to human use has arisen from these non-clinical data.
Reproductive/development Toxicity	
There was no evidence of adverse effects of resmetirom on fertility, reproductive function, embryofoetal, or perinatal/postnatal development, which included behavioural testing,	No safety concern relevant to human use has arisen from these non-clinical data.
Phototoxicity	
Resmetirom did not demonstrate phototoxic potential in an in vitro neutral red uptake phototoxicity assay in BALB/c 3T3 Mouse Fibroblasts.	No safety concern relevant to human use has arisen from these non-clinical data.

Source: Module 2.4-Non-Clinical Overview (NCO)

Part II: Module SIII – Clinical trial exposure

Throughout this document, study names may be shortened for brevity, e.g., MGL-3196-11 may be shortened to Study 11.

SIII.1 Non-cirrhotic NASH Population Pool

Four studies (Study 11, Study 14, Study 18 and Study 05) were pooled to provide a comprehensive safety profile in patients with non-cirrhotic MASH, which comprise the non-cirrhotic MASH patient pool.

- Study 11: A Phase 3, Multinational, Double-Blind, Randomized, Placebo-Controlled Study of MGL-3196 (resmetirom) in 1050 Patients with Non-Alcoholic Steatohepatitis (NASH) and Fibrosis that were treated for 52 weeks with either 80 mg resmetirom, 100 mg resmetirom or placebo.
- Study 14: A Phase 3, Multi-Center, Double-Blind, Randomized, Placebo-Controlled Study of MGL-3196 (resmetirom) in 1143 Patients with Non-Alcoholic Fatty Liver Disease that were treated for 52 weeks with either 80 mg resmetirom, 100 mg resmetirom or placebo.
- Study 18: A Phase 3, Multi-Center, Active-Treatment Rollover Study for patients who completed Study 14 (513 patients who received resmetirom in Study 14 and continued to receive resmetirom in Study 18, and 172 patients who received placebo in Study 14 then resmetirom in Study 18); and Screen Failed Patients from Study 11 or Study 19, and de novo patients meeting eligibility criteria (184 patients).
- Study 05: A Phase 2, Multi-Center, Double-Blind, Randomized, Placebo-Controlled Study of MGL-3196 (resmetirom) in 125 Patients with Non-Alcoholic Steatohepatitis (NASH) that were treated for 36 weeks with either 80 mg resmetirom or placebo.

The Non-Cirrhotic NASH Safety Analysis Population consisted of 2502 randomized patients from the MASH patient pool who received at least one dose of resmetirom or placebo, regardless of their fibrosis stage.

Results

Table 2: Exposure for the Non-Cirrhotic NASH Population

	Resmetirom 80 mg (N=761)	Resmetirom 100 mg (N=1033)	Resmetirom Overall (N=1794)	Placebo (N=708)
Duration of Study Drug Exposure (Weeks)[a]				
n	761	1033	1794	707
Mean (SD)	58.18 (33.179)	53.96 (28.722)	55.75 (30.754)	61.20 (31.439)
Median	52.00	52.00	52.00	52.14
Q1, Q3	37.29, 72.57	40.14, 53.14	40.14, 65.00	51.57, 77.71
Min, Max	0.1, 156.6	0.1, 157.1	0.1, 157.1	0.1, 157.3

Source: Module 5.3.5.3-ISS-Table 14.1.5.1.1

The pooled person-time analysis for the Non-Cirrhotic NASH population is provided in Table 3. Overall, the safety of resmetirom has been evaluated in a total pool of 1794 patients in the Non-cirrhotic NASH population, corresponding to a total duration of exposure of 114803.2 person-weeks.

Table 3: Duration of exposure (Non-Cirrhotic NASH Population Pool)

Indication: Non-cirrhotic MASH with liver fibrosis		
Duration of exposure (weeks)	**Resmetirom overall**	**Person time (weeks)**
0 - <4 weeks	53	82.9
≥4 - <8 weeks	41	226.5
≥8 - <12 weeks	39	352.7
≥12 - <16 weeks	26	352.8
≥16 - <20 weeks	34	586.7
≥20 - <24 weeks	29	622.0
≥24 - <28 weeks	22	562.6
≥28 - <32 weeks	51	1465.9
≥32 - <36 weeks	33	1130.1
≥36 - <40 weeks	89	3319.7
≥40 - <44 weeks	93	3774.4
≥44 - <48 weeks	23	1050.2
≥48 - <52 weeks	101	5165.1
≥52 - <65 weeks	333	18129.0
≥65 - <78 weeks	143	10044.8
≥78 - <91 weeks	171	13865.6
≥91 - <104 weeks	286	26963.1
≥104 - <117 weeks	107	11254.8
≥117 - <130 weeks	42	5068.4
≥130 - <143 weeks	45	5945.5
≥143 - <156 weeks	25	3588.6
≥156 - <169 weeks	8	1251.8
Total	1794	114803.2

Note: Duration of exposure (weeks) = (date of last dose - date of first dose + 1)/7.
Note: For the Week 52 analysis, as the dual primary endpoint is based on the unit time (weeks), the categories in this table are also presented in weeks.
Source: Study 11, Study 14, Study 18, Study 05, RMP-Table SIII.1a

SIII.2 Non-Cirrhotic NASH Extended Analysis Population Pool

The Non-Cirrhotic NASH Extended Safety Analysis pool consisted of 420 patients from the MASH non-cirrhotic patient pool who received resmetirom (double-blind [DB] 100 mg, DB 80 mg, or open-label [OL] 100 mg, whether randomized or not) in Study 14 and received at least one dose of resmetirom in Study 18. In essence, this pool provides long term safety data in patients with non-cirrhotic MASH.

Table 4: Study Drug Exposure (Non-Cirrhotic NASH Extended Population)

	Resmetirom 80 mg (N=6)	Resmetirom 100 mg (N=414)	Overall (N=420)
Duration of Study Drug Exposure (Weeks)[a]			
n	6	414	420
Mean (SD)	68.5 (18.56)	90.3 (11.61)	89.9 (11.98)
Median	59.5	92.1	92.1
Q1, Q3	54.9, 92.0	81.3, 98.7	81.1, 97.6
Min, Max	53, 92	52, 109	52, 109
≥52 weeks – <13 months	2 (33.3)	6 (1.4)	8 (1.9)
≥13 months - <14 months	1 (16.7)	7 (1.7)	8 (1.9)
≥14 months - <15 months	1 (16.7)	8 (1.9)	9 (2.1)
≥15 months - <16 months	0	10 (2.4)	10 (2.4)
≥16 months - <17 months	0	3 (0.7)	3 (0.7)
≥17 months - <18 months	0	12 (2.9)	12 (2.9)
≥18 months - <19 months	0	69 (16.7)	69 (16.4)
≥19 months - <20 months	0	4 (1.0)	4 (1.0)
≥20 months - <21 months	0	31 (7.5)	31 (7.4)
≥21 months - <22 months	2 (33.3)	157 (37.9)	159 (37.9)
≥22 months - <23 months	0	8 (1.9)	8 (1.9)
≥23 months - <24 months	0	61 (14.7)	61 (14.5)
≥24 months	0	38 (9.2)	38 (9.0)

[a] Duration of exposure (weeks) = (date of last dose - date of first dose + 1)/7. The time gap (if any) between Study 14 and Study 18 is excluded from the duration of exposure.
Note: Percentages are based on the number of subjects indicated in each column header.
Source: Module 5.3.5.3-ISS-Table 14.1.5.1.2

SIII.3 Healthy Volunteer Safety Analysis Population Pool

The Healthy Volunteer Safety Analysis Population consisted of all subjects from the Phase 1 studies (except subjects from Study 10) who received at least one dose of resmetirom or placebo. A total of 275 healthy volunteers were exposed to at least one dose of resmetirom ranging between 40 mg and 200 mg compared to 30 total subjects exposed to placebo in Phase 1 studies.

SIII.4 Special Populations

Hepatic Impairment Patients

Safety in hepatic impairment (HI) patients with cirrhosis or MASH cirrhosis (Study 10, a Phase 1 study) was of much shorter duration (1 week of dosing). Given the short dosing duration, their safety data were not pooled with the MASH cirrhotic population cohort.

Table 5: Study MGL-3196-10 Study Drug Exposure

Treatment Group Characteristics	40 mg (N=7)	60 mg (N=9)	80 mg (N=42)	80 mg – 40 mg (N=1)	100 mg (N=28)	Overall (N=87)
Non-NASH (Includes Cohorts 1, 2, 3, 4)						
Normal	2 (28.6%)	3 (33.3%)	8 (19.0%)	0 (0.0%)	0 (0.0%)	13 (14.9%)
Mild	0 (0.0%)	0 (0.0%)	10 (23.8%)	0 (0.0%)	0 (0.0%)	10 (11.5%)
Moderate	0 (0.0%)	0 (0.0%)	10 (23.8%)	0 (0.0%)	0 (0.0%)	10 (11.5%)
Severe	5 (71.4%)	6 (66.7%)	3 (7.1%)	1 (100.0%)	0 (0.0%)	15 (17.2%)
NASH						
NASH Non-cirrhosis (Cohort 5)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	8 (28.6%)	8 (9.2%)
NASH Cirrhosis (Cohort 6)						
Mild	0 (0.0%)	0 (0.0%)	10 (23.8%)	0 (0.0%)	20 (71.4%)	30 (34.5%)
Moderate	0 (0.0%)	0 (0.0%)	1 (2.4%)	0 (0.0%)	0 (0.0%)	1 (1.1%)
Severe	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)

Abbreviations: NASH = non-alcoholic steatohepatitis
Source: Study 10-Table 14.1.1.2
Note: Hepatic function is based on the last non-missing value prior to the first dose of study medication.

Severe Renal Impairment Patients

Safety in severe renal impairment (RI) patients (Study 21, a Phase 1 study) was also of much shorter duration (1 week of dosing). Given the short dosing duration, their safety data were not pooled with the MASH population cohorts.

Table 6: Study MGL-3196-21 Study Drug Exposure

	Group		
Category	Healthy Control (N = 14)	Severe RI (N = 14)	Overall (N = 28)
Dosed	14 (100%)	14 (100%)	28 (100%)

RI = Renal impairment
Healthy Control: Administration of multiple oral doses of 100 mg resmetirom once daily on Days 1 through 6 in matched healthy control subjects with normal renal function
Severe RI: Administration of multiple oral doses of 100 mg resmetirom once daily on Days 1 through 6 in subjects with severe renal impairment
Source: Study 21-Table 14.1.1

SIII.5 Clinical Trial Exposure Subgroup Analyses

RMP subgroup analyses were only performed for the pooled Non-Cirrhotic NASH population.

By Age and Sex

The person-time analyses of exposure by age group and sex are provided in Table 7. Overall, a total of 786 male patients and 1008 female patients received resmetirom across studies within the pooled Non-Cirrhotic NASH Population, corresponding to a total person-time exposure of 50218.3 and 64584.9 person-weeks, respectively. A small subset of elderly patients who were ≥75 years (24 males and 27 females) were exposed to resmetirom corresponding to a cumulative exposure of 1644.0 and 2044.5 person-weeks, respectively.

Table 7: Exposure subgroup analyses by age and sex (Non-cirrhotic NASH Population Pool)

Indication: Non-cirrhotic MASH with liver fibrosis	Resmetirom overall			
Age group	Patients		Person time (weeks)	
	Male (N)	Female (N)	Male	Female
Adults (18 to 64 years)	599	762	37740.1	48847.9
Elderly people	187	246	12478.2	15737.0
65-74 years	163	219	10834.2	13692.5
≥75 years	24	27	1644.0	2044.5
Total	786	1008	50218.3	64584.9

Source: RMP-Table SIII.2a

By Dose Level Received

The person-time analysis of exposure by dose level received for the pooled Non-Cirrhotic NASH Population is provided in Table 8. More patients overall were exposed to resmetirom 100 mg compared to resmetirom 80 mg (1197 and 597 total patients, respectively) corresponding to 79515.6 and 35287.6 person-weeks, respectively.

Table 8: Exposure subgroup analysis by dose level received (Non-Cirrhotic NASH Population Pool)

Indication: Non-cirrhotic MASH with liver fibrosis	Resmetirom overall	
Dose of exposure	Patients	Person time (weeks)
80 mg resmetirom	597	35287.6
100 mg resmetirom	1197	79515.6
Total	1794	114803.2

Note: Patients were assigned to the highest dose of resmetirom received.
Source: RMP-Table SIII.3a

By Ethnic Origin

The pooled Non-Cirrhotic NASH population consisted mainly of Caucasian patients (~90%) and were not Hispanic or Latino (~69%). Person-time analysis of the pooled Non-cirrhotic NASH Population by ethnic origin is provided in Table 9, which showed overall that the majority of patients who received resmetirom were non-Hispanic or Latino (1232 patients total), corresponding to 81470.5 person-weeks of exposure.

Table 9: Ethnic origin (Non-cirrhotic NASH Population Pool)

Indication: Non-Cirrhotic MASH with Liver Fibrosis	Resmetirom Overall	
Ethnic origin	**Patients**	**Person time (weeks)**
Hispanic or Latino	543	31939.6
Not Hispanic or Latino	1232	81470.5
Not reported	15	1231.1
Unknown	4	162.0
Total	1794	114803.2

Source: RMP-Table SIII.4a

Part II: Module SIV – Populations not studied in clinical trials

Very Elderly population

Specific studies in the elderly population have not been conducted and are not planned. There was no upper age limit restriction in resmetirom Phase 2 and 3 clinical trials; in the Non-Cirrhotic NASH Population, a small subset of very elderly patients (i.e., those who were ≥75 years) were enrolled (N=54) and treated with resmetirom as of the DLP for this RMP. Ongoing double-blinded Phase 3 studies continued enrolment and data are pending as of the DLP of this RMP (i.e., 31-Jul-2022).

Women of child-bearing potential

Women of child-bearing potential were allowed into the Phase 3 registrational studies; however, these patients had to use 2 methods of highly effective contraception. Per protocol, if at any time post-randomization a patient became pregnant, the patient discontinued study treatment but was followed until the pregnancy completed.

As of the DLP of this RMP, no pregnancies have occurred in patients during treatment with resmetirom. There were 3 pregnancies reported in partners of male patients. Of those, 2 reported deliveries of full-term neonates without complications; one outcome was not obtainable as the partner did not consent to provide outcome data.

SIV.1. Exclusion criteria in pivotal clinical studies within the development program

The important exclusion criteria across the registrational Phase 3 studies were as follows:

Criterion	Missing Information (Yes or No)	Reason and Rationale for Exclusion
History of significant alcohol consumption for ≥3 months within 1 year of screening. Significant alcohol consumption is defined as equal to or greater than approximately 2 alcoholic drinks per day for males, and approximately 1.5 alcoholic drinks per day for females. One	No	Patients who had a history of significant alcohol consumption were excluded due to the synergy between pathophysiology of liver damage due to alcohol and nonalcoholic liver disease. MASH is defined according to the quantity of alcohol intake as

alcoholic drink is equal to 12 ounces (355 mL) of 5% alcohol by volume (ABV) beer, 5 ounces (148 mL) of 12% ABV wine, or 1.5 ounces (44.4 mL) of 40% ABV distilled spirits		compared with various stages of MetALD or ALD (Rinella et al 2023). However, patients with elevated CDT or PEth at baseline or during the trial were allowed to continue in the trial. This comprised at least 10% of the enrolled population.
≥5% weight gain or loss within 12 weeks of randomization	No	Weight reduction ≥5% was associated with significant improvement in the NAFLD activity score (NAS) in MASH patients. Excluding patients with recent change in weight allowed for a more meaningful assessment of the treatment effect of resmetirom in MASH. Acute weight gain, by analogy, might be expected to impact MASH adversely; however, patients with ≥5% weight gain during the trial showed similar relative benefit of resmetirom compared with placebo as patients with weight loss or no change in weight.
MELD score ≥12 due to liver disease (not due to Gilbert, underlying renal disease, anti-coagulant therapy, etc)	No	MELD score ≥12 that is not due to artifactual (non-liver disease) factors is associated with advanced MASH cirrhosis, not non-cirrhotic MASH

SIV.2. Limitations to detect adverse reactions in clinical trial development programs

At this point in the clinical development program, given the size of the studies and duration of treatment, the clinical development program is unlikely to detect certain types of adverse reactions such as very rare adverse reactions (<1/10000), or adverse reactions with a long latency (>2 years).

SIV.3. Limitations in respect to populations typically under-represented in clinical trial development programs

Table 10: Exposure of special populations included or not in clinical trial development programs

Type of special population	Exposure
Pregnant women	Neither pregnant nor breastfeeding women were included in the clinical development program
Breastfeeding women	
Patients with relevant comorbidities: 1. Patients with hepatic impairment 2. Patients with moderate to severe renal impairment 3. Patients with MASH cirrhosis 4. Patients with cardiovascular disease 5. Immunocompromised patients	1. Phase 1 Study 10 enrolled 35 patients with hepatic impairment, 8 patients with non-cirrhotic MASH, and 31 patients with MASH cirrhosis. 2. Phase 3 Study 14, a 52-week study, enrolled 14 patients with moderate renal impairment (eGFR ≥30 and <45). 3. In Study 14, there were 180 patients who had well-compensated MASH cirrhosis (generally Child-Pugh A, mild hepatic impairment, a few were more advanced), in open-label arms. 4. A high percentage of MASH patients have evidence of atherosclerotic cardiovascular disease and <10 percent of enrolled patients had a prior CV event such as stroke or myocardial infarction. Thus, patients with cardiovascular disease were included in resmetirom clinical trials; however, patients with uncontrolled hypertension, New York Heart Association Class III or IV heart failure, known left ventricular ejection fraction <30%, uncontrolled arrhythmia, or confirmed QTcF >450 for males or >470 for females were excluded. 5. Autoimmune and inflammatory bowel disease was allowed but some immunosuppressive therapies were limited that might impact liver inflammation. Immunocompromised patients such as those with HIV were not included in the clinical development program.

Type of special population	Exposure
Population with relevant different ethnic origin	The majority of patients in the resmetirom Non-cirrhotic NASH Population were white (N=1608), Black or African American (N=78), Asian (N=40), or Other Race Category (N=34). In addition, the majority of patients in this pool were not Hispanic or Latino (N=1232), with 543 patients who were Hispanic or Latino.
Subpopulations carrying relevant genetic polymorphisms	Gilbert syndrome is a type of genetic polymorphism that was determined by DNA analysis in consenting patients at the time of study enrolment to determine how to assess laboratory values such as bilirubin. UGT1a1 allele testing for Gilbert was performed in Study 11 and 14. A total of 136/1118 (12.2%) patients had genetics consistent with Gilbert syndrome.
Other	Not included in the clinical development program.

Part II: Module SV – Post-authorization experience

Not applicable.

Part II: Module SVI – Additional EU requirements for the safety specification

Potential for misuse for illegal purposes

Resmetirom is not considered a controlled substance and is not expected to cause psychological or physical dependence.

Part II: Module SVII – Identified and potential risks

SVII.1. Identification of safety concerns in the initial RMP submission

SVII.1.1. Risks not considered important for inclusion in the list of safety concerns in the RMP

Diarrhea

Evidence Source:

Diarrhea is a known adverse reaction for resmetirom; however, it is not considered an important identified or potential risk for the RMP as it was mild to moderate in severity, self-limiting, not serious, usually resolved quickly within the first two to three weeks of treatment and can easily be managed through standard of care.

Other known risks that require no further characterisation as they are mild to moderate, non-serious and are followed up via routine pharmacovigilance namely through signal detection and adverse reaction reporting:

- Nausea
- Vomiting
- Abdominal pain
- Constipation
- Pruritus
- Rash
- Urticaria
- Dizziness

SVII.1.2. Risks considered important for inclusion in the list of safety concerns in the RMP

Important Identified Risk:

Cholelithiasis, including complications such as cholecystitis and obstructive pancreatitis

Risk-benefit impact:

Resmetirom has a risk of rarely occurring cholelithiasis, cholecystitis and obstructive pancreatitis. The incidence of acute events is low (i.e., cholecystitis), with the majority of gallbladder disease events non-acute (i.e., gallbladder polyp, cholelithiasis). 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 with resmetirom. The SmPC advises that if cholelithiasis is suspected, gallbladder diagnostic studies and appropriate clinical follow-up are indicated. This is expected to avoid any unfavourable change to the risk-benefit balance.

Hepatotoxicity

Risk-benefit impact:

Resmetirom has a risk of rarely occurring, readily reversible hepatotoxicity that is detectable with routine monitoring of MASH patients. The SmPC advises health care providers to conduct liver enzyme monitoring periodically during treatment. If hepatotoxicity is suspected, discontinue resmetirom treatment and continue to monitor liver chemistry. The SmPC also advises that 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. These precautions are expected to avoid any unfavourable change to the risk-benefit balance.

Important Potential Risk:

Hepatocellular Carcinoma (HCC)

Risk-benefit impact:

HCC occurred rarely in clinical trials in non-cirrhotic MASH patients. Completion of Study 19 in patients with well-compensated MASH cirrhosis and routine pharmacovigilance activities will further characterise the risk of HCC with respect to number of reports, seriousness, outcome,

risk factors, and whether experience in the post marketing setting is consistent with the information already known for this risk from clinical study data.

Cardiovascular (CV) Safety

Risk-benefit impact:

Cardiovascular events were rare in clinical trials and not increased with resmetirom versus placebo. Because of the importance of CV risk in MASH, additional CV data will be collected in clinical trials and post marketing.

Routine pharmacovigilance activities will further characterise the risk of CV safety with respect to the number of reports, seriousness, outcome, risk factors, and whether experience in the post marketing setting is consistent with the information already known for this risk from clinical study data. A pooled meta-analysis of CV events from two randomized placebo-controlled studies will be undertaken to evaluate composite endpoint of MACE events including CV mortality, non-fatal stroke and non-fatal myocardial infarction.

Missing information 1: Long-term safety (i.e., ≥1 year) in very elderly

- Summary: There was no upper age limit restriction in Phase 2 and 3 clinical trials. A small subset of elderly (≥75 years) patients was enrolled and treated with resmetirom (N=54) in the Phase 2 and 3 studies as of the DLP (31-Jul-2022); however, only two very elderly patients were treated with resmetirom for longer than 1 year.
- Risk-benefit impact of missing information: Limited long-term safety in very elderly patients is available as of the DLP; however, no additional risks have been identified in this population. The proportion of MASH responders compared with placebo was consistently higher for the 100 mg dose than for the 80 mg dose across all subgroups except for patients ≥65 years of age.

Missing information 2: Use in patients with severe renal impairment

- Summary: Renal excretion is a minor route of elimination for resmetirom, as discussed in Section SVII.1.2. Population PK analyses showed minimal impact of mild to moderate renal impairment on PK, and clinically completed study in severe renal impairment will assess the impact of severe renal impairment. Based on initial data in a cohort of Phase 3 patients (n=14) with moderate renal impairment, there is no impact of resmetirom in moderate renal impairment.
- The recommended dosage in patients with mild or moderate renal impairment is the same as in patients with normal kidney function. Resmetirom has not been studied in patients with severe renal impairment.
- Population PK analyses indicated no clinically significant difference in the pharmacokinetics of resmetirom by mild to moderate renal impairment (eGFR 30 to 89 mL/min/1.73 m^2, Modification of Diet in Renal Disease (MDRD)). The effect of severe renal impairment (eGFR < 30 mL/min/1.73 m2, MDRD) on resmetirom pharmacokinetics is unknown.
- Risk-benefit impact of missing information: Full data from Study 21 are pending as of the DLP for this RMP; therefore, in consideration of the missing information in patients with severe renal impairment, the risk/benefit impact remains unknown at this time. No dose adjustment is considered necessary in patients with renal impairment.

SVII.2. New safety concerns and reclassification with a submission of an updated RMP

Not applicable.

SVII.3. Details of important identified risks, important potential risks, and missing information

SVII.3.1. Presentation of important identified risks and important potential risks

Important Identified Risk: Cholelithiasis, including complications such as cholecystitis and obstructive pancreatitis.

Note: the term "cholecystitis" includes PTs of bile duct stone, biliary colic, biliary dilation, cholecystitis, cholecystitis acute, cholecystitis chronic, and cholangitis.

Potential mechanisms:

Resmetirom, a lipid lowering drug via the THR-β pathway, is expected to have an important effect to promote bile formation and secretion including balanced production of all components of the pathway, increased cholesterol metabolism and formation of bile acids, as well as direct cholesterol secretion into bile. These effects are largely mediated by transcriptional regulation of enzymes and transporters (Sinha et al, 2019).

Evidence source(s) and strength of evidence:

In the randomized, double-blind studies of patients with non-cirrhotic MASH, the number of patients with either cholelithiasis, cholecystitis or obstructive pancreatitis was low across treatment groups but more common in resmetirom treatment groups compared with placebo.

- Cholelithiasis: resmetirom 80 mg (8/679 [1.2%]) and resmetirom 100 mg (6/673 [0.9%]) vs placebo (5/667 [0.7%])
- Acute events of cholecystitis (i.e., bile duct stone, biliary colic, biliary dilatation, cholecystitis, cholecystitis acute, cholecystitis chronic, and cholangitis) and obstructive pancreatitis: resmetirom 80 mg (4/679 [0.6%]) and resmetirom 100 mg (7/673 [1.0%]) vs placebo (2/667 [0.3%])

Risk factors and risk groups:

MASH patients are at high risk of existing gallstone disease with approximately 24% of Study 11 and 14 patients with a history of gallbladder disease and approximately 16% of patients with a history of cholecystectomy at baseline.

Preventability:

Strategies to prevent cholecystitis with resmetirom are based on mitigation. As stated in the SmPC, if cholelithiasis is suspected, gallbladder diagnostic studies and appropriate follow-up should be conducted as clinically indicated.

Impact on the risk-benefit balance of the product:

Resmetirom has a risk of rarely occurring cholelithiasis, cholecystitis and obstructive pancreatitis. The incidence of acute events is low (i.e., cholecystitis), with the majority of gallbladder disease events non-acute (i.e., gallbladder polyp, cholelithiasis). 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 with resmetirom. The SmPC advises that if cholelithiasis is suspected, gallbladder diagnostic studies and appropriate clinical follow-up are indicated. This is expected to avoid any unfavourable change to the risk-benefit balance.

Public health impact:

Cholecystitis is not expected to have a significant impact on public health given the low incidence of acute events.

Important Identified Risk: Hepatotoxicity

Potential mechanisms:

Hepatotoxicity occurs rarely with resmetirom treatment and any potential mechanism is unknown.

Evidence source(s) and strength of evidence:

Increases in ALT and AST commonly occur as part of the disease pathophysiology of MASH and can be variable over time. As stated in the SmPC, mild transient increases in mean alanine aminotransferase (ALT) and aspartate aminotransferase (AST) levels were observed in the first 4 weeks after initiating treatment with resmetirom that resolved by Week 8 and were more common in patients on concomitant statin therapy. The number of patients with 3x or 5x ULN increases in ALT or AST in resmetirom-treated patients was similar to placebo.

One resmetirom-treated patient in the double-blind period of Study 14 was adjudicated as possible drug-induced hepatotoxicity and met Hy's law criteria (defined as having any post-baseline total bilirubin equal to or exceeding 2x ULN within 30 days after a post-baseline ALT or AST equal to or exceeding 3x ULN). No other case adjudicated as possible drug-induced hepatotoxicity met Hy's law criteria. Other cases of resmetirom-treated patients adjudicated as possible drug-induced hepatotoxicity included one case in a randomized, double-blind arm of Study 11, one case in the randomized open-label arm of Study 14, and one case in the open-label cirrhotic arm of Study 14. No cases adjudicated as drug-induced hepatotoxicity occurred in placebo-treated patients.

All events resolved. These cases had confounding factors including autoimmune liver disease in two cases that may suggest alternative causality; however, drug-induced hepatotoxicity could not be excluded.

Risk factors and risk groups:

Risk factors associated with hepatotoxicity include age, female gender, pregnancy, smoking, alcohol consumption, and drug interactions (Chalasani 2018, Li 2022).

Preventability:

As directed in the SmPC, conduct liver enzyme monitoring periodically during treatment. If hepatotoxicity is suspected, discontinue resmetirom treatment and continue to monitor liver chemistry.

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.

Impact on the risk-benefit balance of the product:

Resmetirom has a risk of rarely occurring, readily reversible hepatotoxicity that is detectable with routine monitoring of MASH patients. The SmPC advises health care providers to conduct liver enzyme monitoring periodically during treatment. If hepatotoxicity is suspected, discontinue resmetirom treatment and continue to monitor liver chemistry. The SmPC also advises that 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. These precautions are expected to avoid any unfavourable change to the risk-benefit balance.

Public health impact:

Given the low occurrence of hepatotoxicity events in the clinical development programme and with periodic monitoring of liver enzymes, the public health impact of this risk is considered to be low.

Important Potential Risk: Hepatocellular Carcinoma (HCC)

Potential mechanisms:

The mechanism for HCC is unknown at this time.

Evidence source(s) and strength of evidence:

Hepatocellular carcinoma was observed in three cases during the Non-cirrhotic NASH, randomized, double-blind studies and was pre-existing and not treatment-emergent in 2 of the 3 cases.

Risk factors and risk groups:

MASH patients have an increased incidence of cancers in general, including hepatocellular cancer (HCC), as the disease progresses. One-third of cirrhotic patients will develop HCC during their lifetime. Long-term follow-up studies have demonstrated that approximately 1–8% per year of patients with cirrhosis develop HCC (e.g. 2% in HBV-infected cirrhotic patients and 3–8% in HCV infected cirrhotic patients). In general, features of liver disease severity (low platelet count of less than 100 $X10^3$, presence of oesophageal varices), in addition to older age and male gender, correlate with the risk of developing HCC among patients with cirrhosis. Other risk factors include excessive alcohol consumption, diabetes, obesity, and smoking (EASL-EORTC Clinical Practice Guidelines, 2012).

Preventability:

Most HCCs develop in a cirrhotic liver, so interventions to reduce prevalence of cirrhosis will lead to significant reductions in the incidence of HCC. Lifestyle modifications and routine screening will also mitigate the risk (EASL Clinical Practice Guidelines, 2024).

Impact on the risk-benefit balance of the product:

Completion of Study 19 in patients with well-compensated MASH cirrhosis and routine pharmacovigilance activities will further characterize the risk of HCC with respect to the number of reports, seriousness, outcome, risk factors, and whether experience in the post marketing setting is consistent with the information already known for this risk from clinical study data.

Public health impact:

Given the low occurrence of HCC events in the clinical development programme, the public health impact of this risk is low.

Important potential risk: Cardiovascular safety

Potential mechanisms:

The mechanism for resmetirom affecting CV safety is unknown at this time.

Evidence source(s) and strength of evidence:

Resmetirom is liver-directed and has high THR-β/THR-α selectivity with little penetration into tissues outside of the liver. Preclinical studies, including a dog CV pharmacology study, showed no adverse CV effects or adverse effects on thyroid function. In humans, a thorough QT study demonstrated no CV liability at high multiples of exposure and extensive evaluation in Phase 2 and 3 studies has not revealed CV safety issues. In contrast, resmetirom potentially reduces CV risk through observed reductions in blood pressure, in hepatic steatosis, an independent risk factor CV disease, and in atherogenic apolipoprotein B and Lp (a) particles. As of the DLP of this RMP, the randomized clinical trial experience is limited to 52-weeks, which is inadequate to definitively determine the CV risk profile of resmetirom in MASH patients. In addition, the incidence of adjudicated MACE and other CV events in the Phase 2 and 3 studies was low, and incidence in the treatment groups was not substantively different from placebo. Longer-term exposure to resmetirom up to 54 months is currently being evaluated in Study 11 (in non-cirrhotic MASH patients) and Study 19 (in cirrhotic MASH patients).

Safety data as of Day 120 for the pivotal trial (Study 11) showed the most common (≥2 patients in any arm) adjudicated treatment-emergent CV events by PT were low across the resmetirom 80 mg and 100 mg groups, and numerically higher in the placebo group (1 (0.3%) and 1 (0.3%), vs 5 (1.6%), respectively).

Risk factors and risk groups:

Recent European data confirm that patients with NAFLD—particularly those with MASH—are at elevated risk for a range of CV events, including myocardial infarction, ischemic stroke, heart failure, and atrial fibrillation, independent of traditional risk factors such as obesity or diabetes (Tagher et al, 2010, Li et al, 2023). The mechanisms implicated in this association include systemic low-grade inflammation, endothelial dysfunction, insulin resistance, and pro-atherogenic lipid profiles, all of which foster an atherogenic environment.

Preventability:

Current guidelines from the European Society of Cardiology (2021) and the American College of Cardiology (2022) emphasize routine ASCVD risk assessment in NASH patients to guide therapeutic intensity for CV risk management. Smoking cessation and alcohol moderation are universally advised.

Integration of these approaches into personalized care plans can significantly reduce the burden of CV disease in MASH populations.

Impact on the risk-benefit balance of the product:

Completion of Studies 11,18,19, the planned cardiovascular meta-analysis and routine pharmacovigilance activities will further characterize the risk of cardiovascular safety with respect to the number of reports, seriousness, outcome, risk factors, and whether experience in the post marketing setting is consistent with the information already known for this risk from clinical study data.

Public health impact:

Given the low occurrence of adjudicated CV events in the clinical development programme (across the pooled Non-Cirrhotic NASH population), the public health impact of this risk is low.

SVII.3.2. Presentation of the missing information

Missing information 1: Long-term safety in very elderly

Anticipated risk/consequence of the missing information:

Long-term safety in very elderly (i.e., ≥75 years old) are limited (N=2) as of the DLP of this RMP (i.e., 31-Jul-2022) and therefore, is considered missing information. In terms of the anticipated risk or consequence of this missing information, in patients ≥65 years of age, no overall difference in effectiveness of resmetirom but numerically higher incidence of adverse reactions has been observed compared to younger adults. Based on the mildness and increase in only known AEs, it is not anticipated that the difference in age between ≥65 and ≥75 will identify new AE risks. Routine pharmacovigilance surveillance will determine any additional risks.

Missing information 2: Use in patients with severe renal impairment

Anticipated risk/consequence of the missing information:

A study in patients with severe renal impairment has been clinically completed but final data is not available as of the DLP of this RMP and therefore is considered missing information. However, data shows that in patients with severe renal impairment (eGFR <30 mL/min/1.73 m²), repeated dosing resulted in an approximately 1.5-fold increase in AUC and a 1.3-fold increase in C_{max} for resmetirom compared to matched healthy controls. Exposure to the metabolite MGL-3623 was increased to a lesser extent. These increases remained within the variability observed in the general population at the recommended dose. Importantly, the observed changes in exposure were not associated with clinically meaningful alterations in pharmacodynamic markers (including thyroid hormones, lipids, and SHBG) or safety signals. Therefore, in terms of overall risk, no dose adjustment is considered necessary in patients with renal impairment.

Part II: Module SVIII – Summary of the safety concerns

Table 11: Summary of safety concerns

Summary of safety concerns	
Important identified risk	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 very elderly

Summary of safety concerns	
	Use in patients with severe renal impairment

Part III: Pharmacovigilance plan (including post-authorization safety studies)

III.1. Routine pharmacovigilance activities

Routine pharmacovigilance activities beyond adverse reactions reporting and signal detection:

Not applicable

III.2. Additional pharmacovigilance activities

Cardiovascular meta-analysis

Study short name and title:

Meta-analysis to evaluate the cardiovascular safety of resmetirom via composite endpoint of MACE events including CV mortality, non-fatal stroke and non-fatal myocardial infarction

Rationale and study objectives:

Rationale:

To provide evidence of cardiovascular safety of treatment with resmetirom in patients with MASH

Primary objective:

To evaluate the cardiovascular safety of resmetirom via composite endpoint of MACE events including CV mortality, non-fatal stroke and non-fatal myocardial infarction

Study design:

A pooled analysis of cardiovascular events obtained from resmetirom, international multicentre, randomized, placebo-controlled trials.

Study population:

The study includes patients who participated in completed non-cirrhotic MASH randomized, placebo-controlled trials: Maestro NASH (Study 11) and the non-cirrhotic patients from Study 14. Data from extension trial to Study 14 will also be included. These studies enrolled approximately 3,000 patients. Patients in these trials could be followed for more than 4 to 5 years.

Milestones:

Protocol submission: Q3 2028

Statistical Analysis Plan: Q1 2029

Analysis Completion: Q2 2029

Final report: Q4 2029

III.3. Summary table of additional pharmacovigilance activities

Table 12: 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

[redacted]

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Part IV: Plans for post-authorization efficacy studies

Table 13: 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 complete; Month 54 analysis ongoing	Week 52 Dual Primary: To determine the effect of once-daily resmetirom versus 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	To evaluate the effect of resmetirom on histologic conversion to NASH cirrhosis To evaluate the effect of resmetirom on clinical outcomes in patients with MASH	Interim study report Study Completion Final study report	30-Jun-2023 (data cut off 31-Jul-2022) Q3 2028 Q1 2029

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Study Status	Summary of Objectives	Efficacy uncertainties addressed	Milestones	Due Date
	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 (composted of all-cause mortality, liver transplant, and significant hepatic decompensation events [ascites, encephalopathy or gastroesophageal variceal haemorrhage] or confirmed increase of MELD score from <12 to ≥15			
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

Part V: Risk minimization measures (including evaluation of the effectiveness of risk minimization activities)

Risk minimization plan

Not applicable

V.1. Routine risk minimization measures

Table 14: Description of Routine Risk Minimisation Measures by Safety Concern

Safety Concern	Routine risk minimisation activities
Important Identified Risks:	
Cholelithiasis, including complications such as cholecystitis and obstructive pancreatitis	Routine risk communication: EU SmPC Section 4.4 Special warnings and precautions for use Package leaflet Section 2 Routine risk minimisation activities recommending specific clinical measures to address the risk: EU SmPC Section 4.4 includes recommendations that if cholelithiasis is suspected, gallbladder diagnostic studies and appropriate clinical follow-up are indicated. Other routine risk minimisation measures beyond Product Information: Medicine's legal status: Prescription only medicine.
Hepatotoxicity	Routine risk communication: EU SmPC Section 4.4 Special warnings and precautions for use Package leaflet Section 2 Routine risk minimisation activities recommending specific clinical measures to address the risk: 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. Other routine risk minimisation measures beyond Product Information: Medicine's legal status: Prescription only medicine.

Important Potential Risks:	
Hepatocellular carcinoma	Routine risk communication: Not applicable Routine risk minimisation activities recommending specific clinical measures to address the risk: Interventions to reduce prevalence of cirrhosis will lead to reductions in HCC. Lifestyle modifications and routine screening also mitigate risk. Other routine risk minimisation measures beyond Product Information: Medicine's legal status: Prescription only medicine.
Cardiovascular safety	Routine risk communication: Not applicable Routine risk minimisation activities recommending specific clinical measures to address the risk: None Other routine risk minimisation measures beyond Product Information: Medicine's legal status: Prescription only medicine.
Missing Information:	
Long term safety (i.e., ≥1 year) in very elderly	Routine risk communication: None Routine risk minimisation activities recommending specific clinical measures to address the risk: None Other routine risk minimisation measures beyond Product Information: Medicine's legal status: Prescription only medicine.
Use in patients with severe renal impairment	Routine risk communication: None Routine risk minimisation activities recommending specific clinical measures to address the risk: None Other routine risk minimisation measures beyond Product Information: Medicine's legal status: Prescription only medicine.

V.2. Additional risk minimization measures

Routine risk minimization activities as described above in Section V.1 are sufficient to manage the safety concerns of the medicinal product.

V.3 Summary of risk minimization measures

Table 15: Summary Table of Pharmacovigilance Activities and Risk Minimisation Activities by Safety Concern

Safety concern	Risk minimisation measures	Pharmacovigilance activities
Important Identified Risks:		
Cholelithiasis, including complications such as cholecystitis and obstructive pancreatitis	Routine risk communication: EU SmPC Section 4.4 Special warnings and precautions for use; Package leaflet Section 2 Other routine risk minimisation measures beyond the Product Information: Medicine's legal status: Prescription only medicine Additional risk minimisation measures: None	Routine pharmacovigilance activities beyond adverse reactions reporting and signal detection: None Additional pharmacovigilance activities: None
Hepatotoxicity	Routine risk communication: EU SmPC Section 4.4 Special warnings and precautions for use; Package leaflet Section 2 Other routine risk minimisation measures beyond the Product Information: Medicine's legal status: Prescription only medicine Additional risk minimisation measures: None	Routine pharmacovigilance activities beyond adverse reactions reporting and signal detection: None Additional pharmacovigilance activities: None
Important Potential Risks:		
Hepatocellular carcinoma	Routine risk communication: Not applicable Other routine risk minimisation measures beyond the Product Information: Medicine's legal status: Prescription only medicine Additional risk minimisation measures: None	Routine pharmacovigilance activities beyond adverse reactions reporting and signal detection: None Additional pharmacovigilance activities: None

Cardiovascular safety	Routine risk communication: Not applicable Other routine risk minimisation measures beyond the Product Information: **Medicine's legal status:** Prescription only medicine Additional risk minimisation measures: None	Routine pharmacovigilance activities beyond adverse reactions reporting and signal detection: None Additional pharmacovigilance activities: Cardiovascular meta-analysis
Missing Information:		
Long term safety (i.e., ≥1 year) in very elderly	Routine risk communication: None Other routine risk minimisation measures beyond Product Information: **Medicine's legal status:** Prescription only medicine Additional risk minimisation measures: None	Routine pharmacovigilance activities beyond adverse reactions reporting and signal detection: None Additional pharmacovigilance activities: None
Use in patients with severe renal impairment	Routine risk communication: None Other routine risk minimisation measures beyond Product Information: **Medicine's legal status:** Prescription only medicine Additional risk minimisation measures: None	Routine pharmacovigilance activities beyond adverse reactions reporting and signal detection: None Additional pharmacovigilance activities: None

Part VI: Summary of the risk management plan

Summary of risk management plan for resmetirom

This is a summary of the risk management plan (RMP) for resmetirom. The RMP details important risks of resmetirom, how these risks can be minimized, and how more information will be obtained about resmetirom's risks and uncertainties (missing information).

Resmetirom 's summary of product characteristics (SmPC) and its package leaflet give essential information to healthcare professionals and patients on how resmetirom should be used.

This summary of the RMP for resmetirom should be read in the context of all this information including the assessment report of the evaluation and its plain-language summary, all which is part of the European Public Assessment Report (EPAR).

Important new concerns or changes to the current ones will be included in updates of resmetirom 's RMP.

I. The medicine and what it is used for

Resmetirom is authorized for the treatment of adults with non-cirrhotic nonalcoholic steatohepatitis/metabolic dysfunction-associated steatohepatitis (MASH) with liver fibrosis. (see SmPC for the full indication). It contains resmetirom as the active substance and it is given by oral route of administration.

Further information about the evaluation of resmetirom's benefits can be found in resmetirom's EPAR, including in its plain-language summary, available on the EMA website, under the medicine's webpage link to the EPAR summary landing page: *<link to the EPAR summary ending page>*.

II. Risks associated with the medicine and activities to minimize or further characterize the risks

Important risks of resmetirom, together with measures to minimize such risks and the proposed studies for learning more about resmetirom's risks, are outlined below.

Measures to minimize the risks identified for medicinal products can be:

- Specific information, such as warnings, precautions, and advice on correct use, in the package leaflet and SmPC addressed to patients and healthcare professionals;
- Important advice on the medicine's packaging;
- The authorized pack size — the amount of medicine in a pack is chosen so to ensure that the medicine is used correctly;
- The medicine's legal status — the way a medicine is supplied to the patient (e.g. with or without prescription) can help to minimize its risks.

Together, these measures constitute *routine risk minimization* measures.

In addition to these measures, information about adverse reactions is collected continuously and regularly analysed, including Periodic Safety Update Report (PSUR) assessment so that immediate action can be taken as necessary. These measures constitute *routine pharmacovigilance activities*.

If important information that may affect the safe use of resmetirom is not yet available, it is listed under "missing information" below.

II.A. List of important risks and missing information

Important risks of resmetirom are risks that need special risk management activities to further investigate or minimize the risk, so that the medicinal product can be safely taken. Important risks can be regarded as identified or potential. Identified risks are concerns for which there is sufficient proof of a link with the use of resmetirom. Potential risks are concerns for which an association with the use of this medicine is possible based on available data, but this association has not been established yet and needs further evaluation. Missing information refers to information on the safety of the medicinal product that is currently missing and needs to be collected (e.g., on the long-term use of the medicine).

List of important risks and missing information	
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 very elderly patients Use in patients with severe renal impairment

II.B. Summary of important risks

Important identified risks

Cholelithiasis, including complications such as cholecystitis and obstructive pancreatitis	
Evidence for linking the event to the medicine	Patients with acute events of cholecystitis (i.e., bile duct stone, biliary colic, biliary dilatation, cholecystitis, cholecystitis acute, cholecystitis chronic, cholangitis, and obstructive pancreatitis) were low across treatment groups but was more common in resmetirom 80 mg and 100 mg (5/761 [0.7%] and 8/1033 [0.8%], respectively) compared with placebo (3/708 [0.4%])
Risk factors and risk groups	MASH patients are at high risk of existing gallstone disease with approximately 25% of Study 11 and 14 patients with a history of gallbladder disease at baseline.
Risk minimisation measures	Routine risk communication: EU SmPC Section 4.4 Special warnings and precautions for use Package leaflet Section 2 Other routine risk minimisation measures beyond the Product Information: Medicine's legal status: Prescription only medicine Additional risk minimisation measures: None
Additional pharmacovigilance activities	None
Hepatotoxicity	

Evidence for linking the event to the medicine	Two cases of possible DILI were observed in the Non-cirrhotic MASH, randomized, double-blind studies, one in the randomized open-label arm of Study 14, and one additional in the open-label MASH cirrhosis arm of Study 14.
Risk factors and risk groups	Risk factors associated with hepatotoxicity include age, female gender, pregnancy, daily dose of offending medication including analgesics (acetaminophen), antimicrobials and central nervous system agents (antiepileptic agents, antidepressants, antipsychotics), drugs with high lipophilicity, metabolism characteristics, metabolism genetics, smoking, alcohol consumption, and drug interactions.
Risk minimisation measures	Routine risk communication: EU SmPC Section 4.4 Special warnings and precautions for use Package leaflet Section 2 Other routine risk minimisation measures beyond the Product Information: **Medicine's legal status:** Prescription only medicine Additional risk minimisation measures: None
Additional pharmacovigilance activities	None

Important potential risks

Hepatocellular carcinoma	
Evidence for linking the event to the medicine	Hepatocellular carcinoma was observed in three cases during the Non-cirrhotic NASH, randomized, double-blind studies and was pre-existing and not treatment-emergent in 2 of the 3 cases.
Risk factors and risk groups	MASH patients have an increased incidence of cancers in general, including hepatocellular cancer (HCC), as the disease progresses. One-third of cirrhotic patients will develop HCC during their lifetime. Long-term follow-up studies have demonstrated that approximately 1–8% per year of patients with cirrhosis develop HCC (e.g. 2% in HBV-infected cirrhotic patients and 3–8% in HCV infected cirrhotic patients). In general, features of liver disease severity (low platelet count of less than 100 $X10^3$, presence of oesophageal varices), in addition to older age and male gender, correlate with the risk of development of HCC among patients with cirrhosis. Other risk factors include excessive alcohol consumption, diabetes, obesity, and smoking
Risk minimisation measures	Routine risk communication: Not applicable Other routine risk minimisation measures beyond the Product Information: **Medicine's legal status:** Prescription only medicine Additional risk minimisation measures: None
Additional pharmacovigilance activities	None
Cardiovascular safety	
Evidence for linking the event to the medicine	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.
Risk factors and risk groups	Recent European data confirm that patients with NAFLD—particularly those with MASH—are at elevated risk for a range of CV events, including myocardial infarction, ischemic stroke, heart failure, and atrial fibrillation, independent of traditional risk factors such as obesity or diabetes.

	The mechanisms implicated in this association include systemic low-grade inflammation, endothelial dysfunction, insulin resistance, and pro-atherogenic lipid profiles, all of which foster an atherogenic environment
Risk minimisation measures	Routine risk communication: Not applicable Other routine risk minimisation measures beyond the Product Information: **Medicine's legal status:** Prescription only medicine Additional risk minimisation measures: None
Additional pharmacovigilance activities	Cardiovascular meta-analysis

Missing Information

Long term safety (i.e., ≥1 year) in very elderly	
Risk minimisation measures	Routine risk communication: None Other routine risk minimisation measures beyond Product Information: **Medicine's legal status:** Prescription only medicine. Additional risk minimisation measures: None
Additional pharmacovigilance activities	None
Use in patients with severe renal impairment	
Risk minimisation measures	Routine risk communication: None Other routine risk minimisation measures beyond Product Information: **Medicine's legal status:** Prescription only medicine. Additional risk minimisation measures: None
Additional pharmacovigilance activities	None

II.C. Post-authorization development plan

II.C.1. Studies which are conditions of the marketing authorization

The following studies are conditions of the marketing authorization:

Study 11 (MAESTRO-NASH):

Purpose of the study:

To assess the efficacy of resmetirom 80 mg and 100 mg vs placebo in patients with non-cirrhotic NASH. The primary objective is the time to experiencing an adjudicated Composite Clinical Outcome event (Final Primary Endpoint, at 54 months).

Study 19 (MAESTRO-OUTCOMES):

Purpose of the study:

To evaluate the effect of resmetirom on liver-related Outcomes in patients with Well-compensated (Child-Pugh A) NASH Cirrhosis (MAESTRO-NASH OUTCOMES).

II.C.2. Other studies in post-authorization development plan

Cardiovascular meta-analysis:

Purpose of the analysis:

To evaluate the cardiovascular safety of resmetirom via composite endpoint of MACE events including CV mortality, non-fatal stroke and non-fatal myocardial infarction from two completed randomized, placebo-controlled clinical trials in patients with MASH (Study 11 and Study 14) and data from extension safety study (Study 18) will also be included.

Part VII: Annexes

Table of contents

Annex 4 – Specific adverse drug reaction follow-up forms

Not applicable.

[redacted]

Annex 6 – Details of proposed additional risk minimization activities (if applicable)

Not applicable.

Annex 7 – Other supporting data (including referenced material)

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SPONSOR'S RESPONSIBLE MEDICAL OFFICER APPROVAL

REZDIFFRA (resmetirom) Risk Management Plan

I have read this report and confirm that it is accurate to the best of my knowledge.

[redacted]

Madrigal Pharmaceuticals EU Limited

Signed by:
Maria Traikova
Signer Name: Maria Traikova
Signing Reason: I approve this document
Signing Time: 07-Jul-2025 | 10:40 EDT
37C50D3DD9C348CFBC90E19C6D3A1EBA

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