

Resmetirom (metabolic dysfunction-associated steatohepatitis)

Addendum to Project A25-117
(dossier assessment)¹

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Institut für Qualität und Wirtschaftlichkeit im Gesundheitswesen
Siegburger Str. 237
50679 Köln
Germany

Phone: +49 221 35685-0

Fax: +49 221 35685-1

E-mail: info@iqwig.de

Internet: www.iqwig.de

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IQWiG employees involved in the addendum

- Alina Reese
- Katharina Hirsch
- Lisa Junge
- Petra Kohlepp
- Daniela Preukschat

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List of abbreviations

Abbreviation	Meaning
ACT	appropriate comparator therapy
AE	adverse event
BMI	body mass index
CHMP	Committee for Medicinal Products for Human Use
CLDQ	Chronic Liver Disease Questionnaire
CTCAE	Common Terminology Criteria for Adverse Events
EMA	European Medicines Agency
FDA	Food and Drug Administration
G-BA	Gemeinsamer Bundesausschuss (Federal Joint Committee)
GLP-1	glucagon-like peptide-1
HbA1c	haemoglobin A1c
IQWiG	Institut für Qualität und Wirtschaftlichkeit im Gesundheitswesen (Institute for Quality and Efficiency in Health Care)
LDL-C	low-density lipoprotein cholesterol
MACE	major adverse cardiovascular events
MASH	metabolic dysfunction-associated steatohepatitis
MASLD	metabolic dysfunction-associated steatotic liver disease
MCS	Mental Component Summary
MELD	Model for End-Stage Liver Disease
NAS	non-alcoholic fatty liver disease activity score
PCS	Physical Component Summary
PT	Preferred Term
RCT	randomized controlled trial
RR	relative risk
SAE	serious adverse event
SF-36v2	Short Form 36-version 2
SF- LDQOL	Short Form Liver Disease Quality of Life
SGB	Sozialgesetzbuch (Social Code Book)
SGLT2	sodium-glucose cotransporter 2
SLD	steatotic liver disease
SOC	System Organ Class

Abbreviation	Meaning
VCTE	vibration-controlled transient elastography
WPAI	Work Productivity and Activity Impairment

1 Background

On 27 January 2026, the Federal Joint Committee (G-BA) commissioned the Institute for Quality and Efficiency in Health Care (IQWiG) to conduct supplementary assessments for Project A25-117 (Resmetirom – Benefit assessment according to §35a Social Code Book V) [1].

In its comments and following the oral hearing, the pharmaceutical company (hereinafter referred to as ‘the company’) presented supplementary data to provide evidence for the added benefit [2-4], which went beyond the information provided in the dossier [5]. The commission comprises the analysis of the MAESTRO-NASH study, taking into account the data contained in the dossier, the data submitted subsequently during the commenting procedure, and the information submitted after the oral hearing.

The responsibility for this assessment and the assessment result lies exclusively with IQWiG. The assessment is forwarded to the G-BA. The G-BA decides on the added benefit.

2 Assessment

In its dossier [5] the company used the randomized controlled trial (RCT) MAESTRO-NASH (MGL-3196-11) [6-9] for the benefit assessment, and presented the RCTs MAESTRO-NAFLD-1 (MGL-3196-14) [10] and MGL-3196-05 [11] as supporting information.

In dossier assessment A25-117 [1], the review of the completeness of the study pool was based on a minimum study duration of 52 weeks. With an observation period of 36 weeks, the MGL-3196-05 study, presented by the company as supporting information, was therefore clearly too short for the assessment of the added benefit of resmetirom in the given therapeutic indication. A conclusive assessment of the relevance of MAESTRO-NASH and MAESTRO-NAFLD-1 for the benefit assessment was not possible based on the available information. In particular, it was unclear to what extent optimized standard therapy for comorbidities, as per the appropriate comparator therapy (ACT), was ensured in the studies. The dossier assessment additionally described that it was unclear whether – due to the slow progression of the disease – the respective study periods taken into account for the benefit assessment (52 weeks) might be too short to meaningfully capture results on patient-relevant outcomes that would allow the positive and negative effects to be weighed up and thus ultimately permit a conclusion on the added benefit of resmetirom. Irrespective of this, the analyses of the respective subpopulations considered by the company presented for the benefit assessment were not appropriate. The data from MAESTRO-NASH and MAESTRO-NAFLD-1 were therefore not used for the assessment of the added benefit of resmetirom in the dossier assessment.

Overall, at the time of the dossier assessment, there were no suitable data available for comparing resmetirom with the comparator therapy specified by the G-BA (optimized standard therapy for the treatment of comorbidities such as diabetes mellitus, hypertension, obesity and lipid metabolism disorders).

As part of the comments and following the oral hearing, the company provided further data on the MAESTRO-NASH study [2-4]. The company did not provide any further data regarding the MAESTRO-NAFLD-1 study, which was presented as supporting information in the dossier, but was of questionable relevance and involved only a small number of patients (see dossier assessment).

With regard to the data on the subpopulation of the MAESTRO-NASH study submitted as part of the comments (see Section 2.2.2), it was assumed for the available analysis timepoints (Week 52) that the uncertainties – some of which remained – concerning the administration of optimized standard therapy (see Section 2.2.3) did not have a relevant impact on the results overall. However, given the slow progression of the disease in this therapeutic indication, the available results at this early analysis date and without any appropriate surrogate outcomes

were not suitable for the benefit assessment. The reasons for this are provided below. In compliance with the commission, the MAESTRO-NASH study is then described in Sections 2.2 to 2.5, and the results are presented.

2.1 Unsuitability of the available analysis date

Two key analysis dates were planned for the MAESTRO-NASH study, one at Week 52 and one at Month 54. The primary outcomes at Week 52 were NASH resolution response and fibrosis response. The primary outcome of the analysis at Month 54 was a composite outcome consisting of all-cause mortality, liver transplantation, other important liver-related events including hepatic decompensation, histological progression to hepatic cirrhosis and an increase in the Model for End-Stage Liver Disease (MELD) score from below 12 to 15 or higher.

According to the company, the available analyses of the ongoing MAESTRO-NASH study were based on the data cut of 13 January 2023 (Food and Drug Administration [FDA] 120-day safety update), which represented an observation period of up to 3.5 years for the outcomes in the side effects category. The company did not provide any information on the outcome-specific observation period. When considering the side effect outcomes (including all-cause mortality and major adverse cardiovascular events [MACE]), it should be noted that 17% of patients in the resmetirom arm and 13% in the placebo arm discontinued treatment prematurely. Given the available data, it was not anticipated that this would result in any relevant differences between the treatment arms in the observation periods for these outcomes; consequently, the relative risk effect measure presented could be used.

The prespecified analyses at Week 52 (data cut-off: 31 July 2022) are currently available for the health-related quality of life outcomes presented by the company. Provided they had not discontinued the study beforehand, all patients had been under observation for at least 52 weeks at the data cut-off (31 July 2022).

Based on the timepoints of recording specified in the study protocol, analyses at later timepoints of recording (at least at Week 64) were possible for the health-related quality of life outcomes at the 13 January 2023 data cut-off. However, it was not anticipated that such analyses would yield any relevant new information.

The therapeutic indication to be assessed includes patients with noncirrhotic metabolic dysfunction-associated steatohepatitis (MASH) with moderate to advanced liver fibrosis (fibrosis stages F2 to F3). In general, the progression of the disease is slow and without prominent and specific symptoms. As described in the dossier assessment, the European Medicines Agency (EMA) Reflection paper on regulatory requirements for the development of medicinal products for MASH therefore considers long-term outcomes to be difficult to study [12]. According to this paper, the question of an appropriate study duration in the therapeutic indication cannot be answered unequivocally and the final analysis should

therefore be event-driven. For interim analyses based on intermediate outcomes used as a substitute, the EMA recommends a 2-year study duration as a general rule, which can be modified based on phase 2 data, the size of the study, patient characteristics, and statistical rigor. For such outcomes defined by the EMA, it must first be ensured that they have been validated using appropriate statistical methods within a sufficiently well-defined patient group and in the context of comparable interventions (e.g. drugs with a comparable mechanism of action) [13]. The FDA Guidance ‘Noncirrhotic Nonalcoholic Steatohepatitis With Liver Fibrosis; Developing Drugs for Treatment’ also does not state a specific minimum study duration. For phase 2 studies, however, the FDA recommends a duration of at least 12 to 18 months [14].

It was already described in the dossier assessment that it is questionable whether, based on the analysis timepoints underlying the available data cuts (Week 52 for outcomes on morbidity and health-related quality of life; up to 3.5 years of observation period for adverse events [AEs], see above), results on patient-relevant outcomes can be meaningfully interpreted and thus allow the positive and negative effects to be weighed up and ultimately permit a conclusion on the added benefit of resmetirom.

In the morbidity category, the company used the primary outcomes of the interim analysis – NASH resolution response and fibrosis response – to derive the added benefit. However, the data presented by the company with the dossier, as well as the publications referred to in the comments, did not, on the whole, provide sufficient evidence to demonstrate that these outcomes are sufficiently valid surrogates for patient-relevant outcomes such as mortality, avoidance or delay of liver transplantation, or the symptomatic progression to hepatic cirrhosis (see Section 2.3.1). Although, in general, MAESTRO-NASH did record patient-relevant outcomes in the categories of mortality, morbidity and health-related quality of life, the slow progression of the disease means that it was not possible to interpret the results meaningfully on the basis of the available analysis dates. The outcomes of all-cause mortality and MACE were recorded as AEs in the study and therefore covered a follow-up period of more than 52 weeks (although it was unclear how long the median follow-up duration was for these outcomes); nevertheless, very few events occurred for these outcomes during the period under consideration (see Table 8 in Section 2.3.3). Overall, the period for which results were available at the time of this assessment was considered too short, and the available results were therefore not taken into account when assessing the added benefit of resmetirom.

In compliance with the commission, the MAESTRO-NASH study is described in Sections 2.2 to 2.5, and the results are presented.

2.2 Evidence presented by the company – MAESTRO-NASH

2.2.1 Study characteristics

A detailed description of the MAESTRO-NASH study can be found in dossier assessment A25-117.

2.2.2 Subpopulation presented

As described in the dossier assessment, the analyses of the subpopulation used in the company's dossier were not suitable for the benefit assessment. The company compared patients with MASH fibrosis stage F2 and F3 as well as subpopulations modified in accordance with the marketing authorization from the individual resmetirom arms (80 mg resmetirom arm: all patients with a body weight < 100 kg; 100 mg resmetirom arm: all patients with a body weight ≥ 100 kg) with the entire control arm. Due to the selection criterion (weight) that was applied differently in the study arms, structural equality between the study arms, which was achieved through the randomized allocation of patients to the study arms, was not certain to have been maintained.

With the comments, the company subsequently submitted analyses for the subpopulation presented in the dossier, in which the 2 resmetirom arms (80 mg resmetirom and 100 mg resmetirom) were pooled into a single patient population (N = 318) and compared with the placebo arm (N = 303). This approach was appropriate. Unless otherwise stated, all information regarding the MAESTRO-NASH study set out below relates to the subpopulation described.

Characteristics of the subpopulation presented by the company

Table 1 shows the patient characteristics of the study.

Table 1: Characteristics of the study population and study/treatment discontinuation – RCT, direct comparison: resmetirom + concomitant treatment vs. placebo + concomitant treatment (multipage table)

Study Characteristic Category	resmetirom N ^a = 318	placebo N ^a = 303
MAESTRO-NASH study		
Age [years], mean (SD)	56 (11)	57 (10)
Sex [F/M], %	59/41	56/44
Family origin		
Caucasian	291 (92)	265 (88)
Black or African American	3 (< 1)	7 (2)
Asian	9 (3)	9 (3)
Other / not recorded	15 (5) ^b	22 (7) ^b
BMI [kg/m ²], mean (SD)	36.2 (7.1)	35.2 (6.4)
< 25 kg/m ²	7 (2)	8 (3)
≥ 25–30 kg/m ²	47 (15)	62 (21)
≥ 30 kg/m ²	264 (83)	233 (77)
NAS ≥ 5 at screening, n (%)	280 (88)	239 (79)
Fibrosis stage at baseline ^c , n (%)		
2	117 (37)	111 (37)
3	195 (61)	187 (62)
4	6 (2)	5 (2)
Fibroscan VCTE value [kPa] at screening, median (Q1; Q3)	11.54 (9.4; 15.5)	11.8 (9.5; 14.9)
Type 2 diabetes mellitus at baseline, n (%)	218 (67)	201 (66)
HbA1c at baseline ^d , mean (SD)	7.1 (1.0)	6.9 (1.0)
Documented ASCVD ^d	13 (6)	9 (5)
Hypertension at baseline, n (%)	245 (77)	243 (80)
Dyslipidaemia at baseline, n (%)	238 (75)	212 (70)
LDL-C [mg/dL] at baseline ^e , mean (SD)	101.6 (37.2)	99.8 (39.0)
Triglycerides [mg/dL] at baseline ^e , mean (SD)	200.5 (146.2)	195.1 (136.7)
History of documented ASCVD, n (%)	18 (6)	13 (4)
10-year ASCVD risk score, median (Q1; Q3)	10.9 (5.5; 20.4)	12.8 (6.4; 22.1)
Treatment discontinuation, n (%) ^f	53 (17)	38 (13)
Study discontinuation, n (%) ^g	44 (14)	35 (12)

Table 1: Characteristics of the study population and study/treatment discontinuation – RCT, direct comparison: resmetirom + concomitant treatment vs. placebo + concomitant treatment (multipage table)

Study Characteristic Category	resmetirom N ^a = 318	placebo N ^a = 303
a. Number of analysed patients. Values that are based on other patient numbers are marked in the corresponding line if the deviation is relevant. b. Institute's calculations. c. The fibrosis stage at baseline was determined by the analysis performed by Pathologist A and Pathologist B. The maximum stage of fibrosis was used for this presentation. d. Analyses relating to patients with type 2 diabetes mellitus at baseline. e. Analyses relating to patients with dyslipidaemia at baseline. f. Frequent reasons for treatment discontinuation in the intervention arm vs. the control arm (percentages refer to randomized patients): patient request (7% vs. 5%), AEs (6% vs. 4%), lost to follow-up (3% vs. 2%). g. Frequent reasons for study discontinuation in the intervention arm vs. the control arm (percentages refer to randomized patients): patient request (6% vs. 6%), AEs (4% vs. 3%), lost to follow-up (3% vs. 2%). ASCVD: atherosclerotic cardiovascular disease; BMI: body mass index; F: female; HbA1c: haemoglobin A1c; kPa: kilopascals; LDL-C: low-density lipoprotein cholesterol; M: male; n: number of patients in the category; N: number of analysed patients; NAS: non-alcoholic fatty liver disease activity score; Q1: 1st quartile; Q3: 3rd quartile; RCT: randomized controlled trial; SD: standard deviation; VCTE: vibration-controlled transient elastography		

Both treatment arms were largely balanced in terms of the demographic and clinical characteristics of the patients in the subpopulation presented. The mean patient age was 56 years; most patients were women and almost all patients were of Caucasian family origin. At the time of screening, a higher proportion of patients in the resmetirom arm had a non-alcoholic fatty liver disease activity score (NAS) of ≥ 5 than in the placebo arm (88% versus 79%). The majority of patients in both study arms had fibrosis stage 3 at baseline (approximately 60%). Overall, 67% of patients in the subpopulation had type 2 diabetes mellitus at baseline, 79% had hypertension and 72% had dyslipidaemia.

Treatment discontinuation occurred in 17% of patients in the intervention arm, compared with 13% in the comparator arm. The most common reasons were patient request, discontinuation due to AEs, and lost to follow-up. The proportion of patients who discontinued the study was comparable between the study arms (14% in the resmetirom arm and 12% in the placebo arm).

Table 2 shows the treatment of comorbidities at baseline.

Table 2: Treatment of comorbidities at baseline – RCT, direct comparison: resmetirom + concomitant treatment vs. placebo + concomitant treatment

Study	Patients with therapy n (%)	
	resmetirom N = 318	placebo N = 303
MAESTRO-NASH study		
Statins	162 (51)	147 (49)
Other lipid-lowering therapy	84 (26)	72 (24)
GLP-1 analogues	49 (15)	39 (13)
SGLT2 inhibitors	53 (17)	35 (12)
Insulin therapy	34 (11)	36 (12)
Antihypertensive therapy	225 (71)	222 (73)
GLP-1: glucagon-like peptide 1; n: number of patients in the category; N: number of analysed patients; RCT: randomized controlled trial; SGLT2: sodium-glucose cotransporter 2		

Some of the patients were receiving drug treatment for their comorbidities at baseline. The drugs used included statins (approximately 50% of patients), glucagon-like peptide-1 (GLP-1) receptor agonists (14%), sodium-glucose cotransporter-2 (SGLT2) inhibitors (14%), insulin, and others. Other antidiabetic treatments not listed in Table 2 were also used (see Table 3).

Notes on the subpopulation

In MAESTRO-NASH, the diagnosis of MASH with fibrosis (F1, F2 or F3) had to be confirmed by a recent liver biopsy. Whilst this is in line with the recommendations of the regulatory authorities [12,14] for the conduct of clinical studies, biopsy-based confirmation is not necessary according to the amendment to the S2k guideline [15]. The presence of significant liver stiffness measured by vibration-controlled transient elastography (VCTE), magnetic resonance elastography or other ultrasound-based elastography procedures is cited as a selection criterion for resmetirom therapy, as an alternative to biopsy-confirmed MASH with liver fibrosis (F2 and F3). At the same time, it is stated that guideline-based risk stratification is probably unable to correctly classify a major proportion of patients because non-invasive procedures are not sufficiently reliable. It is therefore unclear whether, and to what extent, the patient population in the study differed from patients in everyday German health care practice.

2.2.3 Appropriate comparator therapy

The G-BA defined optimized standard therapy for the treatment of comorbidities such as diabetes mellitus, hypertension, obesity and lipid metabolism disorders as the ACT. This is understood to mean individualized treatment in accordance with the current state of medical knowledge, taking into account the specific characteristics of the actual disease and the

German health care context. The study protocol should explicitly allow for modifications to the basic/concomitant medication.

As described in the dossier assessment, the MAESTRO-NASH study protocol restricted the drug treatment of type 2 diabetes mellitus and dyslipidaemia in particular:

- A dose increase or initiation of GLP-1 therapy was prohibited during the first 52 weeks.
- The use of statins was restricted in terms of the permitted drugs and their maximum doses.

As part of the commenting procedure, the company submitted further data on treatment modifications and laboratory results (including haemoglobin A1c [HbA1c] and low-density lipoprotein cholesterol [LDL-C]) during the course of the study, which it considered to demonstrate that optimum treatment of comorbidities was administered despite the limitations described. Furthermore, the company compared the data from the MAESTRO-NASH subpopulation presented with data on a sub-cohort from the Steatotic Liver Disease (SLD) registry [16]. The sub-cohort comprises 360 patients with metabolic dysfunction-associated steatotic liver disease (MASLD) and liver stiffness, as measured by VCTE, ranging from 8.5 to 20 kPa (treatment-eligible MASH cohort) and is hereinafter referred to as 'MASH cohort'.

The data subsequently submitted for the MAESTRO-NASH study were taken into account below when assessing whether, at the analysis dates currently available, treatment was administered in accordance with the ACT specified by the G-BA. In addition, a comparison was carried out with the MASH cohort. In this regard, however, it should be noted at the outset that, in accordance with the inclusion criteria, patients in the MAESTRO-NASH study were required to have at least 3 metabolic risk factors and therefore tended to have more comorbidities than those in the MASH cohort; for example, the proportion of patients with type 2 diabetes mellitus was higher in MAESTRO-NASH (67% versus 52%) (see Table 11 in Appendix A). Furthermore, patients in the SLD registry were selected solely on the basis of a non-invasive measurement of liver stiffness, whereas patients in MAESTRO-NASH also had a liver biopsy. Other inclusion criteria for the study were also not taken into account when selecting the MASH cohort. Consequently, it is unclear to what extent the patients in the MAESTRO-NASH study were in fact sufficiently similar to those in the registry cohort.

Drug treatment of type 2 diabetes mellitus

The dossier assessment described that, based on the information available, it was not possible to assess whether adequate treatment of type 2 diabetes mellitus was ensured despite the restricted antidiabetic treatment optimization in the study. In its comments, the company

provided information on treatment modifications during the course of the study for patients with type 2 diabetes mellitus at baseline (see Table 3).

Table 3: Treatment modifications in patients with type 2 diabetes mellitus at baseline – RCT, direct comparison: resmetirom + concomitant therapy vs. placebo + concomitant therapy

Study Characteristic Category	resmetirom N = 218	placebo N = 201
MAESTRO-NASH		
No treatment received, n (%)	15 (6.9)	7 (3.5)
Treatment received, n (%)	203 (93.1)	194 (96.5)
No modification of treatment	99 (48.8)	79 (40.7)
Any modification of treatment	104 (51.2)	115 (59.3)
Medication	88 (84.6)	88 (76.5)
Discontinuation of medication	58 (55.8)	59 (51.3)
Initiation of new medication	71 (68.3)	70 (60.9)
Dosage	33 (31.7)	45 (39.1)
Frequency	17 (16.3)	33 (28.7)
Route of administration	2 (1.9)	3 (2.6)
n: number of patients in the category; N: number of analysed patients with type 2 diabetes mellitus at baseline; RCT: randomized controlled trial		

The data showed that approximately 95% of patients with type 2 diabetes mellitus at baseline received concomitant treatment by the data cut-off of 13 January 2023. Based on further information contained in the dossier, it was assumed that this referred to the antidiabetic treatment. Treatment was modified for more than half of these patients. The most common change was to the medication (initiation or discontinuation; 80% across both study arms) or the dosage (36% across both study arms). However, the available data did not allow any conclusions to be drawn regarding the extent to which GLP-1 receptor agonists were affected by the modifications despite the restriction stipulated in the protocol (see above).

The data provided by the company on the treatment of comorbidities at baseline referred to the entire subpopulation in each case (see Table 2). Assuming that every patient receiving a GLP-1 receptor agonist at baseline also had type 2 diabetes mellitus, a maximum of approximately 21% of patients with type 2 diabetes mellitus received a GLP-1 receptor agonist. In the MASH cohort, the proportion of patients with diabetes who were treated with a GLP-1 receptor agonist was slightly higher, at 29% (see Table 12 in Appendix A). The situation was similar with regard to treatment with SGLT2 inhibitors (a maximum of 21% of patients with diabetes at baseline, compared with 27%). In the subpopulation of the study, a maximum

of approximately 17% of patients with type 2 diabetes mellitus received insulin; in the SLD cohort, the figure was around 25%.

According to various guidelines, GLP-1 receptor agonists are a central component of the treatment of type 2 diabetes mellitus with concomitant cardiovascular disorder or overweight/obesity [17-19]. The guidelines explicitly recommend combination therapy with metformin and GLP-1 receptor agonists or SGLT2 inhibitors for patients with type 2 diabetes mellitus and a clinically relevant cardiovascular disorder [17,18]. In the MAESTRO-NASH study, only 13 patients (6%) in the resmetirom arm and 9 (5%) in the placebo arm had atherosclerotic cardiovascular disease in addition to type 2 diabetes mellitus. However, based on the comments made during the oral hearing, it can be assumed that, due to comorbidities, combination therapy was considered to be indicated for a substantially larger number of patients [20].

A total of 24 of the 621 patients (4%) in the MAESTRO-NASH subpopulation presented developed type 2 diabetes mellitus during the course of the study. Of these 24 patients, 63% received metformin, 21% GLP-1 receptor agonists and 17% SGLT2 inhibitors.

Throughout the study, the HbA1c level (in patients with type 2 diabetes mellitus at baseline) remained largely constant. The mean HbA1c value at baseline was 7.05% in the resmetirom arm and 6.90% in the placebo arm. At Week 52, these values were 7.15% and 6.99% respectively. The observed mean HbA1c values were therefore within the target range of 6.5% to 8.5% set out in the National Care Guideline for type 2 diabetes [17]. The mean HbA1c level in the MASH cohort was 6.9% (patients < 100 kg) and 7.2% (patients ≥ 100 kg), and was therefore within a similar range.

Overall, there was no indication that the antidiabetic treatment administered in the study was inadequate for a relevant proportion of patients during the period taken into account.

It should also be noted that, according to the G-BA, it was assumed that optimized standard treatment was administered in both treatment arms (i.e. the use of resmetirom as an add-on), and the question arises to what extent the effects of resmetirom and SGLT2 inhibitors or GLP-1 receptor agonists complement or reinforce one another. This should also be seen against the backdrop of the recent positive EU marketing authorization recommendation for the GLP-1 receptor agonist semaglutide for MASH [21]. One publication [22] analysed relevant subgroup analyses from the MAESTRO-NASH study, which suggested that the concomitant use of SGLT2 inhibitors or GLP-1 receptor agonists does not, but relevant weight loss does enhance the effect of resmetirom, although the informative value of the analyses was limited by the smaller size of the subgroup populations. GLP-1 receptor agonists are also used for weight loss; SGLT2 inhibitors can lead to a slight reduction in weight [19].

Drug treatment of dyslipidaemia

As described above, the use of statins in the MAESTRO-NASH study was restricted in terms of the permitted drugs and their maximum doses. Overall, around 75% of patients with dyslipidaemia at baseline received treatment to lower their LDL-C and/or triglycerides. Concomitant treatment was changed in 18% of patients in the subpopulation with this condition. Based on further information contained in the dossier, it was assumed that this referred to modifications of the lipid-lowering therapy.

Table 4: Treatment modifications in patients with dyslipidaemia at baseline – RCT, direct comparison: resmetirom + concomitant therapy vs. placebo + concomitant therapy

Study Characteristic Category	resmetirom N = 238	placebo N = 212
MAESTRO-NASH		
No treatment received, n (%)	66 (27.7)	45 (21.2)
Treatment received, n (%)	172 (72.3)	167 (78.8)
No modification of treatment	135 (78.5)	123 (73.7)
Any modification of treatment	37 (21.5)	44 (26.3)
Medication	30 (81.1)	34 (77.3)
Discontinuation of medication	27 (73.0)	27 (61.4)
Initiation of new medication	12 (32.4)	23 (52.3)
Dosage	7 (18.9)	8 (18.2)
Frequency	2 (5.4)	5 (11.4)
Route of administration	1 (2.7)	1 (2.3)
n: number of patients in the category; N: number of analysed patients with dyslipidaemia at baseline; RCT: randomized controlled trial		

The subsequently submitted trends in LDL-C and triglyceride levels in patients with dyslipidaemia at baseline showed an early and marked decline in these levels in the resmetirom arm. The mean LDL-C level at baseline was 102 mg/dL and fell to 80 mg/dL by Week 52, whilst the mean triglyceride level at baseline was 200 mg/dl and fell to 136 mg/dL by Week 52. In the placebo arm, the levels fluctuated and fell only slightly. The mean LDL-C level was 100 mg/dL at baseline and 96 mg/dL at Week 52; the mean triglyceride level was 195 mg/dL at baseline and 187 mg/dL at Week 52. The data confirmed that the potential effects of limiting the dose of statins affected the placebo arm in particular. After 52 weeks, despite treatment modifications in some patients, there were marked differences between the treatment arms with regard to both LDL-C levels and triglycerides. Compared with patients in the MASH cohort, however, LDL-C and triglyceride levels in the MAESTRO-NASH study were lower (see Table 11). According to the guideline, LDL-C target levels are based on the patient's cardiovascular risk, which is determined by factors such as the presence of cardiovascular

disease or type 2 diabetes mellitus (depending on the patient's age and the time since diagnosis) [23]. The target level is < 70 mg/dL for patients at high risk, for example, and < 100 mg/dL for patients at intermediate risk. It was unclear how large the proportion of patients at high risk was in the MAESTRO-NASH subpopulation presented; however, based on the ASCVD score at baseline it was highly likely that this was a relevant proportion (see Table 1). Considering a possible assessment of the final analysis at Month 54, individual patient data regarding target values would be desirable.

The company's comments did not address which additional interventions could be used to ensure optimal treatment of LDL dyslipidaemia in particular for patients in the placebo arm despite these limited dosing options for statins. According to guideline recommendations, the addition of ezetimibe may be considered if LDL-C target levels are not achieved with the maximum tolerated dose of a statin [23]. In the MAESTRO-NASH study, ezetimibe was used in a small number of patients in the placebo arm (relative to the number of patients with dyslipidaemia at baseline) (up to 11%). For at least some patients with dyslipidaemia, ezetimibe would have been another option for further reducing LDL-C levels if needed.

Conclusion

As already described in dossier assessment A25-117, there were no restrictions regarding the drug treatment of hypertension, and bariatric or intestinal bypass surgery was indicated only in individual cases, based on the body mass index (BMI) of the patients in the MAESTRO-NASH study.

Overall, there was no indication that the antidiabetic treatment administered in the study was inadequate for a relevant proportion of patients during the period taken into account. The data subsequently submitted on the treatment of dyslipidaemia, however, could not fully dispel the uncertainty already described in the dossier assessment as to whether optimal treatment was guaranteed for patients in the placebo arm, despite the limited dosing options for statins. The implications of the restricted use of statins in the study must be considered in the context of the results. For the available analysis dates, no relevant impact on the results was anticipated. The impact on the results for outcomes recorded in the final analysis at Month 54 must then be reassessed when these data are available.

Risk of bias across outcomes (study level)

Table 5 shows the risk of bias across outcomes (risk of bias at study level).

Table 5: Risk of bias across outcomes (study level) – RCT, direct comparison: resmetirom + concomitant therapy vs. placebo + concomitant therapy

Study	Adequate random sequence generation	Allocation concealment	Blinding		Reporting independent of the results	Absence of other aspects	Risk of bias at study level
			Patients	Treating staff			
MAESTRO-NASH	Yes	Yes	Yes	Yes	Yes	Yes ^a	Low
a. Changes to the SAP and the study protocol following the database lock for the interim analysis and the unblinding of the data (see running text).							
RCT: randomized controlled trial; SAP: statistical analysis plan							

During the course of the study, a number of changes were made to the study protocol and statistical analysis plan; some of these were made after the database lock of the interim analysis on 18 November 2022 for the 31 July 2022 data cut, and after unblinding at the Clinical Research Organization on 2 December 2022. This was also criticized in the European Public Assessment Report on resmetirom [24]. Although the latest amendment to the study protocol applicable to the European Union, from 27 June 2023, and to the statistical analysis plan, from 5 December 2022, were dated more than 6 months and 2 weeks, respectively, after the database lock, the Committee for Medicinal Products for Human Use (CHMP) considered the analyses of the outcomes at Week 52 to have been sufficiently prespecified, and the risk of limited reliability of the study results at Week 52 as low [24]. For the benefit assessment, the company submitted a further amendment to the statistical analysis plan dated 26 May 2023, which did not contain any relevant changes compared with the previous version, however.

The risk of bias across outcomes for MAESTRO-NASH was rated as low.

2.3 Results

2.3.1 Presented outcomes

The following patient-relevant outcomes are presented in the present addendum:

- Mortality
 - All-cause mortality
- Morbidity
 - MACE, composite cardiovascular outcome consisting of the following components:
 - Cardiovascular death

- Non-fatal myocardial infarction
- Non-fatal stroke
- Activity impairment (recorded using the Work Productivity and Activity Impairment [WPAI]-NASH question 6)
- Health-related quality of life
 - measured using the Short Form 36-version 2 (SF-36v2)
 - measured using the Chronic Liver Disease Questionnaire for non-alcoholic fatty liver disease – non-alcoholic steatohepatitis (CLDQ NAFLD-NASH)
- Side effects
 - Serious adverse events (SAEs)
 - Severe AEs, operationalized as Common Terminology Criteria for Adverse Events (CTCAE) grade ≥ 3
 - Discontinuation due to AEs
 - Other specific AEs, if any

The selection of patient-relevant outcomes deviates from that of the company, which used further outcomes.

Table 6 shows for which outcomes data were available in the study.

Table 6: Matrix of outcomes – RCT, direct comparison: resmetirom + concomitant therapy vs. placebo + concomitant therapy

Study	Outcomes										
	All-cause mortality ^a	MACE ^{b, c}	Activity impairment (WPAI-NASH question 6)	Health-related quality of life (SF-36v2)	Health-related quality of life (CLDQ-NAFLD/NASH)	SAEs ^d	Severe AEs ^{d, e}	Discontinuation due to AEs ^d	Diarrhoea (PT, AEs)	Gastrointestinal disorders (SOC, SAEs)	Vascular disorders (SOC, severe AEs ^e)
MAESTRO-NASH	Yes	Yes	No ^f	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes
a. The results on all-cause mortality are based on the information on fatal AEs. b. Composite cardiovascular outcome consisting of the following components: cardiovascular death, non-fatal myocardial infarction and non-fatal stroke; after review by an adjudication committee. c. Recorded as part of the AEs. d. Without taking into account the following disease-related events: hepatic cirrhosis, ascites, oesophageal varices, haemorrhage and hepatic encephalopathy. e. Operationalized as CTCAE grade ≥ 3. f. No suitable data available; see running text for reasons. AE: adverse event; CLDQ: Chronic Liver Disease Questionnaire; CTCAE: Common Terminology Criteria for Adverse Events; MACE: major adverse cardiovascular event; NAFLD: non-alcoholic fatty liver disease; NASH: non-alcoholic steatohepatitis; PT: Preferred Term; RCT: randomized controlled trial; SAE: serious adverse event; SF-36v2: Short Form 36-version 2; SOC: System Organ Class; WPAI: Work Productivity and Activity Impairment											

Notes on outcomes

NASH resolution response and fibrosis response

The primary outcomes of the interim analysis at Week 52 in MAESTRO-NASH were NASH resolution response and fibrosis response. In each case, histological improvement was assessed on the basis of liver biopsies taken at Week 52 (± 10 days) compared with baseline. For patients who discontinued the study early, the liver biopsy was performed at the time of study discontinuation. If the study was discontinued within 36 weeks after starting study treatment, a biopsy was not required at the end of treatment.

The analysis of the liver biopsies was performed centrally by 2 blinded pathologists, who evaluated MASH and fibrosis independently of each another. Changes in the severity of MASH were determined using the NAS. The NAS (on a scale of 0 to 8 points) was calculated as the unweighted sum of the following components: steatosis (0 to 3 points), lobular inflammation

(0 to 3 points) and ballooning (0 to 2 points). The stage of fibrosis was determined using the NASH Clinical Research Network scale [25].

In the study, a NASH resolution response was operationalized as

- total absence of ballooning (score = 0) and absent or mild inflammatory process (score 0 to 1) with a reduction in NAS of ≥ 2 points, and
- without worsening of fibrosis, defined as progression of ≥ 1 stage compared with baseline

A fibrosis response was operationalized as an improvement of ≥ 1 fibrosis stage with no worsening of NAS compared with baseline. For the benefit assessment, the company also presented the post-hoc-defined operationalizations of 1-stage fibrosis response without worsening of a NAS component, and 1-stage fibrosis response without worsening of activity, without defining these in further detail. It was assumed that activity refers to the sum of ballooning and lobular inflammation.

Outcomes based on imaging, such as the NASH resolution response and fibrosis response, are not, in themselves, patient-relevant. The publications referred to by the company in the dossier and in the comments [26-43] did not, on the whole, provide sufficient evidence to demonstrate that these outcomes are sufficiently valid surrogates for patient-relevant outcomes such as mortality, avoidance or delay of liver transplantation, or the symptomatic progression to hepatic cirrhosis.

The analyses and publications submitted subsequently were not validation studies in the sense of a correlation analysis between a treatment effect on a surrogate outcome (NASH resolution response or fibrosis response) and a treatment effect on a patient-relevant outcome [13,44]. Some of the publications presented by the company [26-31,34,37,38] as well as the meta-analysis presented by the company [45] merely show that the stage of fibrosis is a prognostic marker for various clinical outcomes, such as mortality or liver carcinoma. A common, fundamental misunderstanding is the equation of a prognostic marker and a surrogate outcome. In terms of surrogate validation, it is not sufficient to demonstrate that an outcome has a prognostic character, because a prognostic marker only indicates that there is a higher probability of dying earlier or of the disease becoming more severe. However, this does not mean that an effect on the prognostic marker can simultaneously be quantitatively translated into or transferred to an effect on the clinically relevant outcome.

In special situations, however, validity can be recognized even without a validation study (i.e. a study in terms of an RCT-based correlation analysis). For this, it is necessary that the relationship between the patient-relevant outcome and the surrogate outcome is biologically/medically clearly plausible and that results are available, at least from cohort

studies, that show that the occurrence of the surrogate outcome leads to a dramatically reduced risk (point estimate factor 1/10 or smaller) with regard to the actual outcome. In the event of only a substantially reduced risk (point estimate factor 1/5 or smaller), the risk with regard to the actual outcome must reach a minimal level, e.g. that of a non-diseased population. The cohort studies must relate to patients undergoing treatment; data on the natural course of the disease are not sufficient. Close specificity of intervention and indication is not required. In addition, the follow-up period must be sufficiently long to accurately assess the risk of the actual outcome occurring. Furthermore, at least a focused search should have been conducted to obtain the evidence base; see, for example, explanations in rapid report A24-61 [44] and dossier assessment A11-17 [46].

Although one study [47], which was cited by another company during the commenting procedure, did show a notable reduction in the risk of liver-related complications for patients with MASH and ≥ 1 stage regression of fibrosis, this study was not based on a focused search and therefore did not have a sufficiently comprehensive evidence base. However, this is an important prerequisite in order that the data is not presented in a biased manner. Furthermore, this study was based on 2 placebo-controlled RCTs, which would also have allowed for a correlation analysis – generally the preferred approach – between the treatment effect on the surrogate outcome and the treatment effect on a patient-relevant outcome.

Whilst the EMA accepts the outcomes ‘NASH resolution response’ and ‘fibrosis response’ as so-called ‘intermediate endpoints’ within the framework of an accelerated authorization procedure, it pointed out, both in the Reflection paper on regulatory requirements for the development of medicinal products for non-alcoholic steatohepatitis and in the European Public Assessment Report on resmetirom, that neither of the primary outcomes at Week 52 were validated surrogates [12]. This is in line with the FDA Guidance ‘Noncirrhotic Nonalcoholic Steatohepatitis With Liver Fibrosis; Developing Drugs for Treatment’, which states that ‘the relationship between liver histological improvement and clinical outcomes has not been characterized’ [14].

The results for the outcomes of NASH resolution response and fibrosis response are presented in Table 13 in Appendix A as supplementary information.

MACE

In the MAESTRO-NASH study, MACE was defined as a composite outcome comprising the 3 individual components of cardiovascular mortality, non-fatal myocardial infarction and non-fatal stroke. The events were adjudicated by a blinded committee (Endpoint Adjudication Committee). No information was provided in either the dossier or the study protocol regarding the operationalization of the individual components.

Activity impairment (recorded using the Work Productivity and Activity Impairment [WPAI]-NASH question 6)

The company did not provide any analyses of the WPAI-NASH domain of activity impairment, as the response rates for all timepoints of recording were less than 70%. This approach was appropriate. Hence, no suitable data were available for the outcome of activity impairment.

Health-related quality of life

In the MAESTRO-NASH study, health-related quality of life was assessed using the instruments SF-36v2, Short Form Liver Disease Quality of Life (SF-LDQOL) and CLDQ-NAFLD/NASH.

SF-LDQOL

The SF-LDQOL is an instrument for assessing health-related quality of life in people with advanced liver disease. It was not developed specifically for patients with MASH, but for those with advanced liver disease of various aetiologies who are awaiting a liver transplantation. The questionnaire includes 36 items representing 9 domains (symptoms of liver disease, effects of liver disease on activities of daily living, concentration/memory, sleep, hopelessness, health distress, loneliness, stigma of liver disease, sexual problems).

As it was validated in a different patient population, the SF-LDQOL was not used as a tool for assessing health-related quality of life in adults with noncirrhotic MASH with moderate to advanced liver fibrosis (fibrosis stages F2 to F3).

CLDQ-NAFLD/NASH

The CLDQ NAFLD/NASH is an instrument for assessing health-related quality of life in patients with MASLD/MASH. Following the oral hearing, the company clarified that, contrary to the information provided in the dossier and the study protocol, the MAESTRO-NASH study used a version of the instrument [48] that includes 36 items across 6 scales (abdominal symptoms, activity/energy, emotional health, fatigue, systemic symptoms and worry), rather than one that includes 29 items. Each item was answered on a 1 to 7 Likert scale. The total score used had a scale range of 6 points.

Responder analyses

With regard to the analyses of the pooled resmetirom arms submitted subsequently during the commenting procedure, the company provided responder analyses of the instruments mentioned above on the proportion of patients with an improvement of at least 15% of the scale range at Week 52 compared with the baseline. Following the oral hearing, the company also presented responder analyses on the proportion of patients with a deterioration of at least 15% of the scale range at Week 52.

Given the expected course of disease in this therapeutic indication, and taking into account the distribution of the absolute scale values at baseline, an analysis of the deterioration in health-related quality of life is of primary relevance in the long term. The results regarding improvements in health-related quality of life are presented in Table 14 in Appendix A.

For the outcomes in the health-related quality of life category, analyses of the change at Week 52 were prespecified in the study protocol. The company used an improvement or a deterioration of at least 15% of the respective scale range of the instrument as the response criterion defined post hoc. This meets the requirements for response criteria for reflecting with sufficient certainty a change that is perceivable for patients, as described in the General Methods of the Institute [13]. The company did not specify for the instruments which score this threshold value was based on. Furthermore, for the SF-36v2, the score range of the Physical Component Summary (PCS) and of the Mental Component Summary (MCS) was unclear, as no information was available on the norm sample the analyses were based on.

Side effects

For the overall rates (AEs, SAEs and severe AEs), analyses excluding disease-related events were used in each case. The company defined the following events as disease-related: hepatic cirrhosis, ascites, oesophageal varices, haemorrhage and hepatic encephalitis.

2.3.2 Risk of bias

Table 7 describes the risk of bias for the results of the relevant outcomes.

Table 7: Risk of bias across outcomes and outcome-specific risk of bias – RCT, direct comparison: resmetirom + concomitant therapy vs. placebo + concomitant therapy

Study	Study level	Outcomes										
		All-cause mortality ^a	MACE ^{b, c}	Activity impairment (WPAI-NASH question 6)	Health-related quality of life (SF-36v2)	Health-related quality of life (CLDQ-NAFLD/NASH)	SAEs ^d	Severe AEs ^{d, e}	Discontinuation due to AEs ^d	Diarrhoea (PT, AEs)	Gastrointestinal disorders (SOC, SAEs)	Vascular disorders (SOC, severe AEs) ^e
MAESTRO-NASH	L	H ^f	H ^f	— ^g	H ^h	H ^h	H ^f	H ^f	L ⁱ	H ^f	H ^f	H ^f

a. The results on all-cause mortality are based on the information on fatal AEs.
 b. Composite cardiovascular outcome consisting of the following components: cardiovascular death, non-fatal myocardial infarction and non-fatal stroke; after review by an adjudication committee.
 c. Recorded as part of the AEs.
 d. Without taking into account the following disease-related events: hepatic cirrhosis, ascites, oesophageal varices, haemorrhage and hepatic encephalopathy.
 e. Operationalized as CTCAE grade ≥ 3.
 f. Incomplete observations for potentially informative reasons.
 g. No suitable data available; see Section 2.3.1 for the reasoning.
 h. High proportion of patients excluded from the analysis (> 10%).
 i. Despite low risk of bias, the certainty of results for the outcome of discontinuation due to AEs was assumed to be limited (see running text).
 AE: adverse event; CLDQ: Chronic Liver Disease Questionnaire; CTCAE: Common Terminology Criteria for Adverse Events; H: high; L: low; MACE: major adverse cardiovascular event; NAFLD: non-alcoholic fatty liver disease; NASH: non-alcoholic steatohepatitis; PT: Preferred Term; RCT: randomized controlled trial; SAE: serious adverse event; SF-36v2: Short Form 36-version 2; SOC: System Organ Class; WPAI: Work Productivity and Activity Impairment

The risk of bias in the results for the following outcomes was assessed as high: all-cause mortality (recorded under side effects), MACE (recorded under side effects), SAEs, severe AEs, and specific AEs (diarrhoea [PT, AEs], gastrointestinal disorders [SOC, SAEs] and vascular disorders [SOC, severe AEs]). Side effects were recorded up to 30 days after the last dose of the study medication. During the course of the study, 17% and 13% of patients, respectively, discontinued treatment. As the observations were linked to the treatment duration, there were incomplete observations for potentially informative reasons.

The risk of bias in the results relating to health-related quality of life outcomes (recorded using the SF-36v2 and CLDQ-NAFLD/NASH), operationalized as deterioration at Week 52, was assessed as high. The results were based on a complete-case analysis, which only included

patients with complete data. As a result, 25% to 28% of patients were not included in the analyses.

The risk of bias was not assessed for the outcome of activity impairment because suitable data were missing.

Although the risk of bias is low for the results on the outcome of discontinuation due to AEs, the certainty of results is reduced for this outcome. Premature treatment discontinuation for reasons other than AEs is a competing event for the outcome discontinuation due to AEs to be recorded. This means that, although AEs that would have led to discontinuation of therapy may occur after discontinuation for other reasons, the criterion discontinuation is no longer applicable to them. It was impossible to estimate how many AEs this affected.

2.3.3 Results

Table 8 summarizes the results of the comparison of resmetirom with the ACT in adult patients with non-cirrhotic MASH with moderate to advanced liver fibrosis (fibrosis stages F2 to F3). Where necessary, calculations conducted by the Institute are provided in addition to the data from the company's dossier.

Tables on common AEs, common SAEs, common severe AEs (CTCAE ≥ 3) and discontinuations due to AEs are presented in Appendix C.

Table 8: Results (mortality, morbidity, health-related quality of life and side effects, dichotomous) – RCT, direct comparison: resmetirom + concomitant therapy vs. placebo + concomitant therapy (multipage table)

Study	resmetirom		placebo		resmetirom vs. placebo
Outcome category	N	Patients with event n (%)	N	Patients with event n (%)	RR [95% CI]; p-value ^a
Outcome					
MAESTRO-NASH (data cut: 13 January 2023)					
Mortality					
All-cause mortality ^b	318	2 (0.6)	303	1 (0.3)	1.91 [0.17; 20.91]; 0.683
Morbidity					
MACE ^{c, d}	318	2 (0.6)	303	1 (0.3)	1.91 [0.17; 20.91]; 0.683
Cardiovascular death	ND	ND	ND	ND	ND
Non-fatal myocardial infarction	ND	ND	ND	ND	ND
Non-fatal stroke	ND	ND	ND	ND	ND
Health-related quality of life					
SF-36v2 (deterioration at Week 52) ^{e, f}					
Physical Component Summary (PCS)	238 ^g	16 (6.7 ^g)	223 ^g	9 (4.0 ^g)	1.67 [0.75; 3.69]; 0.248
Mental Component Summary (MCS)	238 ^g	19 (8.0 ^g)	223 ^g	23 (10.3 ^g)	0.77 [0.43; 1.38]; 0.531
Physical functioning	238 ^g	29 (12.2 ^g)	223 ^g	36 (16.1 ^g)	0.75 [0.48; 1.18]
Physical role functioning	238 ^g	40 (16.8 ^g)	223 ^g	43 (19.3 ^g)	0.87 [0.59; 1.28]
Physical pain	238 ^g	37 (15.5 ^g)	223 ^g	48 (21.5 ^g)	0.72 [0.49; 1.06]
General health perception	238 ^g	29 (12.2 ^g)	223 ^g	26 (11.7 ^g)	1.04 [0.63; 1.71]
Vitality	238 ^g	27 (11.3 ^g)	223 ^g	30 (13.5 ^g)	0.84 [0.52; 1.37]
Social functioning	238 ^g	38 (16.0 ^g)	223 ^g	31 (13.9 ^g)	1.14 [0.74; 1.77]
Emotional role functioning	238 ^g	40 (16.8 ^g)	223 ^g	52 (23.3 ^g)	0.72 [0.50; 1.04]
Mental well-being	238 ^g	34 (14.3 ^g)	223 ^g	31 (13.9 ^g)	1.02 [0.65; 1.61]

Table 8: Results (mortality, morbidity, health-related quality of life and side effects, dichotomous) – RCT, direct comparison: resmetirom + concomitant therapy vs. placebo + concomitant therapy (multipage table)

Study	resmetirom		placebo		resmetirom vs. placebo
Outcome category	N	Patients with event n (%)	N	Patients with event n (%)	RR [95% CI]; p-value ^a
Outcome					
CLDQ-NAFLD/NASH (deterioration at Week 52) ^{f, h}					
Total score	234 ^g	21 (9.0 ^g)	217 ^g	13 (6.0 ^g)	1.50 [0.77; 2.92]; 0.257
Abdominal symptoms	234 ^g	41 (17.5 ^g)	217 ^g	37 (17.1 ^g)	1.03 [0.69; 1.54]
Activity/energy	234 ^g	39 (16.7 ^g)	217 ^g	42 (19.4 ^g)	0.86 [0.58; 1.28]
Emotional health	234 ^g	24 (10.3 ^g)	217 ^g	32 (14.7 ^g)	0.70 [0.42; 1.14]
Fatigue	234 ^g	38 (16.2 ^g)	217 ^g	37 (17.1 ^g)	0.95 [0.63; 1.44]
Systemic symptoms	234 ^g	34 (14.5 ^g)	217 ^g	28 (12.9 ^g)	1.13 [0.71; 1.79]
Worry	234 ^g	18 (7.7 ^g)	217 ^g	18 (8.3 ^g)	0.93 [0.50; 1.74]
Side effects					
AEs ⁱ (supplementary information)	318	295 (92.8)	303	281 (92.7)	–
SAEs ⁱ	318	37 (11.6)	303	43 (14.2)	0.82 [0.54; 1.24]; 0.530
Severe AEs ^{i, j}	318	44 (13.8)	303	52 (17.2)	0.81 [0.56; 1.17]; 0.260
Discontinuation due to AEs ⁱ	318	25 (7.9)	303	16 (5.3)	1.49 [0.81; 2.73]; 0.226
Diarrhoea (PT, AEs)	318	93 (29.2)	303	49 (16.2)	1.81 [1.33; 2.46]; < 0.001
Gastrointestinal disorders (SOC, SAEs)	318	3 (0.9)	303	10 (3.3)	0.29 [0.08; 1.03]; 0.041
Vascular disorders (SOC, severe AEs ^j)	318	4 (1.3)	303	12 (4.0)	0.32 [0.10; 0.97]; 0.035
a. Institute's calculation (unconditional exact test [CSZ method according to [49]]). b. The results on all-cause mortality are based on the data on fatal AEs. c. Recorded as part of the AEs. d. Composite cardiovascular outcome consisting of the following components: cardiovascular death, non-fatal myocardial infarction and non-fatal stroke; after review by an adjudication committee. e. A score decrease of $\geq 15\%$ (PCS/MCS) from baseline is considered a clinically relevant deterioration (scale range: ND). f. Complete-case analysis; missing values are not imputed. g. Institute's calculations. h. A score decrease of $\geq 15\%$ from baseline is considered a clinically relevant deterioration (scale range: 1 to 7). i. Without taking into account the following disease-related events: hepatic cirrhosis, ascites, oesophageal varices, haemorrhage and hepatic encephalopathy. j. Operationalized as CTCAE grade ≥ 3. AE: adverse event; CI: confidence interval; CSZ: convexity, symmetry, z-score; CTCAE: Common Terminology Criteria for Adverse Events; MACE: major adverse cardiovascular event; MCS: Mental Component Summary; n: number of patients with (at least one) event; N: number of analysed patients; NAFLD: non-alcoholic fatty liver disease; NASH: non-alcoholic steatohepatitis; CLDQ-NAFLD/NASH: Chronic Liver Disease Questionnaire-NAFLD/NASH; PCS: Physical Component Summary; PT: Preferred Term; RCT: randomized controlled trial; RR: relative risk; SAE: serious adverse event; SF-36v2: Short Form 36-version 2; SOC: System Organ Class					

Mortality

In MAESTRO-NASH, deaths were recorded as part of the AEs. No statistically significant difference between treatment groups was found.

Morbidity

MACE

The MACE outcome (comprising the individual components of cardiovascular death, non-fatal myocardial infarction or non-fatal stroke) was recorded in the MAESTRO-NASH study as part of the side effects. No statistically significant difference between treatment groups was found.

Health-related quality of life

SF-36v2

For health-related quality of life recorded using the SF-36v2, there was no statistically significant difference between the treatment groups for either the PCS or the MCS.

CLDQ-NAFLD/NASH

For health-related quality of life recorded using the CLDQ-NAFLD/NASH, there was no statistically significant difference between treatment groups.

Side effects

SAEs, severe AEs, and discontinuation due to AEs

No statistically significant difference between treatment groups was found for any of the outcomes of SAEs, severe AEs, or discontinuation due to AEs.

Specific AEs

A statistically significant difference between the treatment groups to the disadvantage of resmetirom + concomitant therapy in comparison with placebo + concomitant therapy was found for the outcome of diarrhoea (PT, AEs). There was an effect modification by the characteristic of sex for this outcome, however (see Section 2.4). A statistically significant difference between the treatment groups to the disadvantage of resmetirom + concomitant therapy in comparison with placebo + concomitant therapy was found for men. For women, however, there was no statistically significant difference between the treatment groups.

A statistically significant difference between the treatment groups in favour of resmetirom + concomitant therapy in comparison with placebo + concomitant therapy was found for each of the outcomes of gastrointestinal disorders (SOC, SAEs) and vascular disorders (SOC, severe AEs).

2.4 Subgroups and other effect modifiers

The following subgroup characteristics were taken into account for this benefit assessment:

- Age (< 65 years versus ≥ 65 years)
- Sex (men versus women)
- Fibrosis stage at baseline (F2 versus F3)

The characteristics of sex and fibrosis stage at baseline were defined a priori.

No interaction tests or subgroup analyses were available for the outcomes in the health-related quality of life category (SF-36v2 and CLDQ-NAFLD/NASH), operationalized as deterioration at Week 52, or for the specific AEs of gastrointestinal disorders (SOC, SAEs) and vascular disorders (SOC, severe AEs).

Interaction tests are performed when at least 10 patients per subgroup are included in the analysis. For binary data, there must also be at least 10 events in at least one subgroup.

Only the results with an effect modification with a statistically significant interaction between treatment and subgroup characteristic (p-value < 0.05) are presented. In addition, subgroup results are only presented if there is a statistically significant and relevant effect in at least one subgroup.

The subgroup analyses conducted by the company used the Breslow-Day test for homogeneity. The company stated in the dossier that this was conducted on the basis of the (inverse) relative risk (RR). This test is suitable when using the effect measure odds ratio, but not for the effect measure RR. The company's subgroup results that were statistically significant at the 0.2 level were therefore checked. No relevant differences were found; the subgroup analyses carried out by the company using the Breslow-Day test are therefore presented below.

Table 9 presents the subgroup results of resmetirom + concomitant therapy in comparison with placebo + concomitant therapy.

Table 9: Subgroups (side effects, dichotomous) – RCT, direct comparison: resmetirom + concomitant therapy vs. placebo + concomitant therapy

Study Outcome Characteristic Subgroup	resmetirom		placebo		resmetirom vs. placebo	
	N	Patients with event n (%)	N	Patients with event n (%)	RR [95% CI]	p-value
MAESTRO-NASH						
Diarrhoea (PT, AEs)						
Sex						
Men	129	38 (29.5)	132	12 (9.1)	3.24 [1.77; 5.92]	< 0.001 ^a
Women	189	55 (29.1)	171	37 (21.6)	1.34 [0.94; 1.93]	0.105 ^a
Total					Interaction ^b :	0.017
a. Chi-square test.						
b. p-value based on the Breslow-Day test, with subgroup as a stratification factor.						
AE: adverse event; CI: confidence interval; n: number of patients with (at least one) event; N: number of analysed patients; PT: Preferred Term; RCT: randomized controlled trial; RR: relative risk						

There was an effect modification by the characteristic of sex for the outcome diarrhoea (PT, AEs). A statistically significant difference to the disadvantage of resmetirom + concomitant therapy in comparison with placebo + concomitant therapy was found for men. For women, however, there was no statistically significant difference between the treatment groups.

When applying the methods described above, there were no effect modifications for the outcomes and outcome operationalizations presented as supplementary information in Table 13 and Table 14 in Appendix B.

2.5 Summary of the results

Overall, there are advantages of resmetirom + concomitant therapy in comparison with placebo + concomitant therapy for the outcomes of gastrointestinal disorders (SOC, SAEs) and vascular disorders (SOC, severe AEs). For men, however there is a disadvantage of with resmetirom + concomitant therapy compared with placebo + concomitant therapy for the outcome diarrhoea (PT, AEs).

2.6 Summary

The data subsequently submitted by the company in the commenting procedure did not alter the conclusion on the added benefit of resmetirom drawn in dossier assessment A25-117.

The following Table 10 shows the result of the benefit assessment of resmetirom, taking into account dossier assessment A25-117 and this addendum.

Table 10: Resmetirom – probability and extent of added benefit

Therapeutic indication	ACT ^{a-d}	Probability and extent of added benefit
Adults with noncirrhotic metabolic dysfunction-associated steatohepatitis (MASH) with moderate to advanced liver fibrosis (fibrosis stages F2 to F3)	Optimized standard therapy for the treatment of comorbidities such as diabetes mellitus, hypertension, obesity and lipid metabolism disorders	Added benefit not proven
a. Presented is the ACT specified by the G-BA. b. According to the G-BA, it is assumed that individualized treatment of comorbidities such as diabetes mellitus, hypertension, obesity and lipid metabolism disorders is carried out in accordance with the current state of medical knowledge, taking into account the specific characteristics of the actual disease and the German health care context. According to the G-BA, it is assumed that the optimized standard therapy is provided in both treatment arms. According to the G-BA, standard therapy should also include non-drug measures such as recommendations for weight reduction and exercise, where indicated. The SmPC of resmetirom [50] also describes its administration in conjunction with diet and exercise. c. In individual cases, surgical intervention (e.g. bariatric surgery) may be indicated for severely obese people. This is not a standard treatment option in this therapeutic indication. d. According to the G-BA, a therapy adjustment can include both dose modifications and treatment switches or treatment initiation when new symptoms occur or existing symptoms worsen. The study protocol should explicitly allow for modifications to the basic/concomitant medication. If no optimization is performed, it must be documented or explained that any remaining treatment options are not suitable, are not tolerated or have been exhausted. ACT: appropriate comparator therapy; G-BA: Federal Joint Committee; MASH: metabolic dysfunction-associated steatohepatitis; SmPC: summary of product characteristics		

The G-BA decides on the added benefit.

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Appendix A Characteristics of the MASH cohort from the SLD registry

Table 11: Characteristics of the population – MASH cohort from the SLD registry

Registry Characteristic	Patients in the MASH cohort N = 360	
	< 100 kg N = 163	≥ 100 kg N = 197
SLD registry		
BMI > 30 [kg/m ²], n (%)	68 (41.7)	192 (97.5)
Liver stiffness [kPa], n (%)		
8.5 to 12	103 (64.8)	124 (64.2)
HbA1c [%], mean (SD)	6.9 (0.9)	7.2 (1.3)
Triglycerides [mg/dL], mean (SD)	200.6 (112.9)	219.9 (324.0)
LDL [mg/dL], mean (SD)	112.0 (43.5)	104.7 (36.1)
Type 2 diabetes mellitus, n (%)	83 (51.6)	105 (53.3)
Hypertension, n (%)	101 (62.0)	137 (69.5)
Dyslipidaemia, n (%)	N = 105 88 (83.8)	N = 148 114 (77.0)
BMI: body mass index; HbA1c: haemoglobin A1c; kPa: kilopascals; LDL: low-density lipoprotein; MASH: metabolic dysfunction-associated steatohepatitis; n: number of patients in the category; N: number of analysed patients; SD: standard deviation; SLD: steatotic liver disease		

Table 12: Treatment of comorbidities – MASH cohort from the SLD registry

Registry Comorbidity Comedication	Patients in the MASH cohort N = 360	
	N	n (%)
SLD registry		
Type 2 diabetes mellitus		
GLP-1 agonist	187	54 (28.9)
SGLT2 inhibitor	186	50 (26.9)
insulin	185	47 (25.4)
Hypertension		
ACE inhibitors	235	80 (34.0)
AT1 receptor antagonists	235	100 (42.6)
Calcium antagonists	236	82 (34.7)
Other antihypertensive therapy	234	29 (12.4)
Dyslipidaemia		
Statin therapy	202	61 (30.2)
Fibrates	202	2 (1.0)
ACE: angiotensin converting enzyme; AT1: angiotensin I; GLP-1: glucagon-like peptide 1; MASH: metabolic dysfunction-associated steatohepatitis; n: number of patients with treatment; N: number of analysed patients with the relevant comorbidity; SLD: steatotic liver disease; SGLT2: sodium-glucose cotransporter 2		

Appendix B Results presented as supplementary information

Table 13: Results (morbidity, dichotomous) – RCT, direct comparison: resmetirom + concomitant therapy vs. placebo + concomitant therapy (multipage table)

Study Outcome category Outcome	resmetirom		placebo		resmetirom vs. placebo
	N	Patients with event n (%)	N	Patients with event n (%)	RR [95% CI]; p-value
MAESTRO-NASH (data cut: 13 January 2023)					
Morbidity					
NASH resolution response					
1 ^{a, b}	315	70 (22.2)	300	17 (5.7)	3.92 [2.36; 6.50] ^c ; < 0.001 ^d
1 ^{a, b} + 0.5 ^{e, a}	315	117 (37.1) ^f	300	40 (13.3) ^f	2.79 [2.02; 3.85] ^c ; < 0.001 ^d
As observed ^g					
1 ^b	256	70 (27.3)	258	17 (6.6)	4.15 [2.51; 6.85] ^c ; < 0.001 ^d
1 ^b + 0.5 ^e	256	117 (45.7) ^f	258	40 (15.5) ^f	2.95 [2.15; 4.04] ^c ; < 0.001 ^d
NRI ^h					
1 ^b	318	70 (22.0)	303	17 (5.6)	3.92 [2.37; 6.51] ^c ; < 0.001 ^d
1 ^b + 0.5 ^e	318	117 (36.8) ^f	303	40 (13.2) ^f	2.79 [2.02; 3.85] ^c ; < 0.001 ^d
Fibrosis response					
1 ^{a, b}	315	57 (18.1)	300	27 (9.0)	2.01 [1.31; 3.09] ^c ; 0.001 ^d
1 ^{a, b} + 0.5 ^{e, a}	315	116 (36.8) ^f	300	61 (20.3) ^f	1.81 [1.39; 2.36] ^c ; < 0.001 ^d
As observed ^g					
1 ^b	256	57 (22.3)	258	27 (10.5)	2.13 [1.39; 3.25] ^c ; < 0.001 ^d
1 ^b + 0.5 ^e	256	116 (45.3) ^f	258	61 (23.6) ^f	1.92 [1.48; 2.48] ^c ; < 0.001 ^d
NRI ^h					
1 ^b	318	57 (17.9)	303	27 (8.9)	2.01 [1.31; 3.09] ^c ; 0.001 ^d
1 ^b + 0.5 ^e	318	116 (36.5) ^f	303	61 (20.1) ^f	1.81 [1.39; 2.37] ^c ; < 0.001 ^d
1-stage fibrosis response without worsening of a NAS component ^a					
1 ^b	315	52 (16.5)	300	20 (6.7)	2.48 [1.52; 4.05] ^c ; < 0.001 ^d
1 ^b + 0.5 ^e	315	111 (35.2) ^f	300	56 (18.7) ^f	1.89 [1.43; 2.50] ^c ; < 0.001 ^d
1-stage fibrosis response without worsening of activity ^a					
1 ^b	315	56 (17.8)	300	26 (8.7)	2.05 [1.32; 3.18] ^c ; < 0.001 ^d
1 ^b + 0.5 ^e	315	116 (36.8) ^f	300	61 (20.3) ^f	1.81 [1.39; 2.36] ^c ; < 0.001 ^d

Table 13: Results (morbidity, dichotomous) – RCT, direct comparison: resmetirom + concomitant therapy vs. placebo + concomitant therapy (multipage table)

Study Outcome category Outcome	resmetirom		placebo		resmetirom vs. placebo
	N	Patients with event n (%)	N	Patients with event n (%)	RR [95% CI]; p-value
a. Patients who had no valid biopsy within the time window of Week 52 or who experienced an event of the composite outcome of the final analysis (e.g. liver transplantation, death) prior to their Week 52 biopsy were considered non-responders. b. A value of 1 means that Pathologist A and Pathologist B classified the patient as a responder (1,1). c. Institute's calculations, CI asymptotic. d. Institute's calculation (unconditional exact test [CSZ method according to [49]]). e. A value of 0.5 means that one pathologist classified the patient as a responder and the other as a non-responder (1,0 or 0,1). f. Institute's calculation. g. Patients who experienced an event of the composite outcome of the final analysis (e.g. liver transplantation, death) prior to their Week 52 biopsy were considered non-responders. The analysis includes all patients with valid biopsies taken within the specified time window at baseline and at Week 52. h. All missing data, including any visits outside the specified time window in Week 52 due to COVID-19, were considered non-responders. Patients who had no valid biopsy within the time window of Week 52 or who experienced an event of the composite outcome of the final analysis (e.g. liver transplantation, death) prior to their Week 52 biopsy were considered non-responders. CI: confidence interval; COVID: coronavirus disease; n: number of patients with (at least one) event; N: number of analysed patients; NAFLD: non-alcoholic fatty liver disease; NAS: NAFLD activity score; NASH: non-alcoholic steatohepatitis; NRI: non-responder imputation; RCT: randomized controlled trial; RR: relative risk					

Table 14: Results (health-related quality of life, dichotomous) – RCT, direct comparison: resmetirom + concomitant therapy vs. placebo + concomitant therapy

Study Outcome category Outcome	resmetirom		placebo		resmetirom vs. placebo
	N	Patients with event n (%)	N	Patients with event n (%)	RR [95% CI]; p-value
MAESTRO-NASH (data cut: 13 January 2023)					
Health-related quality of life					
SF-36v2 (improvement at Week 52) ^a					
Physical Component Summary (PCS)	318	19 (6.0)	303	14 (4.6)	0.77 [0.39; 1.51] ^b ; 0.533 ^c
Mental Component Summary (MCS)	318	20 (6.3)	303	17 (5.6)	0.89 [0.48; 1.67] ^b ; 0.776 ^c
Physical functioning	318	40 (12.6)	303	37 (12.2)	0.97 [0.64; 1.48] ^b
Physical role functioning	318	33 (10.4)	303	38 (12.5)	1.21 [0.78; 1.87] ^b
Physical pain	318	46 (14.5)	303	53 (17.5)	1.21 [0.84; 1.74] ^b
General health perception	318	53 (16.7)	303	45 (14.9)	0.89 [0.62; 1.28] ^b
Vitality	318	30 (9.4)	303	36 (11.9)	1.26 [0.80; 1.99] ^b
Social functioning	318	36 (11.3)	303	25 (8.3)	0.73 [0.45; 1.18] ^b
Emotional role functioning	318	49 (15.4)	303	38 (12.5)	0.81 [0.55; 1.21] ^b
Mental well-being	318	33 (10.4)	303	40 (13.2)	1.27 [0.82; 1.96] ^b
CLDQ-NAFLD/NASH (improvement at Week 52) ^d					
Total score	318	22 (6.9)	303	26 (8.6)	1.24 [0.72; 2.14] ^b ; 0.531 ^c
Abdominal symptoms	318	48 (15.1)	303	54 (17.8)	1.18 [0.83; 1.68] ^b
Activity/energy	318	34 (10.7)	303	23 (7.6)	0.71 [0.43; 1.18] ^b
Emotional health	318	33 (10.4)	303	26 (8.6)	0.83 [0.51; 1.35] ^b
Fatigue	318	36 (11.3)	303	38 (12.5)	1.11 [0.72; 1.70] ^b
Systemic symptoms	318	20 (6.3)	303	28 (9.2)	1.47 [0.85; 2.55] ^b
Worry	318	57 (17.9)	303	53 (17.5)	0.98 [0.70; 1.37] ^b
a. A score increase of $\geq 15\%$ (PCS/MCS) from baseline is considered a clinically relevant improvement (scale range: ND). b. The company indicates the inverse direction of effect. c. Institute's calculation (unconditional exact test [CSZ method according to [49]]). d. A score increase of $\geq 15\%$ from baseline is considered a clinically relevant improvement (scale range: 1 to 7). CI: confidence interval; CLDQ: Chronic Liver Disease Questionnaire; CSZ: convexity, symmetry, z-score; MCS: Mental Component Summary; n: number of patients with (at least one) event; N: number of analysed patients; NAFLD: non-alcoholic fatty liver disease; NASH: non-alcoholic steatohepatitis; PCS: Physical Component Summary; RCT: randomized controlled trial; RR: relative risk; SF-36v2: Short Form 36-version 2					

Appendix C Results on side effects

For AEs, SAEs and severe AEs (e.g. CTCAE grade ≥ 3), the following tables present the proportion of events for System Organ Classes (SOCs) and Preferred Terms (PTs) according to the Medical Dictionary for Regulatory Activities (MedDRA), each on the basis of the following criteria:

- AEs (irrespective of severity grade): events that occurred in at least 10% of patients in one study arm
- Severe AEs (e.g. CTCAE grade ≥ 3) and SAEs: events that occurred in at least 5% of patients in one study arm
- Additionally, for all events irrespective of severity: events that occurred in at least 10 patients and in at least 1% of patients in one study arm

For the outcome of discontinuation due to AEs, a complete presentation of all events (SOCs/PTs) that resulted in discontinuation is provided.

Table 15: Common AEs^a – RCT, direct comparison: resmetirom + concomitant therapy vs. placebo + concomitant therapy (multipage table)

Study SOC ^b PT ^b	Patients with event n (%)	
	resmetirom N = 318	placebo N = 303
MAESTRO-NASH		
Overall AE rate	296 (93.1)	283 (93.4)
Gastrointestinal disorders	193 (60.7)	172 (56.8)
Diarrhoea	93 (29.2)	49 (16.2)
Nausea	64 (20.1)	39 (12.9)
Abdominal pain upper	24 (7.5)	32 (10.6)
Abdominal pain	29 (9.1)	19 (6.3)
Vomiting	29 (9.1)	17 (5.6)
Constipation	26 (8.2)	18 (5.9)
Abdominal distension	13 (4.1)	16 (5.3)
Toothache	12 (3.8)	11 (3.6)
Gastrooesophageal reflux disease	14 (4.4)	8 (2.6)
Abdominal discomfort	4 (1.3)	13 (4.3)
Haemorrhoids	4 (1.3)	11 (3.6)

Table 15: Common AEs^a – RCT, direct comparison: resmetirom + concomitant therapy vs. placebo + concomitant therapy (multipage table)

Study SOC ^b PT ^b	Patients with event n (%)	
	resmetirom N = 318	placebo N = 303
Infections and infestations	177 (55.7)	171 (56.4)
COVID-19	81 (25.5)	72 (23.8)
Urinary tract infection	30 (9.4)	29 (9.6)
Upper respiratory tract infection	20 (6.3)	16 (5.3)
Nasopharyngitis	19 (6.0)	15 (5.0)
Sinusitis	13 (4.1)	15 (5.0)
Bronchitis	9 (2.8)	13 (4.3)
Musculoskeletal and connective tissue disorders	135 (42.5)	126 (41.6)
Arthralgia	47 (14.8)	43 (14.2)
Back pain	30 (9.4)	37 (12.2)
Muscle spasms	17 (5.3)	20 (6.6)
Pain in extremity	11 (3.5)	24 (7.9)
Myalgia	12 (3.8)	11 (3.6)
Metabolism and nutrition disorders	91 (28.6)	79 (26.1)
Diabetes mellitus inadequate control	37 (11.6)	29 (9.6)
Type 2 diabetes mellitus	12 (3.8)	10 (3.3)
Decreased appetite	10 (3.1)	4 (1.3)
Skin and subcutaneous tissue disorders	92 (28.9)	77 (25.4)
Pruritus	30 (9.4)	23 (7.6)
Rash	24 (7.5)	12 (4.0)
Alopecia	4 (1.3)	10 (3.3)
Nervous system disorders	78 (24.5)	87 (28.7)
Headache	32 (10.1)	24 (7.9)
Dizziness	19 (6.0)	15 (5.0)
Injury, poisoning and procedural complications	75 (23.6)	82 (27.1)
Procedural pain	20 (6.3)	19 (6.3)
Fall	9 (2.8)	16 (5.3)
Contusion	2 (0.6)	10 (3.3)
General disorders and administration site conditions	64 (20.1)	85 (28.1)
Fatigue	30 (9.4)	31 (10.2)
Pyrexia	8 (2.5)	15 (5.0)
Oedema peripheral	11 (3.5)	10 (3.3)

Table 15: Common AEs^a – RCT, direct comparison: resmetirom + concomitant therapy vs. placebo + concomitant therapy (multipage table)

Study SOC ^b PT ^b	Patients with event n (%)	
	resmetirom N = 318	placebo N = 303
Investigations	61 (19.2)	69 (22.8)
SARS-CoV-2 test positive	6 (1.9)	10 (3.3)
Respiratory, thoracic and mediastinal disorders	51 (16.0)	50 (16.5)
Cough	14 (4.4)	15 (5.0)
Oropharyngeal pain	9 (2.8)	10 (3.3)
Psychiatric disorders	34 (10.7)	36 (11.9)
Insomnia	8 (2.5)	14 (4.6)
Anxiety	9 (2.8)	11 (3.6)
Depression	13 (4.1)	5 (1.7)
Vascular disorders	31 (9.7)	39 (12.9)
Hypertension	17 (5.3)	23 (7.6)
Hepatobiliary disorders	30 (9.4)	33 (10.9)
Hepatic cirrhosis	19 (6.0)	23 (7.6)
Eye disorders	22 (6.9)	30 (9.9)
Renal and urinary disorders	25 (7.9)	27 (8.9)
Blood and lymphatic system disorders	19 (6.0)	27 (8.9)
Anaemia	10 (3.1)	12 (4.0)
Neoplasms benign, malignant and unspecified (incl cysts and polyps)	21 (6.6)	21 (6.9)
Reproductive system and breast disorders	22 (6.9)	18 (5.9)
Cardiac disorders	19 (6.0)	19 (6.3)
Immune system disorders	22 (6.9)	15 (5.0)
Immunisation reaction	10 (3.1)	4 (1.3)
Ear and labyrinth disorders	17 (5.3)	12 (4.0)
a. Events that occurred in ≥ 10 patients in at least one study arm. b. MedDRA version 25.0; SOC and PT notation taken without adaptation from the comments provided by the company. AE: adverse event; MedDRA: Medical Dictionary for Regulatory Activities; n: number of patients with at least one event; N: number of analysed patients; PT: Preferred Term; RCT: randomized controlled trial; SOC: System Organ Class		

Table 16: Common SAEs^a – RCT, direct comparison: resmetirom + concomitant therapy vs. placebo + concomitant therapy

Study SOC ^b	Patients with event n (%)	
	resmetirom N = 318	placebo N = 303
MAESTRO-NASH		
Overall SAE rate	37 (11.6)	43 (14.2)
Infections and infestations	7 (2.2)	16 (5.3)
Gastrointestinal disorders	3 (0.9)	10 (3.3)
a. Events that occurred in ≥ 10 patients in at least one study arm. b. MedDRA version 25.0; SOC notation taken without adaptation from the comments provided by the company. MedDRA: Medical Dictionary for Regulatory Activities; n: number of patients with at least one event; N: number of analysed patients; RCT: randomized controlled trial; SAE: serious adverse event; SOC: System Organ Class		

Table 17: Common severe AEs (CTCAE ≥ 3)^a – RCT, direct comparison: resmetirom + concomitant therapy vs. placebo + concomitant therapy

Study SOC ^b	Patients with event n (%)	
	resmetirom N = 318	placebo N = 303
MAESTRO-NASH		
Overall rate of severe AEs (CTCAE grade ≥ 3)	48 (15.1)	55 (18.2)
Infections and infestations	7 (2.2)	14 (4.6)
Injury, poisoning and procedural complications	10 (3.1)	6 (2.0)
Vascular disorders	4 (1.3)	12 (4.0)
a. Events that occurred in ≥ 10 patients in at least one study arm. b. MedDRA version 25.0; SOC notation taken without adaptation from the comments provided by the company. AE: adverse event; CTCAE: Common Terminology Criteria for Adverse Events; MedDRA: Medical Dictionary for Regulatory Activities; n: number of patients with at least one event; N: number of analysed patients; RCT: randomized controlled trial; SOC: System Organ Class		

Table 18: Discontinuations due to AEs – RCT, direct comparison: resmetirom + concomitant therapy vs. placebo + concomitant therapy (multipage table)

Study SOCa PTa	Patients with event n (%)	
	resmetirom N = 318	placebo N = 303
MAESTRO-NASH		
Overall rate of discontinuations due to AEs	30 (9.4)	21 (6.9)
Gastrointestinal disorders	10 (3.1)	3 (1.0)
Diarrhoea	5 (1.6)	1 (0.3)
Nausea	3 (0.9)	0 (0)
Abdominal pain	1 (0.3)	1 (0.3)
Vomiting	1 (0.3)	1 (0.3)
Abdominal pain upper	0 (0)	1 (0.3)
Dyspepsia	1 (0.3)	0 (0)
Hepatobiliary disorders	5 (1.6)	5 (1.7)
Hepatic cirrhosis	5 (1.6)	5 (1.7)
General disorders and administration site conditions	4 (1.3)	3 (1.0)
Fatigue	2 (0.6)	1 (0.3)
Chest discomfort	0 (0)	1 (0.3)
Death	0 (0)	1 (0.3)
Multiple organ dysfunction syndrome	1 (0.3)	0 (0)
Prosthetic cardiac valve thrombosis	1 (0.3)	0 (0)
Skin and subcutaneous tissue disorders	5 (1.6)	2 (0.7)
Pruritus	1 (0.3)	1 (0.3)
Rash	1 (0.3)	1 (0.3)
Urticaria	2 (0.6)	0 (0)
Hyperhidrosis	0 (0)	1 (0.3)
Psoriasis	1 (0.3)	0 (0)
Nervous system disorders	2 (0.6)	3 (1.0)
Headache	1 (0.3)	1 (0.3)
Hypoglycaemic coma	1 (0.3)	0 (0)
Neuromyopathy	0 (0)	1 (0.3)
Parkinsonism	0 (0)	1 (0.3)
Cardiac disorders	2 (0.6)	1 (0.3)
Angina pectoris	0 (0)	1 (0.3)
Intracardiac thrombus	1 (0.3)	0 (0)
Ventricular extrasystoles	1 (0.3)	0 (0)

Table 18: Discontinuations due to AEs – RCT, direct comparison: resmetirom + concomitant therapy vs. placebo + concomitant therapy (multipage table)

Study SOCa PTa	Patients with event n (%)	
	resmetirom N = 318	placebo N = 303
Musculoskeletal and connective tissue disorders	1 (0.3)	2 (0.7)
Arthralgia	1 (0.3)	1 (0.3)
Bone pain	1 (0.3)	0 (0)
Osteitis deformans	0 (0)	1 (0.3)
Metabolism and nutrition disorders	2 (0.6)	0 (0)
Obesity	2 (0.6)	0 (0)
Neoplasms benign, malignant and unspecified (incl cysts and polyps)	1 (0.3)	1 (0.3)
Bladder transitional cell carcinoma	0 (0)	1 (0.3)
Hepatocellular carcinoma	1 (0.3)	0 (0)
Immune system disorders	0 (0)	1 (0.3)
Anaphylactic shock	0 (0)	1 (0.3)
Infections and infestations	1 (0.3)	0 (0)
Pneumonia	1 (0.3)	0 (0)
Septic shock	1 (0.3)	0 (0)
Injury, poisoning and procedural complications	1 (0.3)	0 (0)
Fall	1 (0.3)	0 (0)
Investigations	0 (0)	1 (0.3)
Hepatic enzyme increased	0 (0)	1 (0.3)
Renal and urinary disorders	1 (0.3)	0 (0)
Renal impairment	1 (0.3)	0 (0)
Vascular disorders	0 (0)	1 (0.3)
Poor venous access	0 (0)	1 (0.3)
a. MedDRA version 25.0; SOC and PT notation taken without adaptation from the comments provided by the company.		
AE: adverse event; MedDRA: Medical Dictionary for Regulatory Activities; n: number of patients with at least one event; N: number of analysed patients; PT: Preferred Term; RCT: randomized controlled trial; SOC: System Organ Class		