

Resmetirom (metabolic dysfunction-associated steatohepatitis)

Benefit assessment according to §35a SGB V¹

A decorative horizontal bar composed of 20 squares of varying shades of blue and grey. The word 'EXTRACT' is centered in white text on a dark blue rectangular background that spans the width of the bar.

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Patient and family involvement

The questionnaire on the disease and its treatment was answered by one person.

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Part I: Benefit assessment

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I List of abbreviations

Abbreviation	Meaning
ACT	appropriate comparator therapy
AE	adverse event
BMI	body mass index
ELF	enhanced liver fibrosis
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
MASH	metabolic dysfunction-associated steatohepatitis
MASLD	metabolic dysfunction-associated steatotic liver disease
MELD	Model for End-Stage Liver Disease
MRE	magnetic resonance elastography
MRI-PDFF	magnetic resonance imaging proton density fat fraction
NAS	non-alcoholic fatty liver disease activity score
PCSK9	proprotein convertase subtilisin/kexin type 9
PRO-C3	N-terminal type III collagen propeptide
RCT	randomized controlled trial
SAE	serious adverse event
SGB	Sozialgesetzbuch (Social Code Book)
SGLT2	sodium-glucose cotransporter 2
VCTE	vibration-controlled transient elastography

I 1 **Executive summary of the benefit assessment**

Background

In accordance with §35a Social Code Book V, the Federal Joint Committee (G-BA) commissioned the Institute for Quality and Efficiency in Health Care (IQWiG) to assess the benefit of the drug resmetirom. The assessment is based on a dossier compiled by the pharmaceutical company (hereinafter referred to as the ‘company’). The dossier was sent to IQWiG on 15 September 2025.

Research question

The aim of this report is to assess the added benefit of resmetirom in conjunction with diet and exercise, in comparison with the appropriate comparator therapy (ACT), in adult patients with noncirrhotic metabolic dysfunction-associated steatohepatitis (MASH) with moderate to advanced liver fibrosis (fibrosis stages F2 to F3).

The research question shown in Table 2 was defined in accordance with the ACT specified by the G-BA.

Table 2: Research question for the benefit assessment of resmetirom

Therapeutic indication	ACT ^{a-d}
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
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 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 company followed the ACT specified by the G-BA. The assessment was conducted by means of patient-relevant outcomes on the basis of the data provided by the company in the dossier.

For the derivation of an added benefit, randomized controlled trials (RCTs) with an event-driven study duration on longer-term outcomes such as progression to symptomatic hepatic cirrhosis or the avoidance or delay of liver transplantation are preferable in this therapeutic indication. The review of the completeness of the study pool was based on a minimum study duration of 52 weeks. However, it is questionable whether results on patient-relevant outcomes can be meaningfully interpreted in this period, and thus allow positive and negative effects to be weighed up to ultimately permit a conclusion on the added benefit of resmetirom. This deviated from the company's inclusion criteria, which included studies with a duration of at least 24 weeks.

Study pool

The company identified the RCTs MAESTRO-NASH (MGL-3196-11), MAESTRO-NAFLD-1 (MGL-3196-14) and the study MGL-3196-05 on the comparison of resmetirom versus placebo. For the benefit assessment, the company used the MAESTRO-NASH study and presented the other 2 studies as supportive information.

The review of the completeness of the study pool did not identify any further studies comparing resmetirom with the ACT for this benefit assessment.

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. Irrespective of this, due to inappropriate analyses of the subpopulations presented in the dossier, no suitable data were available from either study for the benefit assessment comparing resmetirom with the comparator therapy specified by the G-BA. The data from MAESTRO-NASH and MAESTRO-NAFLD-1 were therefore not used for the derivation of the added benefit of resmetirom in this benefit assessment.

The study MGL-3196-05 with a treatment period of 36 weeks was too short in this therapeutic indication for the assessment of the added benefit of resmetirom and was therefore not used for the derivation of the added benefit.

The section below describes the evidence provided by the company, and then justifies why the data provided were unsuitable for the benefit assessment.

MAESTRO-NASH

Study characteristics

The MAESTRO NASH study is an ongoing, double-blind RCT comparing resmetirom with placebo. A total of 1050 patients were included in the study and randomly assigned in a 1:1:1 ratio to treatment with resmetirom 80 mg (N = 352), resmetirom 100 mg (N = 349) or the placebo arm (N = 349). Randomization was stratified according to type 2 diabetes mellitus status (yes versus no) and biopsy-based fibrosis stage (F1 versus F2 versus F3).

In the study, patients underwent a prescreening and a multi-stage screening procedure. After screening, patients were included in the study if they had a diagnosis of MASH with liver fibrosis (fibrosis stages F1 to F3) confirmed by a recent liver biopsy (≤ 6 months) and a non-alcoholic fatty liver disease activity score (NAS) of at least 4, with a score of at least 1 in each of the NAS components of steatosis (0 to 3 points), ballooning (0 to 3 points) and lobular inflammation (0 to 2 points).

Patients with a haemoglobin A1c (HbA1c) > 9 , weight gain or loss of $\geq 5\%$ within 12 weeks prior to randomization, active hyperthyroidism or untreated clinical hypothyroidism, or a history of bariatric surgery were excluded.

In both study arms, the resmetirom doses used in MAESTRO-NASH deviated from the specifications of the summary of product characteristics (SmPC) for some of the patients in the included population. A placebo was used in the control arm. At study start, all patients in the 3 study arms additionally received lifestyle counselling, which included diet and exercise recommendations, by the investigator. In addition, stable medication for the treatment of comorbidities (e.g. diabetes mellitus, hypertension or hypothyroidism) could be continued during the study. The treatment duration with the study medication was up to 54 months.

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 information in Module 4 A, secondary outcomes at Week 52 and Month 54 were recorded in the categories of morbidity, health-related quality of life and side effects. A liver biopsy was conducted at Week 52 and Month 54 for outcome recording.

Notes on the patient population

In the study, the diagnosis of MASH with fibrosis (F1, F2 or F3) had to be confirmed by a recent liver biopsy. This is in line with the recommendation of the European Medicines Agency (EMA). The amendment to the S2k guideline contains various information on the need to conduct a liver biopsy in all patients with suspected MASH, however. On the one hand, it is described that a biopsy-based confirmation is not necessary for the treatment decision. On the other hand, the guideline points out the limitations of non-invasive procedures in the classification of the relevant patient population. Overall, the inclusion criteria selected by the company appeared sufficient to identify the patient population relevant for this benefit assessment.

Notes on study duration

The planned study duration of MAESTRO-NASH is 54 months. This analysis date has not yet been reached. For the benefit assessment, the company presented the prespecified analyses at Week 52 currently available for various outcomes on morbidity and health-related quality of life. The analyses of side effects, on the other hand, represented a longer period of up to 3.5 years.

Even though the review of the completeness of the study pool in the given therapeutic indication was based on a minimum study duration of 52 weeks, it is questionable overall whether results on patient-relevant outcomes can be meaningfully interpreted with a study duration of 52 weeks and thus allow the positive and negative effects to be weighed up, and ultimately allow a conclusion to be drawn on the added benefit of resmetirom. Longer studies are needed to adequately investigate, for example, the progression to symptomatic hepatic cirrhosis, the avoidance or delay of liver transplantation or all-cause mortality. Therefore, the analyses presented for Week 52 were potentially too short to draw a conclusion on the added benefit of resmetirom.

Data cut-off

According to the company, the analyses presented in the dossier were based on the data cut of 13 January 2023 (Food and Drug Administration [FDA] 120-day safety update), and for outcomes in the morbidity and health-related quality of life categories, 31 July 2022 was still the most recent analysis date by definition of the analysis populations.

Assessment of the data presented for MAESTRO-NASH

Appropriate comparator therapy

Although the interventions in the MAESTRO-NASH study represented the lifestyle counselling recommended in the guidelines, they were not designed to optimize standard therapy for accompanying diseases during the course of the study. Drug treatment of diabetes mellitus and dyslipidaemia in particular was restricted in the study. Patients could only be included if their concomitant treatment had been administered at a stable dose for a specified period prior to randomization. Furthermore, the study protocol prohibited a dose increase or the initiation of glucagon-like peptide-1 (GLP-1) therapy within the first 52 weeks, which according to various guidelines is a central component in the treatment of type 2 diabetes mellitus with concomitant cardiovascular disease or overweight/obesity. There was no information on whether and, if so, to what extent, modifications were made to antidiabetic therapy during the course of the study.

Furthermore, the use of statins in the study was restricted with regard to the permitted drugs and their maximum dose. For the statins to be used, a maximum of around half of the authorized maximum dose of the respective drugs was allowed. The company explained in

Module 4 A that the dosage of statins had to be reduced in the MAESTRO-NASH study due to the common metabolic pathway of resmetirom and statins. The dosage restrictions for statins also applied to the patients in the placebo arm. It was not possible to assess the relevance of the restricted dosing options based on the available data.

Overall, there was no information in Module 4 A that any remaining treatment options were not suitable for the patients, were not tolerated or had been exhausted. Based on the information available, it was therefore not possible to conclusively assess the extent to which the optimization of standard therapy was ensured in the study despite the limitations described.

Analyses of the presented subpopulation not suitable

For the benefit assessment, the company presented analyses based on a subpopulation of the MAESTRO-NASH study. To form the subpopulation, the company considered patients with moderate to advanced liver fibrosis (stage F2 or F3) from all 3 study arms. In addition, from the 2 resmetirom arms, the company only considered patients who received an approval-compliant resmetirom dosage based on their body weight. For the control arm, the company did not make any additional adjustments to the patient population with regard to body weight. For the comparison of resmetirom and placebo, the company used the weight-adjusted subpopulations of the resmetirom arms (80 mg resmetirom: patients < 100 kg body weight; 100 mg resmetirom: patients ≥ 100 kg body weight) and compared these separately with the entire control arm (weight-independent; contains both patients with a body weight < 100 kg and ≥ 100 kg).

The comparison of the weight-adjusted subpopulations of the resmetirom arms with the entire control arm presented by the company was not appropriate. Due to the selection criterion (weight) differently applied in the study arms, it was not ensured that the structural equality between the study arms, which was achieved through the randomized allocation of patients to the study arms, was maintained. It would have been useful to carry out an analysis in which the same weight-adjusted subdivision was made for the control arm (< 100 kg or ≥ 100 kg body weight) and the effect estimate was compared with the corresponding weight-adjusted resmetirom arm. In order to draw conclusions on the added benefit, a meta-analytical analysis of the 2 effect estimates would be generally required.

Irrespective of this, an analysis in which the 2 subpopulations of the resmetirom arms were pooled as a common patient population and analysed versus the placebo arm would have been more useful overall. A prerequisite for this would have been comparable proportions of patients with a body weight < 100 kg and ≥ 100 kg in the placebo arm and in the pooled resmetirom arm. Corresponding information on body weight at baseline (< 100 kg versus

≥ 100 kg) was not available in the dossier. However, taking into account the 1:1:1 randomization in the study, a comparable distribution was assumed.

Overall, the data presented by the company were not suitable for the benefit assessment for the reasons mentioned.

Further notes on the data presented by the company

The assessment of the added benefit was based on the impact on patient-relevant outcomes that allow to determine the changes related to disease and treatment. These include outcomes in the categories of mortality, morbidity, health-related quality of life and side effects. It should be noted that not all outcomes presented by the company in the dossier were assessed as patient-relevant per se and that no surrogate validations were presented.

Summary

A conclusive assessment of the relevance of MAESTRO-NASH for the benefit assessment was not possible based on the available information. It was unclear to what extent an optimized standard therapy was ensured in the study due to the previously described limitations in the treatment of accompanying diseases. Irrespective of this, the analyses of the subpopulation considered by the company presented for the benefit assessment were not appropriate. This means that no suitable data were available for the comparison of resmetirom with the G-BA's comparator therapy.

MAESTRO-NAFLD-1

Study characteristics

The MAESTRO-NAFLD-1 study consists of a double-blind randomized comparison of the 3 study arms resmetirom 80 mg, resmetirom 100 mg and placebo, as well as several open-label study arms. The company only presented results of the double-blind study arms in Module 4 A. The company's approach was appropriate; for this reason, the open-label arms are not considered further for the benefit assessment. A total of 972 patients were included in the double-blind comparison and randomly assigned in a 1:1:1 ratio to treatment with resmetirom 80 mg (N = 327), resmetirom 100 mg (N = 325) or the placebo arm (N = 320).

The study population comprised patients with a suspected or confirmed diagnosis of MASLD/MASH based on findings in the patient's medical history. According to the inclusion criteria, steatosis and fibrosis could be determined either based on non-invasive procedures (Fibroscan or MRE with MRI-PDFF) or liver biopsy (< 2 years). In principle, patients with fibrosis stage F1 to F3 could be included.

The resmetirom doses used in MAESTRO-NAFLD-1 deviated from the specifications of the SmPC for some of the patients in the included population. A placebo was used in the control arm. The treatment duration with the study medication was up to 52 weeks. At study start

and in the course of the study, all patients received lifestyle counselling, which included diet and exercise recommendations, by the investigator. In addition, stable medication for the treatment of comorbidities (e.g. diabetes mellitus, hypertension or hypothyroidism) could be continued during the study.

The primary outcome of the study was the incidence of adverse events within the treatment period of 52 weeks and a 30-day follow-up. According to the information in Module 4 A, secondary outcomes were recorded in the categories of morbidity, health-related quality of life and side effects.

Notes on the patient population

The MAESTRO-NAFLD-1 study also included patients whose diagnosis was based solely on non-invasive procedures.

Information varies on the need to conduct a liver biopsy in all patients with suspected MASH. For example, the EMA requires a liver biopsy to be conducted for the inclusion of patients in clinical studies to confirm an existing MASH. On the one hand, the amendment to the S2k guideline lists non-invasive procedures as an alternative to biopsy-confirmed MASH with liver fibrosis (F2 and F3). On the other hand, the guideline points out incorrect risk stratification due to insufficiently reliable non-invasive procedures.

Notes on study duration

The study duration of MAESTRO-NAFLD-1 was 52 weeks. It is questionable whether results on patient-relevant outcomes can be meaningfully interpreted in this period, and thus allow positive and negative effects to be weighed up to ultimately permit a conclusion on the added benefit of resmetirom (see also explanation regarding MAESTRO-NASH).

Assessment of the supportive data presented for the MAESTRO-NAFLD-1 study

The company presented results of a subpopulation of the MAESTRO-NAFLD-1 study as supporting information.

Patients with fibrosis stage F2 or F3 who received a resmetirom dosage corresponding to their body weight, in compliance with the SmPC, were to be considered in this subpopulation. According to the company, it therefore determined the fibrosis stage post hoc on the basis of the VCTE measured at baseline using Fibroscan to form the subpopulation. According to the company, > 8.5 kPa was set as a cut-off value on the basis of literature data and feedback from experts.

The cut-off value used by the company deviated from the recommendations in the amendment to the S2k guideline. According to the guideline, significant fibrosis (F2 or F3) can be assumed with a VCTE-measured liver stiffness of 10 to 19.9 kPa. In patients with a liver

stiffness (VCTE) of 8 to 10 kPa, the measurement should be repeated after 6 months. It was therefore not sufficiently certain whether resmetirom therapy was indicated in the patients included in the subpopulation.

Appropriate comparator therapy

The restrictions on the treatment of comorbidities in the MAESTRO-NASH study described above also largely applied to the MAESTRO-NAFLD-1 study. However, if medically indicated, it was possible in the MAESTRO-NAFLD-1 study to make adjustments to the antidiabetic treatment after randomization (with the exception of GLP-1 agonists). Overall, there was no information in Module 4 A that any remaining treatment options were not suitable for the patients, were not tolerated or had been exhausted. Based on the information available, it was therefore not possible to conclusively assess the extent to which the optimization of standard therapy was ensured in the study despite the limitations described.

Subpopulation presented by the company as supportive information

The analyses of the subpopulation presented by the company were unsuitable. As in the MAESTRO-NASH study, and in accordance with the specifications of the SmPC, the company considered all patients with a body weight < 100 kg from the 80 mg resmetirom arm and all patients with a body weight ≥ 100 kg from the 100 mg resmetirom arm. For the control arm, the company did not make any additional adjustments to the patient population with regard to body weight. For the comparison of resmetirom versus placebo, the company used the weight-adjusted subpopulations of the resmetirom arms and compared them separately with the entire control arm. This approach was not appropriate.

Overall, it should be noted that the subpopulation used by the company for supportive purposes comprised 9 patients in the 80 mg resmetirom arm, 15 in the 100 mg resmetirom arm and 29 in the placebo arm. Even assuming that, after clarification of the uncertainties described, this was a relevant study for the given research question, it was assumed that the influence of the results of the subpopulation on the results of this benefit assessment was low.

Summary

A conclusive assessment of the relevance of MAESTRO-NAFLD-1, and of the subpopulation presented by the company in the dossier, for the benefit assessment was not possible based on the available information.

MGL-3196-05

Study characteristics

MGL-3196-05 is a completed double-blind RCT on the comparison of resmetirom with placebo. A total of 125 patients were included in the study and randomly assigned in a 2:1 ratio to the intervention arm (N = 84) or the control arm (N = 41).

Adult patients with biopsy-confirmed MASH defined as NAS ≥ 4 with at least a score of 1 in each of the components steatosis, ballooning and lobular inflammation and liver fibrosis (stage F1 to F3) were included.

In contrast to the specifications in the SmPC, in the study, all patients in the intervention arm received 80 mg resmetirom per day, regardless of body weight. A placebo was used in the control arm. In addition to the study medication, nutritional and lifestyle counselling took place during the visits in both study arms.

The primary outcome of study MGL-3196-05 was the percentage change in liver fat content (MRI-PDFF) at Week 12 from baseline. According to the information in Module 4 A, secondary outcomes were recorded in the categories of morbidity, health-related quality of life and side effects.

Assessment of the MGL-3196-05 study presented by the company as supportive information

The study phase of direct comparison only lasted 36 weeks and was therefore too short to draw any conclusions about positive and negative effects. The data presented for study MGL-3196-05 were therefore not suitable for the benefit assessment. A detailed description of the study is therefore not provided.

Results on added benefit

Since no suitable data were available for the benefit assessment, there is no hint of an added benefit of resmetirom in comparison with the ACT; an added benefit is therefore not proven.

Probability and extent of added benefit, patient groups with therapeutically important added benefit³

Table 3 shows a summary of the probability and extent of the added benefit of resmetirom.

³ On the basis of the scientific data analysed, IQWiG draws conclusions on the (added) benefit or harm of an intervention for each patient-relevant outcome. Depending on the number of studies analysed, the certainty of their results, and the direction and statistical significance of treatment effects, conclusions on the probability of (added) benefit or harm are graded into 4 categories: (1) "proof", (2) "indication", (3) "hint", or (4) none of the first 3 categories applies (i.e., no data available or conclusions 1 to 3 cannot be drawn from the available data). The extent of added benefit or harm is graded into 3 categories: (1) major, (2) considerable, (3) minor (in addition, 3 further categories may apply: non-quantifiable extent of added benefit, added benefit not proven, or less benefit). For further details see [1,2].

Table 3: 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 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.

I 2 Research question

The aim of this report is to assess the added benefit of resmetirom in conjunction with diet and exercise, in comparison with the appropriate comparator therapy (ACT), in adult patients with noncirrhotic metabolic dysfunction-associated steatohepatitis (MASH) with moderate to advanced liver fibrosis (fibrosis stages F2 to F3).

The research question shown in Table 4 was defined in accordance with the ACT specified by the G-BA.

Table 4: Research question for the benefit assessment of resmetirom

Therapeutic indication	ACT ^{a-d}
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
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 [3] 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 company followed the ACT specified by the G-BA. The assessment was conducted by means of patient-relevant outcomes on the basis of the data provided by the company in the dossier.

For the derivation of an added benefit, randomized controlled trials (RCTs) with an event-driven study duration on longer-term outcomes such as progression to symptomatic hepatic cirrhosis or the avoidance or delay of liver transplantation are preferable in this therapeutic indication. The review of the completeness of the study pool was based on a minimum study duration of 52 weeks. However, it is questionable whether results on patient-relevant outcomes can be meaningfully interpreted in this period, and thus allow positive and negative effects to be weighed up to ultimately permit a conclusion on the added benefit of resmetirom (see also Section I 4.1.1). This deviated from the company's inclusion criteria, which included studies with a duration of at least 24 weeks.

I 3 Information retrieval and study pool

The study pool for the assessment was compiled on the basis of the following information:

Sources used by the company in the dossier:

- Study list on resmetirom (status: 9 July 2025)
- Bibliographical literature search on resmetirom (last search on 9 July 2025)
- Search of trial registries / trial results databases for studies on resmetirom (last search on 9 July 2025)
- Search on the G-BA website for resmetirom (last search on 9 July 2025)

To check the completeness of the study pool:

- Search of trial registries for studies on resmetirom (last search on 23 September 2025); for search strategies, see I Appendix A of the full dossier assessment

The company identified the RCTs MAESTRO-NASH (MGL-3196-11) [4-8], MAESTRO-NAFLD-1 (MGL-3196-14) [9] and the study MGL-3196-05 [10] on the comparison of resmetirom versus placebo. For the benefit assessment, the company used the MAESTRO-NASH study and presented the other 2 studies as supportive information.

The review of the completeness of the study pool did not identify any further studies comparing resmetirom with the ACT for this benefit assessment.

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 (for justification, see Sections I 4.1 and I 4.2). Irrespective of this, due to inappropriate analyses of the subpopulations presented in the dossier, no suitable data were available from either study for the benefit assessment comparing resmetirom with the comparator therapy specified by the G-BA. The data from MAESTRO-NASH and MAESTRO-NAFLD-1 were therefore not used for the assessment of the added benefit of resmetirom in this benefit assessment.

The study MGL-3196-05 with a treatment period of 36 weeks was too short in this therapeutic indication for the assessment of the added benefit of resmetirom and was therefore not used for the derivation of the added benefit.

Chapter I 4 describes the evidence provided by the company, and then justifies why the data provided were unsuitable for the benefit assessment.

I 4 Evidence provided by the company

I 4.1 MAESTRO-NASH study

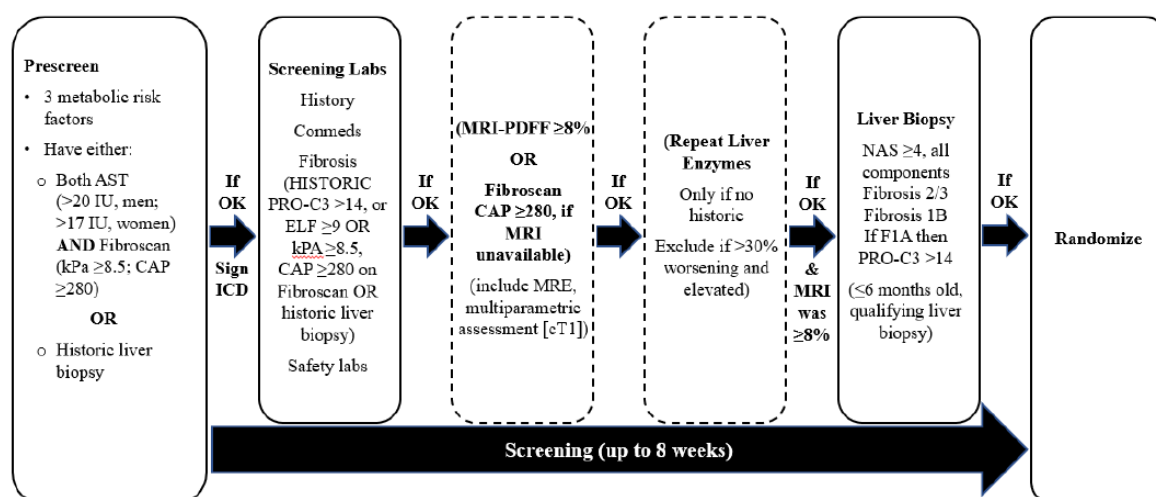
I 4.1.1 Study characteristics

The MAESTRO NASH study is an ongoing, double-blind RCT comparing resmetirom with placebo. A total of 1050 patients were included in the study and randomly assigned in a 1:1:1 ratio to treatment with resmetirom 80 mg (N = 352), resmetirom 100 mg (N = 349) or the placebo arm (N = 349). Randomization was stratified according to type 2 diabetes mellitus status (yes versus no) and biopsy-based fibrosis stage (F1 versus F2 versus F3).

In the study, patients underwent a prescreening and a multi-stage screening procedure with the aim of identifying the patient population with a suspected or confirmed diagnosis of MASH with liver fibrosis, based on historical biochemical tests such as the measurement of the N-terminal type III collagen propeptide (PRO-C3) or an enhanced liver fibrosis (ELF) test, a Fibroscan examination (vibration-controlled transient elastography [VCTE] and controlled attenuation parameter) or a historical liver biopsy (< 2 years). In addition, the liver fat content (determined using the magnetic resonance imaging proton density fat fraction [MRI-PDFF]) had to be at least 8%. The complete screening procedure in the MAESTRO-NASH study is shown in Figure 1.

After screening, patients were included in the study if they had a diagnosis of MASH with liver fibrosis (fibrosis stages F1 to F3) confirmed by a recent liver biopsy ($\leq$ 6 months) and a non-alcoholic fatty liver disease activity score (NAS) of at least 4, with a score of at least 1 in each of the NAS components of steatosis (0 to 3 points), ballooning (0 to 3 points) and lobular inflammation (0 to 2 points).

Patients with a haemoglobin A1c (HbA1c) > 9, weight gain or loss of $\geq$ 5% within 12 weeks prior to randomization, active hyperthyroidism or untreated clinical hypothyroidism, or a history of bariatric surgery were excluded.



Dotted box or parentheses, test not mandatory; prescreening Fibroscan values may be used for liver biopsy eligibility.

NOTE: Repeat liver enzymes are to be collected where indicated in an attempt to establish a stable baseline of ALT and AST with no >30% worsening of elevated values.

ALT: alanine aminotransferase; AST: aspartate aminotransferase; CAP: controlled attenuation parameter; cT1: liver corrected T1; ELF enhanced liver fibrosis; IU: international units; kPa: kilopascal; MRE: magnetic resonance elastography; MRI: magnetic resonance imaging, NAS: non-alcoholic fatty liver disease activity score; PRO-C3: N-terminal type III collagen propeptide

Figure 1: Screening procedure in MAESTRO-NASH

The resmetirom doses used in MAESTRO-NASH deviated from the specifications of the summary of product characteristics (SmPC) [3] for some of the patients in the included population. Patients received either 80 mg or 100 mg resmetirom depending on their allocation to one of the 2 intervention arms. However, according to the SmPC, the dosage must be based on the patient's body weight (< 100 kg: 80 mg resmetirom; ≥ 100 kg: 100 mg resmetirom). Both study arms therefore included patients who received a dosage that was not in compliance with the marketing authorization (see Section 4.1.2). In addition, the dosage was reduced in the study if the free thyroxine in the blood decreased by at least 30% from baseline and the laboratory value was below 0.7 ng/dL. The daily resmetirom dose could be reduced to a maximum of 60 mg. Such a dose reduction is not specified in the SmPC, however [3]. A placebo was used in the control arm.

At study start, all patients in the 3 study arms additionally received lifestyle counselling, which included diet and exercise recommendations, by the investigator. At each visit, any necessary changes had to be pointed out, such as changes in diet and the amount of food eaten, as well as changes in the intensity and frequency of exercise. Extreme changes were to be avoided once the patient followed these recommendations as part of his/her daily lifestyle. In addition, stable medication for the treatment of comorbidities (e.g. diabetes mellitus, hypertension or hypothyroidism) could be continued during the study.

The planned treatment duration with the study medication was up to 54 months. Patients with histological progression to hepatic cirrhosis or any other qualifying event of the primary outcome of the final analysis at Month 54 could switch to an open-label arm after Week 52 and before Month 54, or discontinue the study. All patients in the open-label arm were to receive treatment with resmetirom at a starting dose of 80 mg, with possible dose modifications at a later timepoint. The planned visits up to Month 54 also had to be attended by patients in the open-label arm and data were continued to be recorded.

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 information in Module 4 A, secondary outcomes at Week 52 and Month 54 were recorded in the categories of morbidity, health-related quality of life and side effects. A liver biopsy was conducted at Week 52 and Month 54 for outcome recording.

For a characterization of the study, see also Table 6 and Table 7 in I Appendix B of the full dossier assessment.

Notes on the patient population

In the study, the diagnosis of MASH with fibrosis (F1, F2 or F3) had to be confirmed by a recent liver biopsy.

A liver biopsy can be used to directly assess inflammatory activity, ballooning and fibrosis stage, enabling a more reliable differentiation between metabolic dysfunction-associated steatotic liver disease (MASLD) and MASH as well as the exact staging of liver fibrosis [11,12] than is the case when conducting non-invasive procedures.

This is in line with the recommendation of the European Medicines Agency (EMA) not to include patients in clinical studies solely based on non-invasive methods without conducting a liver biopsy to confirm existing MASH with liver fibrosis. EMA recommends to determine MASH using a histology-based NAS score of ≥ 4 with at least a score of 1 for ballooning and lobular inflammation [13]. The SmPC of resmetirom [3] does not provide any specific recommendations for identifying the patient population for the therapeutic indication, such as conducting a liver biopsy.

The amendment to the S2k guideline [14] contains various information on the need to conduct a liver biopsy in all patients with suspected MASH, however. On the one hand, it is pointed out that a biopsy-based confirmation is not necessary for the treatment decision. The

presence of significant liver stiffness measured by VCTE, magnetic resonance elastography (MRE) 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). On the other hand, the guideline points out the limitations of non-invasive procedures, describing, for example, that guideline-based risk stratification is probably unable to correctly classify a major proportion of patients because non-invasive procedures are not sufficiently reliable. According to the guideline, this could lead to inappropriate treatment decisions regarding novel MASLD therapies. In cases of doubt, liver biopsy is still available for grading (MASH) and staging (fibrosis) according to the information in the S2k guideline [14].

It should also be noted that the patients in the study had to have at least 3 of the metabolic risk factors type 2 diabetes mellitus, obesity, hypertension or dyslipidaemia. According to the guidelines, there is sufficient suspicion of steatotic liver disease if at least 1 or 2 risk factors are present [12,15]. According to information provided by the company, it additionally used a modified version of the International Diabetes Foundation criteria in the study protocol to define the risk factors, which include, for example, overweight patients with a body mass index (BMI) $\geq 30 \text{ kg/m}^2$. This deviates from the guidelines, which describe a BMI $\geq 25 \text{ kg/m}^2$ as a metabolic risk factor [12,15].

In addition, patients with baseline haemoglobin A1c (HbA1c) > 9 were excluded. The company did not justify these restrictions in Module 4 A.

Overall, the inclusion criteria selected by the company appeared sufficient to identify the patient population relevant for this benefit assessment.

Notes on study duration

The planned study duration of MAESTRO-NASH is 54 months. This analysis date has not yet been reached. For the benefit assessment, the company presented the prespecified analyses at Week 52 currently available for various outcomes on morbidity and health-related quality of life. The analyses of side effects, on the other hand, represented a longer period of up to 3.5 years (see information on data cuts).

It should be noted that the EMA Reflection paper on regulatory requirements for the development of medicinal products for MASH considers long-term outcomes to be difficult to study due to the slow progression of the disease without prominent and specific symptoms [13]. 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) [1]. The Food and Drug Administration (FDA) Guidance 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 [16].

Even though, in the given therapeutic indication, the review of the completeness of the study pool was based on a minimum study duration of 52 weeks to derive the added benefit, it is questionable overall whether results on patient-relevant outcomes can be meaningfully interpreted with a study duration of 52 weeks and thus allow the positive and negative effects to be weighed up, and, in principle, ultimately allow a conclusion to be drawn on the added benefit of resmetirom. Longer studies are needed to adequately investigate, for example, the progression to symptomatic hepatic cirrhosis, the avoidance or delay of liver transplantation or all-cause mortality. Therefore, the analyses presented for Week 52 were potentially too short to draw a conclusion on the added benefit of resmetirom.

Data cuts

According to information in Module 4 A, 2 data cuts were available for MAESTRO-NASH:

- Data cut from 31 July 2022: planned after all patients have either passed the visit after 52 weeks or have discontinued the study early
- Data cut from 13 January 2023: requested by the FDA as part of the 120-day safety update

In addition, an interim analysis was planned after occurrence of 110 events for the primary composite outcome of the 54-month analysis, consisting of the components of all-cause mortality, liver transplantation, other important liver-related events including hepatic decompensation, histological progression to hepatic cirrhosis and an increase in MELD score from below 12 to 15 or higher. The final analysis of the ongoing study is planned for the timepoint when all patients have completed the visit at Month 54 or have discontinued the study early.

The company stated that the analyses presented in the dossier were based on the data cut of 13 January 2023 (FDA 120-day safety update), and that for outcomes in the morbidity and health-related quality of life categories, 31 July 2022 was still the most recent analysis date by definition of the analysis populations.

I 4.1.2 Assessment of the data presented for the MAESTRO-NASH study

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.

According to national and international guidelines, overweight or obese patients with MASLD should first aim to reduce their weight by modification to their diet and exercise [11,12]. The S2k guideline on MASLD recommends the following drugs for the treatment of patients with comorbidities: glucagon-like peptide 1 (GLP-1) agonists (type 2 diabetes mellitus and/or obesity [BMI $\geq$ 30 kg/m²]), sodium-glucose cotransporter 2 (SGLT2) inhibitors (type 2 diabetes mellitus) and statins (dyslipidaemia). In obese patients, bariatric surgery or endoscopic interventions can also be considered [15].

Although the interventions in the MAESTRO-NASH study represented the lifestyle counselling recommended in the guidelines, they were not designed to optimize standard therapy for accompanying diseases during the course of the study. This is explained below.

Lifestyle counselling

Patients with at least 3 of the following comorbidities were included in the MAESTRO-NASH study: type 2 diabetes mellitus, hypertension, obesity and dyslipidaemia. At each visit during the first 52 weeks, patients in all 3 study arms received lifestyle counselling, which included diet and exercise recommendation, by the investigator. Overall, the recommendations described in the study protocol adequately represented the guideline recommendations, even if, for example, no behavioural therapy was offered [12,15].

Drug treatment of diabetes mellitus

In the MAESTRO-NASH study, patients requiring drug treatment for diabetes mellitus could only be included if they had been on stable treatment for the disease in the 30 days prior to randomization. Patients on GLP-1 agonists even had to be on a stable dose for 24 weeks prior to randomization. In addition, a dose increase or initiation of GLP-1 therapy was prohibited during the first 52 weeks of the study. The use of the other drug therapies recommended in the S2k guideline was also only possible in the study under certain conditions (see Table 7 in I Appendix B of the full dossier assessment). Only for the use of SGLT2 inhibitors were there no further restrictions in the study protocol.

According to various guidelines, GLP-1 agonists are a central component of the treatment of type 2 diabetes mellitus with concomitant cardiovascular disorder or overweight/obesity [17-19]. The information in Module 4 A shows that 14% of the patients in the MAESTRO-NASH subpopulation considered by the company were treated with a GLP-1 agonist at baseline. Information on other antidiabetic medications at baseline was missing. There was also no information on whether and, if so, to what extent, modifications were made to antidiabetic therapy during the course of the study.

In Module 4 A, the company pointed out that the patients had adequate HbA1c values throughout the entire 52 weeks. However, for the MAESTRO-NASH subpopulation considered by the company, the company only provided information on the HbA1c value at baseline. It was not clear in how many patients a modification of GLP-1 therapy (initiation, change or dose modification) was indicated up to Week 52.

Overall, 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.

Drug treatment of dyslipidaemia

The administration of statins and fenofibrate in patients with dyslipidaemia was only permitted in the MAESTRO-NASH study if the treatment was given at a stable dose prior to randomization. Furthermore, the use was restricted with regard to the permitted statin drugs and their maximum dose (see Table 7). For the statins to be used, a maximum of around half of the authorized maximum dose of the respective drugs was allowed [20-25]. The use of proprotein convertase subtilisin/kexin type 9 (PCSK9) inhibitors was not restricted, however.

The company explained in Module 4 A that the dosage of statins had to be reduced in the MAESTRO-NASH study due to the common metabolic pathway of resmetirom and statins in order to avoid a concentration of the respective statin that would increase the risk of adverse side effects. However, due to the low-density lipoprotein cholesterol (LDL-C)-lowering effect of resmetirom, the company considered optimal treatment of LDL dyslipidaemia to be maintained in the study. A limited dosage level for the 4 statins simvastatin, rosuvastatin, pravastatin and atorvastatin is also pointed out in the SmPC of resmetirom [3].

The dosage restrictions for statins also applied to the patients in the placebo arm. The company did not address which interventions ensured optimal treatment of LDL dyslipidaemia for patients in the placebo arm despite these limited dosing options for statins. The information in Module 4 A shows that 48% of the patients in the subpopulation considered by the company received statin therapy at baseline, of which 23% received high statin intensity and 62% received moderate statin intensity. It was not possible to assess the relevance of the restricted dosing options based on the available data. It was unclear for how many patients in

the placebo arm higher statin intensity would have been indicated, but was not permitted according to the study protocol. Furthermore, there was no information on whether and, if so, to what extent patients in the placebo arm had their statin dose reduced prior to study inclusion due to the dosage restrictions in the study.

Bariatric or intestinal bypass surgery

The inclusion of patients with a planned, or with a history of bariatric surgery or intestinal bypass surgery within the 5 years prior to randomization was not permitted in the study. According to the S3 guideline on surgery for obesity and metabolic diseases, obesity surgery may be indicated in individual cases for patients with a BMI ≥ 35 kg/m² and comorbidities such as those present in some of the patients in the study [18,26].

Treatment of hypertension

There were no restrictions in the study protocol with regard to the treatment of hypertension.

Further notes on concomitant treatments

In principle, all concomitant treatments had to be administered at a stable dosage during the study and especially up to Week 52, if possible. All therapies that were not explicitly prohibited could be used at the discretion of the investigator. In certain situations, a non-permitted therapy could also be given after consultation with the sponsor. In the overall population, around 10% of patients received a therapy that was not permitted according to the specifications in the study (31 July 2022 data cut).

Summary

Overall, there was no information in Module 4 A that any remaining treatment options were not suitable for the patients, were not tolerated or had been exhausted. Based on the information available, it was therefore not possible to conclusively assess the extent to which the optimization of standard therapy was ensured in the study despite the limitations described.

Analyses of the presented subpopulation not suitable

For the benefit assessment, the company presented analyses based on a subpopulation of the MAESTRO-NASH study.

To form the subpopulation, the company considered patients with moderate to advanced liver fibrosis (stage F2 or F3) from all 3 study arms. In addition, from the 2 resmetirom arms, the company only considered patients who received a resmetirom dosage in compliance with the marketing authorization [3]. In the 80 mg resmetirom arm, these were all patients with a body weight < 100 kg, and in the 100 mg resmetirom arm all patients with a body weight ≥ 100 kg. For the control arm, the company did not make any additional adjustments to the patient

population with regard to body weight. For the comparison of resmetirom and placebo, the company used the weight-adjusted subpopulations of the resmetirom arms (80 mg resmetirom: patients < 100 kg body weight; 100 mg resmetirom: patients ≥ 100 kg body weight) and compared these separately with the entire control arm (weight-independent; contains both patients with a body weight < 100 kg and ≥ 100 kg).

The subpopulation presented by the company comprised 167 patients in the 80 mg resmetirom arm, 151 patients in the 100 mg resmetirom arm and 303 patients in the placebo arm.

The consideration of an on-label treated subpopulation of the MAESTRO NASH study for the benefit assessment was generally appropriate. Accordingly, it was appropriate to analyse only patients with MASH fibrosis stage F2 and F3 in accordance with the authorized therapeutic indication. In contrast, the on-label weight-adapted adjustment of the resmetirom dosage only affected the 2 intervention arms.

The comparison of the weight-adjusted subpopulations of the resmetirom arms with the entire control arm presented by the company was not appropriate. Due to the selection criterion (weight) differently applied in the study arms, it was not ensured that the structural equality between the study arms, which was achieved through the randomized allocation of patients to the study arms, was maintained. It would have been useful to carry out an analysis in which the same weight-adjusted subdivision was made for the control arm (< 100 kg or ≥ 100 kg body weight) and the effect estimate was compared with the corresponding weight-adjusted resmetirom arm. In order to draw conclusions on the added benefit, a meta-analytical analysis of the 2 effect estimates would be generally required.

Irrespective of this, an analysis in which the 2 subpopulations of the resmetirom arms were pooled as a common patient population and analysed versus the placebo arm would have been more useful overall. A prerequisite for this would have been comparable proportions of patients with a body weight < 100 kg and ≥ 100 kg in the placebo arm and in the pooled resmetirom arm. Corresponding information on body weight at baseline (< 100 kg versus ≥ 100 kg) was not available in the dossier. However, taking into account the 1:1:1 randomization in the study, a comparable distribution was assumed.

Overall, the data presented by the company were not suitable for the benefit assessment for the reasons mentioned.

Further notes on the data presented by the company

When assessing the added benefit, consideration is given to both the intentional and unintentional effects of the interventions that allow an assessment of the impact on patient-relevant outcomes to determine the changes related to disease and treatment. These include

outcomes in the categories of mortality, morbidity, health-related quality of life and side effects. It should be noted that not all outcomes presented by the company in the dossier were assessed as patient-relevant per se and that no surrogate validations were presented.

Summary

A conclusive assessment of the relevance of MAESTRO-NASH for the benefit assessment was not possible based on the available information. It was unclear to what extent an optimized standard therapy was ensured in the study due to the previously described limitations in the treatment of accompanying diseases. Furthermore, it was unclear whether the study period 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 in principle. Irrespective of this, the analyses of the subpopulation considered by the company presented for the benefit assessment were not appropriate. This means that no suitable data were available for the comparison of resmetirom with the G-BA's comparator therapy.

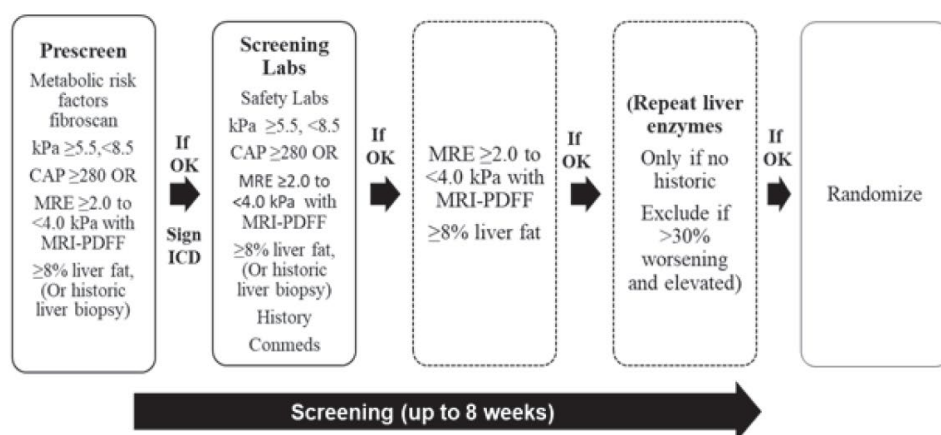
I 4.2 MAESTRO-NAFLD-1

I 4.2.1 Study characteristics

The MAESTRO-NAFLD-1 study consists of a double-blind randomized comparison of the 3 study arms resmetirom 80 mg, resmetirom 100 mg and placebo, as well as several open-label study arms. The company only presented results of the double-blind study arms in Module 4 A. The company's approach was appropriate; for this reason, the open-label arms are not considered further for the benefit assessment. A total of 972 patients were included in the double-blind comparison and randomly assigned in a 1:1:1 ratio to treatment with resmetirom 80 mg (N = 327), resmetirom 100 mg (N = 325) or the placebo arm (N = 320).

The study population comprised patients with a suspected or confirmed diagnosis of MASLD/MASH based on findings in the patient's medical history. According to the inclusion criteria, steatosis and fibrosis could be determined either based on non-invasive procedures (Fibroscan or MRE with MRI-PDFF) or liver biopsy (< 2 years). In principle, patients with fibrosis stage F1 to F3 could be included. The inclusion of patients with fibrosis stage F0 was also possible under certain conditions. Another inclusion criterion was a liver fat content (MRI-PDFF) of at least 8%.

The complete screening procedure in the MAESTRO-NAFLD-1 study is shown in Figure 2.



Dotted box or parentheses, test not mandatory; if eligible prescreening fibroscan, no need to repeat at screening; Patients screened for MGL-3196-11 who failed eligibility because of liver biopsy do not need to repeat screening. Labs if within 10 weeks of randomization. Patients with an eligible MRI-PDFF if within 8 weeks (+3 days) of randomization do not need a repeat MRI-PDFF for eligibility.

CAP: controlled attenuation parameter; kPa: kilopascal; MRE: magnetic resonance elastography; MRI-PDFF: magnetic resonance imaging proton density fat fraction

Figure 2: Screening procedure in MAESTRO-NAFLD-1

The resmetirom doses used in MAESTRO-NAFLD-1 deviated from the specifications of the SmPC [20] for some of the patients in the included population. Patients received either 80 mg or 100 mg resmetirom depending on their allocation to one of the 2 intervention arms. However, according to the SmPC, the dosage must be based on the patient's body weight (< 100 kg: 80 mg resmetirom; ≥ 100 kg: 100 mg resmetirom). Both study arms therefore included patients who received a dosage that was not in compliance with the marketing authorization (see Section I 4.2.2). In addition, the dosage was reduced in the study if the free thyroxine in the blood decreased by at least 30% from baseline and the laboratory value was below 0.7 ng/dL. The daily resmetirom dose could be reduced to a maximum of 60 mg. Such a dose reduction is not found in the recommendations of the SmPC, however [3]. A placebo was used in the control arm. The treatment duration with the study medication was up to 52 weeks.

As in the MAESTRO-NASH study, all patients received lifestyle counselling at study start and in the course of the study, which included diet and exercise recommendation, by the investigator. In addition, stable medication for the treatment of comorbidities (e.g. diabetes mellitus, hypertension or hypothyroidism) could be continued during the study.

The primary outcome of the study was the incidence of adverse events within the treatment period of 52 weeks and a 30-day follow-up. According to the information in Module 4 A, secondary outcomes were recorded in the categories of morbidity, health-related quality of life and side effects.

Notes on the patient population

The MAESTRO-NAFLD-1 study also included patients whose diagnosis was based solely on non-invasive procedures. With regard to fibrosis stage, the inclusion criteria in the MAESTRO-NAFLD-1 study required lower liver stiffness measurements (VCTE by Fibroscan and MRE) than in the MAESTRO-NASH study. The inclusion criteria of the MAESTRO-NAFLD-1 study tended to represent fibrosis stages F1 or F2.

As described in Section I 4.1.1 on the MAESTRO-NASH study, information differs on the need to conduct a liver biopsy in all patients with suspected MASH. For example, the EMA requires a liver biopsy to be conducted for the inclusion of patients in clinical studies to confirm an existing MASH [13]. On the one hand, the amendment to the S2k guideline [14], lists non-invasive procedures as an alternative to biopsy-confirmed MASH with liver fibrosis (F2 and F3). On the other hand, the guideline points out incorrect risk stratification due to insufficiently reliable non-invasive procedures.

Notes on study duration

The study duration of MAESTRO-NAFLD-1 was 52 weeks. As described in Section I 4.1.1, it is questionable whether results on patient-relevant outcomes can be meaningfully interpreted in this period and thus allow the positive and negative effects to be weighed up and ultimately permit a conclusion on the added benefit of resmetirom.

I 4.2.2 Assessment of the supportive data presented for the MAESTRO-NAFLD-1 study

In the dossier, the company presented the results of a subpopulation of the MAESTRO-NAFLD-1 study as supportive information, stating it would not claim an added benefit on the basis of this study due to methodological limitations.

Patients with fibrosis stage F2 or F3 who received a resmetirom dosage corresponding to their body weight, in compliance with the SmPC, were to be considered in this subpopulation [3].

The company justified the supportive presentation of the MAESTRO-NAFLD-1 study with uncertainties in the informative value, as the liver fibrosis did not have to be confirmed by biopsy in the study and there was no stratification by fibrosis stage. According to the company, it therefore determined the fibrosis stage post hoc on the basis of the VCTE measured at baseline using Fibroscan to form the subpopulation. According to the company, > 8.5 kPa was set as a cut-off value on the basis of literature data and feedback from experts. In the company's view, these patients were most likely to be within the therapeutic indication.

The cut-off value used by the company deviated from the recommendations in the amendment to the S2k guideline [14]. According to the guideline, significant fibrosis (F2 or F3) can be assumed with a VCTE-measured liver stiffness of 10 to 19.9 kPa. In patients with a liver stiffness (VCTE) of 8 to 10 kPa, the measurement should be repeated after 6 months. It was

therefore not sufficiently certain whether resmetirom therapy was indicated in the patients included in the subpopulation.

Appropriate comparator therapy

The restrictions on the treatment of comorbidities in the MAESTRO-NASH study described in Section I 4.1 also largely applied to the MAESTRO-NAFLD-1 study. However, if medically indicated, it was possible in the MAESTRO-NAFLD-1 study to make adjustments to the antidiabetic treatment after randomization. Dose modifications, therapy changes or the addition of an additional antidiabetic were permitted. However, the initiation of therapy with GLP-1 agonists, which according to various guidelines [17-19] are a central component in the treatment of type 2 diabetes mellitus with concomitant cardiovascular disease or overweight/obesity, was not permitted. In addition to the restrictions already described regarding lipid therapy (statins, ezetimibe, omega-3 fatty acids, bile acid-binding agents and fenofibrate), the dose used at baseline had to be stable for the duration of the 52-week study. This did not include necessary therapy adjustments due to side effects.

Overall, there was no information in Module 4 A that any remaining treatment options were not suitable for the patients, were not tolerated or had been exhausted. Based on the information available, it was therefore not possible to conclusively assess the extent to which the optimization of standard therapy was ensured in the study despite the limitations described.

Subpopulation presented by the company as supportive information

The analyses of the subpopulation presented by the company were unsuitable. As in the MAESTRO-NASH study, and in accordance with the specifications of the SmPC, the company considered all patients with a body weight < 100 kg from the 80 mg resmetirom arm and all patients with a body weight ≥ 100 kg from the 100 mg resmetirom arm. For the control arm, the company did not make any additional adjustments to the patient population with regard to body weight. For the comparison of resmetirom versus placebo, the company used the weight-adjusted subpopulations of the resmetirom arms and compared them separately with the entire control arm. As described in Section I 4.1.2, this approach was not appropriate.

Overall, it should be noted that the subpopulation used by the company for supportive purposes comprised 9 patients in the 80 mg resmetirom arm, 15 in the 100 mg resmetirom arm and 29 in the placebo arm. Even assuming that, after clarification of the uncertainties described, this was a relevant study for the given research question, it was assumed that the influence of the results of the subpopulation on the results of this benefit assessment was low.

Summary

A conclusive assessment of the relevance of MAESTRO-NAFLD-1, and of the subpopulation presented by the company in the dossier, for the benefit assessment was not possible based on the available information.

I 4.3 MGL-3196-05

I 4.3.1 Study characteristics

MGL-3196-05 is a completed double-blind RCT on the comparison of resmetirom with placebo. A total of 125 patients were included in the study and randomly assigned in a 2:1 ratio to the intervention arm (N = 84) or the control arm (N = 41).

Adult patients with biopsy-confirmed MASH defined as NAS ≥ 4 with at least a score of 1 in each of the components steatosis, ballooning and lobular inflammation and liver fibrosis (stage F1 to F3) were included. Furthermore, inclusion was limited to patients with a liver fat content of at least 10% as measured by MRI-PDFF.

The study consisted of a screening period of 42 days, followed by a 36-week treatment phase. This was followed by the opportunity to take part in a 36-week extension study. In the extension study, patients who had previously received placebo switched to treatment with resmetirom.

In the study, all patients in the intervention arm received 80 mg resmetirom per day, regardless of body weight. This did not comply with the specifications of the SmPC, according to which this dosage should only be used in patients with a body weight of < 100 kg (see Section I 4.3.2) [3]. A placebo was used in the control arm. In addition to the study medication, nutritional and lifestyle counselling took place during the visits in both study arms.

The primary outcome of study MGL-3196-05 was the percentage change in liver fat content (MRI-PDFF) at Week 12 from baseline. According to the information in Module 4 A, secondary outcomes were recorded in the categories of morbidity, health-related quality of life and side effects.

I 4.3.2 Assessment of the MGL-3196-05 study presented by the company as supportive information

For the MGL-3196-05 study – analogous to MAESTRO NASH and MARSTRO-NAFLD-1 – the company only considered the patients with stages F2 and F3 liver fibrosis and on-label resmetirom dosing. The subpopulation presented included 18 patients in the resmetirom arm and 20 patients in the placebo arm. The company justified the merely supportive presentation of the study results by stating that the population available for analyses was greatly reduced due to the definition of the subpopulation and that the study arms were not balanced.

The study phase of direct comparison only lasted 36 weeks and was therefore too short to draw any conclusions about positive and negative effects (see Section I 4.1.1 for the reasons). The data presented for study MGL-3196-05 were therefore not suitable for the benefit assessment. A detailed description of the study is therefore not provided.

I 5 Results on added benefit

No suitable data were available for the assessment of the added benefit of resmetirom compared with the ACT in adult patients with non-cirrhotic MASH with moderate to advanced liver fibrosis (fibrosis stages F2 to F3). There is no hint of an added benefit of resmetirom in comparison with the ACT; an added benefit is therefore not proven.

I 6 Probability and extent of added benefit

The result of the assessment of the added benefit of resmetirom in comparison with the ACT is summarized in Table 5.

Table 5: 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 [3] 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 assessment described above deviates from that of the company, which, based on the results of the MAESTRO-NASH study, derived an indication of a considerable added benefit of resmetirom versus the ACT for adult patients with non-cirrhotic MASH with moderate to advanced liver fibrosis (fibrosis stages F2 to F3).

The approach for the derivation of an overall conclusion on added benefit is a proposal by IQWiG. The G-BA decides on the added benefit.

I 7 References for English extract

Please see full dossier assessment for full reference list.

The reference list contains citations provided by the company in which bibliographical information may be missing.

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