Lomitapide –
Benefit assessment according to §35a Social Code Book V

Extract

1 Translation of Sections 2.1 to 2.5 of the dossier assessment Lomitapid – Nutzenbewertung gemäß § 35a SGB V (Version 1.0; Status: 10 September 2015). Please note: This translation is provided as a service by IQWiG to English-language readers. However, solely the German original text is absolutely authoritative and legally binding.
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2 Due to legal data protection regulations, employees have the right not to be named.
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## List of abbreviations

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<thead>
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<th>Abbreviation</th>
<th>Meaning</th>
</tr>
</thead>
<tbody>
<tr>
<td>ACT</td>
<td>appropriate comparator therapy</td>
</tr>
<tr>
<td>AE</td>
<td>adverse event</td>
</tr>
<tr>
<td>G-BA</td>
<td>Gemeinsamer Bundesausschuss (Federal Joint Committee)</td>
</tr>
<tr>
<td>HoFH</td>
<td>homozygous familial hypercholesterolaemia</td>
</tr>
<tr>
<td>IQWiG</td>
<td>Institut für Qualität und Wirtschaftlichkeit im Gesundheitswesen (Institute for Quality and Efficiency in Health Care)</td>
</tr>
<tr>
<td>LDL</td>
<td>low density lipoprotein</td>
</tr>
<tr>
<td>LDL-C</td>
<td>LDL cholesterol</td>
</tr>
<tr>
<td>RCT</td>
<td>randomized controlled trial</td>
</tr>
<tr>
<td>SAE</td>
<td>serious adverse event</td>
</tr>
<tr>
<td>SGB</td>
<td>Sozialgesetzbuch (Social Code Book)</td>
</tr>
</tbody>
</table>
2 Benefit assessment

2.1 Executive summary of the benefit assessment

Background
In accordance with §35a Social Code Book (SGB) 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 lomitapide. The assessment was based on a dossier compiled by the pharmaceutical company (hereinafter referred to as “the company”). The dossier was sent to IQWiG on 15 June 2015.

The company submitted a first dossier of the drug to be evaluated on 13 December 2013 for the early benefit assessment. In this procedure, by decision of 5 June 2014, the G-BA limited its decision until 15 June 2015.

Research question
The aim of the present report was to assess the added benefit of lomitapide as an adjunct to a low-fat diet and other lipid-lowering medicinal products with or without low density lipoprotein (LDL) apheresis in comparison with the appropriate comparator therapy (ACT) in adult patients with homozygous familial hypercholesterolaemia (HoFH).

Genetic confirmation of HoFH should be obtained whenever possible. Other forms of primary hyperlipoproteinaemia and secondary causes of hypercholesterolaemia (e.g., nephrotic syndrome, hypothyroidism) must be excluded.

Two research questions resulted from the ACT specified by the G-BA. Research question 1 included patients in whom drug and dietary options to reduce lipid levels have been exhausted; research question 2 included patients in whom these options have not been exhausted. Research question 1 was subdivided into patients who have not yet received LDL apheresis (1A) and patients who have already received LDL apheresis (1B).

Table 4 shows the research questions relevant for the present benefit assessment and the respective ACTs.
Table 2: Research questions and ACTs for the benefit assessment of lomitapide

<table>
<thead>
<tr>
<th>Research question</th>
<th>Subindication</th>
<th>Experimental intervention</th>
<th>ACT specified by the G-BA</th>
</tr>
</thead>
<tbody>
<tr>
<td>1A</td>
<td>Adult patients with HoFH in whom drug and dietary options to reduce lipid</td>
<td>Lomitapide</td>
<td>LDL apheresis (as “ultima ratio” in refractory disease), if necessary with concomitant</td>
</tr>
<tr>
<td></td>
<td>levels have been exhausted and who do not receive LDL apheresis treatment</td>
<td></td>
<td>lipid-lowering drug treatment</td>
</tr>
<tr>
<td>1B</td>
<td>Adult patients with HoFH in whom drug and dietary options to reduce lipid</td>
<td>Lomitapide as add-on therapy to LDL</td>
<td></td>
</tr>
<tr>
<td></td>
<td>levels have been exhausted and who receive concomitant LDL apheresis treatment</td>
<td>apheresis</td>
<td></td>
</tr>
<tr>
<td>2</td>
<td>Adult patients with HoFH in whom drug and dietary options to reduce lipid</td>
<td>Lomitapide</td>
<td>Maximum tolerated drug and dietary treatment to reduce lipid levels</td>
</tr>
<tr>
<td></td>
<td>levels have not been exhausted</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

ACT: appropriate comparator therapy; G-BA: Federal Joint Committee; HoFH: homozygous familial hypercholesterolaemia; LDL: low density lipoprotein

The research questions deviate from the research question of the company. The company did not subdivide research question 1, and did not investigate research question 2.

The assessment was conducted based on patient-relevant outcomes and on the data provided by the company in the dossier. Minimum study duration for all research questions was defined as 12 months.

Results

Study pool of the company

The company presented no data for research questions 1A and 2.

The company identified no study of direct comparison on lomitapide in comparison with the ACT for research question 1B. The company also presented no adjusted indirect comparison from randomized controlled trials (RCTs). For this reason, the company tried to derive an added benefit on the basis of different analyses for before-after comparisons under consideration of the one-arm lomitapide study AEGR-733-005 (hereinafter referred to as “study 005”) and its extension study AEGR-733-012 (hereinafter referred to as “study 012”) mainly for the outcome “LDL cholesterol (LDL-C)”. For this purpose, it also used historical LDL-C reference values from studies on LDL apheresis.

To support this, the company presented results of the lomitapide registry (study AEGR-733-025, hereinafter referred to as “LOWER”) und of 2 pharmacokinetic studies (AEGR-733-024 and AEGR-733-029).

The studies AEGR-733-024 und AEGR-733-029 were conducted in healthy subjects and were therefore not relevant for further considerations. Relevant selection bias was possible for the
012 extension study because of the selective choice of patients from the 005 study. The data of the 012 study were therefore not evaluable for the benefit assessment.

**Analyses of the company on research question 1B**

The company termed its different analyses for before-after comparisons “option A” to “option C”. The company’s 3 options A, B and C differed in the following aspects:

- Option A: The LDL-C value at the start of lomitapide treatment in comparison with the values after 26 and 78 weeks in the sense of a before-after comparison was considered.
- Option B: The difference between the result from option A and the change in LDL-C within the 6-week run-in phase was considered.
- The company used option C in particular to prove that the LDL-C values of the patients treated with LDL apheresis in the 005 study were in a magnitude that can be expected due to the previous LDL apheresis.

Option B is conceptually unsuitable to answer the research question of the benefit assessment and was therefore not considered further.

Option A is conceptually oriented towards research question 1B of the benefit assessment. Apart from the low informative value of a before-after comparison, the concrete approach of the company in the dossier was inadequate:

- The evidence presented by the company was incomplete with regard to content because potentially relevant data from the LOWER study were not processed together with the data from the 005 study without justification. The company had presented the results of this study only as supplementary information separately elsewhere in the dossier. Up to 6 HoFH patients from this study may have been treated with LDL apheresis and would therefore be potentially relevant for the benefit assessment. The 6 potentially relevant patients in the LOWER study represent a relevant amount of data besides the 10 patients with LDL apheresis from the 005 study.
- Furthermore, the company did not prove for the most important outcome in its rationale, the LDL-C value, that a reduction represents a valid surrogate outcome for cardiovascular risk reduction in the present situation. Moreover, it presented no adequate analyses for this outcome. In the 005 study, LDL-C values in patients under LDL apheresis treatment were measured before an apheresis procedure if possible. Such analyses are principally suitable to explore whether additional treatment results in lower LDL-C values also in patients with LDL apheresis. Due to the rebound effect, however, several measurements of the LDL-C value at different time points between 2 apheresis procedures would be necessary for a meaningful determination of LDL-C levels. This is the only way to determine the LDL-C burden, i.e. the mean LDL-C concentration over time.
Furthermore, it remained unclear whether all patients in the 005 study with LDL apheresis are relevant for the assessment of research question 1B. There was no information about whether the lipid-lowering pretreatment of the patients had been exhausted. Moreover it is doubtful whether the LDL apheresis treatment of the respective patients was optimized according to the options available in Germany. The analyses on historical LDL-C reference values of patients from the 005 study (option C) were unsuitable for the corresponding proof. No meaningful historical reference value for the reduction of the LDL-C value that can be achieved under apheresis could be inferred from the studies on LDL apheresis either. On the one hand, treatment did not concur with the current state of medicine, on the other, the analyses on LDL-C between the studies were too different so that a meta-analysis as conducted by the company is inadequate.

In addition, the company presented no adequate analysis on adverse events (AEs).

Summary

In summary, the company presented no suitable data for any of the research questions. Hence there was no hint of an added benefit for all 3 research questions 1A, 1B and 2; the added benefit is therefore not proven.

Extent and probability of added benefit, patient groups with therapeutically important added benefit

Table 3 presents a summary of the extent and probability of the added benefit of lomitapide.

4 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, no added benefit, or less benefit). For further details see [1,2].
Table 3: Lomitapide – extent and probability of added benefit

<table>
<thead>
<tr>
<th>Therapeutic indication</th>
<th>ACT(^a)</th>
<th>Extent and probability of added benefit</th>
</tr>
</thead>
<tbody>
<tr>
<td>Adult patients with HoFH in whom drug and dietary options to reduce lipid levels have been <strong>exhausted</strong> and who do <strong>not</strong> receive <strong>LDL apheresis treatment</strong></td>
<td>LDL apheresis (as “ultima ratio” in refractory disease), if necessary with concomitant lipid-lowering drug treatment</td>
<td>Added benefit not proven</td>
</tr>
<tr>
<td>Adult patients with HoFH in whom drug and dietary options to reduce lipid levels have been <strong>exhausted</strong> and who receive <strong>concomitant LDL apheresis treatment</strong></td>
<td></td>
<td><strong>Added benefit not proven</strong></td>
</tr>
<tr>
<td>Adult patients with HoFH in whom drug and dietary options to reduce lipid levels have not been <strong>exhausted</strong></td>
<td>Maximum tolerated drug and dietary treatment to reduce lipid levels</td>
<td><strong>Added benefit not proven</strong></td>
</tr>
</tbody>
</table>

\(^a\): Presentation of the respective ACT specified by the G-BA.

ACT: appropriate comparator therapy; G-BA: Federal Joint Committee; HoFH: homozygous familial hypercholesterolaemia; LDL: low density lipoprotein

The G-BA decides on the added benefit.

### 2.2 Research question

The aim of the present report was to assess the added benefit of lomitapide as an adjunct to a low-fat diet and other lipid-lowering medicinal products with or without LDL apheresis in comparison with the ACT in adult patients with HoFH.

Genetic confirmation of HoFH should be obtained whenever possible. Other forms of primary hyperlipoproteinaemia and secondary causes of hypercholesterolaemia (e.g., nephrotic syndrome, hypothyroidism) must be excluded.

In its specification of the ACT, the G-BA distinguished between patients in whom drug and dietary options to reduce lipid levels have been exhausted and patients in whom these options have not been exhausted.

Two research questions resulted from this in the assessment. Research question 1 was subdivided into patients who have not yet received LDL apheresis (1A) and patients who have already received LDL apheresis (1B).

Table 4 shows the research questions relevant for the present benefit assessment and the respective ACTs.
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<th>Experimental intervention</th>
<th>ACT specified by the G-BA</th>
</tr>
</thead>
<tbody>
<tr>
<td>1A</td>
<td>Adult patients with HoFH in whom drug and dietary options to reduce lipid levels have been exhausted and who <strong>do not receive LDL apheresis treatment</strong></td>
<td>Lomitapide</td>
<td>LDL apheresis (as “ultima ratio” in refractory disease), if necessary with concomitant lipid-lowering drug treatment</td>
</tr>
<tr>
<td>1B</td>
<td>Adult patients with HoFH in whom drug and dietary options to reduce lipid levels have been exhausted and who <strong>receive concomitant LDL apheresis treatment</strong></td>
<td>Lomitapide as add-on therapy to LDL apheresis</td>
<td></td>
</tr>
<tr>
<td>2</td>
<td>Adult patients with HoFH in whom drug and dietary options to reduce lipid levels <strong>have not been exhausted</strong></td>
<td>Lomitapide</td>
<td>Maximum tolerated drug and dietary treatment to reduce lipid levels</td>
</tr>
</tbody>
</table>

ACT: appropriate comparator therapy; G-BA: Federal Joint Committee; HoFH: homozygous familial hypercholesterolaemia; LDL: low density lipoprotein

The research questions deviate from the research question of the company. In research question 1, the company did not differentiate between patients who received no LDL apheresis (1A) and patients who received LDL apheresis (1B). The company did not investigate research question 2.

The assessment was conducted based on patient-relevant outcomes and on the data provided by the company in the dossier. Minimum study duration for all research questions was defined as 12 months.

2.3 Research questions 1A and 1B: Adult patients with HoFH in whom drug and dietary options to reduce lipid levels have been exhausted

2.3.1 Information retrieval and study pool

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

Sources of the company in the dossier:

- study list on lomitapide (status: 3 April 2015)
- bibliographical literature search on lomitapide (last search on 7 April 2015)
- search in trial registries for studies on lomitapide (last search on 3 April 2015)
- bibliographical literature search on the ACT (last search on 7 April 2015)
- search in trial registries for studies on the ACT (last search on 6 April 2015)

To check the completeness of the study pool:
search in trial registries for studies on lomitapide (last search on 25 June 2015)

bibliographical literature search on lomitapide (last search on 3 July 2015)

No additional study was identified from the check that had not been found by the company.

**Study pool of the company**

The company did not investigate research question 1A (patients without LDL apheresis pretreatment). Correspondingly, it did not identify any studies on this research question.

For research question 1B (patients with LDL apheresis pretreatment), the company presented the studies listed in Table 5.

**Table 5: Study pool of the company for research question 1B**

<table>
<thead>
<tr>
<th>Study</th>
<th>Sponsored study(^a) (yes/no)</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>RCT of direct comparison</strong></td>
<td></td>
</tr>
<tr>
<td>None</td>
<td></td>
</tr>
<tr>
<td><strong>Indirect comparisons based on RCTs</strong></td>
<td></td>
</tr>
<tr>
<td>None</td>
<td></td>
</tr>
<tr>
<td><strong>Further investigations</strong></td>
<td></td>
</tr>
<tr>
<td>Studies considered by the company in the before-after comparisons</td>
<td></td>
</tr>
<tr>
<td>AEGR-733-005 (005)</td>
<td>Yes (approval study)</td>
</tr>
<tr>
<td>AEGR-733-012, extension AEGR-733-005 (012)</td>
<td>Yes</td>
</tr>
<tr>
<td>Studies with LDL apheresis</td>
<td></td>
</tr>
<tr>
<td>Bosch 2006</td>
<td>No</td>
</tr>
<tr>
<td>Di Minno 1990</td>
<td>No</td>
</tr>
<tr>
<td>Gordon 1992</td>
<td>No</td>
</tr>
<tr>
<td>Graesdal 2012</td>
<td>No</td>
</tr>
<tr>
<td>Koga 1999</td>
<td>No</td>
</tr>
<tr>
<td>Further studies presented by the company as supporting information</td>
<td></td>
</tr>
<tr>
<td>Registry study AEGR-733-025 (LOWER)</td>
<td>Yes</td>
</tr>
<tr>
<td>AEGR-733-024(^c)</td>
<td>Yes</td>
</tr>
<tr>
<td>AEGR-733-029(^c)</td>
<td>Yes</td>
</tr>
</tbody>
</table>

\(\text{a: Study for which the company was sponsor, or in which the company was otherwise financially involved.}\
\(\text{b: The course of LDL-C values during the studies was additionally presented as well as the reduction in apheresis frequency.}\
\(\text{c: Studies on pharmacokinetics in healthy subjects; not relevant for further considerations.}\
LDL: low density lipoprotein; LDL-C: LDL cholesterol; RCT: randomized controlled trial

The company identified no RCT and no non-randomized controlled trial on lomitapide in comparison with the ACT. Correspondingly, it also presented no adjusted indirect comparison
on the basis of RCTs. For this reason, the company tried to derive an added benefit on the basis of different analyses of the one-arm lomitapide study AEGR-733-005 (hereinafter referred to as “study 005”) and its extension study AEGR-733-012 (hereinafter referred to as “study 012”) mainly for the outcome “LDL cholesterol (LDL-C)”.

Irrespective of the question whether these analyses are at all suitable for the benefit assessment of lomitapide, they were incomplete with regard to content because the company did not use the results of the AEGR-733-025 (LOWER) study without providing further justification.

**Analyses of the studies 005 and 012 presented by the company**

The company presented different analyses for before-after comparisons, which it termed “option A” to “option C”. It used the 005 study for this, partly supplemented with the results of the corresponding extension study 012. Due to the selective choice of patients from the 005 study however, relevant selection bias was possible for the 012 study. Hereinafter only the analyses of the 005 study without the 012 study are therefore considered.

The company’s 3 options A, B and C differed in the following aspects:

- **Option A:** The LDL-C value at the start of lomitapide treatment in comparison with the values after 26 and 78 weeks in the sense of a before-after comparison was considered.
- **Option B:** The difference between the result from option A and the change in LDL-C within the 6-week run-in phase was considered.
- **Option C:** The company used option C in particular to prove that the LDL-C values of the patients treated with LDL apheresis in the 005 study were in a magnitude that can be expected due to the previous LDL apheresis.

Option B is conceptually unsuitable to answer the research question of the benefit assessment and was therefore not considered further (see Section 2.6.2.3.2 of the full dossier assessment).

Option A is conceptually oriented towards research question 1B of the benefit assessment. Apart from the low informative value of a before-after comparison, the concrete approach of the company in the dossier was inadequate particularly for the following reasons:

- The evidence presented by the company was incomplete with regard to content because potentially relevant data from the LOWER study were not processed together with the data from the 005 study without justification.
- Furthermore, for the most important outcome in its rationale, the LDL-C value, the company did not prove that a reduction represents a valid surrogate outcome for cardiovascular risk reduction in the present situation. In addition, it presented no adequate analyses.
- It remained unclear whether all patients in the 005 study with LDL apheresis are relevant for the assessment of research question 1B. There was no information about whether the lipid-lowering pretreatment of the patients had been exhausted. Moreover it is doubtful whether the LDL apheresis treatment of the respective patients was optimized according to the options available in Germany. The analyses presented by the company on option C and the studies on LDL apheresis were unsuitable to prove this.

- The company presented no adequate analysis on AEs.

The studies 005, LOWER and the company’s approach in options A and C are described in detail in the following sections 2.3.1.1 and 2.3.1.2.

### 2.3.1.1 Characteristics of the studies 005 and LOWER

Table 6 and Table 7 describe the studies 005 and LOWER.
## Table 6: Characteristics of the studies 005 and LOWER – further investigations: lomitapide (research question 1B)

<table>
<thead>
<tr>
<th>Study</th>
<th>Study design</th>
<th>Population</th>
<th>Interventions (number of patients included)</th>
<th>Study duration</th>
<th>Location and period of study</th>
<th>Outcomes</th>
</tr>
</thead>
<tbody>
<tr>
<td>005</td>
<td>Open-label, one-arm</td>
<td>Adult patients with HoFH</td>
<td>Lomitapide ± apheresis ± lipid-lowering drug + diet (N = 29&lt;sup&gt;a&lt;/sup&gt;) patients thereof with LDL apheresis (n = 10)</td>
<td>Run-in: 6 weeks before the start of treatment</td>
<td>11 centres in Canada, Italy, South Africa, United States 12/2007-10/2011</td>
<td>Primary&lt;sup&gt;b&lt;/sup&gt;: change in LDL-C value Secondary&lt;sup&gt;b&lt;/sup&gt;: adverse events</td>
</tr>
<tr>
<td>LOWER</td>
<td>Registry study</td>
<td>Adult patients with HoFH, HeFH and hyperlipidaemia who are starting treatment with lomitapide, or initiated treatment with lomitapide within 15 months prior to the start of the study</td>
<td>Lomitapide ± apheresis ± lipid-lowering drug + diet (N = 84) patients with HoFH (n = 75) patients thereof with apheresis (n = 6)&lt;sup&gt;d&lt;/sup&gt;</td>
<td>Average exposure time: 14 months</td>
<td>Netherlands, USA&lt;sup&gt;e&lt;/sup&gt; 3/2014–ongoing</td>
<td>LDL-C value, adverse events</td>
</tr>
</tbody>
</table>

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<sup>a</sup>: Of the 31 patients who originally participated in the run-in phase, 2 patients withdrew consent before the start of the treatment phase.

<sup>b</sup>: Primary outcomes contain information without consideration of its relevance for this benefit assessment. Secondary outcomes contain exclusively outcomes that would have been relevant for a benefit assessment.

<sup>c</sup>: Only for patients who did not participate in the 012 extension study.

<sup>d</sup>: It is unclear how many of these patients had HoFH and HeFH and received LDL apheresis or plasmapheresis.

<sup>e</sup>: Further recruitment planned for Asia, Canada, Europe, Latin America.

HeFH: heterozygous familial hypercholesterolaemia; HoFH: homozygous familial hypercholesterolaemia; LDL: low density lipoprotein; LDL-C: LDL cholesterol; N: number of patients included; n: number of patients in a subpopulation
Table 7: Characteristics of the interventions – studies 005 and LOWER – further investigations: lomitapide (research question 1B)

<table>
<thead>
<tr>
<th>Study</th>
<th>Intervention</th>
<th>Prior and concomitant medication</th>
</tr>
</thead>
</table>
| 005    | Run-in phase: stable individual lipid-lowering treatment  
        Treatment phase lomitapide: lomitapide once daily; titration based on tolerability:  
        5 mg for the first 2 weeks, 10 mg for 4 weeks, then increase to 20, 40, and 60 mg, in exceptional cases up to 80 mg\(^a\), in 4-week intervals  
        ± apheresis in a stable frequency\(^b\)  
        ± lipid-lowering drug at a stable dose\(^b\)  
 | Before run-in phase: dietary counselling  
 From run-in phase up to week 26: stable individual lipid-lowering treatment (diet, lipid-lowering drug, if necessary apheresis), then adjustments possible when LDL-C value < 100 mg/dL is achieved |
| LOWER  | Lomitapide once daily from 2.5 mg to maximum dose of 60 mg  
 ± apheresis at individual treatment intervals  
 + lipid-lowering drugs individually at the doctor’s discretion  
 | Ongoing individual lipid-lowering treatment (diet, lipid-lowering drug, if necessary apheresis) is maintained. |

a: Starting in week 26, patients received the maximum tolerated dose. Dose reduction was possible in case of adverse events (e.g. hepatotoxicity). Only one patient received a dose of 80 mg.  
b: The intervals of apheresis and the dose of the lipid-lowering drugs could be reduced in week 26 or later following the responsible doctor’s assessment when the target values (LDL-C value < 100 mg/dL) were achieved.  

LDL: low density lipoprotein; LDL-C: LDL cholesterol

The 005 study was an open-label, one-arm, multicentre study with a treatment duration of 78 weeks, which was conducted in Canada, Italy, South Africa and USA from 2007 to 2011. Adults with HoFH were included in the study. 29 patients received 5 mg lomitapide once daily in the beginning of the treatment phase. In compliance with the approval, this dose was increased over several weeks up to the maximum tolerated or approved dose of 60 mg. Individual lipid-lowering concomitant drug treatment had to be maintained in the 6-week run-in phase and the subsequent 26-week treatment phase. The frequency of apheresis also had to be maintained during the run-in phase and in the first 26 weeks of the lomitapide treatment phase. 10 patients already received LDL apheresis treatment at the start of the run-in phase.

The LOWER study is a multicentre registry study that has been conducted since 2014 and was planned worldwide. Up to date, patients have only been recruited in the Netherlands and in the USA. In March 2015, the registry included a total of 84 adults treated with lomitapide, 75 of which were HoFH patients. Genetic confirmation of the diagnosis is not an inclusion criterion of the registry. Average exposure time of the patients in the registry is 14 months. A
total of 6 patients are additionally treated with apheresis. It remains unclear whether all of these 6 patients are HoFH patients and whether all of them receive LDL apheresis (one patient in the study receives plasmapheresis).

It was not defined as explicit inclusion criterion for the 005 study or the LOWER study that prior therapy (lipid-lowering drug treatment, LDL apheresis) of the patients included had to be exhausted at the start of lomitapide treatment.

2.3.1.2  Data of the LOWER study and before-after comparisons of the company

Inadequate processing of the LOWER study

The company only considered the 005 study in its before-after comparisons. The company separately presented the results of its registry study LOWER elsewhere in its dossier as “further studies with the drug to be assessed” (see Table 5). Up to 6 HoFH patients with LDL apheresis might be included in the LOWER study. Their results were therefore potentially relevant for research question 1B. The exact number of patients could not be derived from the study documents because the study also included patients (about 11%) with other types of hypercholesterolaemia and because the number of patients with LDL apheresis was not differentiated by diagnosis. It was also unclear whether this number also included patients with plasmapheresis.

It is not comprehensible that the company did not include HoFH patients with LDL apheresis from the LOWER study in the analyses it presented. Those patients in whom drug and dietary options to reduce lipid levels had been proven to be exhausted at the start of treatment with lomitapide and whose treatment with LDL apheresis was optimized according to the options available in Germany are potentially relevant. In addition, according to the German approval status, only patients with genetic confirmation of their diagnosis are relevant for the benefit assessment. The 6 potentially relevant patients in the LOWER study represent a relevant amount of data besides the 10 patients with LDL apheresis from the 005 study. Moreover, one of the reasons for the G-BA to limit its decision from the year 2014 was that new data were expected, including those of the LOWER study [3]. Overall, the evidence for research question 1B presented by the company for the benefit assessment was incomplete with regard to content.

Validity of the outcome “LDL-C” unclear

The company based its derivation of the added benefit of lomitapide mainly on data on the LDL-C value, which it considered to be a patient-relevant outcome. The company’s assessment that the outcome in itself is patient-relevant was not followed. LDL-C is at most a surrogate. The literature provided by the company [4-20] also did not show that LDL-C is a (sufficiently) valid surrogate for cardiovascular events in patients with HoFH. In particular it was not proven that, in the present situation (lipid-lowering prior and concomitant treatment, baseline values before lomitapide treatment), the observed extent of the absolute or relative LDL-C reduction with sufficient certainty results in long-term risk reduction for
cardiovascular events. The European regulatory authority (European Medicines Agency [EMA]) also referred to the lowering of LDL-C levels as a surrogate endpoint in its assessment report of lomitapide, and noted that the recording of data on cardiovascular events is a condition to the marketing authorization of lomitapide [21].

**No meaningful interpretation of LDL-C values possible**

Even if the company had proven that LDL-C reduction is a sufficiently valid surrogate outcome in the present case, it would not be possible to interpret the analyses presented by the company in a meaningful way.

In the 005 study, LDL-C values in patients under LDL apheresis treatment were measured at the same time point (before an apheresis procedure) if possible.

Such analyses are principally suitable to initially prove that additional treatment results in lower LDL-C values also in patients with LDL apheresis. However, an analysis of the LDL-C value as the result of one single measurement is no adequate analysis for the achieved LDL-C level under LDL apheresis treatment. LDL-C values acutely decrease after an LDL apheresis procedure, and increase again within a few days (so-called rebound effect, see Figure 1, which was also cited by the company in Module 3 A). The extent of this increase in LDL-C value differs between the patients [22].

![Figure 1: Figure 3-4 from Module 3 A: Cholesterol rebound after LDL apheresis treatment (according to [22])](image)

C: concentration; max: maximum; min: minimum
Hence several measurements of the LDL-C value at different time points between 2 apheresis procedures are necessary for a meaningful determination of the LDL-C level. This is the only way to determine the LDL-C burden, i.e. the mean LDL-C concentration over time. These types of analysis are meaningful and commonly used for the measurement of the LDL-C value under apheresis treatment. The company also used 2 studies on LDL apheresis that used these analyses, for example [23,24]. For both studies, different methods were used to calculate a mean LDL-C value from several values, which were recorded in the course of the LDL-C rebound curve, for patients under apheresis treatment. The company also presented such a value for the case of total cholesterol in the figure shown in Module 3 A (see Figure 1 above) (termed “C mean”).

**Suitability of the population in the 005 study for the benefit assessment unclear**

It is a precondition to investigate research question 1B that drug and dietary options to reduce lipid levels in patients in the 005 study have to be exhausted according to the G-BA’s specification. Furthermore, only patients who receive concomitant LDL apheresis are relevant for research question 1B investigated by the company. It is necessary that this concomitant treatment with LDL apheresis was optimized according to the options available in Germany at the start of the treatment with lomitapide. This ensures that no further reduction of the LDL-C value could be expected in patients with individually optimized apheresis treatment. Only in this case can the LDL-C levels at the start of the treatment phase be regarded as an anchor, principally allowing an interpretation of the changes under lomitapide add-on therapy observed in a before-after comparison (option A of the company).

**Maximum lipid-lowering pretreatment not ensured**

The company postulated in Module 4 A that the patients in the 005 study had received their individual maximum lipid-lowering therapy before initiating lomitapide treatment. It argued that 93% of the total population had received a high dose of statins and 76% had also received ezetimibe. The company also stated that, from its point of view, all HoFH patients can be assumed to receive maximum lipid-lowering therapy. According to the company, LDL apheresis is regularly used in Germany in patients whose lipid-lowering drug treatment provides insufficient LDL-C reduction. This would apply to almost all HoFH patients. It added that the corresponding directive for contracted doctor care includes no recommendations on the frequency of apheresis procedures [13]. Furthermore, the company mentioned that concomitant treatment in the 005 study was allowed to be “optimized” before the start of the run-in phase.

The company’s statement that the patients in the 005 study had received individual maximum lipid-lowering therapy before initiating lomitapide treatment and that concomitant treatment was allowed to be “optimized” before the start of the run-in phase is incomprehensible for several reasons. Maximum lipid-lowering pretreatment was not an inclusion criterion for the 005 study, neither for drug treatment nor for concomitant treatment with LDL apheresis. The corresponding inclusion criterion merely specified that the present lipid-lowering medication...
had to be stable for at least 6 weeks before the baseline examination. It could also not be inferred from any further information of the study that only patients with maximum and optimized treatment were allowed to enter the study. Moreover, there was no differentiated presentation of pretreatment for the potentially relevant patients with LDL apheresis. The company’s statement that the majority (93%) of the patients had been treated with a high dose of statins only applied to the total population of the 005 study. There was no corresponding information for the potentially relevant patients with LDL apheresis. However, the dossier contained the information that 2 apheresis patients (20%) received no lipid-lowering drugs at all (without documentation of reasons).

Optimization of LDL apheresis doubtful

In the framework of its analyses on “option C”, the company tried to show that baseline LDL-C (with diet, exhausted lipid-lowering drug treatment and LDL apheresis) in the 005 study “concur with clinical reality”. For this purpose, it compared LDL-C values from studies on LDL apheresis with historical values of the patients included in the 005 study. It determined post hoc the respective LDL-C value before their first LDL apheresis for 8 of the 10 patients from the 005 study with concomitant LDL apheresis treatment (hereinafter referred to as “LDL-C original value”). The difference between LDL-C original values and LDL-C values at the start of lomitapide treatment were supposed to represent the change under LDL apheresis. To support the magnitude of the LDL-C reduction achieved under LDL apheresis in these patients, the company used results on LDL-C changes from studies on LDL apheresis.

The LDL-C reference values from LDL apheresis studies presented by the company were unsuitable, however. The decisive reasons were that the treatment used in the studies did not concur with the current state of medicine and that the analyses on LDL-C were too different so that a meta-analysis as conducted by the company is inadequate (for detailed justification, see Section 2.6.2.3.2 of the full dossier assessment).

In addition, a current guideline on HoFH [8] states that most centres conduct LDL apheresis treatment twice weekly, and considers once weekly to be the optimum frequency. This recommendation is therefore in the range of 2 to 4 treatments in 4 weeks. The company provided no information on the frequency of LDL apheresis treatments in the 005 study. The dossier only contained the corresponding information for all apheresis patients, i.e. 10 patients with LDL apheresis, 6 patients with plasmapheresis, and 2 patients without information on the type of apheresis. On average, these patients received only 1.4 apheresis procedures in 4 weeks at the start of the lomitapide treatment, which were fewer than recommended in the guideline.

No adequate analysis of adverse events

The company provided no adequate analyses on AEs. Module 4 A of its dossier only contained analyses on AEs for the total population for the studies conducted by the company. Neither Module 4 A nor Module 5 of its dossier contained a presentation of AEs for the
potentially relevant subpopulation of the 005 study and of the LOWER study for research question 1B. Three serious adverse events (SAEs) and 4 discontinuations due to AEs occurred in the total population in the 005 study. In case all of these had occurred in the potentially relevant subpopulation of at most 10 patients, they would have affected a relevant proportion, i.e. 30% and 40% of the patients.

2.3.2 Results on added benefit

In its dossier, the company did not consider research question 1A on adult patients with HoFH in whom drug and dietary options to reduce lipid levels have been exhausted and who do not receive LDL apheresis. Hence it presented no results in Module 4 A.

No suitable data were available for the assessment of the added benefit of lomitapide on research question 1B.

Hence there was no hint of an added benefit of lomitapide in comparison with the ACT for patients with HoFH in whom drug and dietary options to reduce lipid levels have been exhausted; an added benefit is therefore not proven.

2.3.3 Extent and probability of added benefit

Module 4 A of the dossier contained no data for the derivation of an added benefit of lomitapide for research question 1A.

For research question 1B, no suitable data were available for the benefit assessment.

In summary, the added benefit of lomitapide in comparison with the ACT for patients in whom drug and dietary options to reduce lipid levels have been exhausted is not proven. Hence there are also no patient groups for whom a therapeutically important added benefit can be derived.

This deviates from the company’s approach, which within research question 1 did not differentiate between patients who have already received LDL apheresis and patients who have not yet received LDL apheresis. It derived an indication of a non-quantifiable added benefit for its research question.

2.3.4 List of included studies

Not applicable as no studies were included in the benefit assessment.

2.4 Research question 2: Adult patients with HoFH in whom drug and dietary options to reduce lipid levels have not been exhausted

2.4.1 Information retrieval and study pool

For the present benefit assessment, the research question on the added benefit of lomitapide in comparison with the ACT in adult patients with HoFH in whom drug and dietary options to
reduce lipid levels have not been exhausted resulted from the approval of lomitapide [25] and the corresponding specification on the ACT provided by the G-BA. This research question could not be investigated, however. The company did not consider this research question in its dossier. Hence it conducted no information retrieval in Module 4 A and presented no results.

2.4.2 Results on added benefit

Module 4 A of the dossier contained no data for the derivation of an added benefit of lomitapide for research question 2. Hence there was no hint of an added benefit of lomitapide in comparison with the ACT for adult patients with HoFH in whom drug and dietary options to reduce lipid levels have not been exhausted; an added benefit is therefore not proven.

2.4.3 Extent and probability of added benefit

In Module 4 A, the company presented no data on research question 2. Hence the added benefit of lomitapide in comparison with the ACT for adult patients in whom drug and dietary options to reduce lipid levels have not been exhausted is not proven. Hence there are also no patient groups for whom a therapeutically important added benefit can be derived.

The company did not investigate this research question. It considered an added benefit to be unprovable.

2.4.4 List of included studies

Not applicable as no studies were included in the benefit assessment.

2.5 Extent and probability of added benefit – summary

The result of the assessment of the added benefit of lomitapide in comparison with the ACT is summarized in Table 8.
### Table 8: Lomitapide – extent and probability of added benefit

<table>
<thead>
<tr>
<th>Therapeutic indication</th>
<th>ACT*</th>
<th>Extent and probability of added benefit</th>
</tr>
</thead>
<tbody>
<tr>
<td>Adult patients with HoFH in whom drug and dietary options to reduce lipid levels have been exhausted and who do not receive LDL apheresis treatment</td>
<td>LDL apheresis (as “ultima ratio” in refractory disease), if necessary with concomitant lipid-lowering drug treatment</td>
<td>Added benefit not proven</td>
</tr>
<tr>
<td>Adult patients with HoFH in whom drug and dietary options to reduce lipid levels have been exhausted and who receive concomitant LDL apheresis treatment</td>
<td>Maximum tolerated drug and dietary treatment to reduce lipid levels</td>
<td>Added benefit not proven</td>
</tr>
<tr>
<td>Adult patients with HoFH in whom drug and dietary options to reduce lipid levels have not been exhausted</td>
<td></td>
<td>Added benefit not proven</td>
</tr>
</tbody>
</table>

*a: Presentation of the respective ACT specified by the G-BA.

ACT: appropriate comparator therapy; G-BA: Federal Joint Committee; HoFH: homozygous familial hypercholesterolaemia; LDL: low density lipoprotein

This deviates from the company’s approach, which only investigated research question 1B, and derived an indication of a non-quantifiable added benefit for this research question. The G-BA decides on the added benefit.
References for English extract

Please see full dossier assessment for full reference list.


The full report (German version) is published under https://www.iqwig.de/de/projekte-ergebnisse/projekte/arzneimittelbewertung/a15-23-lomitapid-nutzenbewertung-gemaess-35a-sgb-v-dossierbewertung.6746.html.