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Lomitapide (Addendum to Commission A15-23)¹

Addendum

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Table of contents

	Page
List of tables	iv
List of abbreviations.....	v
1 Background	1
2 Assessment of the data.....	2
2.1 Classification of the information subsequently submitted by the company in the comments	2
2.2 Results	4
2.3 Summary	7
3 References.....	8

List of tables

	Page
Table 1: Lomitapide: study 005 – LDL-C values (results on before-after comparison).....	5
Table 2: Lomitapide: study 005 – LDL-C values (country-related results, before-after comparison).....	6
Table 3: Lomitapide: study 005 – results on adverse events.....	6

List of abbreviations

Abbreviation	Meaning
AE	adverse event
CTCAE	Common Terminology Criteria for Adverse Events
G-BA	Gemeinsamer Bundesausschuss (Federal Joint Committee)
IQWiG	Institut für Qualität und Wirtschaftlichkeit im Gesundheitswesen (Institute for Quality and Efficiency in Health Care)
LDL	low-density lipoprotein
LDL-C	low-density lipoprotein cholesterol
SAE	serious adverse event
SGB	Sozialgesetzbuch (Social Code Book)
SPC	Summary of Product Characteristics

1 Background

On 28 October 2015, the Federal Joint Committee (G-BA) commissioned the Institute for Quality and Efficiency in Health Care (IQWiG) to conduct a supplementary assessment for Commission A15-23 (Lomitapide – Benefit assessment according to §35a Social Code Book [SGB] V).

The pharmaceutical company (hereinafter referred to as “the company”) presented further information on study AEGR-733-005 with its written comments [1]. The G-BA therefore commissioned IQWiG to assess the AEGR-733-005 study (hereinafter referred to as “study 005”). The data were to be assessed under the research question of what low-density lipoprotein (LDL) cholesterol concentration and further recorded parameters were shown in the observation and how these were to be assessed.

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

2 Assessment of the data

2.1 Classification of the information subsequently submitted by the company in the comments

In the original dossier on lomitapide, the company had based its conclusions on the added benefit on several analyses it had designated as “option A”, “option B” and “option C”. As described in dossier assessment A15-23, only option A was conceptually oriented towards a research question of the benefit assessment [2], namely towards research question 1B: adult patients with homozygous familial hypercholesterolaemia in whom drug and dietary options to reduce lipid levels have been exhausted and who receive concomitant LDL apheresis treatment. 10 of the 29 patients included in study 005 were treated with LDL apheresis and therefore potentially relevant for this research question. All further conclusions on study 005 in the present addendum refer to these patients and this research question.

Option A of the company is a before-after comparison (considering the low-density lipoprotein cholesterol [LDL-C] value at the start of treatment in comparison with the LDL-C values after 26 and 78 weeks). Apart from the per se low informative value of a before-after comparison, the concrete approach of the company in the dossier was also inadequate. The following deficiencies in particular were named in dossier assessment A15-23 [2]:

- 1) Incompleteness with regard to content: The LOWER study was not included in the analyses.
- 2) No adequate analyses on the LDL-C value³: Only LDL-C values directly before an LDL apheresis were measured. It was therefore not possible to assess the LDL-C burden.
- 3) Suitability of the patients from the 005 study for research question 1B unclear: There was no information on lipid-lowering pretreatment and on the optimization of the LDL apheresis treatment according to the options available in Germany.
- 4) No adequate analysis on adverse events (AEs): Only the results for the total population of study 005 were presented.

Regarding 1), the company argued in its comment that it considered a joint processing of the studies LOWER and 005 as not meaningful [1]. It argued that, among other things, the mean lomitapide dose of 10 mg daily was considerably lower in the LOWER study than in the 005 study, where it was 40 mg daily. According to the company, one of the reasons for this was a “strictly defined dose escalation” in the 005 study, which was “less strict” in the “clinical practice” (in the LOWER study). Even though the meta-analysis of the results of the studies LOWER and 005 can be questioned for the reasons stated above, it would be meaningful to at least compare the results of the 2 individual studies. However, the company presented no new

³ It was also shown in dossier assessment A15-23 that the company had not proven that the lowering of the LDL-C value in the constellation relevant for the assessment constitutes a valid surrogate outcome for cardiovascular risk reduction. However, this is not subject of the present addendum.

data on the LOWER study, which would have made it possible to assess this study for research question 1B. The data presented by the company were therefore incomplete with regard to content also under consideration of its comment.

Regarding 2), the company argued in its comment that it considered the sole consideration of the LDL-C values measured directly before an LDL apheresis adequate for the benefit assessment of lomitapide. To support this rationale, it presented, among other things, an individual course of LDL-C values of a patient for several weeks with and for several weeks without lomitapide treatment (values before and after LDL apheresis; Figure 1 of the company's comment [1]). This course does not support the company's rationale, however. On the contrary, it confirms the explanations in dossier assessment A15-23 by showing that recording the LDL-C values after LDL apheresis (at least recording the LDL-C level directly *after* LDL apheresis, i.e. the trough level) is mandatory for assessing the LDL-C burden. The reason is that no or only marginal additional lowering from lomitapide regarding the LDL-C values after LDL apheresis was shown in this patient. In contrast, considerable lowering of the LDL-C level under lomitapide treatment can be observed in this course regarding the peak levels (LDL-C values directly *before* LDL apheresis). Considering only the LDL-C values directly *before* LDL apheresis, as done by the company, can lead to a notable overestimation of the LDL-C-lowering potency of lomitapide. The data on LDL-C values presented by the company were therefore inadequate also under consideration of its comment.

Regarding 3), the company presented patient-related information in its comment (see Table 2 of the company's comment [1]). Based on this information, the suitability of the patients for research question 1B cannot be finally assessed because information on the intolerance of individual drugs is missing, for example. The suitability can be assessed more accurately, however:

- Regarding the maximum exhaustion of a drug treatment it can be seen that all 10 patients were treated with a statin and ezetimibe, but that only 2 patients were treated with an additional lipid-lowering drug (niacin or bile acid sequestrant). Moreover, the statin was given at a comparatively low dose in 3 of the 10 patients (< 50% of the maximum dose recommended in the respective Summary of Product Characteristics [SPC] [3,4]: rosuvastatin 10 mg [patient 01-004]; simvastatin 20 mg [patients 31-001 and 35-001]). The suitability for research question 1B is questionable for these 3 patients in particular. Sensitivity analyses under exclusion of these 3 patients were therefore conducted in the present addendum.
- Regarding the optimization of LDL apheresis according to the options available in Germany it can be stated that weekly LDL apheresis was only conducted in 2 of the 10 patients. LDL apheresis was conducted every 2 weeks in 6 patients and even less frequently in the remaining patients (every 4 weeks [patient 01-003] or every 6 weeks [patient 31-001]). Optimization of the LDL apheresis according to the options available in Germany can be questioned particularly for the 2 last-mentioned patients. Further

sensitivity analyses under exclusion of these 2 patients were therefore conducted in the present addendum.

Regarding 4), the company presented further information in its comment, from which it can be inferred that no serious adverse events (SAEs) had occurred in the 10 patients with LDL apheresis, which is the subpopulation of interest. However, the company presented no information on treatment discontinuations due to AEs. Based on the patient-related information (the patient numbers) described under 3), these could be inferred from the documents on the 005 study submitted with the original dossier [5]. Similarly, the results on severe gastrointestinal and hepatic AEs (classified according to the Common Terminology Criteria for Adverse Events [CTCAE]: grade 3 or 4) could be inferred for the subpopulation of interest. It is not possible to conduct a comparison with the ACT even with these data, however, because the company presented no information on this.

From the patient-related information (the patient numbers) described above, it could be additionally inferred that the patients in the relevant subpopulation originated exclusively from the USA (centres 01 and 02) and Italy (centres 31, 32 and 35). The consideration of the LDL-C values showed a considerable difference between these 2 countries. The country-related results on the LDL-C level were therefore also presented as additional information.

2.2 Results

The following tables Table 1 and Table 2 describe the results on the LDL-C levels of the 005 study (before-after comparison, option A of the company) including the sensitivity analyses described above. Table 3 contains the results on AEs from the 005 study.

Table 1: Lomitapide: study 005 – LDL-C values (results on before-after comparison)

Analysis Outcome	N	Start of the study Mean (SD) [mg/dL]	Week 26 Mean (SD) [mg/dL]	Absolute change (SD) ^a ; p-value ^b Relative change	Week 78 Mean (SD) [mg/dL]	Absolute change (SD) ^a ; p-value ^b Relative change
All patients with LDL apheresis						
LDL-C burden	10	ND	ND	ND	ND	ND
LDL-C value before apheresis	10	333 (114)	184 (112)	-149 (114); p = 0.003 -43%	240 (153)	-93 (143); p = 0.071 -27%
LDL-C value after apheresis	10	ND	ND	ND	ND	ND
Sensitivity analysis I: patients with LDL apheresis at least every 2 weeks						
LDL-C value before apheresis	8	346 (114)	217 (98)	-129 (101); p = 0.009 -35%	275 (152)	-72 (150); p = 0.219 -18%
Sensitivity analysis II: patients with statin dose \geq 50% of the maximum dose						
LDL-C value before apheresis	7	347 (92)	198 (120)	-149 (134); p = 0.026 -40%	283 (160)	-65 (157); p = 0.318 -16%
Sensitivity analysis III: patients with LDL apheresis at least every 2 weeks and statin dose \geq 50% of the maximum dose						
LDL-C value before apheresis	6	342 (100)	226 (102)	-116 (149); p = 0.049 -31%	307 (161)	-35 (149); p = 0.592 -8%
a: Change in comparison with start of the study (before-after comparison). b: Institute's calculation (paired t-test). N: number of analysed patients (last observation carried forward [LOCF] analysis); ND: no data; SD: standard deviation						

Table 2: Lomitapide: study 005 – LDL-C values (country-related results, before-after comparison)

Country Analysis Outcome	N	Start of the study Mean (SD)	Week 26 Mean (SD)	Absolute change (SD) ^a Relative change	Week 78 Mean (SD)	Absolute change (SD) ^a Relative change
Country: USA						
<i>Patients with LDL apheresis</i>						
LDL-C value before apheresis	6	363 (119)	222 (130)	-141 (143) -35%	296 (159)	-67 (168) -14%
<i>Patients with LDL apheresis at least every 2 weeks and statin dose \geq 50% of the maximum dose</i>						
LDL-C value before apheresis	4	325 (123)	259 (114)	-66 (98) -18%	351 (168)	+26 (110) +8%
Country: Italy						
<i>Patients with LDL apheresis</i>						
LDL-C value before apheresis	4	287 (105)	126 (44)	-161 (68) -56%	157 (112)	-131 (105) -47%
<i>Patients with LDL apheresis at least every 2 weeks and statin dose \geq 50% of the maximum dose</i>						
LDL-C value before apheresis	2	376 (28)	161 (18)	-215 (46) -57%	219 (146)	-157 (173) -40%
a: Relative change in comparison with start of the study (before-after comparison).						
N: number of analysed patients (last observation carried forward [LOCF] analysis); SD: standard deviation						

Table 3: Lomitapide: study 005 – results on adverse events

Outcome	N	Patients with event n (%)
Severe gastrointestinal or hepatic AEs ^a	10	2 (20)
Serious adverse events	10	0 (0)
Discontinuation due to AEs	10	1 (10)
a: Both patients had both severe gastrointestinal and severe hepatic AEs.		
AE: adverse event; N: number of analysed patients		

Change in LDL-C value

Since the company presented no information on LDL-C values after LDL apheresis, no conclusions can be drawn on the LDL-C burden.

Regarding the LDL-C values directly before LDL apheresis, the before-after in the 005 study comparison showed statistically significant lowering under lomitapide in comparison at week 26, but not at week 78.

The sensitivity analyses without consideration of the patients with questionable suitability for research question 1B (sensitivity analyses I to III) also showed statistically significant

lowering at week 26, but not at week 78. The effect of lomitapide in all 3 sensitivity analyses was lower than in the total subpopulation.

The country-related analyses showed a considerable difference between the results in the USA and in Italy. The effect of lomitapide was notably less pronounced in the USA than in Italy.

Adverse events

In the 005 study, no SAEs were observed in the relevant subpopulation (10 patients). Two patients had both severe gastrointestinal and severe hepatic AEs. Lomitapide treatment was discontinued in one patient due to an AE.

2.3 Summary

From the before-after comparison of the 005 study, the hypothesis can be derived that lomitapide has a short-term LDL-C-lowering effect in patients treated with LDL apheresis, which is in a magnitude of about 30 to 40% in relation to the baseline value. No longer-term lowering of LDL-C from lomitapide can be derived from the available data, however. Besides, the short-term lowering of LDL-C only refers to the LDL-C values directly before an LDL apheresis. Due to a lack of data it is unclear whether the overall LDL-C burden, also in the short term, is lowered. It is also unclear whether the short-term LDL-C-lowering effect or its extent is also achieved without strict titration of lomitapide; there were no data on the LOWER study, where no such strict titration was conducted.

Irrespective of the low certainty of conclusions of the before-after comparison, no reliable conclusions on the occurrence of severe and serious AEs and treatment discontinuations due to AEs under lomitapide can be derived from the 005 study because of the very low number of patients. Moreover, neither data from the LOWER study nor data on the ACT were available.

Overall, the information presented by the company with the comments did not change the conclusions of dossier assessment A15-23: There is no proof of an added benefit of lomitapide in comparison with the ACT.

3 References

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