Latanoprost/netarsudil (primary open-angle glaucoma and ocular hypertension)

Benefit assessment according to §35a SGB V[1]

EXTRACT

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IQWiG thanks the medical and scientific advisor for her contribution to the dossier assessment. However, the advisor was not involved in the actual preparation of the dossier assessment. The responsibility for the contents of the dossier assessment lies solely with IQWiG.

Patient and family involvement

The questionnaire on the disease and its treatment was answered by 4 people.

IQWiG thanks the respondents for participating in the written exchange about how they experienced the disease and its treatment and about the treatment goals. The respondents were not involved in the actual preparation of the dossier assessment.

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Part I: Benefit assessment

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[2] Table numbers start with “2” as numbering follows that of the full dossier assessment.

I List of abbreviations

Abbreviation	Meaning
ACT	appropriate comparator therapy
AE	adverse event
ETDRS	Early Treatment of Diabetic Retinopathy Study
G-BA	Gemeinsamer Bundesausschuss (Federal Joint Committee)
IOP	intraocular pressure
IQWiG	Institut für Qualität und Wirtschaftlichkeit im Gesundheitswesen (Institute for Quality and Efficiency in Health Care)
logMAR	logarithm of the minimum angle of resolution
MCS	Mental Component Summary
NEI VFQ-25	National Eye Institute Visual Functioning Questionnaire-25
PCS	Physical Component Summary
PT	Preferred Term
RCT	randomized controlled trial
SAE	serious adverse event
SF-36	Short Form 36 Health Survey
SGB	Sozialgesetzbuch (Social Code Book)
SOC	System Organ Class
SPC	Summary of Product Characteristics
VAS	visual analogue scale

I 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 combination latanoprost/netarsudil. 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 December 2022.

Research question

The present report aims to assess the added benefit of the fixed combination of latanoprost/netarsudil in comparison with the appropriate comparator therapy (ACT), a combination of a beta blocker + prostaglandin analogue or prostamide in the form of a free or fixed combination, in adult patients with primary open-angle glaucoma or ocular hypertension for whom monotherapy with a prostaglandin or netarsudil provides insufficient intraocular pressure (IOP) reduction.

The research question presented in Table 2 results from the ACT specified by the G-BA.

Table 2: Research question of the benefit assessment of latanoprost/netarsudil

Therapeutic indication	**ACT[a]**
Adults with primary open-angle glaucoma or ocular hypertension for whom monotherapy with a prostaglandin[b] or netarsudil provides insufficient IOP reduction	Combination therapy of beta-blocker + prostaglandin analogue or prostamide as non-fixed or fixed combination
a. Presented is the ACT specified by the G-BA. b. For the purposes of the present benefit assessment, prostaglandins are assumed to comprise both prostaglandin analogues and prostamides. ACT: appropriate comparator therapy; G-BA: Federal Joint Committee; IOP: intraocular pressure	

The company followed the G-BA's specification of the ACT.

The assessment is conducted by means of patient-relevant outcomes on the basis of the data provided by the company in the dossier. Randomized controlled trials (RCTs) with a minimum duration of 24 weeks are used for the derivation of added benefit. This concurs with the company's inclusion criteria.

Study pool and study design

The study pool for the present benefit assessment consists of the MERCURY 3 study.

Study design

The MERCURY 3 study is a randomized, double-blind, parallel-group study comparing latanoprost/netarsudil versus bimatoprost/timolol. The study enrolled adult patients with primary open-angle glaucoma and/or ocular hypertension in both eyes who have been treated with local ocular hypotensive agents. Patients' current monotherapy provided insufficient control, and/or, in the investigator's opinion, patients required combination therapy.

The study included 430 patients, who were randomized in a 1:1 ratio to treatment with either latanoprost/netarsudil (N = 218) or bimatoprost/timolol (N = 212). Both eyes were treated for 180 days as per the respective Summaries of Product Characteristics (SPC).

The MERCURY 3 study's primary outcome was the mean IOP within a treatment group at different time points up to Month 3. Patient-relevant secondary outcomes were morbidity, health-related quality of life, and adverse events (AE) outcomes.

Relevant subpopulation of the MERCURY 3 study

As per SPC, the therapeutic indication of latanoprost/netarsudil comprises only adults in whom monotherapy with a prostaglandin analogue or prostamide or netarsudil provided insufficient IOP reduction. The MERCURY 3 study enrolled patients with any prior antihypotensive therapies without implementing any restrictions to specific drug classes. Therefore, the company presents the results of a subpopulation (latanoprost/netarsudil: n = 176, bimatoprost/timolol: n = 160). According to the company, this subpopulation comprises adult patients who had received monotherapy with prostaglandin analogues or prostamides as well as patients who received a prior combination therapy. However, it is unclear whether all patients who received a combination therapy before study enrolment had previously received monotherapy with prostaglandin analogues or prostamides. The benefit assessment of latanoprost/netarsudil therefore uses the MERCURY 3 study data for the subpopulation with prior prostaglandin monotherapy, which the company presents as a subgroup analysis. This subpopulation comprises a total of 211 patients: 116 in the latanoprost/netarsudil arm and 95 in the bimatoprost/timolol arm.

Protocol deviations

Study documents show that 87% of participants experienced at least 1 protocol deviation, with 31% having at least 1 major protocol deviation. The company listed neither the actual protocol deviations nor their classification into major or minor nor their frequencies. The study documents do not show whether some of the protocol deviations (irrespective of their classification as major) concern the survey of patient-relevant outcomes. While both major and minor protocol deviations are largely balanced between the study arms, it remains overall unclear whether the high proportions of protocol deviations affect the MERCURY 3 study results.

Risk of bias

Due to the large number of protocol deviations, the risk of bias on the study level is high for MERCURY 3. The risk of bias for the results of all outcomes was likewise rated as low. The outcomes of health status (National Eye Institute Visual Functioning Questionnaire-25 [NEI VFQ-25]) and health-related quality of life (NEI VFQ-25 and Short Form 36 Health Survey [SF-36]) additionally exhibit a high percentage of missing values; for the outcome of best corrected visual acuity, the percentages of non-responder imputations differ markedly between treatment arms. Based on the MERCURY 3 study, at most hints, e.g. of an added benefit, can be derived for all outcomes.

Results

Mortality

All-cause mortality

In the relevant subpopulation, no data are available for the outcome of all-cause mortality. In the subpopulation analysed by the company, 1 event occurred in the control arm, allowing conclusions on the effects in the relevant subpopulation. This results in no hint of added benefit of latanoprost/netarsudil in comparison with bimatoprost/timolol; an added benefit is therefore not proven.

Morbidity

Visual field loss

For the outcome of visual field deficit, no data are available from the relevant subpopulation. This results in no hint of added benefit of latanoprost/netarsudil in comparison with bimatoprost/timolol; an added benefit is therefore not proven.

Best corrected visual acuity

No statistically significant difference between treatment groups was found for the outcome of best corrected visual acuity (responder analysis on improvement or deterioration by ≥ 0.2 units on the logMAR [logarithm of the minimum angle of resolution] scale; corresponds to ≥ 10 Early Treatment of Diabetic Retinopathy Study [ETDRS] letters). This results in no hint of added benefit of latanoprost/netarsudil in comparison with bimatoprost/timolol; an added benefit is therefore not proven.

Health status (NEI VFQ-25, general health subscale)

There was no statistically significant difference between treatment groups regarding the outcome of health status (recorded with the VFQ-25 visual analogue scale [VAS], general health subscale). This results in no hint of added benefit of latanoprost/netarsudil in comparison with bimatoprost/timolol; an added benefit is therefore not proven.

Health-related quality of life

NEI VFQ-25 (composite score) and SF-36 (Physical and Mental Component Summaries)

No statistically significant difference between treatment groups was found for the outcome of health-related quality of life (surveyed by means of the NEI VFQ-25 composite score and the SF-36 Physical and Mental Component Summaries). This results in no hint of added benefit of latanoprost/netarsudil in comparison with bimatoprost/timolol; an added benefit is therefore not proven.

Side effects

Serious adverse events (SAEs) and ocular AEs

No data on the relevant subpopulation were available for the outcomes of SAEs or ocular AEs. This results in no hint of greater or lesser harm from latanoprost/netarsudil in comparison with bimatoprost/timolol for either of them; greater or lesser harm is therefore not proven.

Ocular SAEs

No statistically significant difference between treatment groups was shown for the outcome of ocular SAEs. This results in no hint of greater or lesser harm from latanoprost/netarsudil in comparison with bimatoprost/timolol; greater or lesser harm is therefore not proven.

Discontinuation due to AEs

A statistically significant difference between treatment groups to the disadvantage of latanoprost/netarsudil was shown for the outcome of discontinuation due to AEs. This results in a hint of greater harm from latanoprost/netarsudil in comparison with bimatoprost/timolol.

Probability and extent of added benefit, patient groups with therapeutically important added benefit[3]

On the basis of the results presented, the probability and extent of added benefit of the drug combination of latanoprost/netarsudil in comparison with the ACT are assessed as follows:

All things considered, the only effect found is an unfavourable one for the outcome of discontinuation of AEs, with an extent of considerable. The outcome is allocated to the category of non-serious/non-severe side effects because insufficient information is available on the allocation to a severity category. For this outcome, the company presents only an

[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].

incomplete list of the included events on the System Organ Class [SOC] and Preferred Term [PT] levels (this incompleteness concerns both the subpopulation relevant for this assessment and – albeit to a lesser extent – the subpopulation relevant as per the company's Module 4 A). Overall, for the majority of discontinuations, it therefore remains unclear which events led to them.

Furthermore, the company's Module 4 A presents no data on ocular AEs despite the fact that they were surveyed in the context of the study and data are available in the study report for the total population. The ocular AE data from the total population suggest an effect to the disadvantage of latanoprost/netarsudil, although it is unclear whether individual PTs included in the analysis of ocular AEs (e.g. conjunctival hyperaemia and cornea verticillata) may be of lesser relevance or asymptomatic. Furthermore, the data on common AEs on the SOC and PT levels are incomplete for the relevant subpopulation. Furthermore, no information is available as to how many and which SAEs occurred in the relevant subpopulation (but no significant effect is found in the overall population or in the subpopulation analysed by the company; in both populations: 3% in the intervention arm versus 3% in the control arm).

Taking into account all available results, the unfavourable effect regarding the outcome of discontinuation due to AEs is therefore insufficient for deriving lesser benefit of latanoprost/netarsudil. Additionally, while incomplete data are available for the relevant subpopulation, the missing analyses presumably would not result in unfavourable effects of an extent which would lead to a derivation of only minor benefit in the overall analysis.

In summary, there is no hint of added benefit of latanoprost/netarsudil in comparison with bimatoprost/timolol for patients with primary open-angle glaucoma or ocular hypertension in whom monotherapy with a prostaglandin analogue or prostamide or netarsudil provides insufficient IOP reduction; hence, there is no proof of added benefit.

Table 3 shows a summary of the probability and extent of added benefit of latanoprost/netarsudil.

Table 3: Latanoprost/netarsudil – probability and extent of added benefit

Therapeutic indication	**ACT[a]**	**Probability and extent of added benefit**
Adults with primary open-angle glaucoma or ocular hypertension for whom monotherapy with a prostaglandin or netarsudil provides insufficient IOP reduction	Combination therapy of beta-blocker + prostaglandin analogue or prostamide as non-fixed or fixed combination	Added benefit not proven[b]

a. Presented is the ACT specified by the G-BA.
b. The MERCURY 3 study analysed only patients with primary open-angle glaucoma or ocular hypertension in whom monotherapy with a prostaglandin analogue or prostamide provides insufficient IOP reduction. It remains unclear whether the observed effects are transferable to patients in whom netarsudil monotherapy is insufficiently effective.

ACT: appropriate comparator therapy; G-BA: Federal Joint Committee; IOP: intraocular pressure

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 2 Research question

The present report aims to assess the added benefit of the fixed combination of latanoprost/netarsudil in comparison with the ACT, a combination of a beta blocker + prostaglandin analogue or prostamide in the form of a free or fixed combination, in adult patients with primary open-angle glaucoma or ocular hypertension for whom monotherapy with a prostaglandin or netarsudil provides insufficient IOP reduction.

The research question presented in Table 4 results from the ACT specified by the G-BA.

Table 4: Research question of the benefit assessment of latanoprost/netarsudil

Therapeutic indication	**ACT[a]**
Adults with primary open-angle glaucoma or ocular hypertension for whom monotherapy with a prostaglandin[b] or netarsudil provides insufficient IOP reduction	Combination therapy of beta-blocker + prostaglandin analogue or prostamide as non-fixed or fixed combination
a. Presented is the ACT specified by the G-BA. b. For the purposes of the present benefit assessment, prostaglandins are assumed to comprise both prostaglandin analogues and prostamides. ACT: appropriate comparator therapy; G-BA: Federal Joint Committee; IOP: intraocular pressure	

The company followed the G-BA's specification on the ACT.

The assessment is conducted by means of patient-relevant outcomes on the basis of the data provided by the company in the dossier. RCTs with a minimum duration of 24 weeks are used for the derivation of added benefit. This concurs with the company’s inclusion criteria.

I 3 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 latanoprost + netarsudil (status: 15 November 2022)
- bibliographical literature search on latanoprost + netarsudil (last search on 15 November 2022)
- search in trial registries / trial results databases for studies on latanoprost + netarsudil (last search on 15 November 2022)
- search on the G-BA website for latanoprost + netarsudil (last search on 15 November 2022)

To check the completeness of the study pool:

- search in trial registries for studies on latanoprost + netarsudil (last search on 21 December 2022); for search strategies, see I Appendix A of the full dossier assessment

The check did not identify any additional relevant studies.

I 3.1 Studies included

The study listed in the following Table 5 was included in the benefit assessment.

Table 5: Study pool – RCT, direct comparison: latanoprost/netarsudil versus bimatoprost/timolol

Study	Study category			Available sources		
	Study for the approval of the drug to be assessed (yes/no)	Sponsored study[a] (yes/no)	Third-party study (yes/no)	CSR (yes/no [citation])	Registry entries[b] (yes/no [citation])	Publication (yes/no [citation])
PG324-CS303 (MERCURY 3[c])	No	No	Yes	Yes [3]	Yes [4,5]	No

a. Study sponsored by the company.
b. References of trial registry entries and any available reports on the study design and/or results listed in the trial registries.
c. In the tables below, the study will be referred to using this acronym.

CSR: clinical study report; RCT: randomized controlled trial

I 3.2 Study characteristics

Table 6 and Table 7 describe the study used for the benefit assessment.Table 6: Characteristics of the study included – RCT, direct comparison: latanoprost/netarsudil versus bimatoprost/timolol

Study	Study design	Population	Interventions (number of randomized patients)	Study duration	Location and period of study	Primary outcome; secondary outcomes[a]
MERCURY 3	RCT, double-blind, parallel-group	Adult patients (≥ 18 years) diagnosed with OAG or OHT in both eyes[b], ▪ Inadequately controlled and/or requiring combination therapy[c, d] ▪ Pharmacologically treated IOP ≥ 17 mmHg in at least 1 eye and < 28 mmHg in both eyes ▪ Untreated (after wash-out phase) IOP > 20 mmHg in at least 1 eye and < 36 mmHg in both eyes	Latanoprost/netarsudil (N = 218) Bimatoprost/timolol (N = 212) Relevant subpopulation thereof[e]: latanoprost/netarsudil (n = 116) bimatoprost/timolol (n = 95)	Screening: ND Wash-out phase: 5 days to 4 weeks[f] Treatment: 180 days Follow-up observation: 30 days	68 study centres[g] in Austria, Belgium, Czech Republic, France, Germany, Hungary, Italy, Latvia, Poland, Spain, United Kingdom 09/2017–11/2020	Primary: mean IOP at the time points 8:00 am, 10:00 am, 4:00 pm at Week 2, Week 6, and Month 3 Secondary: morbidity, health-related quality of life, AEs

a. Primary outcomes comprise information without regard to its relevance for this benefit assessment. Secondary outcomes include only information on relevant available outcomes for this benefit assessment.
b. OAG in 1 eye and OHT in the partner eye was accepted.
c. In the investigator's opinion.
d. Treatment-naive patients were excluded.
e. Relevant subpopulation according to the SPC: adults with OAG or OHT in whom monotherapy with a prostaglandin or netarsudil provides insufficient IOP reduction [6].
f. Depending on prior therapy; longer possible as per investigator's opinion, but maximum of 8 weeks.
g. Diverging from this, Module 4 A of the company's dossier indicates 70 or 60 study centres, without listing the countries.

AE: adverse event; IOP: intraocular pressure; mmHg: millimetres of mercury; n: relevant subpopulation; N: number of randomized patients; ND: no data; OAG: primary open-angle glaucoma; OHT: ocular hypertension; RCT: randomized controlled trial

Table 7: Characteristics of the intervention – RCT, direct comparison: latanoprost/netarsudil versus bimatoprost/timolol

Study	Intervention	Comparison
MERCURY 3	Latanoprost/netarsudil (50 µg / 200 µg) Once daily in the evenings, 1 drop in each eye	Bimatoprost/timolol (0.3 mg/ 5 mg) Once daily in the evenings, 1 drop in each eye
	Prior treatment Required ▪ Ocular hypotensive agents at constant regimens for at least 30 days prior to screening Disallowed ▪ Systemic drugs substantially affecting IOP which were not taken at a constant dose within 30 days prior to screening ▪ Any ophthalmic medication within 30 days before screening[a] ▪ Insufficiently effective prior treatment with bimatoprost/timolol ▪ Prior treatment with more than 2 IOP-lowering medications ▪ Eye surgery for glaucoma treatment[b] or refractive surgery[c]	
	Concomitant treatment Allowed ▪ Intermittent use of over-the-counter artificial tear substitutes with a minimum interval of 10 minutes from study medication ▪ Contact lenses 30 minutes apart from the administration of study medication ▪ Systemic therapies which might affect IOP and are applied at a constant regimen Disallowed ▪ Any other ophthalmic medication[d] ▪ Steroid-containing medications applied to the face or as topical eye drops	

a. With the exception of ocular hypotensive agents at a consistent regimen until screening, eyelid cleansers, and lubricating eye drops.
b. Including selective laser trabeculoplasty or argon laser trabeculoplasty in both eyes.
c. For instance, radial keratotomy, photorefractive keratectomy, laser-assisted in situ keratomileusis (LASIK), corneal cross-linking, keratoplasty.
d. Miotics, epinephrine-like preparations, carbonic anhydrase inhibitors (ocular or systemic), α-sympathomimetics, beta-blockers, parasympathomimetics (e.g. pilocarpine), prostaglandin analogues.

RCT: randomized controlled trial

Study design

The MERCURY-3 study is a randomized, double-blind, parallel-group study comparing the fixed combination of latanoprost and netarsudil (hereinafter: latanoprost/netarsudil) with the fixed combination of bimatoprost and timolol (hereinafter: bimatoprost/timolol). The study enrolled adult patients with primary open-angle glaucoma and/or ocular hypertension in both eyes who have been treated with local ocular hypotensive agents. Patients' current monotherapy provided insufficient control and/or, in the investigator's opinion, patients required combination therapy. The study excluded patients who were treatment-naïve, had an inadequate response to bimatoprost/timolol, or were treated with more than

2 hypotensive agents. After a screening visit, study participants underwent a washout period of their ocular medication (5 days to 4 weeks, depending on the type of therapy). This was followed by 2 qualification visits to measure untreated IOP. The eye which qualified at both visits was selected as the study eye. If both eyes were eligible, the eye with the higher IOP was selected as the study eye.

The study included 430 patients, who were randomized in a 1:1 ratio to treatment with either latanoprost/netarsudil (N = 218) or bimatoprost/timolol (N = 212). Stratification factors were study centre and maximum IOP at baseline (< 25 mmHg versus ≥ 25 mmHg).

The treatment duration was 180 days, with both eyes being treated. Latanoprost/netarsudil or bimatoprost/timolol was administered as per respective SPC [6,7].

The MERCURY 3 study's primary outcome was the mean IOP within a treatment group at different time points up to Month 3. Patient-relevant secondary outcomes were morbidity, health-related quality of life, and adverse event (AE) outcomes.

Relevant subpopulation of the MERCURY 3 study

Regarding patients' prior therapies, the MERCURY 3 inclusion criteria are more lenient than the SPC specifications for latanoprost/netarsudil [6]. As per SPC, the therapeutic indication for latanoprost/netarsudil comprises only adults in whom monotherapy with a prostaglandin analogue or prostamide or netarsudil provided insufficient IOP reduction. For the present benefit assessment, prostaglandins presumably comprise both prostaglandin analogues and prostamides. The MERCURY 3 study enrolled patients with any prior antihypotensive therapies without implementing any restrictions to specific drug classes. However, patients who were previously treated with netarsudil are excluded because netarsudil was approved in the European Union only after the start of the study [8].

The company reports that Module 4 A of its dossier analyses the MERCURY 3 subpopulation, which purportedly matches the target population of latanoprost/netarsudil (latanoprost/netarsudil: n = 176; bimatoprost/timolol n = 160). According to the company, this subpopulation comprises adult patients who had received monotherapy with prostaglandin analogues or prostamides as well as patients who received prior combination therapy. The company justifies its inclusion of patients with prior combination therapy by arguing that they presumably failed to achieve adequate IOP reduction with prior monotherapy. As per the guideline issued by the European Glaucoma Society, this monotherapy was to have included a prostaglandin analogue or prostamide as the drug of 1st choice. However, the company did not present any evidence of the patients having actually received monotherapy with prostaglandin analogues or prostamides before the combination therapy.

The company's approach is not appropriate. According to various guidelines for primary open-angle glaucoma or ocular hypertension, the first-line therapy is to be a monotherapy [9-11]. Drugs from different drug classes are available for this purpose. Alongside prostaglandin analogues or prostamides as drugs of 1st choice, drugs such as beta-blockers are used, taking into account contraindications and the patient's individual situation. But in severe disease, combination therapy may be started immediately. Therefore, it is unclear whether all patients who received combination therapy before study enrolment had previously been on monotherapy with prostaglandin analogues or prostamides.

In Appendix 4 G of its dossier, the company presents data for different subgroups, including for patients who had received prostaglandin monotherapy prior to study inclusion. The study documents show that these monotherapies included prostaglandin analogues and prostamides. This subpopulation corresponds to the relevant therapeutic indication as per SPC. Therefore, the MERCURY 3 data from the subpopulation with prior prostaglandin monotherapy (hereinafter: relevant subpopulation) were used for the benefit assessment of latanoprost/netarsudil. This subpopulation comprises a total of 211 patients: 116 in the latanoprost/netarsudil arm and 95 in the bimatoprost/timolol arm.

Protocol deviations

Protocol deviations were documented in 87% of MERCURY 3 participants. A total of 31% of participants had at least 1 major protocol deviation, and 83% had at least 1 minor one. The study documents show that protocol deviations were defined as violations of inclusion or exclusion criteria, lack of outcome recording, or visits and examinations which were missed or not conducted as per protocol. However, the company failed to itemize the protocol deviations which had actually occurred, their classification as major or minor, and their frequencies. The study documents do not show whether some of the protocol deviations (irrespective of their classification as major) concern the survey of patient-relevant outcomes.

Both the protocol deviations deemed major (latanoprost/netarsudil: 32%; bimatoprost/timolol: 31%) and those deemed minor (latanoprost/netarsudil: 81%; bimatoprost/timolol: 86%) are largely balanced between study arms. Overall, however, it remains unclear whether the high proportions of protocol deviations affect the MERCURY 3 study results. This issue has been taken into account in the assessment of the risk of bias of results (see Section I 4.2).

Characteristics of the study population

Table 8 shows the characteristics of the patients in the included study. No information on patient characteristics was available for the relevant subpopulation of patients who received prior monotherapy with prostaglandin analogues or prostamides. For this reason, Table 8 presents the corresponding data only for the total population of MERCURY 3. Hence all

conclusions regarding patient characteristics which rest on Table 8 can be drawn only for the total population of the included study.

Table 4–12 in Module 4 A provides information on the characteristics of the subpopulation used by the company. The subpopulation used in the present assessment represents a subpopulation of the latter.

Table 8: Characteristics of the study population as well as study/treatment discontinuation – RCT, direct comparison: latanoprost/netarsudil versus bimatoprost/timolol

Study **Characteristic** **Category**	**Latanoprost/netarsudil** **N[a] = 218**	**Bimatoprost/timolol** **N[a] = 212**
MERCURY 3		
Total population		
Age [years], mean (SD)	67 (12)	67 (11)
Sex [F/M], %	60/40	43/57
Family origin, n (%)		
White	210 (96)	200 (94)
Black or African American	4 (2)	5 (2)
Asian	0 (0)	3 (1)
Other	2 (1)	0 (0)
No data	2 (1)	4 (2)
Diagnosis of study eye, n (%)		
OAG	124 (57)	112 (53)
OHT	94 (43)	100 (47)
Disease duration: time since current diagnosis [months], mean (SD)	73.4 (70.7)[b]	79.3 (83.8)[b]
Prior hypotensive therapy, n (%)		
Prostaglandin monotherapy	116 (53)	95 (45)
Other monotherapy	42 (19)	52 (25)
Combination therapy	60 (28)	65 (31)
Duration of current hypotensive therapy [months], mean (SD)	36.1 (44.1)[b]	42.2 (54.1)[b]
Screening IOP [mmHg] – study eye, mean (SD)	20.6 (2.4)	20.5 (2.4)
Central corneal thickness [µm] – study eye, mean (SD)	547.7 (32.5)	550.6 (34.5)
Cup-to-disc ratio – study eye, mean (SD)	0.5 (0.2)	0.5 (0.2)
Visual field loss [dB] – study eye, mean (SD)	–1.7 (4.2)	–2.0 (4.4)
Treatment discontinuation, n (%)	ND	ND
Study discontinuation, n (%)[c]	55 (25)	13 (6)

a. Number of randomized patients. Values which are based on different patient numbers are marked in the corresponding line if the deviation is relevant.
b. Institute's calculation.
c. Common reasons for treatment discontinuation in the intervention versus control arms were: AEs (18% vs. 2%), withdrawal of consent (2% vs. 1%), protocol violations (1% vs. 1%).

AE: adverse event; dB: decibel; IOP: intraocular pressure; F: female; M: male; mmHg: millimetres of mercury; n: number of patients in the category; N: number of randomized patients: OAG: primary open-angle glaucoma; OHT: ocular hypertension; RCT: randomized controlled trial; SD: standard deviation

At baseline, the patient characteristics of the total population were largely comparable in the 2 treatment arms. Almost all patients were of Caucasian family origin; their mean age was 67 years. The study's latanoprost/netarsudil arm enrolled more women than men (60% versus 40%), while the bimatoprost/timolol arm had more men than women (57% versus 43%). Slightly more than half of patients were diagnosed with primary open-angle glaucoma. The mean IOP in the study eye was 20.6 mmHg at baseline, and the mean time since diagnosis was 73 months and 79 months, respectively. Overall, at the time of screening for study inclusion, about half of patients received monotherapy with prostaglandin analogues or prostamides, while about one-third received a combination therapy. The percentage of patients who dropped out of the study was four times as high in the latanoprost/netarsudil arm as in the bimatoprost/timolol arm (25% versus 6%), with AEs being the main reason for dropout.

Risk of bias across outcomes (study level)

Table 9 shows the risk of bias across outcomes (risk of bias at study level).

Table 9: Risk of bias across outcomes (study level) – RCT, direct comparison: latanoprost/netarsudil versus bimatoprost/timolol

Study	Adequate random sequence generation	Allocation concealment	Blinding		Nonselective reporting	Absence of additional aspects	Risk of bias at study level
			Patients	Treatment providers			
MERCURY 3	Yes	Yes	Yes	Yes	Yes	No[a]	High

a. High proportions of protocol deviations in the study population found in both treatment arms (latanoprost/netarsudil: 86%; bimatoprost/timolol: 89%).

ACT: appropriate comparator therapy; RCT: randomized controlled trial

The risk of bias across outcomes was rated as high for MERCURY 3. This is due to the high number of protocol deviations in the study (for a detailed explanation, see protocol deviations section).

Transferability of the study results to the German health care context

The company's Module 4 A provides reasoning as to why the company deems the results of the MERCURY 3 study to be transferable to the German health care context. The company bases its conclusions on a comparison of the study population versus demographic data from an empirical analysis of health insurance data concerning the health services situation in adult patients with primary open-angle glaucoma and ocular hypertension in Germany [12] as well as data from the Gutenberg Health Study [13], which, according to the company, draws

conclusions on the German population. The company argues that the patient characteristics (sex, age, ocular diagnosis, and central corneal thickness) are comparable to the German health services situation. In addition, the company reports that all study centres of the MERCURY 3 were located in European countries, a circumstance which supports comparability with the German population. Overall, the company therefore presumes the study results to be transferable to the German health care context.

However, the information provided by the company is based on the total population of the MERCURY 3 study. The company did not provide any information on the transferability of the study results to the German healthcare context for the relevant subpopulation.

I 4 Results on added benefit

I 4.1 Outcomes included

The following patient-relevant outcomes were to be included in the assessment:

- Mortality
  - all-cause mortality
- Morbidity
  - visual field loss
  - best corrected visual acuity (measured using ETDRS charts)
  - health status (surveyed with the NEI VFQ-25, general health subscale)
- Health-related quality of life
  - health-related quality of life (recorded using NEI VFQ-25)
  - health-related quality of life (surveyed with the Short Form 36 Health Survey [SF-36])
- Side effects
  - serious adverse events (SAEs)
  - discontinuation due to AEs
  - ocular AEs
  - ocular SAEs
  - other specific AEs, if any

The choice of patient-relevant outcomes deviates from that taken by the company, which used other outcomes in the dossier (Module 4A).

Table 10 shows the outcomes for which data were available in the included study.

Table 10: Matrix of outcomes – RCT, direct comparison: latanoprost/netarsudil versus bimatoprost/timolol

Study	Outcomes										
	All-cause mortality[a]	Visual field loss	Best corrected visual acuity	Health status (NEI VFQ-25, general health subscale)	Health-related quality of life (NEI VFQ-25)	Health-related quality of life (SF-36)	SAEs	Discontinuation due to AEs[b]	Ocular AEs	Ocular SAEs	Other specific AEs
MERCURY 3	Yes[c]	No[d]	Yes	Yes	Yes	Yes	No[e]	Yes[f]	No[e]	Yes[g]	No[h]

a. Deaths were surveyed under AEs.
b. Potentially includes events due to the underlying disease; given the available evidence, the disease-related events included in these analyses presumably have no relevant effects on the study results, particularly not on extent.
c. No data available for the relevant subpopulation; however, the data from the subpopulation analysed by the company allow drawing conclusions on the effects in the relevant subpopulation.
d. No usable data available (for justification, see body of text below).
e. No data available for the relevant subpopulation; the data from the total population or the subpopulation analysed by the company are presented as supplementary information.
f. No usable analyses of the outcome of discontinuation due to AEs are available for the relevant subpopulation. Given the available evidence, the analyses of treatment discontinuations due to AEs with subsequent study discontinuation are used as an alternative (see text below for an explanation).
g. The company did not submit any analyses of ocular SAEs; however, the information provided in Module 5 for the overall population shows that no ocular SAEs occurred in the intervention arm or the control arm.
h. No usable analyses available on AEs because for the relevant subpopulation, complete data on common AEs are unavailable at the SOC/PT level. Therefore, selecting specific AEs was not possible.

AE: adverse event; NEI VFQ-25: National Eye Institute Visual Functioning Questionnaire-25; PT: Preferred Term; RCT: randomized controlled trial; SAE: serious adverse event; SF-36: Short Form 36 – Health Survey; SOC: System Organ Class

Notes on the included outcomes and analyses

Visual field loss

The MERCURY 3 study surveyed the visual field with the aid of automated threshold perimetry (Humphrey 30-2 and 24-2, respectively). The Swedish interactive thresholding algorithm (SITA) was used as the algorithm for determining the threshold. The determined thresholds are measured in decibel (dB). For each measured value, the deviation of the respective

threshold from the standard for same-age adults is determined and condensed (mean deviation, MD) across all measured points. The more negative the value, the greater the visual field loss [9,14].

For the outcome of visual field loss, the company's dossier presents continuous analyses of mean change by Month 6. The information provided in Module 5 shows that these data apply only to the study eye despite the fact that the inclusion criteria specify for both eyes to be affected by the disease and treated. Module 5 supplies data on the other eye only for the total population. The company has not submitted data for the complete visual field based on analyses of both eyes.

The presented analyses of the outcome of visual field loss are disregarded in the derivation of added benefit, as justified below. The results are presented as supplementary information in I Appendix C of the full dossier assessment.

The monocular visual field of the affected eye is typically determined in the diagnostics and follow-up of primary open-angle glaucoma or ocular hypertension as well as for the treatment decision [9]. Typically, visual field defects are not located in matching places in both visual fields; therefore, they are compensated by the perception of the other eye [15]. As a consequence, patients often notice visual field defects, particularly those in the weaker eye, only late or not at all. As per the European Glaucoma Society guideline, visual impairment and hence quality of life is largely determined by the binocular visual field or the field of the better eye [9]. An analysis of the binocular visual field would therefore be more suitable for logging visual impairments which are noticeable to patients or symptomatic. Furthermore, the company drew no conclusions as to which changes in the visual field are to be rated as relevant and lead to changes noticeable to patients. The guidelines do not include any standardised thresholds which can be rated as a response or progression [9].

Best corrected visual acuity

The study measured best corrected visual acuity by means of visual charts as per ETDRS standard at a distance of 3 to 6 meters. A vision chart consists of 14 rows of vision signs with 5 letters each and is thus made up of a total of 70 letters. The letter size decreases with each row.

The MERCURY 3 study determined best corrected visual acuity as the logMAR visual acuity. One cell with 5 letters each corresponds to 0.1 logMAR. Values increase with worsening visual acuity.

The company presents both continuous analyses and responder analyses on improvement and deterioration of visual acuity of both eyes. In the present therapeutic indication, deterioration of visual acuity may result from progression of disease. Visual acuity might be

improved by decreasing IOP and hence improved physiological function of the eye [16]. In the present therapeutic indication, analyses of both improvement and deterioration of best corrected visual acuity are therefore taken into account. According to the reasons described in the benefit assessments of ocriplasmin [17,18], the responder analysis of improvement by ≥ 10 ETDRS letters (corresponds to > 10 ETDRS letters or ≥ 2 lines) was used in the present benefit assessment. The responder analyses of improvement as well as deterioration by ≥ 3 logMAR units (corresponds to ≥ 15 ETDRS letters or ≥ 3 lines) are presented as supplementary information.

NEI VFQ-25

The NEI VFQ-25 is a questionnaire for surveying vision-related quality of life; it consists of a total of 26 items and 12 subscales [19]. Among these, 25 items (11 subscales) concern vision, and 1 item (1 subscale) surveys general health.

The scores for all items are transformed to arrive at a score of 0 to 100, and for each subscale, an average score is calculated based on all the items of the subscale. Finally, a composite score is calculated using the mean of the averaged subscale scores, excluding the subscale on general health. The composite score can reach values between 0 and 100, with higher values indicating better vision-related quality of life.

The company presents both prespecified continuous analyses (change by Month 6) and responder analyses conducted *post hoc* on change in the NEI VFQ-25 composite score and the 12 subscales by 15% each. The company does not operationalize the responder analyses in more detail, but merely presents the results and describes them as change from baseline. The data do not show whether this is to include only improvements (in the present indication, both improvements and deteriorations are relevant, but a combined responder analysis would not be appropriate). Therefore, the continuous analyses were used for the present assessment. No statistically significant differences between treatment groups were found in the responder analyses, as was the case in the continuous analyses.

Unlike the company, this assessment assigned the subscale on general health (1 item) to the morbidity category.

SF-36

In Module 4 A, the company presented predefined continuous analyses and post-hoc responder analyses of the Physical Component Summary (PCS) and the Mental Component Summary (MCS). For the responder analyses, the company presents results for the response criterion of 15%, corresponding to a change by 9.4 points (PCS) and 9.6 points (MCS). It identifies the presented results as change from baseline. However, the presented data do not clarify whether this concerns only improvements (in the present therapeutic indication, both improvements and deteriorations are relevant, but a combined responder analysis would not

be appropriate). Therefore, the present assessment relies on the continuous analyses. Like the continuous analyses, the responder analyses showed no statistically significant differences between treatment groups.

Side effects

Discontinuation due to AEs

The company presents results for discontinuation due to AEs in Module 4 A for the overall population and in Appendix 4 G for the subpopulation, referring to them as treatment discontinuation due to AEs. According to Module 5, however, these results are in fact treatment discontinuations due to AEs with subsequent study discontinuation. In the present data situation, the analyses of treatment discontinuations due to AEs with subsequent study discontinuation are used as a substitute for the outcome of discontinuation due to AEs; see Section I 4.3.

Furthermore, the data presented on discontinuation due to AEs in Module 4 A (total population) and Appendix 4 G (relevant subpopulation) are incomplete because they fail to list all events (PT and SOC) which led to discontinuation. For the relevant subpopulation, Appendix 4 G presents only events from the SOC of eye disorders, and the company does not provide a complete list of the included events at the PT level. Regarding the outcome of discontinuation due to AEs, the company furthermore presents data which include each person with a discontinuation only with 1 event. Complete data are available only for the total population in the study report. They show that, in some patients, more than 1 PT from different SOCs may have led to discontinuation. The company does not provide any information as to which events leading to discontinuation may have been disregarded.

Other specific AEs

For the relevant subpopulation, Appendix 4 G provides events for common AEs at SOC and PT levels only regarding the SOC of eye disorders. In addition, it is unclear which other common events occurred in other SOCs. Furthermore, there are discrepancies between the data provided in Module 4 A versus the study report in terms of the AEs which occurred in the overall population and the subpopulation analysed by the company. Hence, there is general ambiguity about common AEs at SOC and PT levels. It is therefore impossible to select specific AEs based on the events which occurred in the relevant study. Hence, it remains unclear whether relevant effects exist concerning individual missing specific SOCs or PTs.

I 4.2 Risk of bias

Table 11 describes the risk of bias for the results of the relevant outcomes.

Table 11: Risk of bias across outcomes and outcome-specific risk of bias – RCT, direct comparison: latanoprost/netarsudil versus bimatoprost/timolol

Study		Outcomes										
	Study level	All-cause mortality[a]	Visual field loss	Best corrected visual acuity	Health status (NEI VFQ-25, general health subscale)	Health-related quality of life (NEI VFQ-25)	Health-related quality of life (SF-36)	SAEs	Discontinuation due to AEs	Ocular AEs	Ocular SAEs	Other specific AEs
MERCURY 3	H[b]	H[b, c]	-[d]	H[b, e]	H[b, f]	H[b, f]	H[b, f]	-[g]	H[b]	-[g]	H[b,i]	-[j]

a. Deaths were surveyed under AEs.
b. High risk of bias across outcomes due to high number of protocol deviations (for explanation, see Section I 3.2)
c. No data available for the relevant subpopulation; however, the data from the subpopulation analysed by the company allow drawing conclusions on the effects in the relevant subpopulation.
d. No usable data available (see Section I 4.1 for reasoning).
e. Markedly different proportions of non-responder imputations between treatment arms (latanoprost/netarsudil vs. bimatoprost/timolol: 21.8% vs. 7.4%)
f. A total of > 10% missing values in the analysis and > 5% difference in missing values between treatment arms both at baseline (latanoprost/netarsudil vs. bimatoprost/timolol: 19.1% vs. 7.4%) and at the time of analysis (latanoprost/netarsudil vs. bimatoprost/timolol: 21.8% vs. 7.4%)
g. No data available for the relevant subpopulation; the data from the total population or the subpopulation analysed by the company are presented as supplementary information.
h. No usable analyses of the outcome of discontinuation due to AEs are available for the relevant subpopulation. Given the available evidence, the analyses of treatment discontinuations due to AEs with subsequent study discontinuation are used as a substitute (see Section I 4.1 below for an explanation).
i. The company did not submit any analyses of ocular SAEs; however, the information provided in Module 5 for the total population show that no ocular SAEs occurred in the intervention or control arm.
j. No usable analyses available on AEs because no complete data are available on common AEs at the SOC/PT level for the relevant subpopulation. Therefore, it was impossible to select specific AEs.

AE: adverse event; H: high; L: low; NEI VFQ-25: National Eye Institute Visual Functioning Questionnaire-25; PT: Preferred Term; RCT: randomized controlled trial; SAE: serious adverse event; SF-36: Short Form-36 Health Survey; SOC: System Organ Class

Due to the high number of protocol deviations, with an unclear effect on the results of the MERCURY 3 study, the risk of bias across outcomes at the study level is rated as high (for an explanation, see Section I 3.2). This also leads to a high risk of bias for the results of all individual outcomes surveyed in the study.

The outcomes of health status (NEI VFQ-25) and health-related quality of life (NEI VFQ-25 and SF-36) additionally suffer from a high proportion of missing values, which further contributes to a high risk of bias for the results of these outcomes. For the outcomes of best-corrected visual acuity, markedly different proportions of non-responder imputations between treatment arms contribute to a high risk of bias of results.

Overall, this reduces the certainty of conclusions of the study results for the present research question. Based on the MERCURY 3 study, at most hints, e.g. of an added benefit, can be derived for all presented outcomes.

I 4.3 Results

Table 12 and Table 13 summarise the results comparing latanoprost/netarsudil versus bimatoprost/timolol in patients with primary open-angle glaucoma or ocular hypertension in whom monotherapy with a prostaglandin analogue or prostamide or netarsudil provides inadequate IOP reduction. Where necessary, calculations conducted by the Institute are provided in addition to the data from the company's dossier.

Tables on common AEs, common SAEs, and discontinuations due to AEs are presented in I Appendix B of the full dossier assessment. Results for the outcome of visual field loss are presented as supplementary information in I Appendix C of the full dossier assessment.

Table 12: Results (mortality, morbidity, side effects) – RCT, direct comparison: latanoprost/netarsudil versus bimatoprost/timolol (multipage table)

Study Outcome category Outcome	Latanoprost/netarsudil		Bimatoprost/timolol		Latanoprost/netarsudil vs. bimatoprost/timolol
	N	Patients with event n (%)	N	Patients with event n (%)	RR [95% CI]; p-value
MERCURY 3					
Mortality					
All-cause mortality	116	0 (0)	95	≤ 1 (≤ 1)	–[a]
Morbidity					
Best corrected visual acuity[b]					
Improvement by ≥ 0.2 logMAR units	110	2 (2)	95	3 (3)	0.6 [0.1; 3.4]; 0.618[c]
Deterioration by ≥ 0.2 logMAR units	110	2 (2)	95	2 (2)	0.9 [0.1; 6.0]; 0.952[c]
Improvement by ≥ 0.3 logMAR units (presented as supplementary information)	*110*	*0 (0)*	*95*	*1 (1)*	0.3 [0.0; 7.0]; 0.358[c]
Deterioration by ≥ 0.3 logMAR units (presented as supplementary information)	*110*	*0 (0)*	*95*	*1 (1)*	0.3 [0.0; 7.0]; 0.358[c]
Side effects					
AEs[d] (supplementary information)	116	93 (80)	95	58 (61)	-
SAEs	116	ND	95	ND	–[e]
Discontinuation due to AEs[d,f]	116	14 (12)	95	1 (1)	11.5 [1.5; 85.6]; 0.002[c]
Ocular AEs	116	ND	95	ND	–[g]
Ocular SAEs	116	0 (0)[h]	95	0 (0)[h]	–
Other specific AEs	No usable data[i]				

Table 12: Results (mortality, morbidity, side effects) – RCT, direct comparison: latanoprost/netarsudil versus bimatoprost/timolol (multipage table)

Study Outcome category Outcome	Latanoprost/netarsudil		Bimatoprost/timolol		Latanoprost/netarsudil vs. bimatoprost/timolol
	N	Patients with event n (%)	N	Patients with event n (%)	RR [95% CI]; p-value
a. Among the subpopulation analysed by the company, only 1 event was observed in the control arm. Under the assumption that this event occurs in the control arm of the relevant subpopulation, the following results are obtained: intervention arm 0% vs. control arm 1%; RR: 0.27 [0.01; 6.64]; p = 0.355[c].					
b. Based on both eyes; proportion of patients with an increase or decrease in visual acuity by ≥ 0.2 logMAR units, corresponding to ≥ 10 EDTRS letters (or shown as supplementary information: ≥ 0.3 logMAR units, corresponding to ≥ 15 EDTRS letters) at Month 6 versus baseline. One line with 5 letters each corresponds to 0.1 logMAR (scale range from –0.3 logMAR to 1.0 logMAR). Lower (decreasing) or higher (increasing) values on the logMAR scale mean an improvement or worsening of symptoms, respectively.					
c. Institute's calculation, unconditional exact test (CSZ method according to [20]).					
d. Potentially includes events which are due to the underlying disease; given the available evidence, the disease-related events included in these analyses can be safely assumed to have no relevant effects on the study results, particularly not on extent.					
e. The company provides data only for the subpopulation it analysed: number of patients with ≥ 1 SAE: intervention arm n = 6 (3%) vs. control arm n = 5 (3%).					
f. No usable analyses of the outcome of discontinuation due to AEs are available for the relevant subpopulation. Given the available evidence, the analyses of treatment discontinuations due to AEs with subsequent study discontinuation are used as a substitute (see Section I 4.1 below for an explanation).					
g. The company's Module 4 A did not present any data on this outcome. Module 5 contains data only for the total population: number of patients with ≥ 1 ocular AE: intervention arm n = 131 (60%) vs. control arm n = 64 (30%), RR: 1.99 [1.58; 2.51]; p < 0.001[c]. The following ocular AEs are common in the total population: conjunctival hyperaemia (33% vs. 11%), cornea verticillata (11% vs. 0%), conjunctival haemorrhage (8% vs. 2%), itchy eye (8% vs. 2%), keratitis punctata (6% vs. 2%), allergic conjunctivitis (6% vs. 1%). It is unclear whether some of the included PTs may be of lesser relevance or asymptomatic.					
h. The company did not submit any analyses of ocular SAEs; however, the information in Module 5 for the total population show that no ocular SAEs occurred in the intervention arm or the control arm.					
i. No usable analyses available on AEs because the available data on common AEs at the SOC/PT level are incomplete for the relevant subpopulation. Therefore, it was impossible to select specific AEs.					
AE: adverse event; CI: confidence interval; ETDRS: Early Treatment Diabetic Retinopathy Study; logMAR: logarithm of the minimum angle of resolution; n: number of patients with (at least 1) event; N: number of analysed patients; ND: no data; NEI VFQ-25: National Eye Institute Visual Functioning Questionnaire-25; PT: Preferred Term; RCT: randomized controlled trial; RR: relative risk; SAE: serious adverse event; SOC: System Organ Class					

Table 13: Results (morbidity, health-related quality of life) – RCT, direct comparison: latanoprost/netarsudil versus bimatoprost/timolol (multipage table)

Study **Outcome category** **Outcome**	**Latanoprost/netarsudil**			**Bimatoprost/timolol**			**Latanoprost/netarsudil vs. bimatoprost/timolol**
	N[a]	**Values at baseline mean (SD)**	**Change by end of study mean[b] (SE)**	**N[a]**	**Values at baseline mean (SD)**	**Change by end of study mean[b] (SE)**	**MD [95% CI]; p-value[b]**
MERCURY 3							
Morbidity							
Visual field loss	No usable data[c]						
NEI VFQ-25[d]							
General health status subscale	86	55.62 (20.90)	0.62 (2.39)	88	55.11 (19.01)	1.27 (2.40)	–0.6 [–5.1; 3.8]; 0.774
Health-related quality of life							
NEI VFQ-25[d]							
Composite score	86	83.52 (11.67)	–0.53 (1.11)	88	84.44 (10.73)	0.48 (1.11)	–1.0 [–3.0; 1.0]; 0.331
Subscales (supplementary information)							
General vision	*86*	*75.06 (11.79)*	*−0.37 (1.97)*	*88*	*74.09 (13.95)*	*0.20 (1.98)*	–0.6 [–4.2; 3.1]
Eye pain	*86*	*81.83 (18.66)*	*−5.14 (2.21)*	*88*	*82.10 (17.76)*	*2.65 (2.21)*	*−7.8 [−11.9; −3.7]*
Near vision	*86*	*84.69 (16.21)*	*0.93 (2.25)*	*88*	*86.74 (13.76)*	*1.12 (2.24)*	–0.2 [–4.3; 3.9]
Distance vision	*86*	*86.53 (14.74)*	*1.45 (1.84)*	*88*	*87.83 (15.59)*	*1.87 (1.84)*	–0.4 [–3.8; 3.0]
Social functioning	*86*	*95.49 (10.49)*	*−1.10 (1.41)*	*88*	*95.74 (11.03)*	*−1.20 (1.41)*	0.1 [–2.5; 2.7]
Mental well-being	*86*	*80.09 (17.48)*	*−2.51 (1.79)*	*88*	*81.04 (16.67)*	*−2.82 (1.79)*	0.3 [–3.0; 3.6]
Exercising social roles	*86*	*84.16 (23.36)*	*−3.37 (2.21)*	*88*	*86.65 (19.49)*	*−0.13 (2.20)*	–3.2 [–7.3; 0.8]
Dependence on others	*86*	*94.96 (14.25)*	*−4.25 (1.69)*	*88*	*95.83 (10.65)*	*−3.78 (1.70)*	–0.5 [–3.6; 2.6]
Driving problems	*No usable data[e]*						
Problems with colour vision	*86*	*96.91 (9.84)*	*−2.13 (1.39)*	*87*	*96.88 (9.14)*	*−2.34 (1.40)*	0.2 [–2.4; 2.8]
Peripheral vision	*85*	*86.80 (19.98)*	*5.15 (2.67)*	*88*	*87.50 (18.57)*	*4.03 (2.67)*	1.1 [–3.8; 6.0]

Table 13: Results (morbidity, health-related quality of life) – RCT, direct comparison: latanoprost/netarsudil versus bimatoprost/timolol (multipage table)

Study Outcome category Outcome	Latanoprost/netarsudil			Bimatoprost/timolol			Latanoprost/netarsudil vs. bimatoprost/timolol
	N[a]	Values at baseline mean (SD)	Change by end of study mean[b] (SE)	N[a]	Values at baseline mean (SD)	Change by end of study mean[b] (SE)	MD [95% CI]; p-value[b]
SF-36[d]							
Physical Component Summary (PCS)	86	49.03 (9.32)	–0.23 (0.88)	88	50.68 (8.06)	–0.76 (0.88)	0.5 [–1.1; 2.2]; 0.521
Mental Component Summary (MCS)	86	51.19 (8.94)	0.85 (1.10)	88	51.35 (8.54)	1.41 (1.11)	–0.6 [–2.6; 1.5]; 0.587
Subscales (supplementary information)							
Physical functioning	*86*	*77.73 (21.76)*	*−1.57 (2.36)*	*88*	*79.60 (21.18)*	*−0.18 (2.37)*	–1.4 [–5.8; 3.0]
Physical role functioning	*86*	*77.69 (26.32)*	*−2.89 (3.10)*	*88*	*78.76 (23.70)*	*0.02 (3.11)*	–2.9 [–8.7; 2.8]
Physical pain	*86*	*66.28 (27.95)*	*2.37 (3.07)*	*88*	*74.35 (25.24)*	*1.58 (3.06)*	0.8 [–4.9; 6.5]
General health perception	*86*	*65.53 (19.17)*	*2.53 (2.00)*	*88*	*67.62 (16.81)*	*−1.86 (2.00)*	*4.4 [0.7; 8.1]*
Vitality	*86*	*63.81 (17.81)*	*−0.72 (2.22)*	*88*	*65.77 (16.98)*	*−0.33 (2.23)*	–0.4 [–4.5; 3.7]
Social functioning	*86*	*84.16 (21.90)*	*1.18 (3.07)*	*88*	*86.79 (18.02)*	*−0.89 (3.06)*	2.1 [–3.6; 7.7]
Emotional role functioning	*86*	*84.40 (22.64)*	*2.53 (2.74)*	*88*	*82.58 (19.92)*	*5.64 (2.75)*	–3.1 [–8.2; 2.0]
Mental well-being	*86*	*72.67 (17.60)*	*0.71 (2.24)*	*88*	*74.77 (16.61)*	*2.16 (2.24)*	–1.4 [–5.6; 2.7]

a. Number of patients taken into account in the analysis for calculating the effect estimation; baseline values may rest on different patient numbers.
b. Unless otherwise stated: MMRM stratified by the factors of randomisation country and maximum IOP at baseline (< 25 mmHg vs. ≥ 25 mmHg); effect estimate based on difference in mean changes by Month 6.
c. See Section I 4.1 of the present dossier assessment for the reasoning.
d. Higher (increasing) values indicate improved symptoms / health-related quality of life; positive effects indicate an advantage for the intervention (scale range 0 to 100).
e. Less than 70% of patients included in the analysis.

CI: confidence interval; dB: decibel; MD: mean difference; MMRM: mixed-effects model with repeated measures; N: number of analysed patients; NEI VFQ-25: National Eye Institute Visual Functioning Questionnaire-25; RCT: randomized controlled trial; SD: standard deviation; SE: standard error; SF-36: Short Form 36 Health Survey

Based on the available information, at most hints, e.g. of an added benefit, can be determined for all outcomes (see Section I 4.2).

Mortality

All-cause mortality

In the relevant subpopulation, no data are available for the outcome of all-cause mortality. In the subpopulation analysed by the company, 1 event occurred in the control arm, allowing conclusions on the effects in the relevant subpopulation. This results in no hint of added benefit of latanoprost/netarsudil in comparison with bimatoprost/timolol; an added benefit is therefore not proven.

Morbidity

Visual field loss

For the outcome of visual field deficit, no data are available from the relevant subpopulation. This results in no hint of added benefit of latanoprost/netarsudil in comparison with bimatoprost/timolol; an added benefit is therefore not proven.

Best corrected visual acuity

No statistically significant difference between treatment groups was found for the outcome of best corrected visual acuity (responder analysis on improvement or deterioration by ≥ 0.2 logMAR units; corresponds to ≥ 10 ETDRS letters). This results in no hint of added benefit of latanoprost/netarsudil in comparison with bimatoprost/timolol; an added benefit is therefore not proven.

Health status (NEI VFQ-25, general health subscale)

There was no statistically significant difference between treatment groups regarding the outcome of health status (recorded with the VFQ-25 VAS, general health subscale). This results in no hint of added benefit of latanoprost/netarsudil in comparison with bimatoprost/timolol; an added benefit is therefore not proven.

Health-related quality of life

NEI VFQ-25 (composite score) and SF-36 (Physical and Mental Component Summaries)

No statistically significant difference between treatment groups was found for the outcome of health-related quality of life (surveyed by means of the NEI VFQ-25 composite score as well as the SF-36 Physical and Mental Component Summaries). This results in no hint of added benefit of latanoprost/netarsudil in comparison with bimatoprost/timolol; an added benefit is therefore not proven.

Side effects

SAEs and ocular AEs

No data for the relevant subpopulation were available for the outcomes of SAEs or ocular AEs. This results in no hint of greater or lesser harm from latanoprost/netarsudil in comparison with bimatoprost/timolol for either of them; greater or lesser harm is therefore not proven.

Ocular SAEs

No statistically significant difference between treatment groups was shown for the outcome of ocular SAEs. This results in no hint of greater or lesser harm from latanoprost/netarsudil in comparison with bimatoprost/timolol; greater or lesser harm is therefore not proven.

Discontinuation due to AEs

A statistically significant difference between treatment groups to the disadvantage of latanoprost/netarsudil was shown for the outcome of discontinuation due to AEs. In the present data situation, the analyses of treatment discontinuations due to AEs with subsequent study discontinuation are used as a substitute for the outcome of discontinuation due to AEs (see Section I 4.1 for reasoning). According to the study report, 4 additional patients with an event in the intervention arm discontinued treatment due to AEs. This does not affect the result because, while it might result in a greater disadvantage for latanoprost/netarsudil in the relevant subpopulation, the same extent would be derived at outcome level (at most considerable for non-serious / non-severe adverse events). This results in a hint of greater harm from latanoprost/netarsudil in comparison with bimatoprost/timolol.

I 4.4 Subgroups and other effect modifiers

The following potential effect modifiers were taken into account in the present assessment:

- age (< 65 years versus ≥ 65 years)
- sex (female versus male)

The company's dossier does not present a suitable subgroup characteristic for disease severity or stage.

The dossier provides no subgroup analyses for the relevant subpopulation of patients who received prior monotherapy with prostaglandin analogues or prostamides.

I 5 Probability and extent of added benefit

The probability and extent of added benefit at outcome level are derived below, taking into account the different outcome categories and effect sizes. The methods used for this purpose are explained in the *General Methods* of IQWiG [1].

The approach for deriving an overall conclusion on the added benefit based on the aggregation of conclusions derived at outcome level is a proposal by IQWiG. The G-BA decides on the added benefit.

I 5.1 Assessment of the added benefit at outcome level

The extent of the respective added benefit at outcome level is estimated from the results presented in Section I 4 (see Table 14).

Determination of the outcome category for the outcomes on side effects

It cannot be inferred from the dossier whether the following outcome is serious/severe or non-serious/non-severe. The classification of this outcome is explained below.

Discontinuation due to AE

As described in Section I 4.1, the results presented for discontinuation due to AEs are treatment discontinuations due to AEs with subsequent study discontinuation. Because the information on included events at SOC and PT levels is incomplete, the severity of AEs leading to discontinuation cannot be conclusively assessed. For the outcome of discontinuation due to AEs, the available severity data are consequently insufficient for a classification as serious/severe. The outcome of discontinuation due to AEs was therefore assigned to the outcome category of non-serious/non-severe side effects.

Table 14: Extent of added benefit at outcome level: latanoprost/netarsudil versus bimatoprost/timolol (multipage table)

Outcome category **Outcome**	**Latanoprost/netarsudil vs. bimatoprost/timolol** **Proportion of events (%) or MD** **Effect estimation [95% CI];** **p-value** **Probability**[a]	**Derivation of extent**[b]
Mortality		
All-cause mortality	No data for relevant subpopulation[c]	Lesser/added benefit not proven
Morbidity		
Visual field loss	No usable data[d]	Lesser/added benefit not proven
Best corrected visual acuity		
Improvement by ≥ 0.2 logMAR (corresponds to ≥ 10 ETDRS letters)	2% vs. 3% RR: 0.6 [0.1; 3.4] p = 0.618	Lesser/added benefit not proven
Deterioration by ≥ 0.2 logMAR (corresponds to ≥ 10 ETDRS letters)	2% vs. 2% RR: 0.9 [0.1; 6.0] p = 0.952	
Health status (NEI VFQ-25, general health subscale)	0.62 vs. 1.27 MD: –0.6 [–5.1; 3.8] p = 0.774	Lesser/added benefit not proven
Health-related quality of life		
NEI VFQ-25 (composite score)	–0.53 vs. 0.48 MD: –1.0 [–3.0; 1.0] p = 0.331	Lesser/added benefit not proven
SF-36 Physical Component Summary (PCS)	–0.23 vs. –0.76 MD: 0.5 [–1.1; 2.2] p = 0.521	Lesser/added benefit not proven
SF-36 Mental Component Summary (MCS)	0.85 vs. 1.41 MD: –0.6 [–2.6; 1.5] p = 0.587	Lesser/added benefit not proven
Side effects		
SAEs	No usable data[d]	Greater/lesser harm not proven
Discontinuation due to AEs[e]	12% vs. 1% RR: 11.5 [1.5; 85.6] RR: 0.09 [0.01; 0.65][f] p = 0.002 Probability: hint	Outcome category: non-serious/non-severe side effects CI_u < 0.80 Greater harm; extent: considerable
Ocular AEs	No usable data[g]	Greater/lesser harm not proven
Ocular SAEs[h]	0% vs. 0% RR: -	Greater/lesser harm not proven
Other specific AEs	No usable data[i]	Greater/lesser harm not proven

Table 14: Extent of added benefit at outcome level: latanoprost/netarsudil versus bimatoprost/timolol (multipage table)

Outcome category **Outcome**	**Latanoprost/netarsudil vs. bimatoprost/timolol** **Proportion of events (%) or MD** **Effect estimation [95% CI];** **p-value** **Probability[a]**	**Derivation of extent[b]**
a. Probability provided if there is a statistically significant and relevant effect. b. Depending on the outcome category, estimations of effect size and the scale of the outcome are made with different limits based on the upper or lower limit of the confidence interval (CI_u or CI_L). c. See Section I 4.1 of the present dossier assessment for the reasoning. In the subpopulation analysed by the company, only 1 event was observed in the control arm. Assuming that this event occurs in the control arm of the relevant subpopulation, this results in the following: intervention arm 0% vs. control arm 1%; RR: 0.27 [0.01; 6.64]; p = 0.355. d. See Section I 4.1 of the present dossier assessment for the reasoning. e. No usable analyses of the outcome of discontinuation due to AEs are available for the relevant subpopulation. Given the available evidence, the analyses of treatment discontinuations due to AEs with subsequent study discontinuation are used as a substitute (see Section I 4.1 below for an explanation). f. Institute's calculation; reversed direction of effect to enable use of limits to derive the extent of the added benefit. g. See Section I 4.1 of the present dossier assessment for the reasoning. Among the total population, 131 (60%) and 64 (30%) patients, respectively, had ≥ 1 ocular AE. This results in the following: RR: 1.99 [1.58; 2.51]; p < 0.001. h. The company did not submit any analyses of ocular SAEs; however, the information in Module 5 for the total population show that no ocular SAEs occurred in the intervention arm or the control arm. i. No usable analyses available on AEs because the available data on common AEs at the SOC/PT level are incomplete for the relevant subpopulation. Therefore, it was impossible to select specific AEs. AE: adverse event; CI: confidence interval; CI_L: lower limit of confidence interval; CI_U: upper limit of confidence interval; ETDRS: Early Treatment Diabetic Retinopathy Study; logMAR: logarithm of the minimum angle of resolution; MD: mean difference; NEI VFQ-25: National Eye Institute Functioning Questionnaire-25; PT: Preferred Term; RR: relative risk; SAE: serious adverse event; SF-36: Short Form 36 Health Survey; SOC: System Organ Class		

I 5.2 Overall conclusion on added benefit

Table 15 summarizes the results taken into account in the overall conclusion on the extent of added benefit.

Table 15: Favourable and unfavourable effects from the assessment of latanoprost/netarsudil in comparison with bimatoprost/timolol

Favourable effects	**Unfavourable effects**
-	Non-serious/non-severe side effects ▪ Discontinuation due to AEs[a]: hint of greater harm – extent: considerable
For the outcomes of visual field loss, SAEs, ocular AEs, and other specific AEs, no suitable data are available for the relevant subpopulation.	
a. The data on treatment discontinuations due to AEs with subsequent study discontinuation are used as supplementary information (see Section I 4.1 below for an explanation). AE: adverse event; SAE: serious adverse event	

All things considered, the only effect found is an unfavourable one for the outcome of discontinuation of AEs, with an extent of considerable. The outcome is allocated to the category of non-serious/non-severe side effects because insufficient information is available on the allocation to a severity category. For this outcome, the company presents only an incomplete list of the included events on the SOC and PT levels (this incompleteness affects both the subpopulation relevant for this assessment and – albeit to a lesser extent – the subpopulation relevant according to the company's Module 4 A). Overall, for the majority of discontinuations, it therefore remains unclear which events led to them.

Furthermore, the company's Module 4 A presents no data on ocular AEs despite the fact that they were surveyed in the context of the study and the study report provides data for the total population. The ocular AE data from the total population suggest an effect to the disadvantage of latanoprost/netarsudil, although it is unclear whether individual PTs included in the analysis of ocular AEs (e.g. conjunctival hyperaemia and cornea verticillata) may be of lesser relevance or asymptomatic. Furthermore, the data on common AEs on the SOC and PT levels are incomplete for the relevant subpopulation. Furthermore, no information is available as to how many and which SAEs occurred in the relevant subpopulation (however, no significant effect is found in the total population or in the subpopulation analysed by the company; in both populations: 3% in the intervention arm versus 3% in the control arm).

Taking into account all available results, the unfavourable effect regarding the outcome of discontinuation due to AEs is therefore insufficient for deriving lesser benefit of latanoprost/netarsudil. Additionally, while incomplete data are available for the relevant subpopulation, the missing analyses presumably would not result in unfavourable effects of an extent which would lead to a derivation of only minor benefit in the overall analysis.

In summary, there is no hint of added benefit of latanoprost/netarsudil in comparison with bimatoprost/timolol for patients with primary open-angle glaucoma or ocular hypertension in

whom monotherapy with a prostaglandin analogue or prostamide or netarsudil provides insufficient IOP reduction; hence, there is no proof of added benefit.

Table 16 summarizes the result of the assessment of added benefit for latanoprost/netarsudil in comparison with the ACT.

Table 16: Latanoprost/netarsudil – probability and extent of added benefit

Therapeutic indication	**ACT**[a]	**Probability and extent of added benefit**
Adults with primary open-angle glaucoma or ocular hypertension for whom monotherapy with a prostaglandin or netarsudil provides insufficient IOP reduction	Combination therapy of beta-blocker + prostaglandin analogue or prostamide as non-fixed or fixed combination	Added benefit not proven[b]

a. Presented is the ACT specified by the G-BA.
b. The MERCURY 3 study analysed only patients with primary open-angle glaucoma or ocular hypertension in whom monotherapy with a prostaglandin analogue or prostamide provides insufficient IOP reduction. It remains unclear whether the observed effects are transferable to patients in whom netarsudil monotherapy is insufficiently effective.

ACT: appropriate comparator therapy; G-BA: Federal Joint Committee

The assessment described above concurs with that by the company.

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 6 References for English extract

Please see full dossier assessment for full reference list.

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