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

Addendum to Project A22-129 (dossier assessment)[1]

ADDENDUM

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Table of contents

List of tables

Page

List of abbreviations

Abbreviation	Meaning
AE	adverse event
G-BA	Gemeinsamer Bundesausschuss (Federal Joint Committee)
IQWiG	Institut für Qualität und Wirtschaftlichkeit im Gesundheitswesen (Institute for Quality and Efficiency in Health Care)
MedDRA	Medical Dictionary for Regulatory Activities
NEI VFQ-25	National Eye Institute Visual Functioning Questionnaire-25
PT	Preferred Term
SAE	serious adverse event
SF-36	Short Form 36 Health Survey
SGB	Sozialgesetzbuch (Social Code Book)
SOC	System Organ Class

1 Background

On 3 May 2023, the Federal Joint Committee (G-BA) commissioned the Institute for Quality and Efficiency in Health Care (IQWiG) to conduct supplementary assessments for Project A22-129 (Latanoprost/netarsudil – Benefit assessment according to § 35a Social Code Book V) [1].

The commission comprised the analysis of the documents subsequently submitted in the commenting procedure regarding the subpopulation of the MERCURY 3 study relevant for the benefit assessment (adult patients with primary open-angle glaucoma or ocular hypertension who had received pretreatment with prostaglandin monotherapy), with the exception of the subsequently submitted documents on the partner eye.

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

2 Assessment

2.1 Background of the analyses subsequently submitted

The benefit assessment of the fixed combination of latanoprost/netarsudil used the MERCURY 3 study, which compared latanoprost/netarsudil with the fixed combination of bimatoprost/timolol. The included patients had received different pretreatments. In its dossier, the pharmaceutical company (hereinafter referred to as "the company") presented analyses of different subpopulations, including analyses of the subpopulation relevant for the benefit assessment (pretreatment with prostaglandin monotherapy). However, the company did not provide separate characteristics for the patients in this subpopulation. These data were subsequently presented in the company's comments [2].

The company's dossier contained prespecified continuous analyses (change at month 6) as well as post hoc responder analyses on the change in composite scores by 15% of the scale range for the outcomes of health status (assessed using the National Eye Institute Visual Functioning Questionnaire-25 [NEI VFQ-25]) and health-related quality of life (assessed using the NEI VFQ-25 and the Short Form 36 Health Survey [SF-36]). However, the data did not show whether this was to include only improvements. In the present therapeutic indication, both improvements and deteriorations are relevant, but a combined responder analysis would not be appropriate. The continuous analyses were therefore used for benefit assessment A22-129. In its comments, the company presented separate analyses of the responder analyses for improvement and deterioration. Referring to the score with values ranging from 0 to 100, the company presented analyses with a response criterion of 15.15 points for the NEI VFQ-25. The approach of the company is not appropriate, as the 15% refers to the scale range of the instrument, resulting in a response criterion of 15 points in the case of the NEI VFQ-25. However, the response criterion of 15.15 points chosen by the company is assessed as a sufficient approximation for a response criterion of 15% of the scale range.

For the outcome of discontinuation due to adverse events (AEs), the company only presented the results on treatment discontinuations due to AEs with subsequent study discontinuation in its dossier. Furthermore, the data presented on discontinuation due to AEs in the dossier are incomplete because they fail to list all events (Preferred Terms [PTs] and System Organ Classes [SOCs]) which led to discontinuation. Similarly, a listing of the most frequent events at PT and SOC level was missing for the AEs. In addition, the dossier contains no data on mortality, serious AEs (SAEs) and ocular AEs for the relevant subpopulation. In its comments, the company presented the missing data of the relevant subpopulation on mortality and side effects.

The data subsequently submitted are used for the present benefit assessment.

2.2 Characteristics of the study population

Table 1 shows the characteristics of the patients in the relevant subpopulation.

Table 1: Characteristics of the relevant subpopulation as well as study/treatment discontinuation – RCT, direct comparison: latanoprost/netarsudil vs. bimatoprost/timolol

Study **Characteristic** **Category**	**Latanoprost/netarsudil** **N[a] = 116**	**Bimatoprost/timolol** **N[a] = 95**
MERCURY 3		
Age [years], mean (SD)	67 (12)	67 (11)
Sex [F/M], %	55/45	35/65
Family origin, n (%)		
Caucasian	110 (95)	89 (94)
Black or African American	3 (3)	2 (2)
Other	1 (1)	1 (1)
No data	2 (2)	3 (3)
Diagnosis of study eye[b], n (%)		
OAG	68 (59)	49 (52)
OHT	48 (41)	46 (48)
Disease duration: time since current diagnosis [months], mean (SD)	61.7 (61.5)[c]	66.0 (71.6)[c]
Prior hypotensive therapy, n (%)		
Prostaglandin monotherapy	116 (100)	95 (100)
Other monotherapy	0 (0)	0 (0)
Combination therapy	0 (0)	0 (0)
Duration of current hypotensive therapy [months], mean (SD)	43.6 (50.2)[c]	47.7 (59.2)[c]
Screening IOP (mmHg) – study eye[b], mean (SD)	20.9 (2.4)	20.5 (2.6)
Central corneal thickness (µm) – study eye[b], mean (SD)	544.6 (30.6)	553.6 (31.8)
Cup-to-disc ratio – study eye[b], mean (SD)	0.5 (0.2)	0.5 (0.2)
Visual field loss [dB] – study eye[b], mean (SD)	−1.5 (3.7)	−1.9 (4.5)
Treatment discontinuation, n (%)	ND	ND
Study discontinuation, n (%)	ND	ND

a. Number of randomized patients. Values that are based on different patient numbers are marked in the corresponding line if the deviation is relevant.
c. If both eyes meet the inclusion criteria of the study, the study eye will be the eye with the higher IOP at 8:00 hours at baseline. If both eyes have the same IOP, then the right eye will be the study eye.
c. Institute's calculation.

AE: adverse event; IOP: intraocular pressure; F: female; M: male; 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 relevant subpopulation 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 (women versus men: 55% versus 45%), while the bimatoprost/timolol arm had more men than women (women versus men: 35% versus 65%). Slightly more than half of patients were diagnosed with primary open-angle glaucoma. The mean intraocular pressure in the study eye was 20.7 mmHg at baseline, and the mean time since diagnosis was 62 months and 66 months, respectively. All patients in the relevant subpopulation were receiving monotherapy with prostaglandin analogues or prostamides at the time of screening for study inclusion. There was no information on treatment and study discontinuations for the relevant subpopulation.

2.3 Risk of bias

The assessment of the risk of bias at study and outcome level corresponds to dossier assessment A22-129. 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 (including ocular AEs and SAEs for which no suitable data were available in the dossier assessment) is also rated as high in each case.

Certainty of conclusions

Based on the available information, at most hints can be derived for the outcomes of mortality, health status (NEI VFQ-25), health-related quality of life (NEI VFQ-25, SF-36), and side effects.

2.4 Results

Table 2 summarizes the results subsequently submitted for the comparison of latanoprost/ netarsudil versus bimatoprost/timolol. Tables on common AEs and discontinuation due to AEs are presented in Appendix A.

Table 2: Results (mortality, morbidity, side effects) – RCT, direct comparison: latanoprost/netarsudil vs. 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]
MERCURY 3					
Mortality					
All-cause mortality	116	0 (0)	95	0 (0)	–
Morbidity					
NEI VFQ-25[b]					
General health subscale					
Improvement	89	16 (18)	88	14 (16)	1.1 [0.6; 2.2]; 0.793
Deterioration	89	17 (19)	88	13 (15)	1.3 [0.7; 2.5]; 0.532
Health-related quality of life					
NEI VFQ-25[b]					
Composite score					
Improvement	86	2 (2)	88	2 (2)	1.0 [0.1; 7.1]; > 0.999
Deterioration	86	2 (2)	88	2 (2)	1.0 [0.1; 7.1]; > 0.999
Subscales					
General vision					
Improvement	89	13 (15)	88	20 (23)	0.6 [0.3; 1.2]
Deterioration	89	13 (15)	88	12 (14)	1.1 [0.5; 2.2]
Eye pain					
Improvement	86	3 (3)	88	12 (14)	0.3 [0.1; 0.9]
Deterioration	86	16 (19)	88	5 (6)	3.3 [1.3; 8.5]
Near vision					
Improvement	86	15 (17)	88	12 (14)	1.3 [0.6; 2.6]
Deterioration	86	12 (14)	88	12 (14)	1.0 [0.5; 2.2]
Distance vision					
Improvement	86	8 (9)	88	11 (12)	0.7 [0.3; 1.8]
Deterioration	86	10 (12)	88	9 (10)	1.1 [0.5; 2.7]
Social functioning					
Improvement	86	3 (3)	88	2 (2)	1.5 [0.3; 9.0]
Deterioration	86	3 (3)	88	2 (2)	1.5 [0.3; 9.0]
Mental well-being					
Improvement	86	10 (12)	88	6 (7)	1.7 [0.6; 4.5]
Deterioration	86	5 (6)	88	4 (5)	1.3 [0.4; 4.6]

Table 2: Results (mortality, morbidity, side effects) – RCT, direct comparison: latanoprost/netarsudil vs. 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]
Exercising social roles					
Improvement	86	4 (5)	88	10 (11)	0.4 [0.1; 1.3]
Deterioration	86	7 (8)	88	8 (9)	0.9 [0.3; 2.4]
Dependence on others					
Improvement	86	4 (5)	88	4 (5)	1.0 [0.3; 4.0]
Deterioration	86	6 (7)	88	2 (2)	3.1 [0.6; 14.8]
Driving problems					
Improvement	57	3 (5)	63	7 (11)	0.5 [0.1; 1.7]
Deterioration	57	7 (12)	63	7 (11)	1.1 [0.4; 3.0]
Problems with colour vision					
Improvement	89	5 (6)	88	7 (8)	0.7 [0.2; 2.1]
Deterioration	89	4 (4)	88	3 (3)	1.3 [0.3; 5.7]
Peripheral vision					
Improvement	89	16 (18)	88	14 (16)	1.1 [0.6; 2.2]
Deterioration	89	14 (16)	88	17 (19)	0.8 [0.4; 1.5]
SF-36					
Physical Component Summary (PCS)[c]					
Improvement	86	5 (6)	88	4 (5)	1.3 [0.4; 4.6]; 0.773
Deterioration	86	1 (1)	88	5 (6)	0.2 [0.0; 1.7]; 0.124
Mental Component Summary (MCS)[d]					
Improvement	86	9 (10)	88	7 (8)	1.3 [0.5; 3.4]; 0.600
Deterioration	86	5 (6)	88	7 (8)	0.7 [0.2; 2.2]; 0.682
Side effects					
SAEs	116	5 (4)	95	1 (1)	4.1 [0.5; 34.5]; 0.184
Discontinuation due to AEs	116	18 (16)	95	1 (1)	14.7 [2.0; 108.4]; < 0.001
Ocular AEs[e]	116	75 (65)	95	35 (37)	1.8 [1.3; 2.4]; < 0.001

Table 2: Results (mortality, morbidity, side effects) – RCT, direct comparison: latanoprost/netarsudil vs. 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]
a. Institute's calculation, unconditional exact test (CSZ method according to [3]). b. Proportion of patients with an increase (improvement) and decrease (deterioration) in score of ≥ 15.15 points at month 6 compared with baseline. c. Proportion of patients with an increase (improvement) or decrease (deterioration) in the PCS score by ≥ 9.4 points (corresponds to 15% of the scale range) at month 6 compared with baseline; no data are available for the SF-36 subscales. d. Proportion of patients with an increase (improvement) or decrease (deterioration) in the MCS score by ≥ 9.6 points (corresponds to 15% of the scale range) at month 6 compared with baseline; no data are available for the SF-36 subscales. e. The most common events (in each case in the intervention vs. comparator arm) are the following: conjunctival hyperaemia (PT) (30% vs. 15%), conjunctival haemorrhage (PT) (12% vs. 3%) and cornea verticillata (PT) (11% vs. 0). AE: adverse event; CI: confidence interval; MCS: Mental Component Summary; n: number of patients with (at least one) event; N: number of analysed patients; ND: no data; NEI VFQ-25: National Eye Institute Visual Functioning Questionnaire-25; PCS: Physical Component Summary; PT: Preferred Term; RCT: randomized controlled trial; RR: relative risk; SAE: serious adverse event					

Mortality

All-cause mortality

No death occurred in the relevant subpopulation. There is no hint of added benefit of latanoprost/netarsudil in comparison with bimatoprost/timolol; an added benefit is therefore not proven.

Morbidity

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

For the outcome of health status (surveyed via NEI VFQ-25 general health subscale), no statistically significant differences between treatment groups were shown for improvement or deterioration. There is 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) for improvement or deterioration.

There is no hint of added benefit of latanoprost/netarsudil in comparison with bimatoprost/timolol; an added benefit is therefore not proven.

Side effects

SAEs

For the outcome of SAEs, no statistically significant difference between treatment groups was found. There is 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. There is a hint of greater harm from latanoprost/netarsudil in comparison with bimatoprost/timolol.

Ocular AEs

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

2.4.1 Subgroups

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 did not present a suitable subgroup characteristic for disease severity or stage.

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

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

Using the methods described above, the available subgroup results do not reveal any effect modifications.

2.5 Probability and extent of added benefit

2.5.1 Assessment of the added benefit at outcome level

On the basis of the results presented in Chapter 2.4 and those in the dossier assessment, the extent of the respective added benefit was estimated at outcome level (see Table 3).

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

The subsequently submitted documents of the company show that only 1 of the 18 events in the latanoprost/netarsudil arm was classified as serious. The event in the bimatoprost/timolol arm was not classified as serious. The outcome of discontinuation due to AEs was therefore assigned to the outcome category of non-serious/non-severe side effects.

Table 3: 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 (%)** **Effect estimation [95% CI];** **p-value** **Probability**[a]	**Derivation of extent**[b]
Mortality		
All-cause mortality	0 vs. 0 RR: -	Lesser/added benefit not proven
Morbidity		
Visual field loss (dB)	No usable data[c]	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	Lesser/added benefit not proven
Health status (NEI VFQ-25, general health subscale)		
Improvement	18% vs. 16% RR: 1.1 [0.6; 2.2] p = 0.793	Lesser/added benefit not proven
Deterioration	19% vs. 15% RR: 1.3 [0.7; 2.5] p = 0.532	Lesser/added benefit not proven
Health-related quality of life		
NEI VFQ-25 (composite score)		
Improvement	2% vs. 2% RR: 1.0 [0.1; 7.1] p > 0.999	Lesser/added benefit not proven
Deterioration	2% vs. 2% RR: 1.0 [0.1; 7.1] p > 0.999	Lesser/added benefit not proven
SF-36 Physical Component Summary (PCS)		
Improvement	6% vs. 5% RR: 1.3 [0.4; 4.6] p = 0.773	Lesser/added benefit not proven
Deterioration	1% vs. 6% RR: 0.2 [0.0; 1.7] p = 0.124	Lesser/added benefit not proven

Table 3: 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 (%)** **Effect estimation [95% CI];** **p-value** **Probability**[a]	**Derivation of extent**[b]
SF-36 Mental Component Summary (MCS)		
Improvement	10% vs. 8% RR: 1.3 [0.5; 3.4] p = 0.600	Lesser/added benefit not proven
Deterioration	6% vs. 8% RR: 0.7 [0.2; 2.2] p = 0.682	Lesser/added benefit not proven
Side effects		
SAEs	4% vs. 1% RR: 4.1 [0.5; 34.5] p = 0.184	Greater/lesser harm not proven
Discontinuation due to AEs	16% vs. 1% RR: 14.7 [2.0; 108.4] RR: 0.07 [0.01; 0.5][d] p < 0.001 Probability: “hint”	Outcome category: non-serious/non-severe side effects CI_u < 0.80 Greater harm; extent: “considerable”
Ocular AEs	65% vs. 37% RR: 1.8 [1.3; 2.4] RR: 0.56 [0.42; 0.77][d] p < 0.001 Probability: “hint”	Outcome category: non-serious/non-severe side effects CI_u < 0.80 Greater harm; extent: “considerable”
Ocular SAEs	0 vs. 0 RR: –	Greater/lesser harm not proven

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 limit of the confidence interval (CI_u).
c. See Section I 4.1 of dossier assessment A22-129 for the reasoning.
d. Institute’s calculation; reversed direction of effect to enable the use of limits to derive the extent of added benefit.

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; NEI VFQ-25: National Eye Institute Visual Functioning Questionnaire-25; RR: relative risk; SAE: serious adverse event; SF-36: Short Form 36 Health Survey

2.6 Overall conclusion on added benefit

Table 4 summarizes the results taken into account in the overall conclusion on the extent of added benefit.

Table 4: 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: hint of greater harm – extent: “considerable” ▪ Ocular AEs: hint of greater harm – extent: “considerable”
No suitable data are available for the outcome of visual field loss	
AE: adverse event	

The subsequently submitted data on the relevant subpopulation do not change the overall conclusion on added benefit drawn in dossier assessment A22-129. In addition to the unfavourable effect in the outcome of discontinuation due to AEs, there is also an unfavourable effect with the extent “considerable” in the outcome of ocular AEs. The most frequently occurring events (conjunctival hyperaemia [PT], conjunctival haemorrhage [PT], and cornea verticillata [PT]) are predominantly asymptomatic events that often mean no impairment for the patients [4]. Taking into account all available results, the unfavourable effects regarding the outcomes of discontinuation due to AEs and ocular AEs are insufficient for deriving lesser benefit of latanoprost/netarsudil. 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 intraocular pressure reduction; hence, there is no proof of added benefit.

2.7 Summary

The data subsequently submitted by the company in the commenting procedure do not change the conclusion on the added benefit of lumacaftor/ivacaftor drawn in dossier assessment A22-129.

The following Table 5 shows the result of the benefit assessment of latanoprost/netarsudil taking into account both dossier assessment A22-129 and the present addendum.

Table 5: 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 G-BA decides on the added benefit.

3 References

1. Institut für Qualität und Wirtschaftlichkeit im Gesundheitswesen. Latanoprost/Netarsudil (primäres Offenwinkelglaukom und okuläre Hypertension) – Nutzenbewertung gemäß § 35a SGB V; Dossierbewertung [online]. 2023 [Accessed: 11.05.2023]. URL: https://www.iqwig.de/download/a22-129_latanoprost-netarsudil_nutzenbewertung-35a-sgb-v_v1-0.pdf.

2. Santen. Stellungnahme zum IQWiG-Bericht Nr. 1520: Latanoprost/Netarsudil (primäres Offenwinkelglaukom und okuläre Hypertension) – Nutzenbewertung gemäß § 35a SGB V; Dossierbewertung. [Soon available under: https://www.g-ba.de/bewertungsverfahren/nutzenbewertung/907/#beschluesse in the document "Zusammenfassende Dokumentation"].

3. Martín Andrés A, Silva Mato A. Choosing the optimal unconditioned test for comparing two independent proportions. Computat Stat Data Anal 1994; 17(5): 555-574. https://dx.doi.org/10.1016/0167-9473(94)90148-1.

4. Gemeinsamer Bundesausschuss. Wirkstoff: Latanoprost/Netarsudil (D-883); Mündliche Anhörung gemäß § 35 a Abs. 3 Satz 2 SGB V des Gemeinsamen Bundesausschusses – Stenografisches Wortprotokoll [online]. 2023 [Accessed: 16.05.2023]. URL: https://www.g-ba.de/downloads/91-1031-907/2023-05-02_Wortprotokoll_Latanoprost-Netarsudil_D-883.pdf.

5. Santen. Addendum II zu Modul 4 A für Teilpopulation mITT-Mono; Latanoprost/Netarsudil (Roclanda); Dossier zur Nutzenbewertung gemäß § 35a SGB V [unpublished]. 2023.

Appendix A Results on side effects

Regarding total rates of AEs, the table below presents events for SOCs and PTs as per Medical Dictionary for Regulatory Activities (MedDRA), each on the basis of the following criteria:

- Overall rate of AEs (irrespective of severity): events that occurred in at least 10% of patients in one study arm
- In addition, for all events irrespective of severity grade: events that occurred in at least 10 patients and in at least 1% of patients in one study arm

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

Table 6: Common AEs[a] – RCT, direct comparison: latanoprost/netarsudil vs. bimatoprost/timolol

Study	**Patients with event n (%)**	
SOC[b] **PT[b]**	**Latanoprost/netarsudil** **N = 116**	**Bimatoprost/timolol** **N = 95**
MERCURY 3		
Overall AE rate	93 (80)	58 (61)
Eye disorders	67 (58)	33 (35)
Cornea verticillata	13 (11)	0 (0)
Conjunctival haemorrhage	14 (12)	3 (3)
Conjunctival hyperaemia	35 (30)	14 (15)
Infections and infestations	19 (16)	17 (18)
Investigations	15 (13)	11 (12)
Vascular disorders	9 (8)	11 (12)

a. Events that occurred in ≥ 10 patients in at least one study arm.
b. MedDRA version 20.0; SOCs and PTs used unmodified from Addendum II to Module 4 A [5].

AE: adverse event; MedDRA: Medical Dictionary for Regulatory Activities; n: number of patients with at least one event; N: number of analysed patients; PT: Preferred Term; RCT: randomized controlled trial; SOC: System Organ Class

Table 7: Discontinuations due to AEs – RCT, direct comparison: latanoprost/netarsudil vs. bimatoprost/timolol (multipage table)

Study	**Patients with event n (%)**	
SOC[a] **PT[a]**	**Latanoprost/netarsudil** **N = 116**	**Bimatoprost/timolol** **N = 95**
MERCURY 3		
Overall rate of discontinuations due to AEs	18 (16)	1 (1)
Eye disorders	14 (12)	1 (1)
Cornea verticillata	2 (2)	0 (0)
Blepharitis	1 (1)	0 (0)
Conjunctival hyperaemia	4 (3)	0 (0)
Eye irritation	1 (1)	0 (0)
Punctate keratitis	1 (1)	0 (0)
Visual acuity reduced	1 (1)	0 (0)
Conjunctivitis allergic	3 (3)	0 (0)
Foreign body sensation in eyes	2 (2)	0 (0)
Conjunctival oedema	2 (2)	0 (0)
Ocular hyperaemia	2 (2)	0 (0)
Optic ischaemic neuropathy	0 (0)	1 (1)
Eye allergy	2 (2)	0 (0)
Gastrointestinal disorders	1 (1)	0 (0)
Vomiting	1 (1)	0 (0)
General disorders and administration site conditions	1 (1)	0 (0)
Instillation site pain	1 (1)	0 (0)
Musculoskeletal and connective tissue disorders	1 (1)	0 (0)
Muscular weakness	1 (1)	0 (0)
Investigations	2 (2)	0 (0)
Intraocular pressure increased	1 (1)	0 (0)
Vital dye staining cornea present	1 (1)	0 (0)

Table 7: Discontinuations due to AEs – RCT, direct comparison: latanoprost/netarsudil vs. bimatoprost/timolol (multipage table)

Study	**Patients with event n (%)**	
SOC[a] **PT[a]**	**Latanoprost/netarsudil** **N = 116**	**Bimatoprost/timolol** **N = 95**
Nervous system disorders	1 (1)	0 (0)
Dizziness	1 (1)	0 (0)
Endocrine disorders	1 (1)	0 (0)
Inappropriate antidiuretic hormone secretion	1 (1)	0 (0)
Cardiac disorders	1 (1)	0 (0)
Atrial flutter	1 (1)	0 (0)

a. MedDRA version 20.0; SOCs and PTs used unmodified from Addendum II to Module 4 A [5].

AE: adverse event; MedDRA: Medical Dictionary for Regulatory Activities; n: number of patients with at least one event; N: number of analysed patients; PT: Preferred Term; RCT: randomized controlled trial; SOC: System Organ Class