ORIGINAL RESEARCH

Cost–Utility Analysis of a Latanoprost Cationic Emulsion (STN1013001) versus Other Latanoprost in the Treatment of Open-Angle Glaucoma or Ocular Hypertension and Concomitant Ocular Surface Disease in Germany

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Purpose: This study aimed to estimate the cost–utility and economic value of STN1013001, a latanoprost cationic emulsion vs other latanoprost formulations (henceforth latanoprost) in patients with open-angle glaucoma (OAG) or ocular hypertension (OHT) and concomitant ocular surface disease (OSD) in Germany.

Methods: An early 5-year Markov model-supported cost–utility analysis was performed to estimate costs, quality-adjusted life years (QALYs) and life-years saved (LYS) for STN1013001 vs latanoprost from the German health system perspective. The model included seven mutually exclusive health states and adopted a 1-year cycle length. The model was populated with pooled data derived, by means of a questionnaire, from a convenience sample of five German glaucoma specialists. Remaining data were derived from published sources. Data provided by the ophthalmologists included annual treatment adherence probabilities, utility values and resource utilization. The half-cycle correction as well as a discount rate of 3.0% per year were applied to costs (expressed in €2020), life-year saved (LYS) and QALYs. The incremental cost–utility ratio (ICUR) was contrasted against the informal willingness-to-pay (WTP) threshold for incremental LYS saved or QALY gained (€30,000) proposed for Germany. One-way and probabilistic sensitivity analyses (OWSA; PSA) tested the robustness of the base case ICUR.

Results: Over the 5-year time horizon, STN1013001 strongly dominates latanoprost as it is less costly (€1003.65 vs €1145.37; −12.37%) and produces more QALYs (2.612 vs 2.365; +10.44%) per notional patient. Baseline findings were robust against all the variations included in OWSA. PSA shows that STN1013001 has a 100% probability of being cost-effective vs Latanoprost at each WTP threshold for incremental QALY gained.

Conclusion: Once on the market, STN1013001 will provide a cost-effective and possibly strongly dominant therapy vs latanoprost for OAG/OHT+OSD patients from a German health system perspective. Future empirical research should confirm these findings.

Keywords: open-angle glaucoma, ocular surface disease, STN1013001, latanoprost, cost–utility analysis, Germany

Introduction

As one of the leading causes of irreversible blindness, glaucoma represents an important public health issue.[1] The clinical and economic burden of glaucoma are expected to increase significantly in the coming years, as the number of affected patients is projected to rise steeply due to rapidly aging populations.[1–3] In 2013, 64.3 million were affected by glaucoma and this number is projected to rise by 74% to 111.8 million affected patients in 2040.[2]

Open-angle glaucoma (OAG) represents about 86% of all glaucoma diagnoses.[1] In Germany, the age-standardized prevalence of OAG in a proportionate age stratified random sample of 250,000 adults aged 50–90+ years was 2.79%.[3]

According to the last available data, the mean annual costs for healthcare resources (drugs; outpatient procedures; ophthalmologist visits; hospitalizations) per patient affected by early, moderate and advanced OAG/ocular hypertension (OHT) in Germany reaches 423 euros (€), €493 and €809 (values expressed in €2009), respectively, with medications and hospitalization being the cost-drivers.[4] Consistent with the epidemiology of OAG/OHT, these costs are expected to increase in the next years.

Glaucoma is characterized by 6 stages. The disease generally starts with OHT and can then progress according to the following stages: stage 1 – early glaucoma; stage 2 – moderate glaucoma; stage 3 – advanced glaucoma; stage 4 – severe glaucoma and stage 5 – end-stage/blindness.[3,5–7] Patients suffering from OAG/OHT generally remain asymptomatic in the early disease stages.[8] The patient usually starts noticing vision loss when the disease is already in a quite advanced stage and the vision loss is irreversible.[8] Therefore, early diagnosis and appropriate therapies are of paramount importance.[3]

However, currently available OAG/OHT therapies do not sufficiently address low treatment adherence rates generally observed in OAG/OHT patients,[9,10] which are likely underestimated.[10]

Additionally, about 60% of OAG/OHT patients on topical intraocular pressure (IOP)-lowering drugs experience concomitant ocular surface disease (OSD) symptoms, including dry eye disease (DED).[11] The effective management of concomitant OSD in OAG/OHT patients still represents an unmet therapeutic need.[12]

The concomitant OSD-symptoms can severely impact patients' daily activities, remarkably decrease their treatment compliance and worsen their health-related quality of life (HRQoL), also known as utility (that usually ranges between 0, ie, death or HRQoL perceived worse than death and 1, ie, perfect health).[13–15] These factors may contribute to a poorer control of IOP and a higher risk of disease progression.[16] Thus, there appears to be a need for new treatment alternatives that address these unmet needs and help prevent irreversible vision loss in OAG/OHT patients.

STN1013001 (Santen, Osaka, Japan), formerly DE-130A, is a latanoprost cationic emulsion (the gold standard in the glaucoma treatment paradigm) for the treatment of OAG/OHT patients with concomitant OSD.[17] The cationic nanoemulsion (Novasorb® technology) has tear film stabilization and anti-inflammatory properties and has the ability to reside on the ocular surface for a prolonged period of time, offering a technical innovation to effectively address OSD in OAG/OHT patients.[12]

In a 3-month Phase 2 trial, STN1013001 was as effective as latanoprost at lowering IOP (−6.0% vs −5.4%; p<0.05) and improved both OSD-related signs and symptoms (−36.0% vs −7.0%; p>0.05) vs baseline in the per protocol study population.[18]

STN1013001 is currently under investigation in a Phase III trial vs latanoprost[19] and thus, not available on the market yet.

Since OSD dramatically affects the treatment adherence and, in turn, utility of OAG/OHT patients, this paper aims to assess the cost–utility of STN1013001 vs other latanoprost formulations available in Germany (henceforth latanoprost) in OAG/OHT+OSD patients from the German health system perspective[20] by means of an early Markov model-supported cost–utility analysis (CUA).[13–15,21–23] We performed this early health economic model to provide healthcare decision makers with evidence about the economic value of STN1013001 before it enters the market.[22,23]

Materials and Methods
Decision Model

The Markov model (Supplemental Material - SM Definition #1) follows two hypothetical cohorts of patients on STN1013001 or latanoprost (1000 notional patients each) over a 5-year time horizon with 1-year cycles (each one lasting 365.25 days to account for leap years)[24] and includes 7 mutually exclusive health states (OAG/OHT stages 0–5 and gender and age-specific all-cause mortality) (Figure 1).[5,6,21,25]

Pooled data based on the expert opinion[26] of a convenience sample[27] of five German ophthalmologists practicing in different settings (private office: 4; private eye clinic: 1) were converted into 1106 parameters that populated the Markov
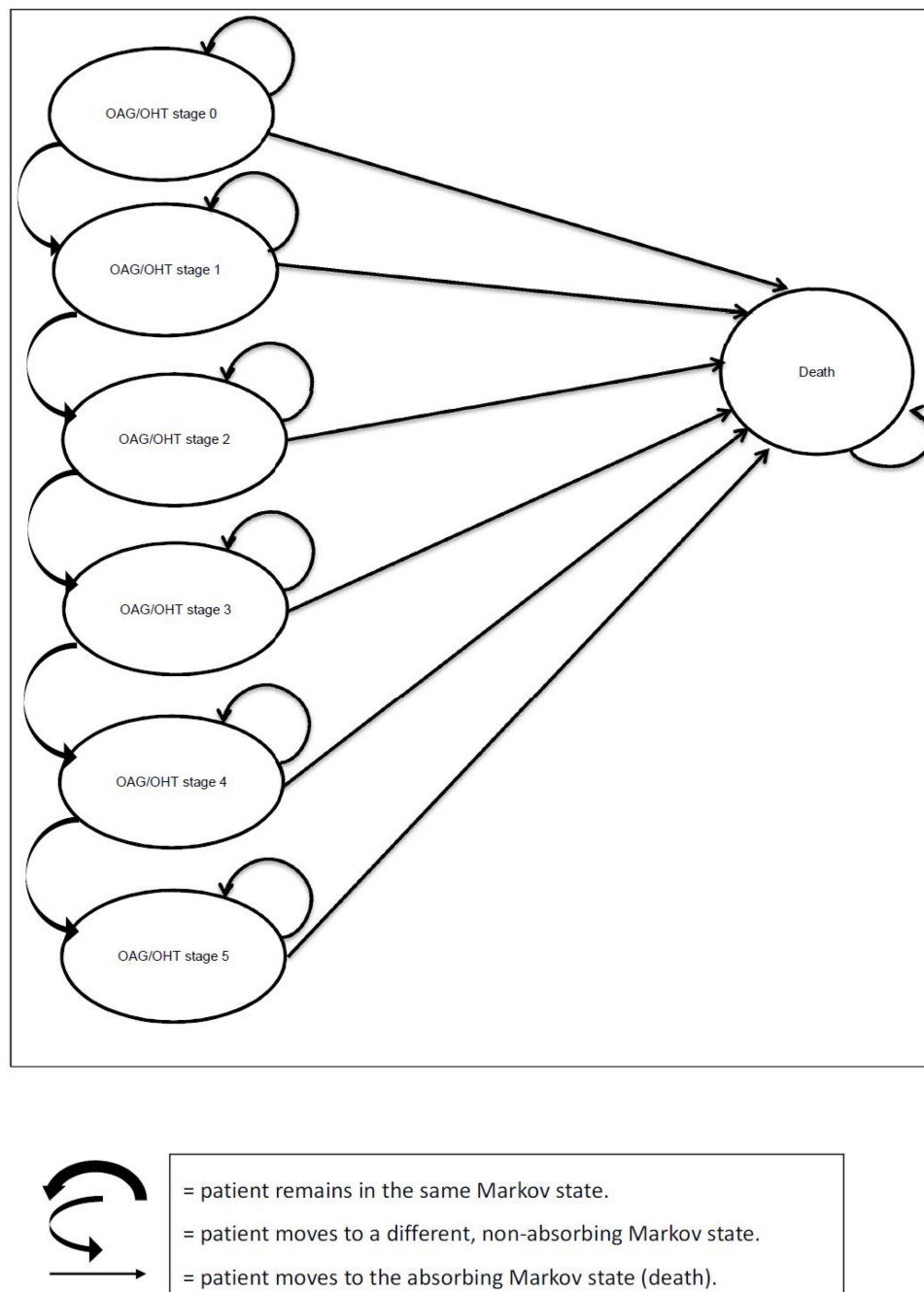
Figure 1 Markov model.
Abbreviation: OAG/OHT, open-angle glaucoma or ocular hypertension.

model. The ophthalmologists are well-renowned glaucoma specialists with extensive experience in diagnosing and treating OAG/OHT (on average 1338 patients followed-up yearly). The Markov model was further populated with data obtained from literature.

OAG/OHT stage 0 represents the initial Markov health state for all the notional patients. During each Markov cycle notional patients can remain in the same OAG/OHT stage, move to more severe OAG/OHT stages or die of all causes according to a transition probability matrix (Table SM1).[13–15,21] Consistent with the natural history of OAG/OHT, backward transitions from more to less severe OAG/OHT stages were not allowed.

The half-cycle correction (ie, the assumption that patients total 6-month costs, life-years saved (LYS) and Quality-Adjusted Life Years (QALYs) the year they pass away) was applied.[15,21] Costs, LYS and QALYs occurring after the first Markov cycle were discounted at 3% real social discount rate in base case CUA.[13,14,28,29] The real social discount rate was set at 0% and 5% in one-way sensitivity analysis (OWSA).[13,14,28,29]

The Markov model-supported CUA was developed in Excel per Windows® 2010 (Microsoft, Redmond, WA, USA).

Data Collection

During July–November 2020, a questionnaire and the target product profile of STN1013001 were sent out by e-mail to each ophthalmologist in the convenience sample. Ophthalmologists were requested to fill in the questionnaire according to their experience with latanoprost and target product profile of STN1013001.

The following OAG/OHT stage-specific data were collected based on the expert opinion of the glaucoma specialists for both hypothetical cohorts of patients: expected annual volume of patients on latanoprost or STN1013001, stratified by gender; annual probability of remaining in the same OAG/OHT stage or transitioning to a more severe disease stage; OAG/OHT stage-specific annual probability of adherence to STN1013001 and latanoprost annual probability of add-on therapies due to insufficient IOP control with STN1013001 or latanoprost alone; single-event or annual probability of consumption, type and volume of healthcare resources (for OAG/OHT and OSD diagnosis, medications, monitoring and follow-up) or therapy duration (for add-on therapies and OSD-related drugs); utility values.

Upon questionnaire completion (response rate: 100.00%), follow-up teleconferences were scheduled with the ophthalmologists when needed for clarifications or missing data management.

The annual probability of OSD (STN1013001=0.762; latanoprost=0.837; p>0.05) was retrieved from the Phase II trial comparing STN1013001 vs latanoprost.[18]

Quality-Adjusted Life Years

QALYs are LYS weighted for their utility.[13,14] OAG/OHT stage-specific utility values and OSD-related disutility were included in the QALYs calculation. Utility values for OAG/OHT stages 0 and 5 were obtained from literature,[30] whereas utility values for OAG/OHT stages 1–4 were elicited from the experts (Table 1).

In accordance with clinical practice, OSD-related disutility value was equaled to that of severe DED (−0.120)[31] and assumed to be the same for both cohorts of patients.

The utility value for death was set at 0.[13,14]

Cost

Consistent with the perspective adopted in the present CUA, only healthcare resources funded by the German health system were valued. For this reason, medications related to the management of OSD were not included in the model, as these are not funded by the German health system. The unit costs per diem for STN1013001 were estimated based on its estimated ex-factory price provided by Santen. One pack of STN1013001 was estimated to cover, on average, 30 days of treatment. The unit cost per diem for latanoprost was based on the ex-factory price, obtained from the Lauer Taxe (November 2020),[32] per month of treatment of all latanoprost formulations currently available on the German market, weighted for their current market share.[33] The market shares were calculated based on IQVIA MIDAS Sales data to moving annual total third quarter of 2020. The same approach was adopted to calculate the unit costs per diem of add-on therapies, such as timolol, in case of insufficient IOP control on STN1013001 or latanoprost monotherapy.

The mean treatment duration of one pack of latanoprost was estimated to be 28.51 days, taking into account the availability of latanoprost formulations covering 30 days (30 unit dose containers) and 28 days (multidose bottles which are generally discarded 28 days after opening).

Following a similar approach, a 29-day mean treatment duration for add-on therapies was estimated.

Drug administrations were not valued as all drugs are self-administered by patient at home.

Tests, specialist visits and day-hospital stay for OAG/OHT diagnosis, patients' follow-up and OSD management were costed at the current outpatient[34] and Diagnosis-Related Group tariffs,[35] that were assumed to be reasonable proxies for

Table 1 Unit Cost for Healthcare Resources, Utility and Disutility Values (Costs in €2020)

Model Main Items	Point Estimate (95% CI)[a,b]		Source
OAG/OHT stages 0–5			
OAG/OHT medications[c,d]			
STN1013001	€0.30		Santen GmbH, 2020
Latanoprost	€0.29		32, 33
Add-on therapies[d,e]			
Acetazolamide	€0.28		32, 33
Brimonidine	€0.38		32, 33
Brinzolamide	€0.29		32, 33
Brinzolamide + brimonidine	€0.64		32, 33
Dorzolamide	€0.27		32, 33
Timolol	€0.06		32, 33
Timolol + dorzolamide	€0.42		32, 33
Healthcare procedures			
Central corneal thickness	€4.33 (€3.48;€5.17)		34 [Code: 1204]
Diurnal curve of intraocular pressure measurement	€19.76 (€15.88;€23.63)		34 [Code: 1257]
Gonioscopy	€14.62 (€11.75;€17.49)		34 [Code: 1241]
Optic disk photographs	€14.42 (€11.59;€17.25)		34 [Code: 1253]
Pachimetry	€4.33 (€3.48;€5.17)		34 [Code: 1204]
Retinal nerve fibre thickness assessment	€69.83 (€56.14;€83.51)		34 [Codes: 1248;1249]
Slit lamp examination	€7.11 (€5.72;€8.50)		34 [Code: 1240]
Tonometry	€5.71 (€4.59;€ 6.83)		34 [Code: 1255]
Specialist visits			
General practitioner	€8.57 (€6.89;€10.24)		Elaborated on 34 [Code: 1201]
Ophthalmologist	€8.57 (€6.89;€10.24)		34 [Code: 1201]
Optometrist	€8.57 (€6.89;€10.24)		Elaborated on 34 [Code: 1201]
Day-hospital access	€435.60 (€350.23;€520.98)		Elaborated on 35
Utility and disutility values[f]	**STN1013001[g]**	**Latanoprost[h]**	
OAG/OHT stage 0	0.900 (0.848;0.942)	0.900 (0.859;0.935)	30
OAG/OHT stage 1	0.900 (0.872;0.925)	0.899 (0.875;0.920)	Experts' opinion
OAG/OHT stage 2	0.894 (0.866;0.919)	0.874 (0.846;0.900)	Experts' opinion
OAG/OHT stage 3	0.873 (0.841;0.901)	0.847 (0.815;0.876)	Experts' opinion
OAG/OHT stage 4	0.844 (0.816;0.869)	0.805 (0.775;0.832)	Experts' opinion
OAG/OHT stage 5	0.790 (0.717;0.855)	0.790 (0.715;0.857)	30
OSD-related disutility	−0.120 (−0.231;-0.045)	−0.120(−0.231;-0.045)	31
Death	0.000 (-)	0.000 (-)	13, 14

Notes: [a]95% CI was calculated assuming a Normal probability distribution[15,39]; [b]95% CI was not calculated for the unit cost of drugs since they are exogenous variables[39]; [c]Medications refer to STN1013001 and latanoprost only; [d]Cost *per diem* calculated based on ex-factory price; [e]Follow-up drugs prescribed in addition to STN1013001 or latanoprost due to poor IOP control; [f]95% CI for utility and disutility values was calculated assuming a Beta and a Gamma probability distribution, respectively[15,39]; [g]Number of observations per OAG/OHT stage (female %): 0=155 (62.65%%); 1=500 (60.00%); 2=510 (61.18%); 3=470 (61.06%); 4=705 (53.62%); 5=131 (70.69%); [h]Number of observations per OAG/OHT stage: 0=235 (64.47%); 1=662 (57.43%); 2=580 (61.12%); 3=530 (61.04%); 4=740 (53.92%); 5=125 (70.40%).
Abbreviations: CI, confidence interval; IOP, intraocular pressure; OAG/OHT, open-angle glaucoma/ocular hypertension; OSD, ocular surface disease.

the real costs borne by the healthcare facilities to provide those healthcare services.[36] Replicating the approach adopted in a recent research on the economic burden of blindness and visual impairment in Germany,[37] the Gebührenordnung für Ärzte tariffs[34] were used for valuing outpatient healthcare procedures for the diagnosis and follow-up of OAG/OHT patients, to allow for more detailed costing compared to Statutory Health Insurance tariffs.[38]

Costs were expressed in €2020 values.

Cost–Utility Analysis

CUA divides the difference in costs (incremental cost - ΔC) of STN1013001 and latanoprost by their difference in QALYs (incremental QALYs - ΔQALYs) and summarizes the results of their comparison via the incremental cost–utility ratio (ICUR).[13,14] ICUR informs decision-makers whether the cost per ΔQALY is affordable and as such, whether the health technology offers the health system good value for money.

As the CUA was supported by a decision model, no patient was enrolled.[15,39] Hence, Ethics Committee approval of the study protocol (questionnaire included) was not required by the current German legislation.[40]

Statistical Analysis

The mean number (along with the standard deviation – SD) of notional patients in each Markov model health state was reported.

Statistical distributions were fitted to most of the parameters included in the Markov model.[15,39]

The Beta distribution was assigned to 2-pathway events (ie, OAG/OHT patient gender) and OAG/OHT stage-specific utility values, whereas the Dirichlet distribution was assigned to polytomous events (ie, transition probabilities from less severe to more severe stages of OAG/OHT).

The Gamma distribution was fitted to the volume of healthcare resources (if different from drugs) as well as to OSD-related disutility value.

Lastly, the Normal distribution fitted to unit cost of healthcare resources other than drugs.

The 95% confidence interval (95% CI) was computed via the percentile method[39] for parameters that were assigned a theoretical probability distribution as well as for adherence probabilities, ΔC, incremental LYS (ΔLYS), and ΔQALYs.

As part of 95% CI calculation, the standard error of the mean was determined on the grounds of the data collected or imposing a coefficient of variation[41] on the baseline sample estimate.[15,39]

For parameters that were not given a statistical distribution, a range was reported.

Sensitivity Analyses

OWSA and probabilistic sensitivity analyses (PSA) were performed to check the robustness of the base case ICUR.[13–15,39]

One-Way Sensitivity Analysis

OWSA was performed on one parameter at a time by replacing its baseline estimate with the lower and upper limits of its 95% CI or range.[13,14] OWSA results were plotted on a Tornado graph.[13]

Probabilistic Sensitivity Analysis

The core of the PSA[13–15,39,42] was a 10,000-iteration Monte Carlo (MC) simulation[15,39] aimed at exploring the conjoint uncertainty of the parameter sample estimates that supported the baseline CUA.[13–15,39]

During each MC trial, a random value for each parameter that was given a theoretical probability distribution was drawn.[15,39]

As these are not subject to uncertainty, parameters set by clinical and methodological guidelines (drug posology; real social discount rate) or national regulatory agencies (drug cost) were not assigned a theoretical probability distribution and were not included in the PSA, as recommended by the reference literature on health economic modelling.[39]

The PSA results were plotted on the cost-effectiveness plane (CEP) (SM Definition #2).[43]

Converting the ICUR into Net Monetary Benefit (NMB) (SM Definition #3),[13–15,39,44,45] the PSA results supported the construction of both the non-parametric Cost-Effectiveness Acceptability Curve (CEAC) (SM Definition #4) and Cost-Effectiveness Acceptability Frontier (CEAF) (SM Definition #5) which show the probability that the healthcare programme under investigation is cost-effective (CEAC) or optimal given the highest expected NMB (CEAF) against a set of willingness to pay (WTP) values decided by the third-party payer.[13–15,39,46,47]

Results

Markov Model

STN1013001- and latanoprost-treated notional patients were assumed to enter the Markov model in OAG/OHT-stage 0 at the age of 44.68 years (range: 40.00;56.00 years) (Table SM2).

Over the 5-year timespan, the Markov traces of notional patients on STN1013001 or latanoprost are similar (Figure 2). For both the hypothetical cohorts of patients, slightly less than 50% remained in OAG/OHT stage 0 (STN1013001: mean: 452; SD: 333; latanoprost: mean: 489; SD: 317). Transition toward OAG/OHT stage 5 was negligible (STN1013001: mean: 7; SD: 9; latanoprost: mean: 5; SD: 7) and all-cause mortality was similar for both the hypothetical cohorts of patients (STN1013001: mean: 153; SD: 98; latanoprost: mean: 145; SD: 93) (Table SM3).

Adherence to STN1013001 and Latanoprost

Across the 5-year time horizon, notional STN1013001 patients were estimated to have higher probabilities of being treatment adherent compared to their latanoprost counterparts for most of the OAG/OHT stages (Table SM4). This trend is most apparent in disease stage 0 and 4. In OAG/OHT stage 0, treatment adherence probabilities are higher in the notional STN1013001 cohort vs latanoprost in years 2–5, with differences ranging from +0.112 (95% CI: 0.023;0.189, year 2) to +0.147 (95% CI: 0.064;0.228, year 3). In OAG/OHT stage 4, higher treatment adherence probabilities were estimated across years 1–4, with differences ranging from +0.100 (0.061;0.140, year 4) to +0.131 (95% CI: 0.094;0.169, year 2) in favor of STN1013001 compared to latanoprost.

Base Case Analysis

Healthcare Resources Consumption

Diagnosis

The most frequently prescribed test for the diagnosis of OAG/OHT is slit lamp examination (STN1013001: 95.16; mean: 1.82; 95% CI: 1.62;2.04; latanoprost: 96.81%; mean: 1.37; 95% CI: 1.20;1.56) (Table SM5).

Almost all notional patients undergo ophthalmologist visits (STN1013001: 100.00%; mean: 1.87; 95% CI: 1.64;2.12; latanoprost: 95.74%; mean: 1.06; 95% CI: 0.90;1.25).

Add-On Therapies and Follow-Up

Based on experts' opinion, notional patients have the same annual probability of ≥1 add-on therapies due to insufficient IOP control on STN1013001 or latanoprost monotherapy. This probability ranges from 40% (OAG/OHT stage 0) to 95% (OAG/OHT stage 5) (Table SM6). Timolol (35% in OAG/OHT stage 0) and timolol+dorzolamide (51% in OAG/OHT stage 1; 60% in OAG/OHT stages 2–5) are the most prescribed medications.
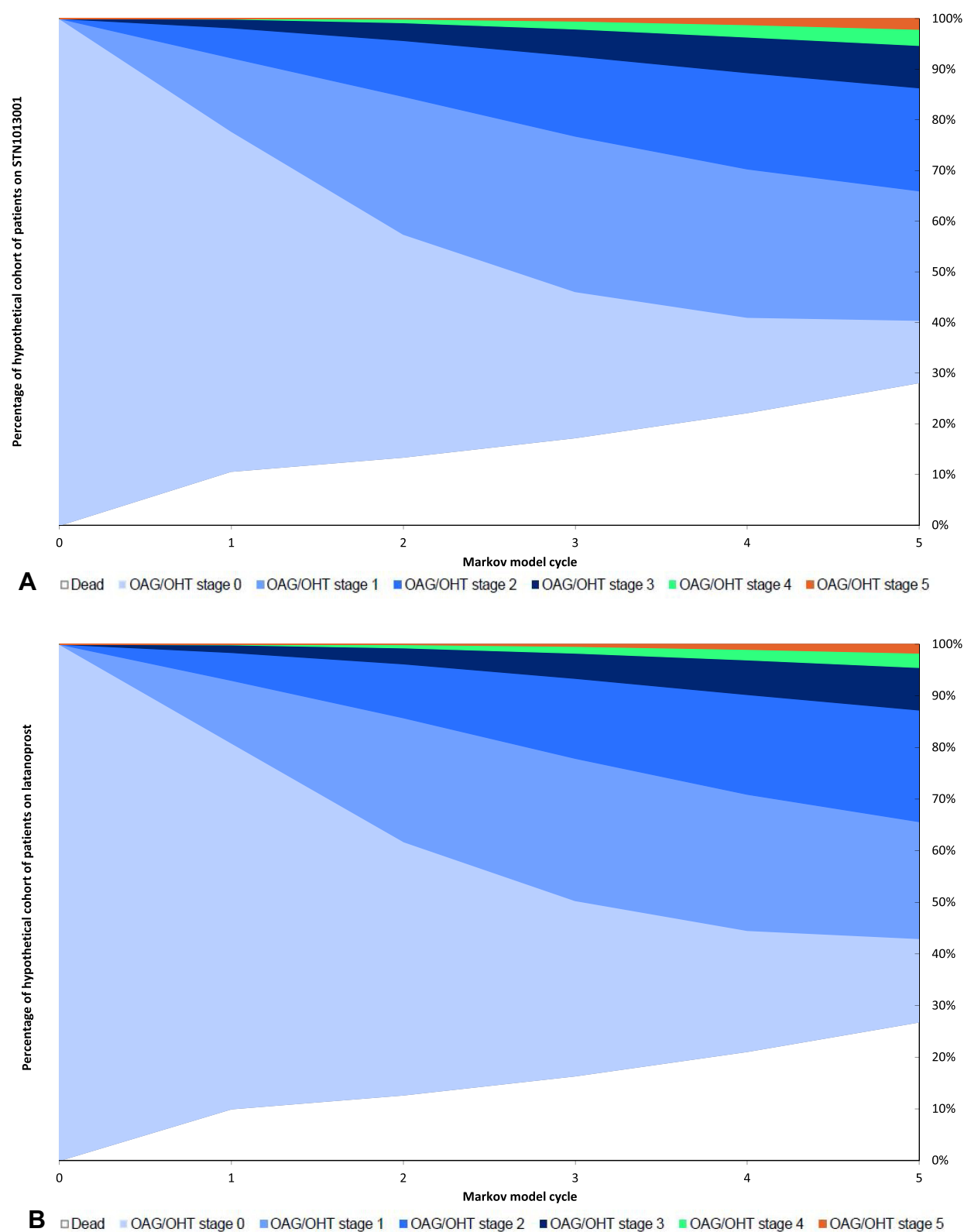
Regardless of OAG/OHT stage, slit lamp examination is the main follow-up test (STN1013001 notional patients: from 29.79% (stage 4) to 100.00% (stage 5); latanoprost notional patients: from 33.11% (stage 4) to 100.00% (stage 5)) (Table SM7). OAG/OHT stage 4 notional patients receive the largest volume of slit lamp examinations (STN1013001: mean: 3.48; 95% CI: 2.39;4.76; latanoprost: mean: 3.54; 95% CI: 2.52;4.74).

All notional patients across all disease stages receive at least one ophthalmologist visit. Notional patients in OAG/OHT stage 4 total the highest number of ophthalmologist visits (STN1013001: mean: 3.82; 95% CI: 2.74;5.06; latanoprost: mean: 3.82; 95% CI: 2.82;4.99).

The proportion of OAG/OHT notional patients who are referred to day-hospital is negligible for both medications.

Management of OSD

Notional patients on STN1013001 have a lower probability of seeking first-line medical care from a General Practitioner (GP) due to OSD symptoms, compared to latanoprost across OAG/OHT stages 0–4. This trend is most visible in disease stages 0 and 1, in which the difference in the proportion of patients with OSD symptoms visiting the GP is −36.10% (95% CI: −43.53%;−28.51%) and −26.12% (95% CI: −30.07%;−22.42%) respectively, in favor of STN1013001. Additionally, notional patients on STN1013001 are less likely to undergo an assessment by an optometrist across stages

A □ Dead ■ OAG/OHT stage 0 ■ OAG/OHT stage 1 ■ OAG/OHT stage 2 ■ OAG/OHT stage 3 ■ OAG/OHT stage 4 ■ OAG/OHT stage 5

B □ Dead ■ OAG/OHT stage 0 ■ OAG/OHT stage 1 ■ OAG/OHT stage 2 ■ OAG/OHT stage 3 ■ OAG/OHT stage 4 ■ OAG/OHT stage 5

Figure 2 (**A**) Markov trace for the hypothetical cohort of patients on STN1013001. (**B**) Markov trace for the hypothetical cohort of patients on latanoprost.
Abbreviation: OAG/OHT, open-angle glaucoma or ocular hypertension.

Table 2 Costs per Patient and Cost–Utility Analysis (Costs in €2020)

Items	STN1013001 (%)	Latanoprost (%)	Difference (%) [95% CI]a,b
German health system viewpoint			
Cost			
Diagnosis	€75.41 (7.51)	€68.90 (6.02)	€6.50 (−4.59) [−€2.05;€15.43]
Medications	€356.18 (35.49)	€319.18 (27.87)	€37.00 (−26.11) [€26.94;€51.77]
Add-on therapies and follow-up	€488.85 (48.71)	€648.82 (56.65)	−€159.96 (112.86) [−€217.88;-€114.23]
OSD management	€83.21 (8.29)	€108.48 (9.47)	−€25.26 (17.84) [−€39.90;−€13.41]
Overall	**€1003.65 (100.00)**	**€1145.37 (100.00)**	**−€141.73 (100) [−€202.51;-€88.33]**
LYS and QALYs			
LYS	3.998	4.035	−0.037 [−0.091;0.028]
QALYs	2.612	2.365	0.247 [0.122;0.407]
Cost–utility analysis - Basecase			
Incremental costs (ΔC)	-€141.73		
Incremental QALYs (ΔQALYs)	0.247		
ICUR (ΔC/ΔQALYs)	STN1013001 is strongly dominant (SE sector of the cost-effectiveness plane)		

Notes: a(STN1013001 – Latanoprost); b95% CI was calculated via the percentile method[39].
Abbreviations: CI, confidence interval; ICUR, Incremental Cost–Utility Ratio; LYS, Life-Years Saved; OAG/OHT, open-angle glaucoma/ocular hypertension; OSD, ocular surface disease; QALYs, Quality-Adjusted Life Years; SE, South-East.

0–4 for OSD symptoms. The biggest difference was projected in OAG/OHT stages 0 and 1 (−26.21% in both disease stages; 95% CI: −30.04%;−22.23%) (Table SM8).

In all the OAG/OHT stages, slit lamp examination is the most frequent test for OSD management (STN1013001 notional patients: from 95.16% to 100.00%; latanoprost notional patients: from 96.81% to 100.00%). OAG/OHT stage 4 notional patients receive the largest volume of slit lamp examination (STN1013001: mean: 3.45; 95% CI: 2.37;4.74; latanoprost: mean: 3.34; 95% CI: 2.31;4.56).

Most of the patients in both hypothetical cohorts visit the ophthalmologist at least once for the management of OSD. Notional patients in OAG/OHT stage 4 undergo the highest number of ophthalmologist visits (STN1013001: mean: 2.69; 95% CI: 1.89;3.65; latanoprost: mean: 2.80; 95% CI: 2.04;3.68).

Cost

Over the 5-year time horizon, the average cost per notional patient is lower for STN1013001 compared to latanoprost (€1003.65 vs €1145.37; ΔC: −€141.73; 95% CI: −€202.51;−€88.33) (Table 2).

The cost-drivers are add-on therapies and the healthcare resources consumed during follow-up (STN1013001: 48.71%; latanoprost: 56.65%) and STN1013001 and latanoprost medications (35.49% and 27.87%, respectively).

Cost of OAG/OHT monotherapy are slightly higher for STN1013001 vs latanoprost (€356.18 vs €319.18; difference: €37.00; 95% CI: €26.94;€51.77) across the 5-year time horizon.

STN1013001 is statistically significantly cost-saving vs latanoprost as far as OAG/OHT follow-up (€488.85 vs €648.82; difference: −€159.96; 95% CI: −€217.88;€114.23) and OSD management are concerned (€83.21 vs €108.48; difference: −€25.26; 95% CI: -€39.90;−€13.41).

Cost–Utility Analysis

After 5 years, the average LYS totaled by both hypothetical cohorts of patients are similar (STN1013001: 3.998; Latanoprost: 4.035; ΔLYS: −0.037; 95% CI: −0.091;0.028), whereas QALYs are higher for STN1013001 (2.612 vs 2.365; ΔQALYs: 0.247; 95% CI: 0.122;0.407) (Table 2).
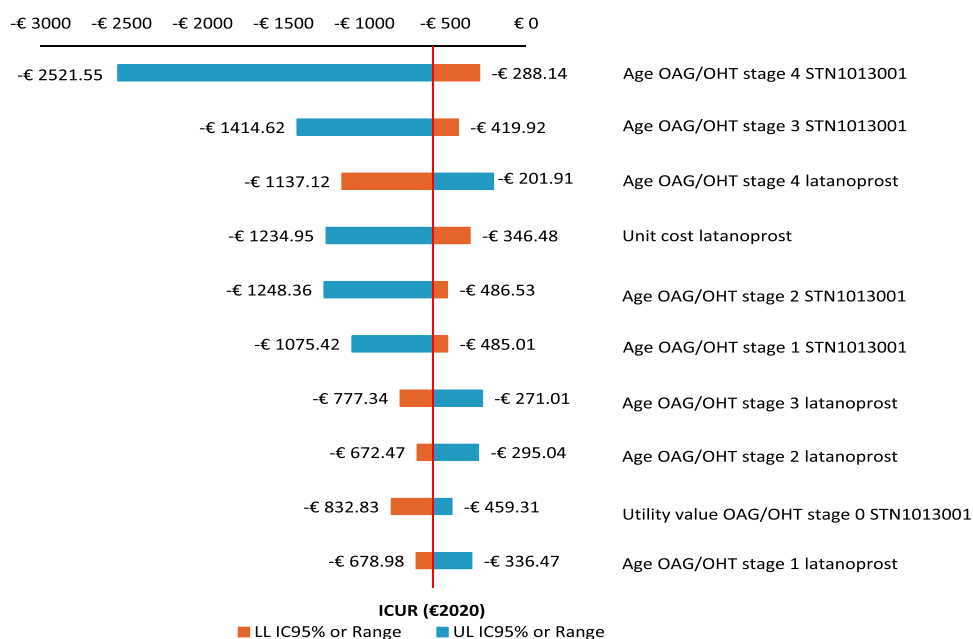
Figure 3 One-way sensitivity analysis: results concerning the first 10 parameters of the Markov model that causes the widest variations in base case ICUR (€2020).[a,b]
Notes: [a]Base case ICUR STN1013001: strongly dominant (SE sector of the cost-effectiveness plane); [b]Y and X-axes intersect at the baseline ICUR.
Abbreviations: ICUR, Incremental Cost–Utility Ratio; LL 95% CI, lower limit 95% confidence interval; OAG/OHT, open-angle glaucoma or ocular hypertension; SE, South-East; UL 95% CI, uUpper limit 95% confidence interval.

Being at the same time cost-saving (-€141.73) and more effective (+0.247 QALYs), STN1013001 strongly dominates latanoprost.

Sensitivity Analyses

One-Way Sensitivity Analysis

OWSA confirms the robustness of the baseline results of the CUA. STN1013001 is highly cost-effective compared to latanoprost, regardless of the OWSA variations that were applied.

OWSA shows that the base case ICUR was most sensitive to variations in STN1013001 notional patients' average age in OAG/OHT stage 4 (−49.87% to +338.69% vs baseline ICUR) and 3 (from −26.94% to +146.11% vs baseline ICUR) (Figure 3) after 1 year from diagnosis. Additionally, OWSA proves the baseline ICUR to be robust to changes in the social discount rate for costs, LYS and QALYs.
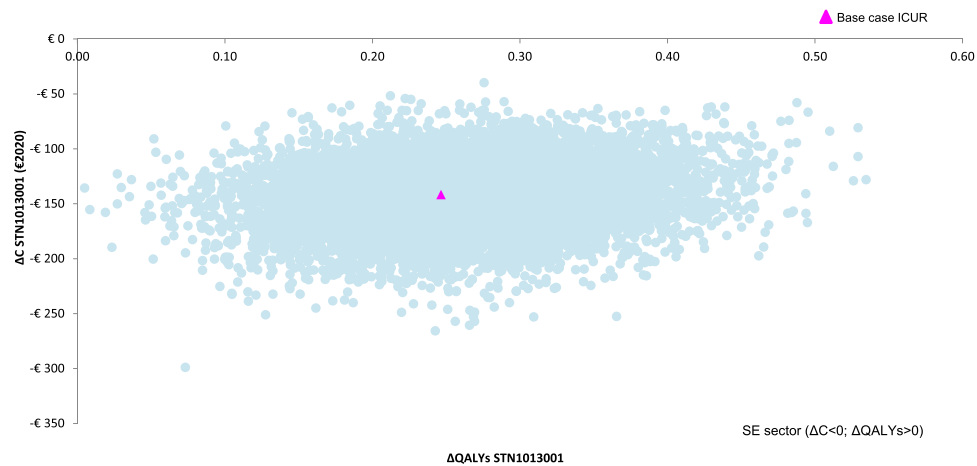
Probabilistic Sensitivity Analysis

PSA shows STN1013001 to be constantly cost-saving vs latanoprost, even at a WTP threshold of €0 per QALY gained (Figure 4). The probability that STN1013001 strongly dominates latanoprost is 100.00% at the last available unofficial acceptability threshold value per QALY gained (€30,000) computed for the German health system (Figure 5).[48]

The CEAF highlights that STN1013001 patients is the optimal alternative for OAG/OHT+OSD patients (that is, the healthcare programme with the highest average NMB) from a WTP for incremental QALY gained of €0.00 onward (Figure 6).

Discussion

This research aimed to estimate the cost–utility of STN1013001 vs latanoprost in OAG/OHT+OSD patients using early health economic modelling to provide evidence of the economic value of STN1013001 and inform healthcare decision-making in the German setting.[22,23]

Figure 4 Probabilistic sensitivity analysis. Cost-effectiveness plane (10,000 out of 10,000 Monte Carlo iterations reported) (ΔC in €2020).[a,b]
Notes: [a]Base case ICUR STN1013001: strongly dominant (SE sector of the cost-effectiveness plane); [b]Number of Monte Carlo iterations (%) for each sector of the cost-effectiveness plane: SE=10,000 (100.00%).
Abbreviations: ΔC, incremental cost; ΔQALYs, incremental quality-adjusted life years; ICUR, Incremental Cost–Utility Ratio; SE, South-East.
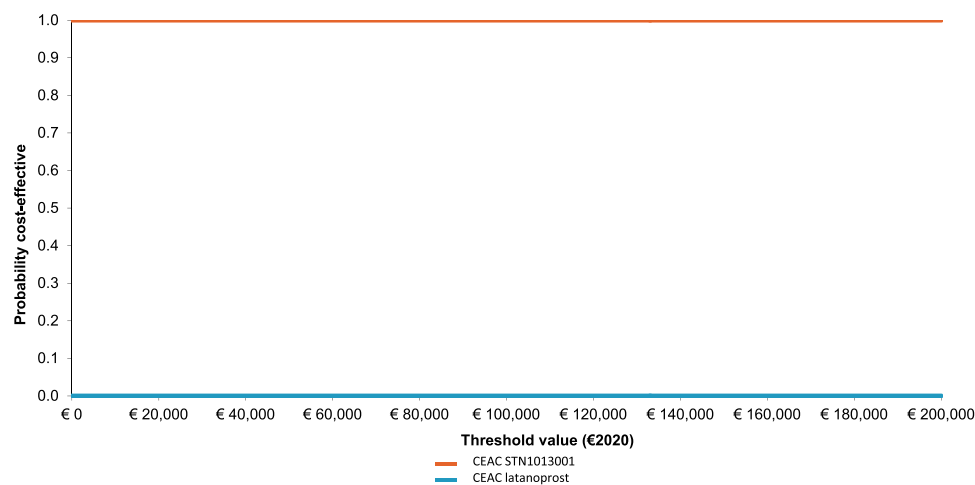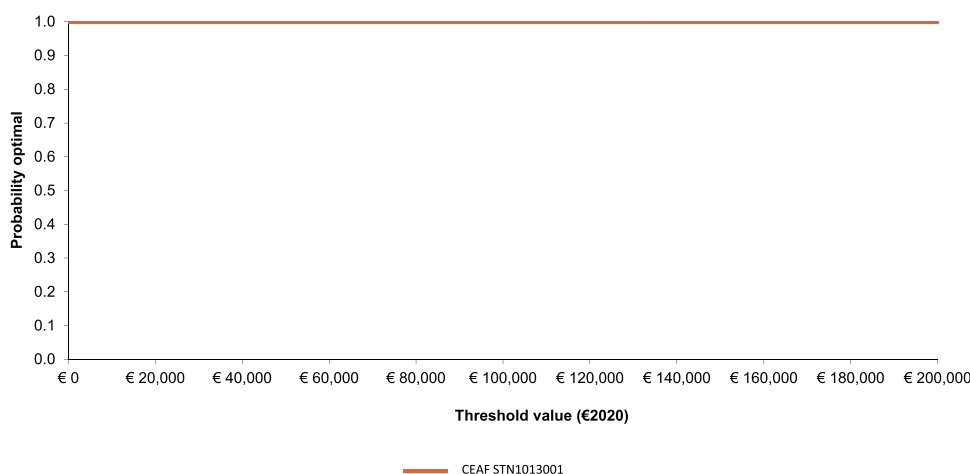

Figure 5 Probabilistic sensitivity analysis. Cost-effectiveness acceptability curve (1000 out of 1000 threshold values reported) (€2020).[a]
Notes: [a]Base case ICUR STN1013001: strongly dominant (SE sector of the cost-effectiveness plane).
Abbreviations: CEAC, cost-effectiveness acceptability curve; ICUR, Incremental Cost–Utility Ratio; SE, South-East.

Over a 5-year time horizon, STN1013001 is a cost-effective treatment option in this patient population vs latanoprost from a German health system perspective. Hence, STN1013001 could provide an effective and economically sustainable treatment option for OAG/OHT+OSD patients.

An important factor contributing to this was the lower probability of developing concomitant OSD in notional patients on STN1013001 vs latanoprost. Consequently, notional STN1013001 patients required less medical treatment for the management of OSD and incurred less costs vs notional latanoprost patients. Additionally, HRQoL was higher in notional STN1013001 patients compared to their latanoprost counterparts. This result is in line with previous research that demonstrated the negative impact of concomitant OSD on HRQoL in OAG/OHT patients.[8] Another factor contributing to the higher number of QALYs gained in the notional STN1013001 cohort vs latanoprost was the higher number of patients in OAG/OHT stage 1 during the 5-year timespan (who, consistent with previous empirical findings,[8] can benefit from a higher utility than notional patients who transitioned to more severe OAG/OHT stages). Furthermore, higher treatment adherence rates were estimated in notional patients on STN1013001 vs latanoprost. The lower probability of OSD[18] (and subsequently reduced discomfort for patients) is expected to further increase adherence to

Figure 6 Probabilistic sensitivity analysis. Cost-effectiveness acceptability frontier (1000 out of 1000 threshold values reported) (€2020).[a,b]
Notes: [a]Base case ICUR STN1013001: strongly dominant (SE sector of the cost-effectiveness plane); [b]CEAF: STN1013001 is the optimal strategy from a threshold value of €0.00 onwards.
Abbreviations: CEAF, cost-effectiveness acceptability frontier; ICUR, Incremental Cost–Utility Ratio; SE, South-East.

therapy for STN1013001 patients in real clinical practice. Moreover, a high adherence is a good predictor of effectiveness and cost-effectiveness of drugs targeted at OAG/OHT patients.[49]

As insufficiently adequate management of OSD as well as low adherence rates in OAG/OHT patients remain persisting unmet needs with currently available treatment options, these results show that STN1013001 can play a relevant role in addressing these unmet needs.

PSA results indicate that STN1013001 has a 100% probability (ie, certainty) of being cost-effective even if local health-care policy-makers allocated no money for a QALY gained (WTP=0). As this probability remains constant regardless the WTP threshold, the likelihood of misallocation of healthcare resources at the unofficial German WTP threshold of €30,000 per QALY gained[48] due to STN1013001 reimbursement is zero.

This research has some limitations.

First, as STN1013001 is currently not available on the German market, an empirical CUA vs latanoprost was unfeasible. In this scenario, early health economic models are a valuable methodological option for supporting OAG/OHT healthcare decision-making.[22,23,50–54]

A second limitation, which is related to the previous one, is due to the lack of OAG/OHT stage-specific utility values obtained from head-to-head clinical trials. Therefore, for stage 0 and 5 the health economic model was populated with utility values that were collected from a Dutch cross-sectional study (537 OAG/OHT patients).[30] For disease stages 1–4, the expert opinion of 5 German ophthalmologists of our convenience sample,[27] was assumed to be a good proxy for the utility experience by patients in OAG/OHT stages 1–4 HRQoL. In addition, as country-specific OSD-related disutility values for Germany were unavailable, a disutility value equal to severe DED was applied in the model to reflect the reduction in HRQoL experienced by OAG/OHT patients suffering from concomitant OSD.[31]

Comprehensive sensitivity analyses demonstrated that base case results where robust to variations induced in both OAG/OHT stage-specific utility values as well as the disutility value for OSD.

Lastly, no surgical or laser treatment was considered as an alternative to OAG/OHT medications,[53] as these are generally second-line treatment options, whereas this research focused on first-line treatment of OAG/OHT+OSD.

Conclusions

Our findings indicate that STN1013001 is highly cost-effective compared to latanoprost in OAG/OHT+OSD patients and support its affordability for the German health system. The favorable results for STN1013001 should be confirmed empirically upon market entry.

Ethics Approval and Informed Consent

As the CUA was supported by a decision model, no patient was enrolled. Hence, Ethics Committee approval of the study protocol (questionnaire included) was not required by the current German legislation.

Author Contributions

All authors contributed to data analysis, drafting or revising the article, have agreed on the journal to which the article will be submitted, gave final approval of the version to be published, and agree to be accountable for all aspects of the work.

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References

1. Kreft D, Doblhammer G, Guthoff RF, Frech S. Prevalence, incidence, and risk factors of primary open-angle glaucoma -a cohort study based on longitudinal data from a German public health insurance. *BMC Public Health*. 2019;19(1):851. doi:10.1186/s12889-019-6935-6
2. Tham YC, Li X, Wong TY, Quigley HA, Aung T, Cheng CY. Global prevalence of glaucoma and projections of glaucoma burden through 2040: a systematic review and meta-analysis. *Ophthalmology*. 2014;121(11):2081–2090. doi:10.1016/j.ophtha.2014.05.013
3. Feldman RM, Cioffi GA, Liebmann JM, Weinreb RN. Current knowledge and attitudes concerning cost-effectiveness in glaucoma pharmacotherapy: a Glaucoma Specialists Focus Group Study. *Clin Ophthalmol*. 2020;14:729–739. doi:10.2147/OPTH.S236030
4. Lorenz K, Wolfram C, Breitscheidel L, Shlaen M, Verboven Y, Pfeiffer N. Direct cost and predictive factors for treatment in patients with ocular hypertension or early, moderate and advanced primary open-angle glaucoma: the CoGIS study in Germany. *Graefes Arch Clin Exp Ophthalmol*. 2013;251(8):2019–2028. doi:10.1007/s00417-013-2354-z
5. Traverso CE, Walt JG, Kelly SP, et al. Direct costs of glaucoma and severity of the disease: a multinational long term study of resource utilisation in Europe. *Br J Ophthalmol*. 2005;89(10):1245–1249. doi:10.1136/bjo.2005.067355
6. Mills RP, Budenz DL, Lee PP, et al. Categorizing the stage of glaucoma from pre-diagnosis to end-stage disease. *Am J Ophthalmol*. 2006;141 (1):24–30. doi:10.1016/j.ajo.2005.07.044
7. European Glaucoma Society. *Terminology and Guidelines for Glaucoma*. 5th ed. Savona (Italy): PubliComm; 2020.
8. van Gestel A, Webers CA, Severens JL, et al. The long-term outcomes of four alternative treatment strategies for primary open-angle glaucoma. *Acta Ophthalmol*. 2012;90(1):20–31. doi:10.1111/j.1755-3768.2011.02318.x
9. Kim CY, Park KH, Ahn J, et al. Treatment patterns and medication adherence of patients with glaucoma in South Korea. *Br J Ophthalmol*. 2017;101(6):801–807. doi:10.1136/bjophthalmol-2016-308505
10. Newman-Casey PA, Niziol LM, Gillespie BW, Janz NK, Lichter PR, Musch DC. The association between medication adherence and visual field progression in the Collaborative Initial Glaucoma Treatment Study. *Ophthalmology*. 2020;127(4):477–483. doi:10.1016/j.ophtha.2019.10.022
11. Pisella PJ, Pouliquen P, Baudouin C. Prevalence of ocular symptoms and signs with preserved and preservative free glaucoma medication. *Br J Ophthalmol*. 2002;86(4):418–423. doi:10.1136/bjo.86.4.418
12. Lallemand F, Daull P, Benita S, Buggage R, Garrigue JS. Successfully improving ocular drug delivery using the cationic nanoemulsion, novasorb. *J Drug Deliv*. 2012;2012:604204. doi:10.1155/2012/604204
13. Drummond MF, Sculpher MJ, Claxton K, Stoddart GL, Torrance GW. *Methods for the Economic Evaluation of Health Care Programmes*. 4th ed. Oxford: Oxford University Press; 2015.
14. Neumann PJ, Ganiats TG, Russell LB, Sanders GD, Siegel JE, eds. *Cost-Effectiveness in Health and Medicine*. 2nd ed. New York: Oxford University Press; 2016.
15. Briggs A, Sculpher M, Claxton K. *Decision Modelling for Health Economic Evaluation*. Oxford: Oxford University Press; 2006.
16. Mylla Boso AL, Gasperi E, Fernandes L, Costa VP, Alves M. Impact of ocular surface disease treatment in patients with glaucoma. *Clin Ophthalmol*. 2020;14:103–111. doi:10.2147/OPTH.S229815
17. Daull P, Amrane M, Garrigue JS. Novasorb® cationic nanoemulsion and latanoprost: the ideal combination for glaucoma management? *J Eye Dis Disord*. 2017;2:14. doi:10.35248/2684-1622.17.2.107
18. Ismail D, Amrane M, Garrigue JS, Buggage R. A phase 2, randomized study evaluating the safety and efficacy of Catioprost® (unpreserved latanoprost 0.005% emulsion) compared to Travatan Z® in subjects with glaucoma and ocular surface disease. *Acta Ophthalmol*. 2011;89(s248 Suppl 227). doi:10.1111/j.1755-3768.2011.227.x

19. Santen. A phase III multinational multicenter investigator-masked randomised active-controlled trial comparing the efficacy and safety of DE-130A with Xalatan® in patients with open-angle glaucoma or ocular hypertension. NLM identifier: NCT04133311. Available from: https://clinicaltrials.gov/ct2/show/NCT04133311. Accessed August 27, 2021.

20. Graf von der Schulenburg JM, Greiner W, Jost F, et al. German recommendations on health economic evaluation: third and updated version of the Hanover consensus. *Value Health*. 2008;11(4):539–544. doi:10.1111/j.1524-4733.2007.00301.x

21. Sonnenberg FA, Beck JR. Markov models in medical decision making: a practical guide. *Med Decis Making*. 1993;13(4):322–338. doi:10.1177/0272989X9301300409

22. Annemans L, Genesté B, Jolain B. Early modelling for assessing health and economic outcomes of drug therapy. *Value Health*. 2000;3(6):427–434. doi:10.1046/j.1524-4733.2000.36007.x

23. IJzerman MJ, Koffijberg H, Fenwick E, Krahn M. Emerging use of early health technology assessment in medical product development: a scoping review of the literature. *Pharmacoeconomics*. 2017;35(7):727–740. doi:10.1007/s40273-017-0509-1

24. Wilkins GA. The IAU style manual (1989). The preparation of astronomical papers and reports. Transactions of the International Astronomical Union; 1990. Available from: https://www.iau.org/static/publications/stylemanual1989.pdf. Accessed July 26, 2020.

25. Statistisches Bundesamt. Sterbetafel (Periodensterbetafel): Deutschland, Jahre, Geschlecht, Vollendetes Alter [Life table (period life table): Germany, period of years, sex, completed age]. Available from: https://www-genesis.destatis.de/genesis/online?operation=abruftabelleBearbeiten&levelindex=2&levelid=1598869665666&auswahloperation=abruftabelleAuspraegungAuswaehlen&auswahlverzeichnis=ordnungsstruktur&auswahlziel=werteabruf&code=12621-0001&auswahltext=&werteabruf=Value+retrieval#abreadcrumb. Accessed August 31, 2020. German.

26. O'Hagan A, Buck CE, Daneshkhah A, et al. *Uncertain Judgements: Eliciting Experts' Probabilities*. Chichester: Wiley; 2006.

27. Lohr SL. *Sampling: Design and Analysis*. 2nd ed. Boston: Brooks/Cole; 2010.

28. European Network for Health Technology Assessment (EUnetHTA). Methods for health economic evaluations – a guideline based on current practices in Europe. Available from: https://eunethta.eu/wp-content/uploads/2018/01/Methods-for-health-economic-evaluations-A-guideline-based-on-current-practices-in-Europe_Guideline_Final-May-2015.pdf. Accessed January 2, 2021.

29. Attema AE, Brouwer WBF, Claxton K. Discounting in economic evaluations. *Pharmacoeconomics*. 2018;36(7):745–758. doi:10.1007/s40273-018-0672-z

30. van Gestel A, Webers CA, Beckers HJ, et al. The relationship between visual field loss in glaucoma and health-related quality-of-life. *Eye (Lond)*. 2010;24(12):1759–1769. doi:10.1038/eye.2010.133

31. Canadian Agency for Drugs and Technology in Health (CADTH). Pharmacoeconomic review report. Cyclosporine (VERKAZIA). Available from: https://cadth.ca/sites/default/files/cdr/pharmacoeconomic/sr0615-verkazia-pharmacoeconomic-review-report.pdf. Accessed February 20, 2020.

32. CompuGroup Medical Deutschland. LAUER-TAXE® download. Available from: https://www.cgm.com/deu_de/produkte/apotheke/lauer-taxe-en.html. Accessed November 30, 2020. German.

33. IQVIA. MIDAS database; 2020. Available from: https://www.iqvia.com/solutions/commercialization/brand-strategy-and-management/market-measurement/midas. Accessed November 30, 2020.

34. Guterman C. Online Ausgabe der Gebührenordnung für Ärzte (GOÄ) [Online edition of healthcare tariffs]. Available from: http://www.e-bis.de/goae/defaultFrame.htm. Accessed November 10, 2020. German.

35. Institut für das Entgeltsystem im Krankenhaus. Fallpauschalen-Katalog 2020 [Institute for the Hospital Remuneration System. Reimbursement tariffs handbook 2020]. Available from: https://www.g-drg.de/aG-DRG-System_2020/Fallpauschalen-Katalog/Fallpauschalen-Katalog_2020. Accessed November 10, 2020. German.

36. Brouwer W, Rutten F, Koopmanschap M. Costing in economic evaluations. In: Drummond M, McGuire A, editors. *Economic Evaluation in Health Care. Merging Theory with Practice*. Oxford: Oxford University Press; 2001:68–93.

37. Chuvarayan Y, Finger RP, Köberlein-Neu J. Economic burden of blindness and visual impairment in Germany from a societal perspective: a cost-of-illness study. *Eur J Health Econ*. 2020;21(1):115–127. doi:10.1007/s10198-019-01115-5

38. Kassenärztliche Bundesvereinigung (KBV). Einheitlicher Bewertungsmaßstab (EBM). Stand: 4. Quartal 2020. [Federal association of statutory health insurance physicians. Uniform evaluation standard. 4th quarter 2000]. Available from: https://www.kbv.de/media/sp/EBM_Gesamt_-_Stand_4._Quartal_2020.pdf. Accessed September 21, 2021. German.

39. Briggs AH. Handling uncertainty in economic evaluation and presenting the results. In: Drummond M, McGuire A, editors. *Economic Evaluation in Health Care. Merging Theory with Practice*. Oxford: Oxford University Press; 2001:172–214.

40. Hoffart J, Teichmann A, Wessler I. Biomedical research in Germany: the role of ethics committee and state medical association. *Anesth Analg*. 2011;112(3):501–503. doi:10.1213/ANE.0b013e31820acb75

41. Pagano M, Gauvreau K. *Principles of Biostatistics*. 2nd ed. Boston: Brooks/Cole; 2000.

42. Stinnett AA, Paltiel AD. Estimating CE ratios under second-order uncertainty: the mean ratio versus the ratio of means. *Med Decis Making*. 1997;17(4):483–489. doi:10.1177/0272989X9701700414

43. Black WC. The CE plane: a graphic representation of cost-effectiveness. *Med Decis Making*. 1990;10(3):212–214. doi:10.1177/0272989X9001000308

44. Stinnett AA, Mullahy J. Net health benefits: a new framework for the analysis of uncertainty in cost-effectiveness analysis. *Med Decis Making*. 1998;18(2 Suppl):S68–S80. doi:10.1177/0272989X98018002S09

45. Glick HA, Doshi JA, Sonnad SA, Polsky D. *Economic Evaluation in Clinical Trials*. 2nd ed. Oxford: Oxford University Press; 2014.

46. Fenwick E, Claxton K, Sculpher M. Representing uncertainty: the role of cost-effectiveness acceptability curves. *Health Econ*. 2001;10(8):779–787. doi:10.1002/hec.635

47. Fenwick E, O'Brien BJ, Briggs A. Cost-effectiveness acceptability curves–facts, fallacies and frequently asked questions. *Health Econ*. 2004;13(5):405–415. doi:10.1002/hec.903

48. Gandjour A. Presenting Germany's drug pricing rule as a cost-per-QALY rule. *Health Care Manag Sci*. 2012;15(2):103–107. doi:10.1007/s10729-011-9186-3

49. Thelen U, Schnober D, Schölzel S, et al. Long-term cost and efficacy analysis of latanoprost versus timolol in glaucoma patients in Germany. *Int J Ophthalmol*. 2013;6(2):155–159. doi:10.3980/j.issn.2222-3959.2013.02.09

50. Buxton MJ, Drummond MF, Van Hout BA, et al. Modelling in economic evaluation: an unavoidable fact of life. *Health Econ*. 1997;6(3):217–227. doi:10.1002/(SICI)1099-1050(199705)6:3<217::AID-HEC267>3.0.CO;2-W

51. Weinstein MC, O'Brien B, Hornberger J, et al. Principles of good practice for decision analytic modeling in health-care evaluation: report of the ISPOR task force on good research practices–modeling studies. *Value Health*. 2003;6(1):9–17. doi:10.1046/j.1524-4733.2003.00234.x

52. Atik A, Barton K, Azuara-Blanco A, Kerr NM. Health economic evaluation in ophthalmology. *Br J Ophthalmol*. 2021;105(5):602–607. doi:10.1136/bjophthalmol-2020-316880

53. Bartelt-Hofer J, Ben-Debba L, Flessa S. Systematic review of economic evaluations in primary open-angle glaucoma: decision analytic modeling insights. *Pharmacoecon Open*. 2020;4(1):5–12. doi:10.1007/s41669-019-0141-4

54. Caro JJ, Briggs AH, Siebert U, Kuntz KM; ISPOR-SMDM Modeling Good Research Practices Task Force. Modeling good research practices–overview: a report of the ISPOR-SMDM modeling good research practices task force–1. *Value Health*. 2012;15(6):796–803. doi:10.1016/j.jval.2012.06.012